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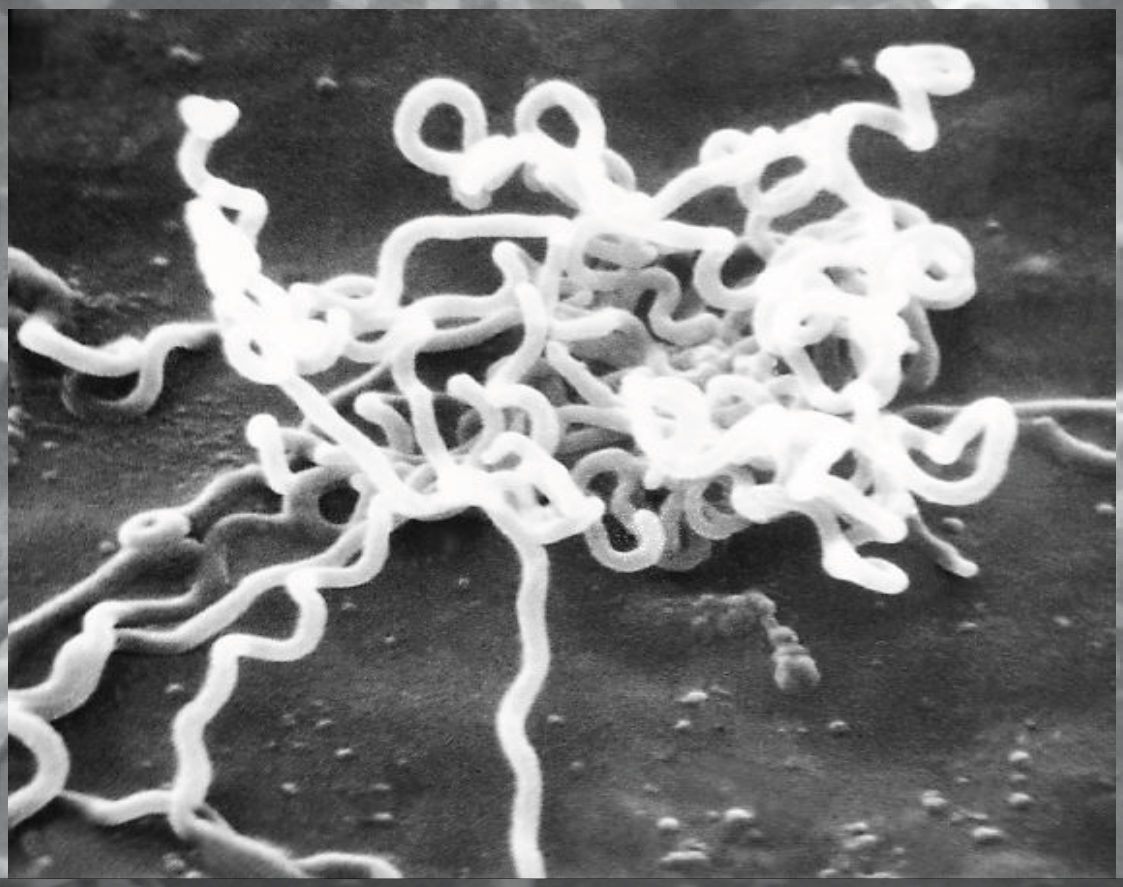

# CONGENITAL SYPHILIS CONFIRMED BY PCR AS RESULT OF FAILURE OF ADEQUATE TREATMENT IN THE PREGNANT WOMAN

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# CONTENTS


## EDITORIAL

Congenital syphilis. New questions about a neglected but re-emerging condition 5
Hernando Gaitán-Duarte
https://doi.org/10.15446/cr.v8n1.99963

## CASE REPORTS

Folliculitis decalvans: a case report of satisfactory recovery after implementing isotretinoin therapy 9
Julián Felipe Porras-Villamil, Ángela Catalina Hinestroza-Ruiz, Gabriela Andrea López-Moreno, Doris Juliana Parra-Sepúlveda
https://doi.org/10.15446/cr.v8n1.88800

De Garengeot's hernia: case report 24
Alejandro Vega-Molina, Kenndy Mawreny Arévalo-Pereira, Daniel Alfonso Fernández-Sandoval, Fabio Felipe Cortés-Díaz
https://doi.org/10.15446/cr.v8n1.90041

Hereditary spastic paraplegia due to NIPA1 gene mutation: case report 32
Dary Jizeth Parra-Párraga, Eugenia Espinosa-García
https://doi.org/10.15446/cr.v8n1.90865

Severe congenital diarrhea secondary to tufting enteropathy. Case report 41
María Angélica Wilches-Cuadros, Laura González-Hakspiel, Paula Nausa-Suárez, María Paula Fernández, Paula Patiño-Ascencio, Alejandra Manrique-Guerrero, Ángela Milena Díaz-Díaz, Derly Liseth Castro-Rojas
https://doi.org/10.15446/cr.v8n1.90883

Congenital syphilis confirmed by PCR as a result of treatment failure for syphilis in pregnancy. Case report 51
Yolanda Cifuentes-Cifuentes, Linda Stefany Gómez-Aristizábal, Gladys Pinilla, Claudia Cruz, Jeannette Navarrete
https://doi.org/10.15446/cr.v8n1.91044

Chronic recurrent multifocal osteomyelitis, a rare disease. Case report 63
Yazmin Paola Martínez-Suárez, José Armando Amador-Gutiérrez
https://doi.org/10.15446/cr.v8n1.91304

Pentalogy of Cantrell. A stillbirth case report 73
Blanca Viviana Fajardo Idrobo, Maribel Palencia Palacios, Valentina López Mosquera, Jaime Antonio Álvarez Soler
https://doi.org/10.15446/cr.v8n1.91323

Successful laparoscopic approach to intraperitoneal bladder injury caused during gynecologic surgery. A case report 85
Carlos Hernán Abonia-Velasco, Juan Camilo Álvarez-Restrepo, David Andrés Castañeda-Millan, Christian Buitrago-Carrascal, Edith Ángel-Muller, Wilfredo Donoso-Donoso
https://doi.org/10.15446/cr.v8n1.91624

Methotrexate nephrotoxicity in a patient with preserved renal function. Case report 96
Juan José Ríos-Valbuena, Paola Karina García-Padilla, Carolina Ardila-Hani
https://doi.org/10.15446/cr.v8n1.92651

Treatment approach to a patient with catamenial epilepsy. Case report 105
Mauricio Andrés Martínez-Ramírez, Karol Zeleny Pinzón-Jaime, Silvia Carolina Rueda-Cataño, Laura Fernanda Sarmiento-Bocanegra, Luisa Cristina Sánchez-Marín, Sara María Lasprilla-Villalobos, Sandra Milena Sánchez-Gutiérrez, Yuly Natalia Guzmán-Yara
https://doi.org/10.15446/cr.v8n1.91649

Metanephric adenoma: differential diagnosis of upper tract urothelial carcinoma. A case report 116
Juan Camilo Álvarez-Restrepo, Víctor Iván Romero-Nieto, Wilfredo Donoso-Donoso, David Andrés Castañeda-Millán, Diego Camacho-Nieto, Jorge Forero-Muñoz
https://doi.org/10.15446/cr.v8n1.92283

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# CONGENITAL SYPHILIS. NEW QUESTIONS ABOUT A NEGLECTED BUT RE-EMERGING CONDITION

**Keywords:** Syphilis, Congenital; Treatment Failure; Penicillin G Benzathine; Syphilis Serodiagnosis; Polymerase Chain Reaction; Nephritis.
**Palabras clave:** Sífilis congénita; Insuficiencia del tratamiento; Penicilina G benzatina; Serodiagnóstico de la sífilis; Reacción en cadena de la polimerasa; Nefritis.

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In this issue of Case Reports, Cifuentes-Cifuentes *et al.* (1) describe a case of congenital syphilis (CS) in a newborn resulting from the first pregnancy of a woman who, despite having been diagnosed with syphilis through serological tests four years earlier, had not received treatment.

At 21 weeks pregnant, the mother attended a prenatal check-up where she was ordered a VDRL test that showed a 1:4 dilution, as well as a treponemal test that was positive. Therefore, she was diagnosed with gestational syphilis (GS) and was prescribed a weekly dose of 2 400 000 IU of benzathine penicillin for 3 weeks.

At the time of delivery, both the mother and the newborn underwent a VDRL test, and although the mother had a 1:1 dilution, which was interpreted as a satisfactory response to treatment, the result in the newborn was a 1:4 dilution. Since the infant also had elevated liver enzyme levels and his urinalysis showed signs of renal failure, he was considered to be a case of CS. Treatment was started with 150 000 IU of intravenous crystalline penicillin every 12 hours for 10 days, which resulted in improvement of the signs of renal failure and liver disease, as well as a negative VDRL test result at 3 months.

This case presents relevant and novel information about the management of CS since Cifuentes-Cifuentes *et al.* (1) concluded that the recommended treatment for GS was insufficient to prevent CS. Consequently, they indicated that clinical and serological follow-up is required to confirm whether maternal treatment was effective in the fetus.

Given the relevance of this publication, I would like to make some reflections that could explain the failure to treat CS when treating GS.

## POSSIBLE MATERNAL RE-INFECTION WITHIN 30 DAYS PRIOR TO DELIVERY

According to the case report, the pregnancy occurred in a woman with late latent syphilis, who became pregnant as a result of a consensual relationship that lasted 3 months; however, it is unclear whether or not the patient had sexual intercourse with this or another partner after the administration of the therapeutic regimen given to her at week 22 of gestation based on the stage of her infection. Thus, reinfection in the mother (primary syphilis) cannot be ruled out as a cause of CS, especially if it was acquired within 30 days after delivery and had little effect on the maternal serological test (2,3). Data about a new sexual contact may not be presented because the patient was not asked for it, or she did not respond or answered incorrectly. In other words, this case report neither confirms nor denies this possibility.

It is important to keep in mind that, as described in Cifuentes-Cifuentes *et al.* (1), international guidelines do not consider the administration of benzathine penicillin to the mother as effective for the treatment of GS if it is administered 30 days before delivery, which is consistent with what has been reported in the literature (2,3).

## UNDERTREATMENT OF CS

According to Workowski *et al.* (2), a single dose of 2 400 000 IU of benzathine penicillin is effective in curing 97% of CS cases if administered more than 30 days before delivery and if there is no reinfection. Therefore, the case of Cifuentes-Cifuentes *et al.* (1) could be among the 3% of patients who do not respond to treatment or could be a case of decreased response of fetal *Treponema pallidum* to benzathine penicillin administered to the mother. However, this cannot be validated because the evidence supporting the effectiveness of GS treatment in terms of fetal or neonatal outcome is considered to be of low certainty since the majority of the information is derived from observational studies (4).

In this regard, in the case published by Cifuentes-Cifuentes et al. (1), more than explaining reinfection, the mechanism that would explain the success of treatment in the mother but the failure of treatment in the fetus remains unclear.

Another interesting aspect of the case presented by Cifuentes-Cifuentes *et al.* (1) is that infection in the newborn was confirmed by a polymerase chain reaction (PCR) test to detect *T. pallidum,* which is one of the most sensitive and specific diagnostic tests to identify this bacterium (2). This is relevant because the diagnosis of syphilis is still based on treponemal and non-treponemal tests, as diagnosis and treatment in a single time have been prioritized for both pregnant women and high-risk populations (5); however, these tests do not perform well in primary syphilis, where microscopy techniques of genital or oral ulcer samples are preferred (2). It is worth mentioning that a very interesting application of PCR tests is that they detect strains resistant to macrolides (2) or tetracyclines (3).

In summary, this case report raises several problems that should be addressed by researchers and public health agencies regarding syphilis infection in Colombia:

For researches, different questions arise, such as: what is the effectiveness, in terms of fetal outcomes, of crystalline penicillin compared with benzathine penicillin in the treatment of CS when detected within 30 days prior to delivery?; what is the resistance profile of *T. pallidum* to macrolides and tetracyclines in Colombia?; and what is the effectiveness of therapeutic alternatives for syphilis in case of penicillin resistance or shortage of this drug?

In turn, health authorities should consider whether it would be important to know the magnitude of the syphilis problem in the general population of the country, given that surveillance reports published by the Ministry of Health and Social Protection of Colombia indicate that the prevalence rate of gestational syphilis is 1.3 cases per 100 live newborns (2). This would allow determining if there is an undeclared epidemic of population-based syphilis, what measures are being taken to control syphilis outbreaks in the general population, and what surveillance methods are being implemented for dealing with antibiotic-resistant *T. pallidum.*

The situation of GS and CS in Colombia may be a warning sign of the syphilis situation in the general population; therefore, it must be viewed as a public health issue, as the disease cannot be eradicated if the foci of infection are not controlled. In this sense, the researchers must work to ensure that the entities responsible for its prevention, treatment, follow-up and control, both individual and collective, provide the necessary resources to seek solutions that enable an interdisciplinary approach to care for patients with syphilis and to generate strategies to prevent and eradicate this infection.

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# FOLLICULITIS DECALVANS: A CASE REPORT OF SATISFACTORY RECOVERY AFTER IMPLEMENTING ISOTRETINOIN THERAPY

**Keywords:** Folliculitis; Hair Follicle; Isotretinoin; Cicatricial alopecia.
**Palabras clave:** Foliculitis; Alopecia Folículo piloso; Isotretinoina.

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## ABSTRACT

**Introduction:** Folliculitis decalvans is a rare skin disease characterized by the presence of painful papules and pustules with an underlying neutrophilic infiltrate, usually on the scalp. Its treatment is lengthy and challenging, and recurrence is relatively common. Although its etiology is unknown, several theories explaining its development have been proposed, including colonization by *Staphylococcus aureus.*

**Case description:** This is the case of a 26-year-old male healthcare worker who visited the outpatient service after experiencing a 4-year history of painful pustules on the scalp; initially these lesions were located in the occipital region, but then also started to appear in the temporal and parietal regions. After being treated for bacterial folliculitis and having several recurrences, a skin biopsy was performed, which allowed diagnosing him with folliculitis decalvans. Once the diagnosis was made, isotretinoin (20mg) treatment was implemented for a year and a half, achieving complete remission of the lesions.

**Conclusion:** Although this case has some limitations, such as the lack of histopathology images and some control laboratory tests, it clearly shows the difficulties faced when treating this type of skin disorders and presents an overview of the use of isotretinoin, evidencing that although this drug is well tolerated, possible adverse reactions from drug interactions with trimethoprim/sulfamethoxazole may arise. In addition, this case is of great importance since the possible presence of a familial cluster of folliculitis decalvans could be confirmed, if further genetic testing is performed.



## RESUMEN

**Introducción.** La *folliculitis decalvans* es una enfermedad dermatológica rara caracterizada por la presencia de pápulas y pústulas dolorosas que están acompañadas de un infiltrado de neutrófilos subyacente. Esta condición suele aparecer en el cuero cabelludo, su recurrencia es relativamente común y su tratamiento, largo y difícil. Aunque su etiología es desconocida, se han propuesto muchas teorías que intentan explicar su aparición, siendo la colonización por *Staphylococcus aureus* una de ellas.

**Presentación del caso.** Hombre de 26 años que se desempeñaba como trabajador de la salud y consultó por un cuadro clínico de 4 años de evolución caracterizado por la aparición de pústulas dolorosas en la región occipital, las cuales posteriormente se extendieron a la región temporal y parietal. Después de tratarlo como una foliculitis infecciosa y tras múltiples recurrencias, se realizó una biopsia de las lesiones que permitió diagnosticarlo con folliculitis decalvans. Se instauró un tratamiento consistente de 20mg de isotretinoina al día por un año y medio, con el cual se logró la resolución de la folicutis. Sin embargo, dos años después tuvo un relapso, pero, según el paciente, esto pudo ocurrir por el consumo de derivados lácteos, ya que,

según indicó, cuando suspende el consumo de esta clase de productos no aparecen más lesiones luego de 2-3 semanas.

**Conclusión.** Aunque este caso tiene algunas limitaciones como la ausencia de imágenes histopatológicas y algunos laboratorios de control, muestra las dificultades para tratar este tipo de condiciones dermatológicas y presenta un panorama del uso de la isotretinoina, ya que evidencia que este medicamento tiene una buena tolerancia, pero presenta interacciones medicamentosas adversas con la trimetoprima/sulfametoxazol. Además, este caso es de gran importancia, ya que, si se realizan más pruebas genéticas, podría confirmarse la posible presencia de un grupo familiar de foliculitis decalvante.

## INTRODUCTION

Folliculitis decalvans, also known as scarring alopecia, is a type of primary cicatricial alopecia (for a description of the different types of primary cicatricial alopecia see Table 1) (1). It is a rare skin disease characterized by the presence of inflammatory neutrophilic infiltrates and scarring that cause perifollicular papules and pustules, and it accounts for approximately 10 % of all primary cicatrizing alopecia cases (2,3). This condition was first described by Quinquaudin 1888 (3,4), but it was only until 1905 that it was named as folliculitis decalvans by Broqc et al. (5)

Table 1. Types of primary scarring alopecia.

| Lymphocytic | Neutrophilic |
|---|---|
| Discoid lupus erythematosus | Folliculitis decalvans |
| Lichen planopilaris<br>Classic<br>With lichen planus and/or spinous lesions<br>With frontal sclerosing alopecia | Acne keloidalis nuchae |
| Pseudopelade of Brocq<br>Classic<br>Non-specific scarring alopecia | Tinea capitis |
| | Tufted folliculitis |
| Follicular degeneration syndrome | Acne necrotica |
| Alopecia mucinosa | Dissecting cellulitis of the scalp |

Source: Own elaboration based on (1).

It generally occurs in middle-aged adults, predominately males, and tends to be more frequent in people with dark skin. Although its etiology is unknown, it has been described that *Staphylococcus aureus* may be a contributing factor; (6-8)

other possible causes include mechanisms involving superantigens or cytotoxins that bind to themajor histocompatibility complex class II (MHC II) molecules (9) and a genetic component, since several familial cases have been reported. (2,10,11)

Folliculitis decalvans management has proven to be a challenge since there is a wide range of treatment alternatives, including antibiotic therapy (tetracycline, trimethoprim/sulfamethoxazole, cephalosporins, ciprofloxacin, minocycline or clindamycin or clarithromycin plus rifampicin) (1,6,9), the use of topical antibiotics (for example erythromycin, mupirocin and clindamycin) (1), antifungals, retinoids, corticosteroids (topical or oral), phototherapy, and laser depilation. (1,7,12)

The occipital region and the vertex are usually the most affected areas in patients with this condition. Generally, folliculitis decalvans starts as a single lesion and then spreads in a centrifugal progression with the development of painful follicular papules and pustules. (2,5) As the disease progresses, a hardened erythematous plaque appears. (7) Follicular keratosis, erosions and hemorrhagic crusts are also observed. (5,13) Furthermore, some patients may experience spontaneous bleeding, pain, and a burning sensation. (5,6) Likewise, polytrichia (tufted hairs), that is, the presence of multiple hair shafts emerging from a single dilated hair follicle, may also be found in some cases. (5,6,9,14)

Dermatoscopy has been shown to be a useful procedure for diagnosing this skin condition. (15) In this regard, trichoscopy can be highly useful. In patients with folliculitis decalvans, the main finding during this examination is the presence of tufted hairs surrounded by perifollicular hyperplasia that may be arranged in a starburst pattern (starburst sign); other findings include the presence of yellowish tubular scaling and follicular pustules with emerging hair shafts in their midpoint. In addition, white and milky red areas lacking follicular openings are predominant in long-lasting lesions. (16,17)

Histopathologically, these lesions are first characterized y by the presence of neutrophilic infiltrates, and, as it progresses, the presence of neutrophilic, lymphocytic and histiocytic infiltrates. (18) At first, the location of the infiltrate is peri-infundibular, but it may affect the entire follicle. (18,19)

Other usual findings in patients with folliculitis decalvanas include the formation of abscesses and the presence of polythrichia and perifollicular fibrosis. (19) Infectious agents are rarely found and differential diagnoses include infectious folliculitis, follicular degeneration syndrome, and acne necrotica. (1) This paper reports the case of a young healthcare worker with folliculitis decalvans.

## CASE PRESENTATION

This is the case of a 26-year-old middle-class male healthcare worker of Hispanic origin, from Bogotá D.C., Colombia, who, in August 2017, visited the outpatient service of a tertiary care hospital due to a history of approximately 4 years of pustules and papules in the scalp.

According to the patient, he did not have any relevant history of disease or surgeries. He reported drinking alcohol occasionally but denied having used psychoactive substances; also, he did not have any known allergy. The patient had the following family history of disease: gastric cancer (paternal grandmother), breast cancer (half-sister), and diabetes mellitus type 2, hypertriglyceridemia, and high blood pressure in other relatives, both maternal and paternal.

The following findings were reported on the physical examination made during the outpatient appointment: blood pressure: 118/76; heart rate: 64 bpm; respiratory rate: 16 bpm; body temperature: 36.6°C; weight: 91kg, and height: 168cm. Likewise, several lesions (approximately 60) compatible with perifollicular papules and pustules were observed mainly on the scalp (in the vertex and the occipital, temporal, and parietal regions), while some others were located in the bordering area between the neck and the scalp.; there were no lesions in other regions different than the scalp, that is, the face, armpits, groin or buttocks. Regarding its mental health status, the patient reported feeling irritable and having a negative attitude due to the lack of sleep experienced as a result of the pain produced by the lesions. There were no other significant findings.

During the 2017 outpatient appointment, the patient reported the following sequence of events.

**August 2015:** The patient reported that he started suffering from individual and extremely painful and suppurating pustules since the second semester of 2015. In addition, according to the patient, each lesion had the same rapid evolution, described as follows: 1) development of painful erythema, 2) increase in the severity of erythema and swelling, 3) appearance of a pustule, and 4) spontaneous pustule rupture with blood and purulent fluid (pus) secretion. (Figure 1A). Most of the lesions appeared in the occipital region of the scalp. This situation persisted over time, but as there were very few lesions, he did not did not seek medical help. According to the patient, the appearance of the first lesions was caused by a prolonged and seriously stressful situation.

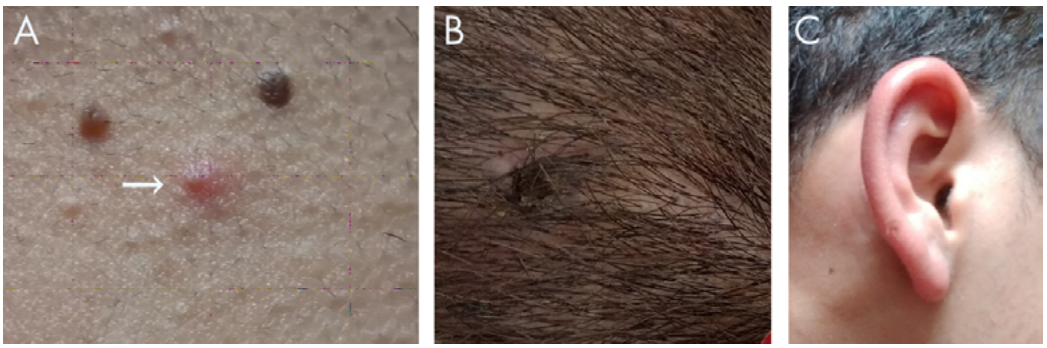


Figure 1. A) A pustule on the scalp, more specifically in the bordering area between the scalp and the neck. B) Site of the skin biopsy, near the vertex. C) Erythematous swelling secondary to the application of fusidic acid.

Source: Images obtained while conducting the study.

**October 2016:** After a trip to the Colombian Pacific region, the patient started to notice an increase in the number, distribution, and size of lesions. At first, he reported that 1 or 2 lesions would appear per week, but that as time passed this number increased to 30 or more per week. Also, not only the number of lesions appearing per week increased, but they started to appear in other regions of the scalp different than the occipital region, including the vertex an the temporal, and parietal regions. As a result of such an increase in the number of lesions and their wider distribution, e pain became almost unbearable, thus affecting his sleep habits and mood.

**Late 2016:** Given this situation, the patient scheduled a medical visit with a general physician who diagnosed him with bacterial folliculitis and started treatment consisting of doxycycline 200mg per os twice per day for 30 days, although he did not have a history of head shaving. In addition, the patient was referred to a dermatologist for further assessment, who agreed with continuing the initial antibiotic therapy for two more months, achieving the complete resolution of the existing lesions.

**February 2017:** Unfortunately, about two to three months after ending the doxycycline therapy, the lesions reappeared, so the patient scheduled another medical appointment with the same dermatologist and a new antibiotic treatment was started, this time consisting of oral trimethoprim/sulfamethoxazole 800mg/125mg twice a day for 15 days, topical mupirocin every 8 hours for 10 days and taking showers/baths with Kelual DS foaming gel (ciclopiroxolamine) and chlorhexidine 2 times per day for a month. As was the case with the initial suggested treatment, lesions disappeared, but they reappeared two to four months later.

**June 2017:** The patient reported that pain intensity and the number and size of lesions increased each time there was a relapse. Also, he said that some lesions were fusing together (3 to 5 at a time), and that he had observed alopecia in some areas. Likewise, he expressed having problems to sleep due to the pain caused by the lesions, as well as subsequent irritability and mood swings, which had a negative impact on his life both personally and the at the workplace. He also reported that his sister had started to experience similar signs and symptoms although less severely.

**November 2017:** Despite the reappearance of the lesions, no pharmacological treatment was prescribed by the dermatologist until a skin biopsy was performed, since folliculitis decalvans was suspected. The skin biopsy was performed using samples taken from two lesions (Figure 1B). Diagnosis was confirmed with biopsy report results (January 2018), in which the following findings were described: neutrophilic infiltrates, perifollicular fibrosis and polytrichia (no cultures were taken). Once the diagnosis was confirmed and routine laboratory tests were performed, that is, late January 2018, the patient was prescribed with oral isotretinoin therapy (20mg daily) for a year and a half due to his weight, as well as the use of topical fusidic acid 3 times per day for 2 weeks and taking baths with chlorhexidine 1 time per day for 1 month; he was also informed of some recommendations, such as stopping alcohol consumption altogether.

After treatment was started, the patient's condition improved significantly as lesions and alopecia areas disappeared. However, he reported having an allergic

reaction to fusidic acid, so its use was immediately suspended (Figure 1C). Approximately 4 months after the treatment was started, a new lesion appeared, but he opted for self-medication (a single dose of trimethoprim/sulfamethoxazole of 160/800mg), which caused a severe adverse reaction (fever, headache, and fatigue), so he suspended the use of this antibiotic; there were no more self-medication cases during the remaining of the treatment after it was finally completed. The results of the laboratory tests taken at different times (diagnosis and treatment over one year and a half), including those performed after the adverse reaction to trimethoprim/sulfamethoxazole occurred, are available in Table 2.

Table 2. Laboratory tests results of the patient.

| Test | 13/01/2018 | 27/03/2018 | 17/06/2018† | 20/09/2018 | 09/07/2019 |
|---|---|---|---|---|---|
| Creatinine urine test (mg/dL) | 0.85 | 0.83 | No information | No information | 0.73 |
| Blood glucose test (mg/dL) | 92.00 | 92.30 | 99.00 | no information | 99.26 |
| Postprandial glucose test (mg/dL) | No information | No information | 115.03 | no information | No information |
| Phosphatase alkaline test (U/L) | No information | 86.10 | No information | 87.50 | No information |
| Creatine phosphokinase (CPK) test (U/L) | No information | No information | 75.00Ŧ | No information | No information |
| Lactic dehydrogenase test (U/L) | No information | No information | 161.30 | No information | No information |
| Alanine Aminotransferase test (ALT) (U/L) | 21.60 | 25.90 | 41.40 * | 32.30 | 43.90 * |
| Aspartate aminotransferase (AST) test(U/L) | 22.30 | 17.20 | 21.30 | 21.00 | 23.20 |
| Total cholesterol test (mg/dL) | 191.50 | No information | 196.50 | 179.10 | 172.3 |
| High-Density Lipoprotein (HDL) Cholesterol Test (mg/dL) | 44.40 | No information | No information | No information | 36.70 |
| Low-density lipoprotein (LDL) test (mg/dL) | 125.08 | No information | No information | No information | 110.15 * |
| Triglycerides test (mg/dL) | 110.10 | No information | 190.50 * | 209.00 ** | 130.39 |
| Complete blood count | Normal limits | Normal limits | No information | No information | Normal limits |
| Urinalysis | Normal limits | No information | No information | No information | Normal limits |

Comments:
* Outside normal reference values; slight increase in values.
** Outside normal reference values, significant increase in values.
† Prior to undergoing these tests, the patient self-medicated.
Ŧ There was no control CPK test, which is another limitation of the case presented here.
Source: own elaboration based on the data obtained from the patient's medical record.

**November 2019:** Treatment was completed without any adverse effects. It should be noted that despite medical treatment was started relatively early and complete remission was achieved, there is always a possibility of relapse. A yearly timeline of the case is described in Table 3.

**November 2021 (follow-up):** The patient reported a mild relapse. However, lesions disappeared after he followed the recommendation of suspending the consumption of milk and other dairy products.

**January 2022 (follow-up):** According to the patient, lesions do not appear unless he consumes dairy products or derivatives, as they usually appear 2 to 3 days after he eats or drinks any of such products, but they disappear within 2 to 3 weeks after suspending said consumption. There was no sign of new lesions during this follow-up examination, and the patient claimed that he is doing his best to continue with a dairy-free diet.

Table 3. Timeline.

| Year | General characteristics | Diagnosis | Treatment | Second treatment | Relapse | Comments | Skin biopsy results |
|---|---|---|---|---|---|---|---|
| 2015 | The first lesion appeared | NA | NA | NA | NA | The patient did not report any travel | N/A |
| 2016 | Lesions continued to appear once or twice per week. After a trip to the Colombian Pacific region, the number and size of lesions appearing per week increased, as well as pain intensity | NA | NA | NA | NA | The patient travelled to the Colombian Pacific Region (Guapi, Cauca) | N/A |
| Late 2016 | The patient sought medical assistance | Bacterial folliculitis | Doxycycline 200mg po twice a day for 30 days, and then for 2 more months | Trimethoprim sulfamethoxazole 800/125mg po twice a day for 15 days, topic mupirocin every 8 hours for 10 days, and 2 baths with Kelual DS and chlorhexidine 2 time per day for a month | Yes, 2 to 3 months after completing each therapy | N/A | |
| 2017 - 2018 | Patient continued attending follow-up visits with the Dermatology Service | Folliculitis decalvans | Isotretinoin 20mg po daily for 1 year and a half, topical fusidic acid and 3 times per day for 2 weeks and baths with chlorhexidine x times per day for 1 month | NA | NA | Allergic reaction to fusidic acid, so it was suspended. Due to the appearance of a new single lesion the patient self- medicated with trimethoprim sulfa-methoxazole 800/125mg; however, he experienced a severe adverse reaction and a slight increase in liver enzymes was evidenced. Isotretinoine is started. | Yes, findings compat-ible with folliculitis decalvans |
| 2019 | Complete remission | Folliculitis decalvans | | | | | |
| 2021 | Mild relapse: smaller and sparser lesions | Folliculitis decalvans | No medication was started. The suspension of dairy products was ordered. | N/A | N/A | N/A | N/A |
| 2022 | Remission. The patient is exercising and losing weight | Folliculitis decalvans | Dairy-free diet | | | | |

po: medication taken orally.
Source: own elaboration.

## DISCUSSION

Folliculitis decalvans is a rare type of primary cicatricial alopecia that mainly affects middle-aged males (18,19,20,21). In addition, although it has been described that *S aureus* infection might be a contributing factor, there is no clear evidence on its association with the occurrence of this disease (18,19,20,21). Most cases seem to be sporadic, and lesions mainly appear on the vertex. (20,21) Its diagnosis and treatment are a challenge since reaching a diagnosis may take several years and sometimes treatment needs to be extended due to folliculitis decalvans being refractory. (22)

In the case reported here, the information provided by the patient allowed the treating physician to make a rather fast diagnosis and start a timely treatment. The clinical manifestations of folliculitis decalvans described here are similar to what have been reported in other case reports (6,9). Likewise, as shown in other case reports (23), treatment with isotretinoin was successful in our case. Other therapeutic options include the use of biological drugs, (24,25) photodynamic therapy (20,21) and even YAG laser (26), especially in cases of recalcitrant folliculits decalvans.

Regarding prognostic factors for severe folliculitis decalvans, our patient presented with tufted hairs (polytrichia); besides it had an early onset (age < 25 years old) and had lasted several years. (20) As mentioned above, proper treatment of this condition has proven to be a challenge (1,7,12), as several therapies have been reported with a varying range of success; in this regard the main clinical characteristics of folliculitis decalvans, as well as some of the therapies described for its treatment (including doses) are available in Table 4. Other therapeutic alternatives include medical honey (27) and adipose tissue transplantation. (22) Primary scarring alopecia refers to a heterogeneous group of rare disorders in which hair follicles are destroyed irreversibly, (28) most of these disorders can be easily recognizable based on their clinical manifestations, however skin biopsies are useful for confirming the diagnosis. (29)

Table 4. Treatment options and main clinical characteristics of folliculitis decalvans and some other types of scarring alopecia.

| Disease | Clinical characteristics | Treatment options |
|---|---|---|
| Folliculitis decalvans | It affects both men and women. | Antimicrobial shampoo<br>Isotretinoin<br>Clarithromycin (4-8 weeks)<br>Doxycycline (4-8 weeks)<br>Clindamycin 300mg plus rifampicin 300mg for 6-12 weeks<br>Dapsone 50mg for several years<br>Removal of all tufted hair follicles to prevent recurrence. |
| | Intense granulocytic inflammation destroys the hair follicles and the skin of the scalp. | |
| | Scarred and atrophic areas, together with severe inflammation are observed during physical inspections. | |
| | Presence of tufted hairs (5-20), which act as a portal of entry for staphylococci. | |

| Disease | Clinical characteristics | Treatment options |
|---|---|---|
| Perifolliculitis capitis abscedens et suffodiens | It mainly affects men. | Aspiration of nodules<br>Injection of triamcinolone crystal suspension (10mg/mL)<br>Systemic glucocorticoids (e.g., methylprednisolone)<br>Isotretinoin |
| | Initial lesions are hemispherical, lividly inflamed, hairless, soft and fluctuant; they are located on the scalp. | |
| | Bloody exudate is generally microbiologically sterile. In extreme cases the entire scalp is undermined by confluent inflammatory exudates. | |
| Lichen planopilaris | A dense collection of T lymphocytes is found under the epidermal and follicular basal laminae. | Class III or IV corticosteroids foams<br>Retinoid actitretin<br>Hydroxychloroquine |
| | Possible autoimmunity to unknown basement membrane antigen. Destruction of follicular stem cells. | |
| | Physical inspection findings: small areas of alopecia with peripheral follicular hyperkeratosis. | |
| | Hairs in the affected area seem to have a tight-fitting white collar. | |
| | Lassueur-Graham-Little-Piccardi syndrome: characterized by the triad of patchy cicatricial alopecia of the scalp, nonscarring of the axilla and groin, and a follicular spinous papule on the body, scalp, or both. Dystrophic changes in fingernails and toenails. | |
| Frontal fibrosing alopecia (first described by Kosard) | This disorder is considered a variant of lichen planopilaris | Therapy analogous to that of lichen planus |
| | It almost exclusively affects elderly women; however, it can occur in men and women in the perimenopuse period. | |
| | The loss of hair resembles the one observed in patients with androgenetic alopecia | |
| | Perifollicular alopecia and hyperkeratosis can often be seen | |
| | Often restricted to frontal regions | |

| Treatment options | |
|---|---|
| **Option *** | **Dosage or Combination** |
| Option 1 | Doxycicline bid 100mg po per day for 3-6 months |
| Option 2 | Rifampicin 300 mg po for 3 months or Rifampicin and Cyndamicin 300mg bid for 10 weeks |
| Option 3 | Minocycline 100mg po per day for 3-6 months |
| Option 4 | Clarithromycin 250 mg bid × 3 months, acitretin 10 mg bid / qd × 1 month, rifampicin 300 mg bid × 1 month |
| Option 5 | Isotretinoin 0.2-0.5mg/kg po once a day for 6 months to a year |
| Option 6 | Cephalexin (500mg per os 3-4 times a day) + Intralesional triamcinolone + Clobetasol propionate lotion for 4 months to 4 years |
| Option 7 | Intralesional triamcinolone + clobetasol propionate lotion + (doxycycline 100mg bid, minocycline 100mg bid, or tetracycline 500mg bid) between 6 months to 4 years |
| Option 8 | Photodynamic therapy |
| Option 9 | Azithromycin 500mg po/day 3 times weekly for 3 months day |
| Option 10 | Dapsone 75-100mg po per day for 4-6 months |

bid: twice a day
po: medication taken orally
qd: every day
* There are many other therapeutic options available. Treatment of the disease is not clear, as it can last even years and there is not strong evidence supporting its implementation. (40)

Source: Own elaboration based on Powell *et al.* (6); Sillani *et al.* (9); Miguel-Gómez *et al.* (20); Tietze *et al.* (23); Trüeb (28); Wolff *et al.* (30); Stokmeier *et al.* (31); Bolz *et al.* (32); Kossard (33); Vaño-Galván *et al.* (34); Harries & Messenger (35); Le Cleach & Chosidow (36); Tan *et al.* (37); Miguel-Gomez et al. (21); Vaño-Galván et al. (2); Bunagan *et al.* (38); Aksoy *et al.* (39), and Rambhia *et al.* (40).

Although the use of isotretinoin is a valid therapeutic alternative for the treatment of folliculitis decalvans, it can cause several adverse effects on the skin and mucous membranes, as well as muscle and skeletal alterations; besides, its teratogenic effect may limit its usefulness. (22)

The management of folliculitis decalvans requires both patience and economic resources, for its treatment is lengthy, and the medications to be used may be expensive. In this regard, it has been estimated that a patient might spend as much as 80 sterling pounds per month ($99 USD) in medications and other products necessary for proper treatment. (20)

On the other hand, patients with this condition need to be aware of the importance of follow-up and their own responsibility in terms of adherence to treatment and the proper care of the lesions; for example, in the case of our patient, he was asked to completely stop drinking alcohol due to the metabolism of isotretinoin. Furthermore, patients must be informed that the possibility of relapse is always present, and that it may take years to achieve full remission (i.e., absence of folliculitis decalvans), or that even treatment will be needed the whole life; making this clear early is important because it may have a toll on the patient's mental health. (20) Likewise, patients must be aware of the challenges of reaching a diagnosis, as folliculitis decalvans is not only a rare disorder, but there are also several differential diagnoses (Table 5).

Table 5. Differential diagnoses of scalp folliculitis.

| Folliculitis and perifolliculitis | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Infectious folliculitis or caused by infestations or Infections** | | **Non-infectious (folliculitis)** | | | **Perifolliculitis** | | |
| **Superficial (generally suppurating lesions)** | **Deep (generally granulomatous lesions)** | **Superficial (generally suppurative)** | **Deep (generally granulomatous)** | **Other possibilities (spongiotic folliculitis)** | **Predominantly lymphocytic** | | **Predominantly granulomatous** |
| Fungi: Dermato-phytes Pityrosporum Candida | Demodicosis | Acne vulgaris | Acne vulgaris | Pruritic folliculitis of pregnancy | Keratosis pilaris atrophi-cans and Keratosis follicularis spinulosa decalvans | Demodi-cosis | Perioral dermatitis |
| Bacteria: Bacteria (Impetigo of Bockhart) Secondary to Syphilis infection | Favus and kerion | Rosacea and perioral dermatitis | Lupoid rosacea | Fox-Fordyce disease | Keratosis pilaris atrophi-cans | Vitamin C deficiency | Acneiform erup-tion secondary to syphilis |

| Folliculitis and perifolliculitis | | | | | | | |
|---|---|---|---|---|---|---|---|
| Infectious folliculitis or caused by infestations or Infections | | Non-infectious (folliculitis) | | | Perifolliculitis | | |
| Superficial (generally suppurating lesions) | Deep (generally granulomatous lesions) | Superficial (generally suppurative) | Deep (generally granulomatous) | Other possibilities (spongiotic folliculitis) | Predominantly lymphocytic | | Predominantly granulomatous |
| Viruses: Herpes simplex virus Varicella zoster virus Molluscum contagiosum | Tinea barbae | Eosinophilic pustular folliculitis | Acne conglobata | Infundibulofollic-ulitis | Lichen planopi-laris | Vitamin A deficiency | |
| | Majocchi's granuloma | Toxic erythema of the newborn | Keloidal acne of the neck | | Pityriasis rubra pilaris | Lithi-um-in-duced folliculitis | |
| | Furuncle | Follicular mucinosis | Perforating folliculitis | | | | |
| | Carbuncle | Mechanical and chemical traumas | Toxicoderma: Halogens Lithium | | | | |
| | Sycosis | Toxicoderma: Halogens Steroids | Pseudofolliculitis | | | | |
| | Pustular acneiform Secondary syphilis | Pseudofollic-ulitis | | | | | |

Source: Own elaboration based on the paper by Lugovic-Mihic *et al.* (41), which in turn used information described by Camacho *et al.* (25)

One of the most important strengths of the case reported here is that the patient was referred to the dermatology service for conducting a comprehensive assessment consisting of a thorough clinical and physical examination and the performance of laboratory tests and a skin biopsy. On the other hand, this case has the following limitations: genetic and immunological aspects were not analyzed; the patient's relatives were not assessed and tested and, therefore, it was not possible to confirm the presence of familiar cluster; there were no follow-up laboratory tests; and there were no photographs depicting the histopathological characteristics and clinical distribution of the lesions.

## CONCLUSION

The case reported here clearly exposes the challenges that treating folliculitis decalvans and other types of primary cicatricial alopecia implies. In addition, this case is of great importance since, if further genetic testing is performed, the possible presence of a familial cluster of folliculitis decalvans could be confirmed.

Furthermore, it was observed that although the patient had an adequate response to retinoid therapy, drug interactions must always be monitored to avoid the occurrence of adverse reactions, as happened when the patient self-medicated with trimethoprim sulfamethoxazole while taking isotretinoin, even though no adverse reactions were reported when such treatment was first implemented.

## ETHICAL CONSIDERATIONS

The patient signed a written informed consent form in which he agreed to the use of his clinical data and photographs for the publication of this case report. Data anonymity was ensured at all times.

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## CONFLICT OF INTERESTS

None declared by the authors.

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CASE REPORTS
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# DE GARENGEOT'S HERNIA: CASE REPORT

**Keywords:** Femoral hernia; Ultrasound; Appendix.
**Palabras clave:** Hernia femoral; Ultrasonido; Apéndice.

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## RESUMEN

**Introducción.** La hernia de Garengeot es una entidad cuyo diagnóstico es principalmente intraoperatorio, se presenta con mayor frecuencia en mujeres y corresponde al hallazgo del apéndice cecal contenido en una hernia femoral. La mayoría de las hernias femorales se identifican mediante diagnóstico clínico, pero para su verificación es importante hacer una valoración con imágenes diagnósticas: el ultrasonido, por ejemplo, es una herramienta valiosa para caracterizar la anatomía de la hernia y su contenido, y para establecer el planeamiento quirúrgico.

**Presentación de caso.** Mujer de 75 años quien asistió al servicio de cirugía general de un hospital de alta complejidad de Bogotá, Colombia, por presentar una masa dolorosa en región inguinal derecha. El estudio ecográfico inicial mostró una hernia femoral conteniendo el apéndice cecal con septos internos que separaban el líquido dentro del saco herniario. La paciente presentó inflamación crónica en el apéndice, por lo que se le practicó herniorrafía femoral con malla y apendicectomía sin complicaciones y con las cuales tuvo una recuperación satisfactoria.

**Conclusiones.** El examen clínico puede ser suficiente para confirmar la presencia de una hernia en un gran número de casos cuando se hace el abordaje diagnóstico de masas inguinales con presencia de dolor; sin embargo, las imágenes diagnósticas, especialmente la ecografía con transductores de alta resolución, constituyen la herramienta de primera línea para caracterizar el tipo de hernia y el contenido del saco herniario, lo que facilita la planeación quirúrgica.

## ABSTRACT

**Introduction:** De Garengeot hernia is an entity mainly diagnosed intraoperatively. It is more frequently observed in women and is defined as the presence of the vermiform appendix inside to femoral hernia. Most femoral hernias are identified based on clinical diagnosis, but diagnostic imaging is necessary for confirmation. Ultrasound, for example, is a valuable tool to characterize the anatomy of the hernia and its content, and to establish surgical planning.

**Case presentation:** A 75-year-old woman attended the general surgery department of a high complexity hospital in Bogotá, Colombia, due to a painful mass in the right inguinal region. The initial ultrasound study showed a femoral hernia containing the incarcerated appendix and periappendiceal fluid in the hernial sac. The patient developed chronic appendiceal inflammation, so she underwent femoral hernia repair with mesh and appendectomy without complications, achieving a satisfactory recovery.

**Conclusion:** Clinical examination may be sufficient to confirm the presence of a hernia in a large number of cases when the diagnostic approach involves the search of inguinal masses with pain. However, to facilitate surgical planning, diagnostic imaging, especially ultrasound with high-resolution transducers, is the primary tool to characterize the type of hernia and the contents of the hernial sac.

## INTRODUCTION

De Garengeot hernia is a femoral hernia that contains the appendix. It was first described in 1731 by René Jacques Croissant de Garengeot and, according to the literature, the first case of appendicectomy due to appendicitis contained in a De Garengeot hernia was published in 1785 by Hevin (1,2). This type of hernia is most common in women, accounts for only 0.5% to 5% of all hernias, and can lead to complications such as strangulation or acute inflammation in some cases (1).

Differential diagnoses of De Garengeot hernia include Amyand hernia, which is defined as an inguinal hernia that contains the appendix; pelvic or venereal infectious diseases associated with adenopathies; incarcerated or strangulated hernias; soft tissue tumors, among others (3-5). Although its diagnosis is usually clinical, diagnostic imaging must be used to establish pre-surgical planning. It is important to keep in mind that in most cases this type of hernia is diagnosed intraoperatively (1-3).

The main approaches proposed for the management of this entity are appendectomy and herniorrhaphy (4,6).

The following is the case of a woman with a De Garengeot hernia and multiple comorbidities, who was diagnosed via ultrasound and had inflammation of the tip of the appendix during her treatment.

## CASE PRESENTATION

A 75-year-old white woman attended a primary health care center due to pain and mass sensation in the right inguinal region for a month. The patient reported the following relevant history: chronic hypertension, active smoking, and pulmonary thromboembolism, which was treated with low molecular weight heparin.

An ultrasound of the inguinal region performed shortly after the onset of symptoms revealed a De Garengeot hernia of 6.3mm in diameter that did not compress with external pressure during the examination. This imaging study also revealed fluid with thin septa inside the hernia sac (Figures 1 and 2), so the patient was advised to go to the emergency department. However, the woman opted to wait and consult on an outpatient basis, and one month later attended the general surgery service of the Hospital Universitario Nacional de Colombia.

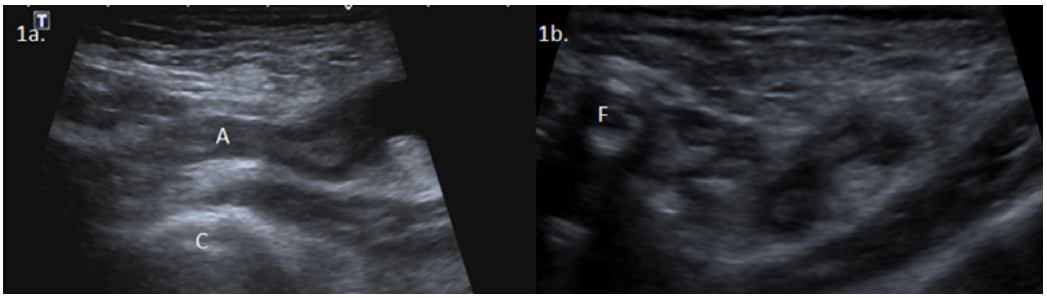


Figure 1 Ultrasound of the inguinal region along the longitudinal axis (1a) and the transverse axis (1b).
A: vermiform appendix; C: femoral head; F: common femoral artery.
Source: Document obtained during the study.

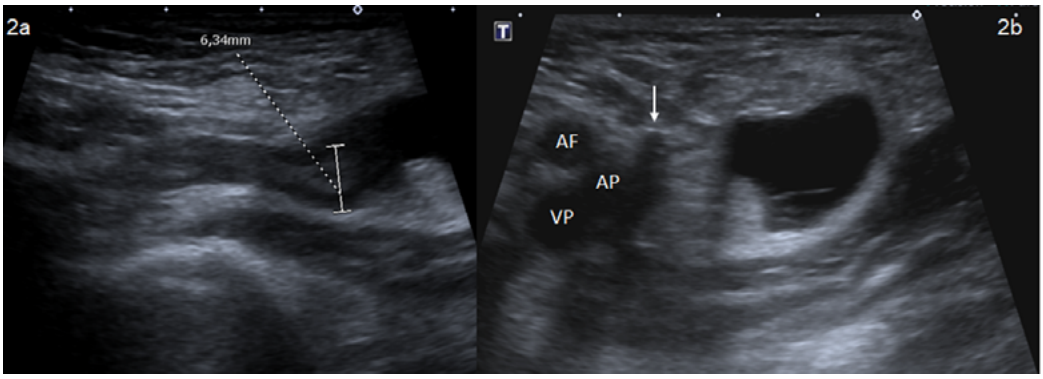


Figure 2 Ultrasound of the inguinal region. 2a) thickening of the tip of the appendix; 2b) fluid with thin septa inside the hernia sac.
Arrow: compression of the medial wall of the femoral vein: AF, superficial femoral artery; AP: deep femoral artery; VP, deep femoral vein.
Source: Document obtained during the study.

On admission examination, vital variables were altered: heart rate of 66 bpm, respiratory rate of 14 rpm, blood pressure of 107/48 mmHg, and oxygen saturation of 88% with $FiO_2$ of 0.28%. On physical examination, the patient was found in acceptable general condition, conscious and hydrated; her abdomen was soft, and, on palpation, there was no evidence of pain, masses, signs of intestinal obstruction, increase in the size of the abdominal organs, or distension. A mass of 3cm in diameter was found in the right inguinal region; it was painful on palpation and did not compress with external pressure. The rest of the examination was normal.

Based on the findings of the physical examination and the initial ultrasound, it was decided to hospitalize the patient and perform a series of pre-surgical laboratory tests, all of which were within normal ranges. An ultrasound study was performed again, confirming the presence of a De Garengeot hernia and showing that the vermiform appendix had a thickening in the walls of its tip, with an anteroposterior diameter of 6.7mm that did not decrease with external pressure, as well as scarce free fluid in the hernia sac (Figure 3).

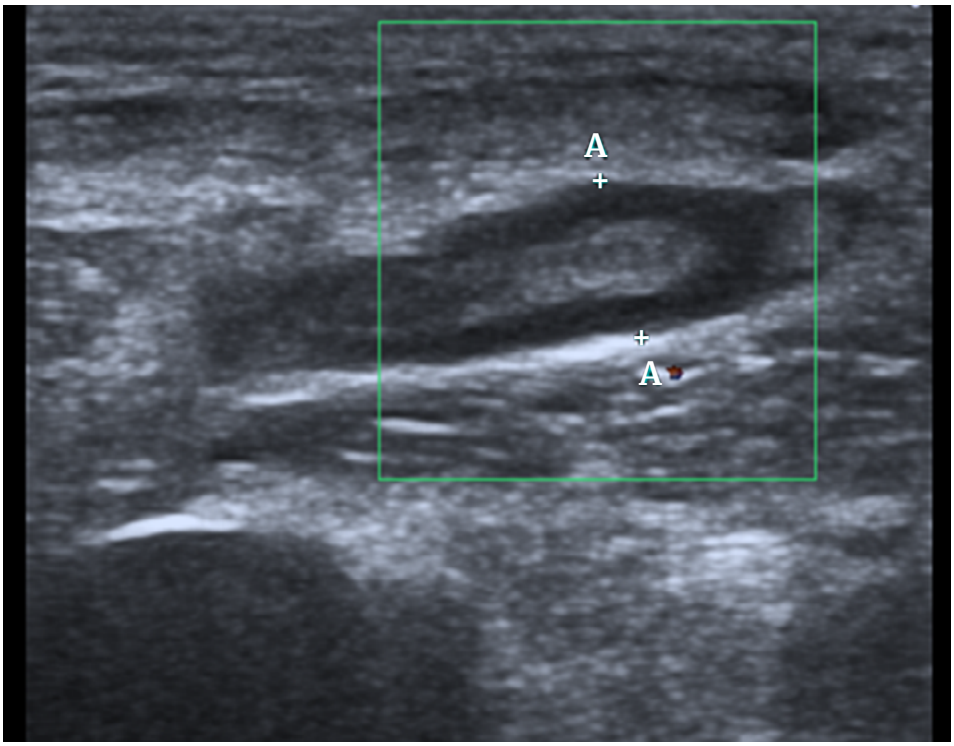


Figure 3 Follow-up ultrasound performed one month after the onset of symptoms showing cecal appendix with thickening of the appendix wall and contained within the hernia sac.

Source: Document obtained during the study.

Following an assessment by the Internal Medicine Service, done considering the patient's comorbidities, and after completing the recommended of anticoagulant suspension, the woman was taken to surgery 24 hours after admission. Under general anesthesia, an appendectomy was performed using a preperitoneal approach with access to the abdominal cavity; a polypropylene preperitoneal mesh was placed to correct the femoral hernia.

The patient recovered well from the surgery and was discharged the following day. During a postoperative follow-up visit performed after 44 days, the woman was asymptomatic, with the surgical wound in good condition, and no hernia reproduction nor signs of infection.

## DISCUSSION

De Garengeot hernia occurs most often in women; some of the conditions that may favor its appearance are pregnancy, smoking, constipation, advanced age, and connective tissue disorders (1,2,4). This entity accounts for about 1% of all femoral hernias and can cause acute appendicitis in up to 0.13% of cases.

One theory proposed to explain the development of De Garengeot hernias refers to the abnormal attachment of the appendix to the cecum, while another

suggests that the presence of a large cecum may push the cecal appendix into an existing femoral defect.

The clinical spectrum and physical examination findings in cases of De Garengeot hernia may include abdominal pain, fever, local inflammation, and inguinal masses that do not diminish in size with external pressure or supine position. Differential diagnoses include Amyand's hernia, adenitis, annexitis, and soft tissue tumors (2-4,7).

Most femoral hernias are diagnosed clinically and further evaluated with diagnostic imaging; however, De Garengeot hernias are usually diagnosed during surgery. In this sense, in the presence of an inguinal mass with clinical suspicion of hernia, a confirmatory ultrasound should be performed, as this is the method of choice for such entities due to its wide availability, low cost, and high efficacy. In this regard, Robinsón et al. (8), in a study of 59 patients performed to investigate the accuracy of ultrasound in patients with symptoms suggestive of hernia, found that although this is an operator-dependent test, it can help characterize the type of hernia with a sensitivity of 90%, a specificity of 91%, a positive predictive value of 68%, and a negative predictive value of 98% if the person performing the test has adequate training.

Ultrasound is also a useful tool in the follow-up of patients with previous surgeries. For an adequate exploration, it is necessary to use equipment with high frequency linear transducers, preferably >10 MHz, which allows us to obtain imaging with high spatial resolution and anatomical detail to identify the structures that delimit the inguinal region, particularly the Hesselbach's triangle: the inferior epigastric vessels, the inguinal ligament, and the lateral border of the rectus abdominis. Moreover, other structures such as the spermatic cord, femoral vessels and the conjoint tendon, formed from the lower part of the common aponeurosis of the abdominal internal oblique muscle and the transversus abdominis muscle, can be assessed using this imaging study. Exploration should be performed carefully to obtain images in orthogonal planes at rest and with the Valsalva maneuver in order to not only locate the structures of the Hasselbach's triangle, but also to determine the size of the defect or neck of the hernia and the hernia sac, as well as the characteristics of its contents (9).

Femoral vein compression is a particular finding described for femoral hernias on ultrasound and tomography; this happens because hernias pass through the lower part of the inguinal ligament, where the hernia sac and its contents exert pressure on this vein. It should be noted that computed axial tomography is useful not only for diagnosing femoral hernias, but also for ruling out other diagnoses (10).

Femoral hernias are associated with an increased risk of incarceration of the herniated contents, which may result in acute appendiceal inflammation, and this is believed to be related to external compression of this organ at the neck of the hernia. Perforation and peritonitis are less frequent complications because pelvic rigidity prevents the spread of inflammation to the peritoneal cavity (4,11); necrotizing fasciitis may also occur on some occasions.

Patients with De Garengeot hernia should be taken to surgery as soon as they are diagnosed and necessary pre-surgical examinations are available. Currently, there are no unified standards about the type of intervention to be performed; therefore, it is recommended that surgeons decide the most appropriate surgical strategy based on their experience and case characteristics. Some of the options for performing the surgery include localized open approaches, midline laparotomy, and laparoscopic-assisted approaches (11,12).

The use of prosthetic materials to repair the hernial defect is controversial when the cecal appendix is inflamed due to the risk of mesh contamination, which can lead to a variety of complications, the most common of which is operative site infection (30% of cases) (4,5,7).

In the case presented here, ultrasound was used to make the diagnosis, as well as to determine the cause of the patient's symptoms and to devise a suitable surgical plan; the surgical intervention included appendectomy and hernia repair with prosthetic material. Similarly, the histopathological report indicated a cecal appendix with follicular lymphoid hyperplasia, that is, the inflammation of the appendix observed on ultrasound was limited. This case was successfully treated and had a favorable outcome, allowing the patient to improve her quality of life as a result of symptom resolution.

## CONCLUSION

De Garengeot hernia is a rare condition that is usually diagnosed intraoperatively; however, diagnostic imaging is the primary tool for characterizing these hernias when performing a mass assessment of the inguinal region. In the case presented, the diagnosis was made using ultrasound, which has a high degree of sensitivity and specificity, and is low cost and easy to perform.

To avoid complications, surgical management of a De Garengeot hernia should be established as soon as possible. In this case, appendectomy and mesh hernia repair were the primary treatments, but it should be noted that the patient did not have appendicitis or infection.

## ETHICAL CONSIDERATIONS

This case report was approved by the Ethics Committee of the Hospital Universitario Nacional de Colombia, in accordance with Minutes No. CEI-HUN- Acta-2020-05b of May 21, 2020.

## CONFLICTS OF INTEREST

None stated by the authors.

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CASE REPORTS
REPORTES DE CASO

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# HEREDITARY SPASTIC PARAPLEGIA DUE TO *NIPA1* GENE MUTATION: CASE REPORT

**Keywords:** Hereditary spastic Paraplegia; Mutation; Genetics.
**Palabras clave:** Paraplejía espástica hereditaria; Mutación; Genética.

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## RESUMEN

**Introducción.** La paraplejía espástica hereditaria (PEH) es un grupo de trastornos neurológicos caracterizados por espasticidad progresiva y debilidad muscular de miembros inferiores. Su etiología es genética y se ha asociado con mutaciones en más de 60 genes. La PEH es poco frecuente y puede ser útil en el diagnóstico diferencial de la parálisis cerebral.

**Presentación de caso.** Adolescente masculino de 16 años con diagnóstico de PEH por mutación del gen *NIPA1*: c. 316G>A (p. Gly106arg), correspondiente a una PEH tipo 6 (SPG6). El paciente presentó signos clínicos de síndrome de motoneurona superior progresivos en miembros inferiores como espasticidad, hiperreflexia y paraparesia, asociados a epilepsia de inicio focal diagnosticada a los 11 años y tratada satisfactoriamente con ácido valproico. El manejo de la espasticidad fue complejo e incluyó baclofeno oral, toxina botulínica intraoperatoria, terapia física y cirugía ortopédica multinivel para manejo de deformidades musculoesqueléticas en miembros inferiores.

**Conclusión.** El presente caso demuestra la importancia de realizar un diagnóstico temprano de la SPG6 (variante más común de la PEH) para realizar intervenciones oportunas en estos pacientes, prevenir complicaciones y evitar un mayor nivel de discapacidad.



## ABSTRACT

**Introduction:** Hereditary spastic paraplegia (HSP) is the term for a group of neurological disorders characterized by progressive spasticity and muscle weakness in the lower limbs. Its etiology is genetic and has been associated with mutations in more than 60 genes. HSP is rare and may be useful in the differential diagnosis of cerebral palsy.

**Case presentation:** 16-year-old male with a diagnosis of HSP due to mutation of the *NIPA1* gene:c.316G>A (p. Gly106arg), which corresponds to HSP type 6 (SPG6). The patient presented with clinical signs of progressive upper motor neuron syndrome in the lower limbs, such as spasticity, hyperreflexia and paraparesis, associated with focal onset seizures diagnosed at age 11 and successfully treated with valproic acid. Spasticity treatment was complex and included oral baclofen, intraoperative botulinum toxin, physical therapy, and multilevel orthopedic surgery for the management of musculoskeletal deformities.

**Conclusion:** This is a rare case of complex HSP, associated with epilepsy, due to the mutation of the *NIPA1* gene (SPG6), the most common pathogenic variant within this type of mutation. The present case demonstrates the importance of making an early diagnosis of GSP6 to perform timely interventions in these patients, prevent complications, and avoid a higher level of disability.

## INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of hereditary neurological disorders characterized by progressive spasticity, lower limb paresis, and hyperreflexia, caused by neurodegeneration in the corticospinal tract, resulting in axonopathy depending on the extension of the injury. These disorders may be autosomal dominant, autosomal recessive, or X-linked (1-5). Variants associated with mutations in more than 60 genes have been identified so far.

HSP is an orphan disease, with a prevalence between 0.5 and 5.3 cases per 100 000 people for the autosomal dominant type and between 0.0 and 5.3 cases per 100 000 people for the autosomal recessive type (6).

Currently, there is no effective treatment to prevent gait disturbances in these patients and the management of spasticity is symptomatic with physiotherapy. Pharmacological treatment includes oral or intrathecal baclofen, botulinum toxin and tizanidine injections, and oral benzodiazepines (5).

This report describes the case of an adolescent with HSP caused by a mutation of the *NIPA1* gene and associated with seizures.

## CASE PRESENTATION

Male patient from a low-income household who was taken for the first time to an outpatient physiatry consultation in a tertiary care center at the age of 8 due to frequent falls with loss of stability in bipedal position, paraparesis, toe walking, and spasticity. On that occasion, it was also reported that he presented with pain in the feet attributed to flat foot at the age of 5.

The patient was the result of a second pregnancy between non-consanguineous parents, and the mother received proper antenatal care throughout her pregnancy; he was born at term by vaginal birth, with a weight of 3 050g and length of 49cm, and his TORCH screen was negative. No perinatal diseases were reported, and psychomotor and language development patterns were normal.

The patient had the following family history: a maternal cousin diagnosed with epilepsy at the age of 14 under treatment with valproic acid, and a sister with epilepsy caused by neurocysticercosis.

On physical examination performed at the first physiatry assessment, when he was 8 years old, the patient was alert with reactive pupils; facial symmetry; normal lower cranial nerves; upper limbs without alterations; left clubfoot with plantar flexion at 10°; increased muscle tone (Ashworth scale 2/4) predominantly distal and in hip adductors; muscle strength of 4/5 in dorsiflexion, plantarflexion and bilateral knee flexors, and 2/5 in hip extensors and flexors; patellar hyperreflexia; bilateral Achilles tendinitis; scissor gait; limping due to left clubfoot discrepancy; and normal sensation in all four limbs. The patient understood simple commands and communicated efficiently with clear, coherent, and fluid language; bilateral ophthalmoscopy was normal.

The patient's IQ was 82 points (low average). During this assessment by physiatry, the patient also presented the reports of the following tests: computed tomography of the skull, magnetic resonance imaging (MRI) of the brain and lumbar region, very long chain fatty acid measurement, plasma amino acid test, urine amino acid test, blood copper test, vitamin B12 test, and creatine phosphokinase test, all with normal results. In addition, he had a negative human T-cell lymphotropic virus type 1 and 2 antibody test. Given the findings and based on hereditary spastic paraplegia panel in which a mutation in the *NIPA1* gene was reported (c. 316G>A [p. Gly106arg), the patient was diagnosed with HSP type 6 (SPG6) at the age of 8 years.

The patient's progress since the time of his first seizure, as reported in the medical records, is described below:

At age 11, the patient had his first focal seizure with right-sided motor involvement (ictal phase semiology: blurred vision, altered state of consciousness with tonic seizures in the right side of the head, right side of the body, and involuntary eye movements on the same side), which was treated with valproic acid. After the treatment was completed, a follow-up electroencephalogram (EGG) was performed, showing normal results.

At age 12, he underwent a computerized gait analysis that reported decreased knee (crouched gait) and hip mobility, femoral anteversion, bilateral foot drop, and paralytic stable valgus flat feet. A 6-minute walk test (distance: 188m, speed: 0.52m/s) and a Timed Up & Go test without orthoses (15.12 seconds) were also performed.

When he was 13 years old, somatosensory evoked potentials studies were carried out, in which a somatosensory pathway impairment was found in the right lower limb causing absolute conduction block through the posterior pathway at distal point C7. In addition, electromyography and nerve conduction studies were performed, and the findings allowed ruling out peripheral neuropathy. However, a decrease in the amplitude of the bilateral tibial and peroneal nerves was observed.

Due to the patient's condition, the dose of oral baclofen (started at 11 years of age with a dose of 20mg/day) was adjusted to 40 mg/day, although it was finally discontinued 3 months later since the desired effect on spasticity was not achieved. Since lower limb spasticity, hyperreflexia, and bilateral Achilles clonus persisted, the patient was instructed to use walking aids and multilevel surgery was proposed to put the feet in plantigrade position. Likewise, the pediatric neurology service indicated to progressively reduce the dose of valproic acid until it was completely discontinued due to the risk of bleeding during surgery, so treatment with carbamazepine was initiated. However, this drug was replaced by levetiracetam because the patient presented with drug dermatitis as an adverse reaction.

At 14 years of age, he underwent multiple reconstructive surgeries of the lower limbs during which botulinum toxin was applied bilaterally to the iliopsoas,

ischiotibial, and gastrocnemius muscles; no complications were reported. At postoperative week six, after removing both casts, the use of knee immobilizers in extension at night and floor reaction ankle–foot orthoses were indicated; additionally, the patient was ordered to walk on elbow crutches.

The alignment of the patient's lower limbs improved three months after surgery; in addition, although he had limited hip abduction on the left side, he was able to perform full knee extension: bilateral 120° flexion.

Although physical therapy was interrupted for a short period, after a year of clinical follow-up, the patient presented hip adduction, marked deformity due to hip flexion contracture, and valgus collapse when walking.

Given the recurrence of hip and knee mobility alterations, which in turn severely affected gait and involved significant energy expenditure, a new computerized gait analysis was performed, finding crouched gait and bilateral calcaneal spur (distance: 157m, energy expenditure index: 1.05, and speed: 0.43 m/s). Since the patient had a score of 2 points on the Ashworth scale for muscle tone and good selective motor control of the lower limbs, including dorsiflexion, he was considered a candidate for treatment with intrathecal baclofen pump to improve performance in the 6-minute walk test (target improvement of 50m) and reduce the degree of spasticity. It was then decided, on the one hand, that if spasticity improved, management would focus on the use of external aids, and, on the other hand, that if it did not improve, further surgery would be necessary.

At 15 years of age, the patient presented with a new seizure with ictal phase semiology similar to the one described above. Therefore, an electroenceph-alogram (EEG) was performed, showing generalized interictal epileptiform discharges. It is important to mention that, at that time, the patient was being treated with levetiracetam 2 000mg daily divided into 3 daily doses, but based on the EEG findings, valproic acid 250mg (every 12 hours) was restarted and the dose of levetiracetam was progressively decreased.

Unfortunately, when the patient was 16 years old, the COVID-19 pandemic was declared and, due to the human mobility restriction and social distancing measures implemented to slow its spread, it was not possible to initiate treatment with intrathecal baclofen pump.

## DISCUSSION

HSP is classified into complex and pure forms depending on the clinical phenotype. The latter are characterized by spasticity (especially in the ischiotibial, quadriceps, gastrocnemius, soleus, and adductor muscles) and slow and progressive weakness of the lower limbs (mainly in the iliopsoas, ischiotibial, and anterior tibial muscles) (3,6), clinical manifestations that were observed in the reported patient. Variable hypertonic urinary disturbances and mild reduction in lower limb vibration sense and proprioception are also symptoms of the pure forms(6).

On the other hand, complex forms of HSP are characterized by the presence of additional neurological or non-neurological symptoms (6) such as neuropathy, seizures, parkinsonism, cognitive impairment, amyotrophy, short stature, visual disturbances (optic atrophy, retinal alterations), among others (5).

The SPG6 variant, identified in the patient described in this report, is caused by mutations in the *NIPA1* gene, located at 15q11.2, and accounts for 1% of all autosomal dominant HSP cases (7); it encodes a magnesium transporter involved in neuronal development and maintenance. Long-term endoplasmic reticulum stress in this variant has been associated with several neurodegenerative disorders, such as Parkinson's disease or amyotrophic lateral sclerosis (ALS) (7).

The pathogenic nonsense variants of the *NIPA1* gene associated with HSP are c.316G>A p. (Gly106Arg), c.316G>C p. (Gly106Arg), c.134C>G p. (Tyr45Arg), c.298G>A p, (Ala100Thr), and c.731A>G p (Gln244Arg) (7,8). The case described here had the most common variant, c.316G>A p. (Gly106Arg).

Mutations of this gene have been reported in 10 families with pure autosomal dominant HSP (with an age of disease onset between 8 and 35 years), of which recurrent mutations have been reported in 9: c.134C>G and c.316G>C or c.316G>A (8). In this sense, it has been described that, in the mutant protein, a nonpolar neutral glycine is changed to a polar-charged arginine, which strengthens the claim that the mutation is pathogenic (9).

There are several proteins associated with the different types of HSP that regulate the signaling pathways that are important for axon function. A compelling candidate for this function that cuts across all types of HSP and widely involved in the development of neurodegenerative diseases is bone morphogenetic protein (BMP) signaling (5). *NIPA1* usually acts by inhibiting synaptic overgrowth at the neuromuscular junction; its function is to inhibit BMP signaling by binding to the BMP type II receptor and to promote endocytosis and lysosomal degradation. *NIPA1* mutations associated with autosomal dominant HSP alter trafficking of BMP type II receptor and are less efficient at promoting BMPRII degradation than wild-type *NIPA1*. The hallmark pathological change is the abnormal accumulation of tubulovesicular membranous organelles in axonal and dendritic nerve endings as the earliest abnormality (10).

Although clinical manifestations of HSP can occur at any age, the first symptoms and signs occur mainly before age 40 (11). However, most cases of HSP are of juvenile or early adult onset (8 to 35 years), with a pure phenotype and urinary disturbances (2,8).

Boutry *et al.* (1) state that the initial symptoms of HSP are subtle and patients usually complain of frequent falls, stiff legs, cramps, and abnormal or unstable gait, which were evident in the patient reported since he was 5 years old, when gait disturbances began. Additionally, de Souza *et al.* (2) describe a complicated phenotype in a large British family that includes adult-onset generalized tonic-clonic seizures and postural tremor in the upper limbs (2).

The progression of HSP is usually slow, but often results in the patient requiring assistance with canes, walkers, or wheelchairs as their gait becomes increasingly spastic and other symptoms appear (1).

In 2011, Svenstrup *et al.*(8), in a study of 52 unrelated HSP patients in Sweden, found that a patient with the *NIPA1* mutation (c.316G> A) belonged to a family that segregated HSP and epilepsy through three generations; this patient was diagnosed at age 11 (normal brain MRI and abnormal EEG. It was presumed that she had idiopathic generalized epilepsy [IGE]). Similarly, although it is unknown whether there is a family history related to HSP in the present case, the patient was diagnosed with epilepsy (focal type) at age 11, with normal brain MRI and abnormal EEG.

In a study conducted in Alberta, Ontario, and Quebec (Canada) between 2012 and 2015, including 526 patients with HSP, Chrestian *et al.* (6) found that seizures were one of the least frequent symptoms and were reported in only 3% of cases.

Likewise, microdeletions of the 15q11.2 region (including the *NIPA1* gene) have been described in patients with IGE, suggesting that changes in one or more genes within this region predispose to this type of epilepsy. Furthermore, the fact that the c.316G> A/C mutation has also been described in patients with autosomal dominant HSP suggests that additional genetic or environmental factors are important for the development of epilepsy (8).

HSP is a rare entity, and this is the first SPG6 case reported in Colombia. In Latin America, Munhoz *et al.* (12) published in 2006 the report of a Brazilian family with the same genetic variant; it is noteworthy that in that case the mean age of onset of symptoms was 23.75±2.98 years. Worldwide, Chen *et al.* (13) reported cases of two independent Chinese families with two mutations linked to the SPG6 locus, c.316G> C and c.316G> A, while Martinez-Lage *et al.* (14) made a neuropathological description *postmortem* of a woman with the same genetic variant who presented with lower limb spasticity, bladder dysfunction, and lower limb weakness at age 13; she also developed dysphagia, facial weakness, and cognitive impairment at age 53 years. This patient had no known family history, but the anatomopathological study showed round neuronal cytoplasmic inclusions in the spinal cord.

Although SPG6 phenotypes associated with epilepsy have been described in the literature, their pathophysiological relationship is still unclear (12-14). Tanti *et al.* (7), by describing the case of a 32-year-old patient with HSP, epilepsy and ALS, reported the first case of a family with *NIPA1* pathogenic variants and ALS segregation; they concluded that *NIPA1* pathogenic variants, particularly c.316G>A p.(Gly106Arg), are associated with pure and complex HSP.

There is no specific treatment for SPG6, so it currently focuses on the management of spasticity using baclofen (both oral and intrathecal) and tizanidine. It has also been established that botulinum toxin type A injections may be useful for relaxing specific muscles, reducing pain, and improving mobility and thus

self-care; benzodiazepines may relieve spasms, but should be used with caution because they generate pharmacodependence; and drugs that include oxybutynin or trospium chloride regulate detrusor overactivity and sphincter dyssynergia (15).

In the same way, it has been determined that an individualized strength training program of 2 sessions per week should be implemented for patients with GPS6, as this favors the maintenance of muscle strength and skills in activities of daily living and posture (16). After surgery, when the patient reaches a walking speed of 0.43 m/s, the use of devices other than or additional to elbow crutches is suggested. In this regard, Van Lith *et al.* (17), in a study in which they analyzed 109 questionnaires completed by patients with pure HSP, found that 35% of them required aids for walking indoors, while 46% required them for walking outdoors; regarding falls, the authors reported that 57% of participants stated that they fell at least twice a year and that 51% had had at least one injury for this reason.

## CONCLUSIONS

Reporting this first case of GSP6 in Colombia, the most common pathogenic variant among all HSP, demonstrates the importance of early diagnosis in order to perform timely pharmacological and rehabilitation interventions to prevent complications, improve the quality of life of patients, and minimize their disability.

## ETHICAL CONSIDERATIONS

The patient's father signed an informed consent form granting permission for publishing this case report.

## CONFLICT OF INTEREST

None stated by the authors.

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# SEVERE CONGENITAL DIARRHEA SECONDARY TO TUFTING ENTEROPATHY. CASE REPORT

**Keywords:** Tufting Enteropathy; Newborn; Infantile Diarrhea; Congenital, Hereditary, and Neonatal Diseases and Abnormalities; Intestinal Diseases.
**Palabras clave:** Diarrea neonatal; Recién nacido; Diarrea infantil; Anomalías congénitas; Enfermedades Intestinales; Enfermedades Raras.

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## RESUMEN

**Introducción.** La enteropatía en penacho es una causa rara de diarrea congénita en neonatos; esta se caracteriza por una alteración de la adhesión epitelial que ocasiona desprendimiento de enterocitos hacia el lumen y, en consecuencia, forma los característicos penachos. Se describe el caso de una paciente con esta patología.

**Presentación del caso.** Neonata de 15 días de vida, quien fue llevada por sus padres al servicio de urgencias de un hospital de tercer nivel debido a que desde su nacimiento tuvo deposiciones diarreicas y a causa de esto presentó deshidratación, pérdida de peso, acidosis metabólica e insuficiencia renal aguda. La paciente recibió manejo con alizaprida, loperamida, sulfato de zinc y probióticos, pero a los 75 días de tratamiento continuaba sintomática. Se le practicó una endoscopia de vías digestivas y una colonoscopia que mostraron aplanamiento de las vellosidades e infiltrado de células linfoides en la lámina propia. Los síntomas continuaron y la menor falleció a los 10 meses de nacida. El resultado del exoma *post mortem* reportó enteropatía en penacho.

**Conclusiones.** Ante la presencia de diarrea congénita, se debe sospechar de una enteropatía en penacho y considerar el estudio molecular temprano, pues este permite evaluar la posibilidad de realizar un trasplante intestinal o modificar el tratamiento según las necesidades de cuidado paliativo del paciente.



## ABSTRACT

**Introduction:** Tufting enteropathy is a rare cause of congenital diarrhea in neonates. It is characterized by the abnormal distribution of epithelial adhesion molecules, which causes enterocytes to shed into the lumen, forming the characteristic tufts.

**Case summary:** A 15-day-old female neonate was taken by her parents to the emergency department of a tertiary care hospital due to diarrheal stools she had been experiencing since birth. The patient presented with dehydration, abnormal weight loss, metabolic acidosis, and acute kidney failure. She received treatment with alizapride, loperamide, zinc sulfate, and probiotics, but after 75 days of treatment she was still symptomatic. An upper tract endoscopy and colonoscopy were performed, finding flattening of the villi and lymphoid cells in the lamina propria. However, the symptoms persisted, and she died at the age of ten months. A post-mortem exome sequencing reported tufting enteropathy.

**Conclusions.** When congenital diarrhea is present, tufting enteropathy should be considered. An early molecular study would allow to evaluate the possibility of performing an intestinal transplant or modifying the treatment to meet the patient's palliative care needs.

## INTRODUCTION

Congenital diarrhea is a rare disorder in neonates (1) and differs from acquired diarrhea due to its severity, chronicity, and dependence on nutritional support (2). This condition is caused by epithelial defects and alterations in neuroendocrine differentiation or immune dysregulation, digestion, and nutrient or electrolyte absorption or transport (1). It is classified as severe chronic diarrhea, with a high mortality rate, a difficult diagnosis, and an intractable course (3).

Tufting enteropathy is a rare cause of congenital diarrhea in neonates and is characterized by the abnormal distribution of epithelial adhesion molecules, which causes enterocytes to shed into the lumen, forming the characteristic tufts (3). The incidence of this disease in Europe varies from 1 cases per 50 000 to 100 000 live births; however, a higher incidence is reported in patients of Arab origin (4).

The following is the case of a neonate with tufting enteropathy who presented with intractable diarrhea of infancy and died at 10 months of age despite receiving multiple treatments.

## CASE PRESENTATION

A 15-day-old female neonate from Bucaramanga (Colombia), mestizo, was taken by her parents to the emergency department of a tertiary care hospital because due to explosive, abundant, watery, yellowish liquid stools without mucus or blood since birth. Seven days prior to the consultation, the patient presented postprandial vomiting, irritability, jaundice, and nursing strike, so the parents started supplementation with milk formula at home.

Relevant perinatal history included that this was the mother's second pregnancy, that she had adequate antenatal care and that the patient was born by vaginal delivery at 40 weeks, weighed 3 245 grams, and Rh incompatibility tests were positive.

The patient was admitted to the emergency room in fair health, with blood pressure of 61/38 mmHg, heart rate of 158 bpm, respiratory rate of 56 rpm, temperature of 35.4°C, oxygen saturation of 90% on room air, glucose level at 232 mg/dL, and weight of 2 800 grams (13% weight loss since birth). Physical examination showed sunken fontanelle, dry oral mucosa, marked intercostal retractions with scarce panniculus adiposus, scaphoid abdomen with hepatomegaly, hypotrophic limbs, and pallor on the elbows; the rest of the examination was normal. Due to the suspicion of late-onset neonatal sepsis, the girl was immediately hospitalized in the neonatal intensive care unit (NICU), where laboratory tests were requested and oxygen support, fluid resuscitation, and empirical antibiotic therapy were initiated.

The test results on admission reported a normal blood count with the following values: hemoglobin: 18.9 g/dL, hematocrit: 56.2%, leukocytes: 18970/mm$^3$,

neutrophils: 6499/µL, lymphocytes: 8157/µL and platelets: 81000/mm$^3$. Prerenal acute kidney failure with creatinine of 1.61 mg/dL and BUN of 40.5 mg/dL was also identified. Total bilirubin was 5.91 mg/dL, direct bilirubin was 1.41 mg/dL, and indirect bilirubin was 4.5 mg/dL. C-reactive protein, transaminases, and electrolytes were normal and arterial blood gas levels showed metabolic acidosis with the following vales: pH: 7.29; $PaCO_2$: 22.7 mmHg; $PaO_2$: 103.4 mmHg; $HCO_3$: 10.8 mmol/L; base excess: -13 µmol/L. On the day of admission, two blood cultures were also taken, which were negative after 5 days of incubation.

Once stable in the NICU, enteral feeding was restarted; although it was initially tolerated, with a gradual increase in intake, the patient again presented with abundant liquid stools and hypovolemic shock. She was given alizapride (3 mg/kg/day for 8 days), loperamide (0.08 mg/kg every 12 hours for 8 days), zinc sulfate (5 mL every day for 10 days), and probiotics; however, no improvement was achieved.

After 15 days of hospitalization, the patient was assessed by the genetics department, which requested further tests to rule out inborn errors of carbohydrate metabolism, aminoacidopathies, metabolic acidemias, cystic fibrosis, among others. Seliwanoff's test was negative, while qualitative amino acid urine tests were positive for sodium nitroprusside. Plasma and urine amino acid quantification tests were also requested, which yielded nonspecific results (Tables 1 and 2).

Table 1 Altered quantitative plasma amino acids

| Amino acid | Value obtained (µmol/L) | Reference value (µmol/L) |
|---|---|---|
| Aspartic acid | 22 | 2-14 |
| Glutamic acid | 230 | 32-185 |
| Serine | 235 | 83-212 |
| α-Aminoadipic acid | 15 | <5 |
| Glycine | 527 | 103-386 |
| Sarcosine | 9 | <5 |
| Arginine | 179 | 30-147 |
| γ-Aminobutyric acid | 1 | <1 |
| α-Aminobutyric acid | 37 | 4-30 |
| Phenylalanine | 103 | 31-92 |
| Ornithine | 206 | 19-139 |
| Lysine | 427 | 70-258 |

Source: Own elaboration.

Table 2 Altered quantitative amino acids in urine.

| Amino acid | Value obtained (µmol/µol creatinine) | Reference values (µmol/µol creatinine) |
|---|---|---|
| Alanine | 431 | 27-313 |
| Glycine | 2988.31 | 133-894 |
| Valine | 56.56 | 3-43 |
| Isoleucine | 23.57 | 2-21 |
| Threonine | 287.52 | 12-145 |
| Serine | 638.67 | 34-329 |
| Phenylalanine | 44.78 | 7-42 |
| α-Aminoadipic acid | 160.26 | 7-110 |
| Ornithine | 120.19 | 2-19 |
| Lysine | 549.11 | 4-80 |
| Histidine | 841.35 | 69-392 |

Source: Own elaboration.

At one week of age, the patient underwent an abdominal ultrasound, followed by a brain magnetic resonance imaging and echocardiogram two weeks later, all of which were normal. There were no cataracts in the fundus and the pilocarpine iontophoresis test (at three different times) was normal.

The patient was also assessed by the pediatric nephrology service at one month of life, which diagnosed high anion gap metabolic acidosis and negative urinary anion gap and suggested a high probability of an inborn error of metabolism rather than tubular acidosis.

After a 75-day hospital stay, during which she was readmitted to the NICU three times due to hypovolemic shock caused by diarrhea following the administration of various nutritional formulas, the patient, who was already 3 months old at that time, weighed 3.59kg and measured 52cm (standard deviations for weight-for-age, height-for-age and weight-for-height were -3.99, -4.03, and -0.61, respectively), which indicated failure to thrive. Additionally, chronic diarrhea and infectious episodes persisted.

At that point, she was evaluated by the pediatric gastroenterology service, which diagnosed intractable diarrhea of infancy and started treatment with ondansetron (0.15 mg/kg/dose for 5 days) and requested a pancreatic enzyme replacement therapy for 2 months (lipase), but no improvement was observed. Endoscopy and colonoscopy were also performed, identifying flattening of the villi in the bulb, in the second portion of the duodenum, and in the last 5 centimeters of the ileum mucosa. Biopsies were taken during these last two examinations, which were processed with electron microscopy, revealing ileum with lymphoid cells in the lamina propria, without microscopic abnormalities. Based on the results, ultrastructural changes suggestive of microvillous inclusion disease or altered lipid transport were ruled out.

As previously stated, the patient developed hypovolemic shock several times as a result of diarrhea, which required fluid resuscitation, prolonged total parenteral nutrition, and gastrostomy feeding. A new amino acid test showed altered aminoaciduria, as well as aminoacidemia with increased oligosaccharides in urine, for which exome sequencing was indicated.

At 10 months of age, vascular access was lost and the only treatment option available was a transhepatic catheter, which her parents rejected due to due to the high morbidity associated with the procedure. The day after this event, the child died without a known diagnosis, but 2 months later, the exome sequencing report indicated a mutation and deletion of the *EPCAM* gene (Table 3), which encodes an epithelial adhesion molecule expressed in the cell membrane. It has been reported that these pathogenic variants cause tufting enteropathy with subsequent diarrhea. Figure 1 shows the clinical course and management of the patient during her hospital stay.

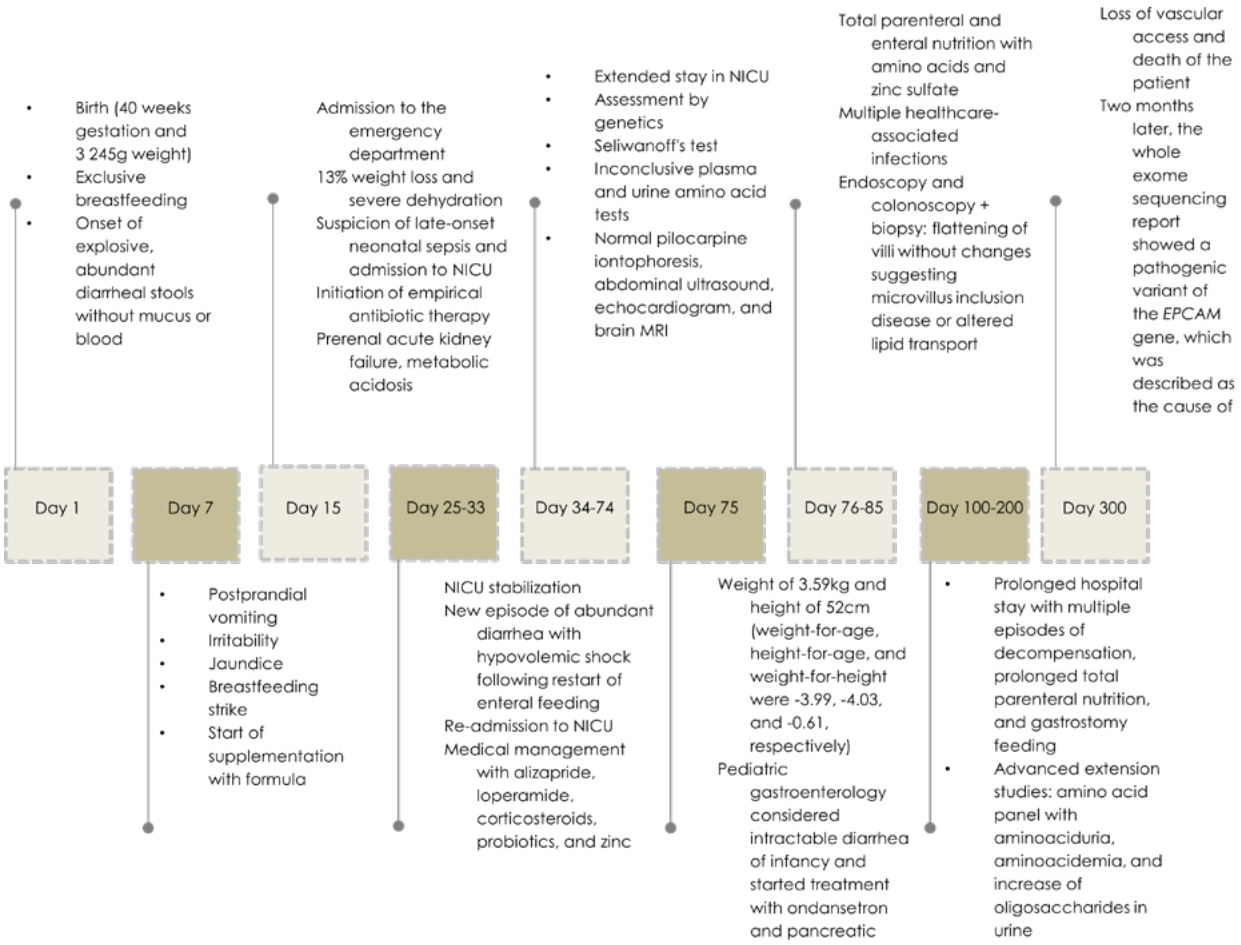


Figure 1 Timeline.
NICU: neonatal intensive care unit; NMR: nuclear magnetic resonance; SD: standard deviation.
Source: Own elaboration.

Table 3 Exome sequencing.

| Gene | Variant | Zygosity | | | Inheritance | MAF (%) | Prediction *In silico* | Classification |
|---|---|---|---|---|---|---|---|---|
| | | Case | Mother | Father | | | | |
| *EPCAM* | c.492-3C>G;p.? | het. | - | het. | AR, AD | - | Affecting splicing | Unknown meaning |
| *EPCAM* | Del.exon 1-3 | het. | het. | - | AR, AD | - | - | Probably deleterious |

HET: heterogeneous; AR: autosomal recessive inheritance; AD: autosomal dominant disorder; MAF: minor allele frequency.

Source: Own elaboration.

## DISCUSSION

Tufting enteropathy, also known as intestinal epithelial dysplasia, is an autosomal recessive genetic disorder that is usually caused by mutations in the *EPCAM* gene, a type I transmembrane surface glycoprotein antigen expressed on the basolateral membrane of multiple epithelial and plasma cells (5). This gene is located in the 2p21 locus, and when it mutates, it causes abnormal development of the intestinal mucosa (6), which is caused by changes in epithelial adhesion molecules and causes enterocytes to shed into the lumen, resulting in the formation of tufts (7). This disease occurs during the first few months of life and manifests with chronic watery diarrhea that persists despite intestinal rest (8) and feeding with breast milk or formula (5). It usually causes a deterioration in the patient's growth and is related to other alterations involving the epithelium (9).

Although mutations in the *SPINT2* gene have also been described, the most involved gene, as in the case presented here, is *EPCAM* (10). It encodes a typical adhesion molecule that is connected to the actin cytoskeleton, is directly associated with the tight junction protein claudin-7 and facilitates intestinal barrier formation by recruiting claudins in cell-to-cell junctions (5). Most mutations are located in exons 3, 4, or 5 and lack the extracellular domain or the transmembrane domain. Some deletions in the gene or exon have also been reported, which are related to the degree of involvement caused by the disease (10).

Mutations associated with tufting enteropathy appear to lead to the loss of cell-surface *EPCAM* protein (4), which is consistent with the immunopathological findings of the present case. Since this is an autosomal recessive disorder, mutations in both alleles are required to express the disease. The exome report in the present case showed a variant of uncertain significance and another probably pathogenic, which, in addition to the clinical findings, allow confirming diagnosis of this condition.

The characteristic feature of tufting enteropathy is the presence of focal epithelial "tufts" composed of tightly packed enterocytes that surround the apical

plasma membrane and result in a tear configuration of the affected epithelial cell (7). Hypoplasia and total or partial villi atrophy are commonly associated complications. Moreover, abnormalities of the basement membrane, accumulation of secretory granules in the apical cytoplasm of enterocytes without inflammatory infiltrate, crypt hyperplasia, and normal or slightly increased density of inflammatory cells in the lamina propria may be observed (5,11,12).

In patients with this disease, electron microscopy identifies pathognomonic changes such as the presence of intracytoplasmic vacuoles with microvilli and absent or abnormal microvilli at the luminal border (13). In cases of tufting enteropathy, the number of intraepithelial lymphocytes is not increased, unlike what happens in celiac disease or autoimmune enteropathy (8). In addition, sometimes the characteristic tufts may be absent in early childhood, as in the case of the patient reported here, so a biopsy is required to establish the correct diagnosis (6,9).

The differential diagnoses for diseases with persistent diarrhea and villous atrophy that should be ruled out include congenital chloride diarrhea, congenital sodium diarrhea, and microvillous inclusion disease. In the latter, besides atrophy, positive periodic acid-Schiff (PAS) stained granules are observed in the apical surface of enterocytes with atrophic bands that represent microvillus inclusion in histology (9,12,14). The first two differ in that there is usually no history of polyhydramnios in tufting enteropathy, but there is a history of consanguinity and no electrolyte alterations in blood and feces (9). Similarly, tufting enteropathy differs from glucose-galactose malabsorption in that the latter improves with one hour of fasting and symptoms can be managed through diet modification (9,14), and from autoimmune enteropathy in that it does not respond to immunosuppressive therapy (9).

Tufting enteropathy rapidly threatens the patient's life due to dehydration and the water-electrolyte disorders it causes (9), as in the reported case, which resulted in the patient's death due to metabolic decompensation. In patients with this disease, administering elemental formulas or hydrolyzed proteins exacerbates diarrhea, so they quickly become dependent on permanent parenteral feeding.

Regarding the management of tufting enteropathy, intestinal transplantation is indicated in patients with liver disease associated with intestinal failure with recurrent catheter-related sepsis (indication still under debate) and thrombosis of two or more central vascular access sites (15). Genetic counseling should be offered since this condition is related to the presence of parental consanguinity or heterozygous carrier status in asymptomatic parents (9). In cases in which transplant is contraindicated, long-term palliative care with home parenteral nutrition is prescribed (9).

Finally, molecular studies are recommended because they have improved diagnostic techniques and reduced the performance of invasive and costly procedures (5).

Among the strengths of this case report, it is noted that a pathogenic approach was taken using different advanced extension tests, which clarified

the various etiological possibilities and, eventually, established a diagnosis of the disease. The patient also received a multidisciplinary treatment, allowing for a comprehensive approach to her disease. On the contrary, limitations include the scarcity of data on the subject due to the few cases reported and the delay in obtaining the results of advanced studies, which led to a late diagnosis that did not allow making interventions aimed at modifying the prognosis and/or improving the patient's survival.

## CONCLUSION

Congenital diarrhea is a rare disease that usually appears in the neonatal period. It is severe, chronic and difficult to treat, and it predisposes to multiple complications due to the nutritional involvement of the patient, resulting in high morbidity and mortality. Furthermore, due to the rarity and scarcity of cases reported in the literature, knowledge about this disorder is limited, as is its diagnosis.

In cases of refractory congenital diarrhea, genetic defects in enterocytes should be suspected early in order to perform a molecular analysis, as these new diagnostic methods are more efficient and have reduced invasive and costly procedures.

In this sense, in the presence of congenital diarrhea, tufting enteropathy should be suspected, and an early molecular study should be considered because it allows evaluating the possibility of performing an intestinal transplant or modifying the treatment based on the patient's palliative care needs.

To date, no specific treatment for tufting enteropathy has been described; however, a timely diagnosis allows for the possibility of performing, if indicated, an intestinal transplant on an experimental basis or providing timely therapy to avoid complications such as advanced life support measures and prolonged suffering of patients and their families. Genetic counseling should also be offered to parents because this is an autosomal recessive disease.

## ETHICAL CONSIDERATIONS

Informed consent was obtained from the mother of the patient, who authorized the publication of the medical history data for the preparation of this case report.

## CONFLICTS OF INTEREST

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# CONGENITAL SYPHILIS CONFIRMED BY PCR AS A RESULT OF TREATMENT FAILURE FOR SYPHILIS IN PREGNANCY. CASE REPORT

**Keywords:** Syphilis, Congenital; Treatment Failure; Penicillin G Benzathine; Syphilis Serodiagnosis; Polymerase Chain Reaction; Nephritis.
**Palabras clave:** Sífilis congénita; Insuficiencia del tratamiento; Penicilina G benzatina; Serodiagnóstico de la sífilis; Reacción en cadena de la polimerasa; Nefritis.

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## RESUMEN

**Introducción.** La sífilis congénita es un importante problema de salud pública y para prevenirla es necesario diagnosticar y tratar la sífilis gestacional de forma temprana. En el presente caso la gestante recibió el tratamiento de elección (penicilina benzatínica), pero este no previno la infección fetal.

**Presentación del caso.** Recién nacido masculino, hijo de una madre con serología negativa para el virus de la inmunodeficiencia humana y positiva para sífilis gestacional diagnosticada en la semana 21 (prueba VDRL con dilución 1:4 y prueba treponémica rápida positiva) y tratada con tres dosis de 2 400 000 UI de penicilina benzatínica. En el parto, la madre presentó VDRL con dilución 1:1 y el recién nacido fue diagnosticado con sífilis congénita por presentar VDRL con dilución 1:4, prueba treponémica rápida positiva, niveles de aspartato aminotransferasa elevados, hipostenuria, proteinuria, hematuria y leucocituria, condiciones que se resolvieron luego de recibir tratamiento con penicilina cristalina durante 10 días. El estudio molecular en sangre realizado al momento del nacimiento evidenció una alta presencia de *Treponema pallidum*. La prueba VDRL a los 3 meses fue no reactiva.

**Conclusiones.** Prevenir la sífilis congénita con el tratamiento recomendado para sífilis gestacional puede fallar, además, diagnosticar sífilis congénita en un recién nacido asintomático es difícil, por lo cual se recomienda hacer un seguimiento clínico y serológico para confirmar si el tratamiento materno fue efectivo en el feto.



## ABSTRACT

**Introduction:** Congenital syphilis is a major public health problem, and early diagnosis and treatment are necessary to prevent it. Penicillin G benzathine is the treatment of choice in pregnant women; however, it may fail to prevent fetal infection, as in the present case.

**Case presentation:** Male newborn, son of an HIV negative mother with gestational syphilis (venereal disease research laboratory (VDRL) 1:4 dilution, positive treponemal test) diagnosed at week 21 of gestation and treated with three doses of 2 400 000 IU of penicillin G benzathine. At delivery, the mother presented VDRL 1:1 dilution. The newborn was diagnosed with congenital syphilis due to VDRL 1:4 dilution, positive treponemal test, elevated aspartate aminotransferases, hyposthenuria, proteinuria, hematuria, and leukocyturia that resolved after treatment with crystalline penicillin for 10 days. The molecular testing in blood showed a high treponemal load. The VDRL test at 3 months was non-reactive.

**Conclusions:** Preventing congenital syphilis with the recommended treatment for gestational syphilis may fail. Moreover, diagnosing this condition in an asymptomatic newborn is difficult. Therefore, clinical and serological tests are recommended to confirm whether maternal treatment was effective in the fetus.

## INTRODUCTION

Congenital syphilis (CS) is a serious public health problem that causes about 305 000 perinatal deaths worldwide each year (1).

According to Korenromp *et al.* (2), in 2016, the estimated global prevalence of gestational syphilis (GS) was 0.69% (95%CI: 0.57-0.81), resulting in an overall CS rate of 473 (95%CI: 385-561) cases per 100 000 births. Furthermore, these authors estimated that there were 661 000 (538 000-784 000) cases of CS, with an estimated 355 000 adverse birth outcomes: 143 000 miscarriages and stillbirths, 61 000 neonatal deaths, 41 000 premature and/or low-weight births, and 109 000 clinical cases of CS. In Colombia, 4 270 cases of GS and 777 cases of CS were reported at the cut-off of epidemiological period VII of 2020, showing an increase in 526 (14%) and 124 cases (19%), respectively, compared with the same period in 2019 (3).

About 50% of newborns (NB) with CS are asymptomatic or have subtle and nonspecific manifestations. In addition, more sensitive and specific diagnostic tests, such as enzyme immunoassays, polymerase chain reaction (PCR) test and immunoblotting, are not available in places where the disease is prevalent (4). It has also been shown that cases are not properly investigated due to pressure on health personnel to discharge patients early and the lack of available resources (4).

In their study, Temmerman *et al.* (5) found that women with GS have a higher risk of adverse obstetric outcomes such as stillbirths or low-weight NBs (OR: 4.1; 95%CI: 2.4-7.2); however, these authors also established that prenatal treatment for this condition with reactive rapid plasma reagin significantly improves pregnancy outcomes, although the risk of adverse outcomes remains 2.5 times higher than that observed in uninfected pregnant women.

Early manifestations of CS include maculopapular rash, lymphadenopathy, and hepatic, splenic, hematologic, renal, bone, and central nervous system involvement, but it is important to note that up to 2/3 of infants infected have no manifestations (6). Organ involvement should therefore be investigated using laboratory tests (7).

Penicillin is the antibiotic of choice for treating GS to prevent maternal-fetal transmission and treat CS (8); its effectiveness depends on the stage of the infection in the mother, the number of spirochetes in blood, the severity of fetal infection, the time of initiation of treatment, and the levels of penicillin in fetal tissues (9). Although it has been reported that, in non-pregnant adults, penicillin concentrations as low as 0.018 µg/mL for 7 days result in treponemacidal activity in almost 100% of cases, (10) Nathan *et al.* (11) stated that after administering 2 400 000 IU of benzathine penicillin G (BPG) to 25 full-term healthy pregnant women (38-39 weeks) scheduled for cesarean section the following week, the serum concentration of this drug was <0.018 µg/mL at 7 days in 36% (11).

Appropriate treatment for GS, according to Cerqueira *et al.* (1), includes administration of BPG 30 days or more before delivery and is established depending

on the clinical stage of the disease in the pregnant woman, the availability of documentation confirming the partner's treatment, and the expected drop in VDRL titers. In Colombia, the Clinical Practice Guideline for the Comprehensive Care of Gestational and Congenital Syphilis (12) establishes a treatment that consists of administering 2 400 000 IU of intramuscular BPG in a single dose for pregnant women with early syphilis (≤1 year of infection) and 2 400 000 IU of intramuscular BPG at a weekly dose for 3 weeks for late syphilis (latent syphilis >1 year of duration since infection) and syphilis of unknown duration. These recommendations, according to De Santis *et al.* (13), are the same for patients co-infected with human immunodeficiency virus (HIV).

It should be noted that, despite the existence of published treatment guidelines for GS and CS, Walker *et al.* (14), in a systematic review that included 25 studies (6 146 patients with GS) aimed at determining the optimal treatment regimen (dose, duration, and method of administration) for GS, concluded that while penicillin is effective at treating this infection and preventing CS, there is insufficient evidence to establish the optimal regimen. Additional research is needed to evaluate cases of treatment failure with suggested regimens and the impact of HIV infection in cases of prenatal syphilis treatment failure (14). It should be kept in mind that for years, there has been a belief that the prescribed treatment for GS is ineffective in preventing or treating CS (15,16), as the reported frequency of penicillin failure fluctuates between 2% and 14%. (17)

The following is a case of a NB with renal involvement due to CS as a result of GS treatment failure in the mother. Infection in the NB was confirmed by PCR test for *Treponema pallidum*.

## CASE PRESENTATION

This is the case of a male newborn, the first child of a 30-year-old single Caucasian mother from Bogotá who receives subsidized health care. At week 21 of pregnancy, the woman was diagnosed with GS by VDRL test with dilution 1:4 and rapid positive treponemal test. Additionally, she was tested for HIV, urinalysis, and toxoplasma IgG, all of which were negative, as well as fasting blood glycemia at 2 hours, which was normal, and blood hemoglobin (Hb) at 12.5 g/dL. At that time, the woman reported a history of diagnosis of syphilis 4 years earlier diagnosed through routine occupational examinations, but she received no treatment. Consequently, treatment was initiated with 1 weekly dose of 2 400 000 IU of intramuscular BPG for 3 weeks. The mother also reported that the relationship with the child's father lasted only 3 months, that he was unaware of the pregnancy and that he was the father, and that he had not received treatment for syphilis either. Prenatal ultrasounds, performed at weeks 25 and 34 of gestation, showed no abnormal findings, and the latter reported an estimated fetal weight of 2 430g.

At the time of delivery, the mother underwent a rapid treponemal test that was positive and a VDRL with a dilution of 1:1. The patient was delivered vaginally, at term, with normal amniotic fluid and cord clamping; his weight was 3 000g; his height was 49cm; and his head and chest circumferences were 35cm and 32cm, respectively. His APGAR scores at 1 minute, 5 minutes, and 10 minutes were 8, 9, and 9, respectively. The placenta was completely removed and showed no signs of infection.

On physical examination at birth, the only finding of relevance was sutural diastasis with wide anterior fontanelle. At 13 hours of life, the patient underwent a blood typing test, which was A+, and a VDRL test with a dilution titer of 1:4. Therefore, the patient was hospitalized, and treatment was started with 150 000 IU of intravenous crystalline penicillin every 12 hours. On the same day, blood count, long bone X-ray and transfontanellar ultrasound were performed, which were normal, and tests for aspartate aminotransferase, alanine aminotransferase, indirect bilirubin and conjugated bilirubin yielded the following results: 57 IU, 13 IU, 7.1 mg/dL, and 0 mg/dL, respectively.

Urinalysis showed pH of 6.5, density of 1 005, proteins at 25, Hb of 150, and leukocyte esterase of 100; nitrite, glucose and ketone tests were negative and urobilinogen was normal. Sediment analysis revealed the following results: epithelial cells: 5-10 HPF, transitional cells: 2-5 HPF, superficial layer of renal epithelial cells: 0-2 HPF, leukocytes: 10-15 HPF, red blood cells: 10-15 HPF, amorphous urate crystals: +++, ammonium biurate crystals: +++; urea nitrogen and creatinine levels were normal. Additionally, a lumbar puncture was performed to rule out neurosyphilis, as well as a rapid treponemal test, which was positive.

Based on the findings, the patient was diagnosed with GS with renal and hepatic involvement.

At eight days of birth, and after receiving treatment, the patient's crystalline penicillin dose interval was switched to every 8 hours according to the protocol; a follow-up analysis carried out the following day showed a significant improvement, which supported the diagnosis of CS with renal involvement. After 10 days of in-hospital treatment with crystalline penicillin, he was discharged and outpatient treatment was indicated.

To establish the molecular diagnosis, the remnant of the serum and whole blood samples taken from the NB were used; DNA was extracted from these samples and the *TpN47* gene was detected. The blood sample tested was considered positive with a threshold cycle of 19.87; this result showed a high presence of initial *T. pallidum*, reaching an exponential amplification of $5.73x10^6$ copies at the end of the reaction.

The follow-up VDRL test performed at 3 months of life was non-reactive.

# DISCUSSION

## Diagnosing the newborn

CS is diagnosed based on the epidemiological link to the infected mother who has not been treated or has received insufficient treatment, and/or on laboratory and physical examination results in an NB born to a mother who has a history of syphilis.

According to the CDC's 2015 Sexually Transmitted Infections Treatment Guidelines (18), a confirmed or highly probable case of CS is considered when the physical examination of an NB shows findings consistent with this condition, the antibody titer blood test is four times higher than the maternal titer, or treponema is identified via dark-field microscopy or PCR test in lesions or body fluids. However, as indicated by Cooper & Sanchez (19), NBs with CS may have lower titers than their mothers.

Routine PCR and multiplex PCR techniques are used to diagnose CS in the early stages of infection, when the serological reaction is negative, whereas nested PCR and real-time PCR are more appropriate for confirmation (20). In addition, several PCR variants have been used to identify different molecular targets, such as the genes *TPF-1, 16S rDNA, Pola, tpp47, bmp, TMPA, tmpB*, and *TpN47*. The additional clinical value of the tr-TaqMan PCR assay targeting the *polA* gene of *T. pallidumin* in diagnosing syphilis using various algorithms is also highlighted (21).

Although the *TpN47* gene has the highest sensitivity and specificity in the diagnosis of CS, molecular typing could be performed using the *16S ADNr* and *polA* genes. Therefore, it becomes an important tool for monitoring the emergence of macrolide-resistant strains, to assess disease subtypes associated with central nervous system disease, to differentiate infection and reinfection processes, and to understand *T. pallidum* transmission and the epidemiological behavior of the disease; the *arp* (acidic repeat protein) gene and the subfamily II *tpr* genes (*tprE, tprG*, and *tprJ*) have been used for the latter purpose (22). Furthermore, the *rpsA* and *tpo548* genes are being studied together to improve the discriminatory ability of *T. pallidum* strain typing (23). It should be noted that there is currently no commercial PCR-based test for the diagnosis of syphilis.

In the case reported, the NB met the following diagnostic criteria for CS: VDRL test 4 times the maternal titer and laboratory tests suggestive of CS due to increased aspartate aminotransferase and urinalysis alterations; in addition, *T. pallidum* was identified based on the detection of the *TpN47* gene using a PCR test, which has been shown to be a more sensitive and specific test.

## Transplacental infection and failure of maternal treatment to prevent CS

Transplacental transmission of *T. pallidum* to the fetus is related to gestational age, stage of infection, and fetal immune response (13). This may occur as early as week 9 or 10 of pregnancy, although the majority of infections occur during the second

trimester (19). Likewise, the risk of fetal infection is higher during the early stages of GS, possibly due to rapid replication of the microorganism and the increased concentration of spirochetes in the bloodstream; thus, a higher risk of transmission has been reported in cases of untreated primary and secondary syphilis (70% to 100%) compared with untreated latent syphilis (40% for the early stage and up to 10% for the late latent stage) (24). In the case reported here, the stage of the infection in the mother, who was diagnosed in the second trimester of pregnancy, was not known.

Based on a study in which 75 women with GS were treated with BPG and treatment failure was demonstrated in 4 of them, resulting in a failure rate of 5.3%, Monif (15) warned of the need for a critical reassessment of the established treatment for syphilis in pregnant women with a high probability of established fetal infection.

Regarding the management of syphilis in pregnant women, Alexander *et al.* (25), through a prospective evaluation of the recommended treatment regimens for syphilis between 1987 and 1989 at Parkland Memorial Hospital in Dallas, Texas, found that 28 552 women gave birth in the institution and 448 of them were diagnosed with the disease; 108 of these women were diagnosed at the time of delivery and treated after delivery, while the remaining 340 received prenatal care. In the latter group, 6 cases of failure in the prevention of congenital syphilis were found, 4 of them in women with secondary syphilis and 2 in early latent syphilis (failure 1.76%).

In a prospective study conducted between January 31, 1982, and December 31, 1998, including all women who received prenatal care at hospitals in Dallas, United States, Sheffield *et al.* (10) identified 43 cases of CS. The authors established that, in all these cases, pregnant women received treatment after the first trimester, with the mean interval from treatment to delivery being 13.5±5.4 days, and 15 women (35%) were treated 30 days or more before delivery (32-183 days). In turn, Rac *et al.* (26), in a retrospective study that included 235 pregnant women with syphilis diagnosed after week 18, found that of the 73 (30%) who had an ultrasound diagnosis of fetal syphilis and were treated before delivery, 32 (18%) gave birth to NBs with CS.

The majority of failed CS treatments appear to occur in cases of secondary syphilis (10,25); when the duration of infection in the pregnant woman is <1 year (27), possibly due to the high number of spirochetes in the blood that occur at this stage (24); or when the mother is diagnosed or treated in the third trimester (28-31). In a systematic review that included 25 observational studies, Blencowe *et al.* (31) found that diagnosing and treating GS after weeks 24 to 28 of gestation is a risk factor for CS, stillbirths, preterm delivery, and neonatal death.

Transplacental transmission of *T. pallidum* is also difficult to prevent when the duration of syphilis in the mother is unknown (32); when the titer of VDRL or RPR (rapid plasma reagin) is very high at diagnosis and during delivery (10,28,29.32); when the time between treatment and delivery is short; when

delivery occurs before week 36 (10,33); and when CS manifestations are detected on antenatal ultrasounds (26,34,35), which are recommended by the CDC in the second half of pregnancy if GS is diagnosed (36), with the most frequent findings being hepatomegaly, ascites, hydrops fetalis, fetal anemia, polyhydramnios, and placentomegaly (27,34).

Donders *et al*. (37) conducted a study of 180 HIV-negative pregnant women diagnosed with syphilis from Petronas, South Africa, in which 108 received 2 or 3 injections of 2 400 000 IU of BPG weekly and had favorable results; however, there was an increase in adverse outcomes in the group that received a single injection. When the authors compared the estimated duration of treponemicidal coverage of 3 weeks or less with that of more than 3 weeks, a decrease in birth weight was observed (2 748g vs. 3 130g); in addition, the relative risks of prematurity (RR: 8.5; 95%CI 2.5-28), perinatal mortality (RR: 20.5 95%CI 2.3-184) and congenital syphilis (RR: 2.0 95%CI: 0.6-6.8) increased when coverage was less than 3 weeks, suggesting that the duration of treatment is more important than the time of the first injection. Therefore, 2 400 000 IU of BPG or treponemicidal concentrations lasting 3 weeks or less is not sufficient to treat GS and prevent CS (37).

Antibiotic treatments other than penicillin (38-40) and reinfection may facilitate transplacental transmission of syphilis. Furthermore, since serology is used to evaluate active infection and requires long-term follow-up to assess the effectiveness of treatment, treatment failures may be undiagnosed reinfections (32). These failures may occur in cases of maternal neurosyphilis, as BPG is not effective for its treatment (41).

In the present case, the diagnosis of GS was made at the beginning of the second half of pregnancy; the VDRL titer was not high (dilution 1:4) and decreased at delivery (dilution 1:1); the stage of infection in the mother was not known and she was treated with 3 doses of 2 400 000 U of BPG weekly; 14 weeks elapsed between the start of treatment and delivery; ultrasounds performed at weeks 25 and 34 were normal; and the mother was HIV-negative and had not received any antibiotics other than penicillin.

Therefore, the only risk for transplacental transmission of the disease would be the unknown duration of infection; however, the decrease in VDRL titers from 4 dilutions to 1 dilution in 3 months met the expected decline for early syphilis (42) and the retention of the same titer at the time of delivery ruled out reinfection according to the Evidence-based Clinical Practice Guideline for the Comprehensive Care of Gestational and Congenital Syphilis. (12) Consequently, it can be concluded that the treatment was effective for the mother but not for the fetus. This is significant because it is assumed that compliance with the criteria for appropriate treatment in a pregnant woman ensures prevention of infection or treatment of the infected fetus (26).

So, what happened in this case to make the mother's treatment ineffective for preventing CS? Since the presence of *T. pallidum* was identified via PCR test

and the VDRL titer in the NB was 4 times higher than the maternal titer (which is evidence of fetal serological response), penicillin levels may not be sufficient to eradicate the bacteria in the fetus. Several factors may contribute to this outcome; for example, if the number of spirochetes in the mother's blood is high, a placental alteration may occur which, together with increased renal flow at the end of pregnancy, may result in decreased penicillin levels (9). In addition, the increase in plasma volume and renal clearance in pregnant women can reduce serum levels between 10% and 50% (43,44).

### Renal involvement in CS

Renal involvement is not a common complication in cases of CS. In a study carried out in 28 NBs with CS treated between August 2011 and February 2012 at the Instituto Materno Infantil of Bogotá, Vallejo & Cifuentes (7) found that only 17.9% of the participants had some renal alterations.

It has been established that when renal alterations occur in cases of GS, the most common involvement is a nephrotic syndrome as an isolated manifestation (45), which is quickly resolved with penicillin treatment, but it can also manifest as a systemic involvement (46) or with proteinuria, hematuria, leukocyturia, and cylindruria (7). Renal involvement, a serological reaction, the presence of *T. pallidum*, and a diagnosis of GS were all observed in the case presented. In addition, alterations were resolved using the penicillin treatment introduced by Scully and Yamazaki in 1949 (47).

## CONCLUSIONS

Syphilis is a complex disease and its treatment during pregnancy must meet several objectives: to eradicate the infection in the mother, to prevent maternal-fetal transmission, and/or to treat CS; therefore, situations involving the risk of maternal treatment failure must be investigated. Thus, given that the diagnosis of CS depends on the diagnosis of the pregnant woman, these risk situations for maternal treatment failure should be considered when treating a NB with a maternal history of treated GS.

In this regard, since preventing CS with the recommended treatment for GS may fail and because diagnosing CS in an asymptomatic NB is difficult, clinical and serological follow-up is recommended to confirm whether maternal treatment was effective for the fetus.

## ETHICAL CONSIDERATIONS

The patient's mother provided an informed consent that allowed preparing this case report.

## CONFLICT OF INTEREST

None stated by the authors.

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To the patients, who always teach us.

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# CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS, A RARE DISEASE. CASE REPORT

**Keywords:** Osteomyelitis; Cytokines; Osteitis.
**Palabras clave:** Osteomielitis; Citocinas; Osteítis.

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## RESUMEN

**Introducción.** La osteomielitis multifocal recurrente crónica (CRMO) es una enfermedad inflamatoria ósea poco frecuente que se presenta principalmente en niños y adolescentes a causa de un desequilibrio entre factores proinflamatorios y antiinflamatorios. Para establecer su diagnóstico se deben integrar elementos clínicos y paraclínicos con el fin de descartar otras entidades, pues su diagnóstico es de exclusión. El tratamiento se basa en antiinflamatorios no esteroideos y otros medicamentos en casos específicos.

**Presentación del caso.** Adolescente femenina de 16 años con cuadro clínico de un año de evolución consistente en episodios de dolor articular, especialmente en rodillas, acompañado de signos de inflamación local, quien ingresó al servicio de urgencias de un hospital de cuarto nivel por presentar fiebre >38.5°, odinofagia, astenia y adinamia durante los dos últimos días. A la paciente se le realizaron múltiples estudios de extensión, incluyendo exámenes de laboratorio, imagenológicos e histopatológicos, con los que se descartaron diversas causas etiológicas. Asimismo, la joven recibió tratamiento antibiótico empírico sin remisión de sus síntomas, por lo que finalmente se estableció el diagnóstico de CRMO y se indicó manejo ambulatorio con antiinflamatorios no esteroideos y corticoesteroides, con el cual se obtuvo respuesta favorable.

**Conclusiones.** La CRMO debe ser considerada en niños y adolescentes con dolor óseo y un cuadro clínico poco definido con hallazgos de laboratorio, imagenológicos e histopatológicos inespecíficos. En la actualidad es poco lo que se conoce sobre la CRMO, por lo que es necesario realizar investigaciones y ampliar los conocimientos relacionados con esta enfermedad.



## ABSTRACT

**Introduction:** Chronic recurrent multifocal osteomyelitis (CRMO) is a rare inflammatory bone disease usually observed in children and adolescents. It is caused by an imbalance between proinflammatory and anti-inflammatory factors. To establish its diagnosis, it is necessary to integrate clinical and laboratory elements that are typically aimed at ruling out other conditions, constituting a diagnosis of exclusion. Treatment is based on non-steroidal anti-inflammatory drugs and other drugs in specific cases.

**Case presentation:** A 16-year-old female patient with a 1-year history of joint pain, especially in the knees, accompanied by signs of local inflammation was admitted to the emergency department of a quaternary care hospital due to a fever >38.5°,

odynophagia, asthenia, and adynamia over the last two days. The patient underwent multiple extension studies, including laboratory, imaging and histopathological tests, which ruled out various etiologic causes. She received empirical antibiotic treatment without remission of symptoms, so a diagnosis of CRMO was finally established and outpatient treatment with non-steroidal anti-inflammatory drugs and corticosteroids was indicated, obtaining a favorable response.

**Conclusions:** CRMO should be considered in children and adolescents with bone pain and a poorly defined clinical history with non-specific laboratory, imaging and histopathological findings. To date, little is known about CRMO, so it is necessary to carry out research and expand the knowledge related to this disease.

## INTRODUCTION

Inflammatory diseases of the bone system include clinical entities characterized by unifocal or multifocal lesions in the bone without evidence of associated infectious involvement (1,2).

Regarding the pathophysiology of such diseases, it has been proposed that dysregulation of the innate immune system is a crucial factor in their genesis and development. Experimental evidence has demonstrated that alterations in the functioning of inflammatory cells can affect any body tissue, including bone tissue, where an abnormally persistent cycle of resorption and remodeling may occur in response to certain chemical mediators secreted by inflammatory cells (2-4). Additionally, specific mutations affecting molecules related to different inflammatory pathways have been described in humans and animal models (3).

Chronic recurrent multifocal osteomyelitis (CMRO) is a rare inflammatory bone disease that mainly affects children and adolescents and can be mild and self-limited or chronic and recurrent, with varying degrees of severity (1,2). Management guidelines to control symptoms, as well as to prevent or slow the progression of bone damage, are defined depending on the stage of the disease and the degree of involvement. Pharmacological therapy includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, sulfasalazine, methotrexate, bisphosphonates, and immunomodulators (2,3).

The following is the case of an adolescent girl with CRMO detailing the diagnostic and therapeutic approaches used, as well as the positive response obtained after providing pharmacological treatment with NSAIDs and corticosteroids.

## CASE PRESENTATION

A 16-year-old female adolescent in the tenth grade from Bogotá, Colombia, of mixed race and from a middle-income family, visited the emergency room of a quaternary care hospital of Bogotá in January 2019 due to a fever >38.5°, odynophagia,

asthenia, and adynamia over the last two days. The patient, who had unintentionally lost 2kg in the previous month, was under medical observation due to a 1-year history of joint pain in the knees, the right ankle and metacarpophalangeal joints of the fourth and fifth fingers of the right hand, accompanied by episodes of erythema, edema, and flushing, especially in the right knee.

As a relevant medical history, the patient reported a bone biopsy in the right distal femur and proximal tibia 5 months before the date of admission; this study ruled out malignancy and showed morphological and structural changes compatible with osteomyelitis, although no microbiological isolation was performed. Based on these results, empirical antibiotic treatment with 300mg of clindamycin every 8 hours for 12 weeks was prescribed, which had already been completed at the time of admission to the emergency room.

In her anamnesis, the adolescent indicated that she had no pathological or traumatic history and reported that her parents were not consanguineous and had no relatives with autoimmune diseases. Physical examination revealed mucocutaneous pallor, skin without lesions, pain on palpation of the distal third of the right femur and pain on mobilization of the right knee, without other signs of local inflammation, no limitation in the mobility arches, and no joint effusion.

On admission to the emergency room, laboratory studies were carried out which yielded the following results: leukocytosis at 18 080 U/microliter (reference value (RV): 4 000-12 000 U/microliter), erythrocyte sedimentation rate (ESR) increased by 48 mm/h (negative value <15 mm/h), and slightly elevated C-reactive protein (CRP) at 10.5 mg/L (negative value <10 mg/L).

On the same day of admission, given the abnormal findings and the course of the disease, and because there was no clear diagnosis, the patient was admitted to the hospital to integrate and expand the studies that were available. At that time, the tests performed during the year prior to admission were also reviewed. As relevant findings, persistent elevation of CRP and ESR, leukocytes in normal ranges, and peripheral blood smear with the presence of microcytes were observed.

In addition, autoantibody studies (anti-Ro, anti-La, anti-RNP, anti-Sm, ANA, anti-DNA, and rheumatoid factor) were performed obtaining negative results, and some predisposing conditions for immunodeficiency, such as complement levels in blood, were ruled out: C3 in 105 mg/dL (RV: 86-206 mg/dL) and C4 in 24 mg/dL (RV: 8-55 mg/dL); and immunoglobulins: IgG in 1625 mg/dL (RV: 700-1600 mg/dL) (IgM in 24 mg (RV: 40-230 mg/dL) and C4 in 226 mg/dL (RV: 70-400 mg/dL); that is, the latter showed mild elevation of IgG, while IgM and IgA were in normal ranges. Human immunodeficiency virus infection was also ruled out.

During the first 3 days of hospitalization, hand and knee X-rays and a nuclear magnetic resonance imaging (MRI) of the lower limbs were performed. The right knee X-ray (Figure 1) showed no fractures, masses, lytic or sclerotic lesions and showed joint space preserved. However, comparative MRI of the legs (Figure 2) showed increased multifocal signal in distal femur and proximal tibia with

osteopenia, no fractures, and a slight increase in joint fluid without involvement of articular cartilage and ligaments (according to the official report).

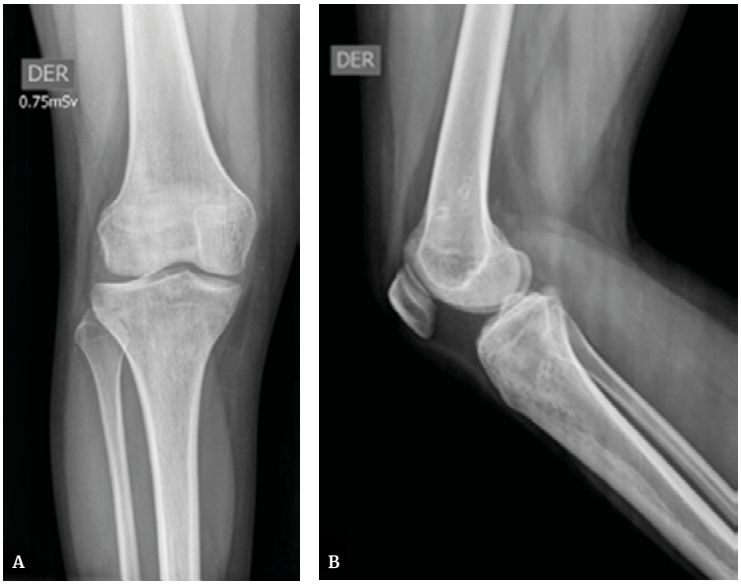


Figure 1 X-ray of the right knee. A) anteroposterior view; B) lateral view.
Source: Document obtained during the study.

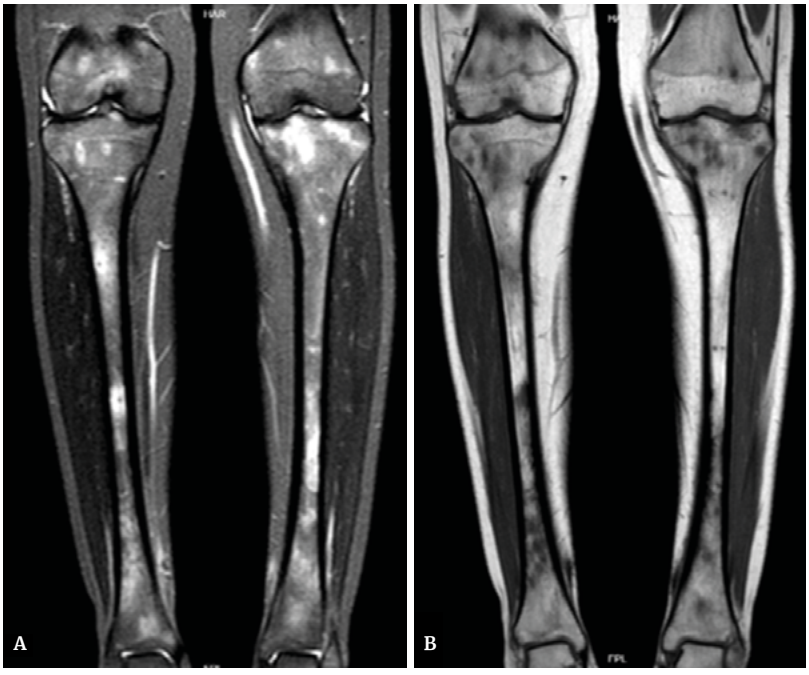


Figure 2 Comparative nuclear MRI of the legs. A) STIR sequence; B) T1 weighted image.
Source: Document obtained during the study.

It should be noted that, one month before admission to the emergency room, the patient underwent a bone scan that showed increased uptake in the left tibia and the metacarpal bones of the right hand, which could be related to multiple foci of osteomyelitis, as indicated in the official report.

On the sixth day of admission, based on intermittent episodes of joint pain, signs of local inflammation, persistence of elevated levels of inflammatory markers, imaging findings of multifocal bone lesions with inflammatory features, presence of sterile inflammation in histopathological study of bone, absence of evidence of neoplastic involvement, lack of microbiological isolation, and non-remission of symptoms after receiving a complete course of antibiotic management, a diagnosis of CRMO was considered.

Thus, once this diagnosis was contemplated and other diseases were ruled out, outpatient management with NSAIDs and corticosteroids was indicated to control symptoms. Therefore, after 6 days of hospitalization, the patient was discharged, and treatment was initiated with 250mg of naproxen every 12 hours and 25mg prednisolone daily (dose: 0.5 mg/kg/day).

Two months later, at a follow-up appointment with pediatric orthopedics, the patient, who was still on the same medical treatment prescribed at discharge, reported persistent episodes of joint pain and inflammation, although with less intensity and frequency. At that time, no local inflammatory changes or limitations in joint mobility were found, and no new studies were requested given the time elapsed since the last studies available and the favorable clinical course described. However, the importance of continuing multidisciplinary follow-up on a regular basis to define the need for adjusting treatment or implementing other interventions based on progress was emphasized.

## DISCUSSION

According to the literature, several hypotheses have been established regarding the pathophysiological mechanisms of CRMO. For example, it has been suggested that dysregulation of the innate immune system leads to an imbalance between proinflammatory cytokines, such as interleukins (IL) IL-1β and IL-6 and tumor necrosis factor (TNF), and anti-inflammatory cytokines, such as interleukins IL-10 and IL-19 (1-4), resulting in chronic inflammation associated with bone resorption and remodeling. This inflammatory process is caused by the modulation exerted by the cellular and humoral components of the immune system in the proliferation and differentiation of osteoclasts. Both processes are mediated by different signaling pathways, among which the one related to the receptor activator of nuclear factor kappa-β ligand (RANKL) stands out (5).

Other hypotheses suggest that it is a polygenic disease originating from the presence of sterile osteomyelitis in some syndromes and the increased frequency

of individuals affected by this condition in some families (5,6). Monogenic disorders leading to the development of bone inflammation have also been described and explain some syndromic forms such as Majeed syndrome; pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; and IL-1 β receptor antagonist deficiency (7,8).

CRMO usually presents with insidious bone pain, signs of local inflammation, fever, weight loss, and fatigue. The bones most commonly affected by this entity are the long bones of the lower limbs, especially the tibia, while the skull is the least affected. The duration of active disease varies from 2 to 5 years, but cases with longer periods of time have been reported (9-15). Furthermore, a strong association has been established between this disease and the presence of skin disorders (such as psoriasis and severe acne), inflammatory bowel diseases, and arthritis (16,17).

CRMO is diagnosed based on clinical and paraclinical parameters, including laboratory and imaging tests, as well as histopathological studies of the bone in many cases. However, there is no consensus to diagnose this disease, and although clinical criteria have been proposed for its operational definition, they have not been widely accepted or adopted. Moreover, there are no biomarkers or specific imaging or histopathological findings for this condition, so it remains an exclusion diagnosis (18,19).

Different groups of drugs are used to treat this disease, including NSAIDs, corticosteroids, sulfasalazine, methotrexate, bisphosphonates, anti-TNFα, and IL-1 receptor antagonists (20,21). It is important to note that the indications and regimes of the aforementioned drugs vary greatly (21).

NSAIDs are widely used in mild and moderate cases of CRMO and are useful in improving pain. More aggressive treatments including TNFα inhibitors or bisphosphonates should be considered in severe cases with inflammation of the vertebrae, structural damage, pathological fractures or damage to the physis (21,22). Nevertheless, the latter should be reserved for specific cases in which there is multifocal, mandibular or vertebral involvement, or the patient has diseases refractory to other drugs (21-23).

CRMO was diagnosed in this case after approximately 12 months of follow-up and multiple extension studies, which is consistent with what has been reported in the literature. According to some case studies, the average time between the onset of symptoms and considering this entity as the likely etiology is 15 to 18 months (23,24).

The fact that CRMO is an exclusion diagnosis can lead to the performance of multiple studies and procedures in short periods of time, as well as the administration of empirical treatments, with the resulting implications for patients and their families, which, when combined with the feelings generated by not having a clear diagnosis and no improvement in symptoms, affects the quality of life of those who suffer from this disease.

The patient in this case had a favorable response after starting combined management with NSAIDs and corticosteroids, which supports the usefulness of this therapy as reported in the literature. For example, Schultz *et al.*, cited by Barral-Mena *et al.* (25), described responses to NSAIDs in 79% of cases in a series of 190 patients without specifying the time of treatment or subsequent recurrences. In this regard, it is critical to conduct laboratory and imaging studies following the start of the indicated treatment in order to evaluate possible modifications in the parameters analyzed. However, in this case, due to the time of follow-up and the absence of signs or symptoms that could suggest disease progression or the appearance of complications, no new studies were carried out, which was a limiting factor for the overall analysis of the case.

Given this scenario, further research on the subject is needed to improve the available knowledge and thus achieve a real impact on outcomes in patients with CRMO. It is also necessary to resolve questions that arise on a daily basis, such as the frequency with which follow-up imaging studies are required, the impact of therapeutic interventions, the decrease in the variability of treatment schemes, remission rates, and individual conditions or findings that may correlate with prognosis and outcome for each patient.

## CONCLUSIONS

CRMO, as well as other inflammatory diseases, should be considered in patients with intermittent bone pain of poorly defined course and accompanied by non-specific symptoms and signs. In this sense, it is necessary to integrate all available tools and initiate available treatments as soon as possible to control the disease and reduce the risk of progression and complications.

To date, little is known about CRMO, so it is essential to carry out new research to expand and deepen knowledge about it, which will allow issuing recommendations based on quality evidence.

## ETHICAL CONSIDERATIONS

For the preparation of this case report, the patient and her legal guardian (mother) signed an informed consent form authorizing the use of their data. Likewise, the Ethics Committee of the Hospital Pediátrico de La Misericordia approved the preparation and publication of this document, according to Minutes No. IEC-222-19 of August 26, 2019.

## CONFLICTS OF INTEREST

None stated by the authors.

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# PENTALOGY OF CANTRELL. A STILLBIRTH CASE REPORT

**Keywords:** Pentalogy of Cantrell; Mesoderm; Gastroschisis.
**Palabras clave:** Pentalogía de Cantrell; Mesodermo; Gastrosquisis.

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## ABSTRACT

**Introduction:** Pentalogy of Cantrell is a rare congenital disorder characterized by midline birth anomalies. Its embryological origins are related to anomalies of the abdominal wall that prevent the closure of the thorax. Its etiology is not yet clear, but it has been associated with a failure of migration of the lateral plate mesoderm to the midline.

**Case description:** A stillbirth at 25.2 weeks of gestation diagnosed with pentalogy of Cantrell. The mother was a 14-year-old teenager with no relevant history of disease. An obstetric ultrasound was performed at 19 weeks of gestation and revealed findings suggestive of pentalogy of Cantrell. The mother was informed of the potential risks and future complications for the fetus, yet she chose to continue with the pregnancy. At 25.2 weeks of gestation, the mother went to the emergency department due to pain in the hypogastrium accompanied by moderate vaginal bleeding and absence of fetal activity. Once fetal death was confirmed by ultrasound, labor was induced, resulting in stillbirth with anencephaly, thoracic hypoplasia, gastroschisis, and eventration of the liver.

**Conclusions:** Adequate antenatal care, including strict ultrasound follow-up, is essential to detect future complications in the fetus; to provide advice on possible malformations incompatible with life, such as pentalogy of Cantrell; and to determine the best therapeutic approach.



## RESUMEN

**Introducción.** La pentalogía de Cantrell es una anomalía congénita rara que se caracteriza por malformaciones en la línea media del cuerpo, y cuyos orígenes embriológicos están relacionados con anormalidades de la pared abdominal que impiden el cierre del tórax. Su etiología aun no es clara, pero se ha asociado con una falla de la migración de los pliegues del mesodermo lateral a la línea media.

**Presentación del caso.** Mortinato de 25.2 semanas de gestación diagnosticado con pentalogía de Cantrell. La madre era una menor de 14 años sin antecedentes patológicos. A las 19 semanas de gestación se realizó ecografía obstétrica que mostró imágenes sugestivas de pentalogía de Cantrell, y se le explicó a la gestante los riesgos y complicaciones futuras que presentaría el feto, pero esta decidió continuar con el embarazo. A las 25.2 semanas de gestación, la joven acudió al servicio de urgencias por dolor en hipogastrio acompañado de sangrado vaginal moderado y ausencia de actividad fetal. Una vez confirmada la muerte fetal mediante ecografía, se indujo el trabajo de parto, obteniéndose mortinato con anencefalia, hipoplasia de caja torácica, gastrosquisis y eventración del hígado.

**Conclusiones.** La realización de adecuados controles prenatales, en los cuales se realice un seguimiento ecográfico estricto, es fundamental para detectar futuras complicaciones en el feto; brindar asesoría sobre posibles malformaciones que sean incompatibles con la vida, como la pentalogía de Cantrell, y establecer las mejores alternativas de manejo.

## INTRODUCTION

Pentalogy of Cantrell was first described in 1958 when Cantrell *et al.* (1) published a series of five cases about this abnormality. It was defined as a collection of four midline body defects (specifically in the abdominal wall, sternum, diaphragm, pericardium and heart) accompanied by some intracardiac defect (2). Regarding intracardiac abnormalities, Madi *et al.* (3) state that ventricular septal and atrial septal defects are present in 100% and 53% of cases with this disorder, respectively, while tetralogy of Fallot and ventricular diverticula are found in 20% each (3).

This is a rare disorder considering that only about 250 cases have been reported worldwide (4). Thus, it is a rare syndrome with an estimated incidence that varies from 1 cases per 65 000 to 200 000 live births in the different reported series (5-7). Its spectrum is variable and depends on the five basic defects that define it: a midline supraumbilical abdominal wall defect, defect of the lower sternum, defect of the anterior diaphragm, defect in the pericardium, and intra-cardiac defects (8).

As described by Mărginean *et al*. (9), pentalogy of Cantrell was classified by Toyama (10) into three classes according to the number of defects in each patient. Class 1 or definitive diagnosis has all 5 defects; class 2 or probable diagnosis involves 4 defects; and class 3 or incomplete expression comprises 3 defects.

Pentalogy of Cantrell or thoracoabdominal syndrome is characterized by the variable association of midline body defects with thoracoabdominal wall defects and its differential diagnosis is limb-body wall complex. Both conditions are of unknown cause and early origin but can be explained by an abnormal mesoderm development (11).

The available literature on pentalogy of Cantrell is scarce, mainly because it is a rare disease with great variability in its signs and symptoms of presentation. Reports on this subject are therefore a valuable resource, as they can serve as a basis for future research (12).

Periodic obstetric ultrasound is recommended to detect and treat fetal anomalies since it allows providing optimal perinatal care, considering that approximately half of structural anomalies can be detected in the first trimester. Some of anomalies include anencephaly, abdominal wall defects, holoprosencephaly, and cystic hygromas. However, due to the stages of embryonic development of some organs, it should be kept in mind that certain anomalies are observed at a later gestational age. Similarly, it is worth noting that, as stated by Saldarriaga-Gil *et al.* (13), the second trimester is the best stage for study to identify fetal structural anomalies.

The following is a case of pentalogy of Cantrell associated with craniofacial, limb and reproductive system defects, which was suspected by ultrasound at week 19 of gestation and confirmed *postmortem*. This is the seventh case of this anomaly reported in Colombia in the last 10 years and the second case in a female patient (8,9,14-17).

## CASE PRESENTATION

Stillbirth of 25.2 weeks in whom multiple malformations were identified at 19 weeks of gestation via obstetric ultrasound, leading to the suspicion of a diagnosis of pentalogy of Cantrell. The mother was a 14-year-old mestizo girl from the rural area of La Sierra, department of Cauca, Colombia. No degree of consanguinity with the father was determined, but it was established that this was the mother's first pregnancy.

The first antenatal check-up was carried out in September 2019, when the mother was 19.4 weeks pregnant, and the laboratory tests ordered at that time showed the following results: negative hepatitis B surface antigen; negative IgG and IgM toxoplasma antibodies; positive IgG and negative IgM antibodies against rubella; and positive IgG and negative IgM antibodies against cytomegalovirus. During this first check-up, an ultrasound was also performed, showing a fetus with anencephaly, ectopia cordis, hypoplastic left heart syndrome, diaphragmatic hernia, hyperlordosis, and equinovarus deformity in the right foot (findings compatible with pentalogy of Cantrell). Thus, counseling on voluntary termination of pregnancy was performed due to the severe malformations in the fetus and the risks and future complications; however, the mother preferred to continue with the pregnancy.

At 25.2 weeks of gestation, the mother was admitted to the emergency department of the Hospital Universitario San José de Popayán Empresa Social del Estado due to an 8-hour history of colicky abdominal pain in the hypogastrium accompanied by moderate vaginal bleeding and absence of fetal movements. Obstetric ultrasound was performed, which confirmed fetal death, so labor was induced.

A dead fetus was obtained after delivery, which was sent to the pathology service, where a female stillbirth with height of 23cm, weight of 555g and external malformations was identified. External malformations included amniotic bands attached to occiput and placenta; exencephaly; asymmetric, separated nostrils with ipsilateral nostril and hypoplastic nasal wings, suggesting arrested facial development; broad and flattened nasal bridge; cleft palate; low-set ears; short neck; hypoplasia of the right upper limb; right ectrodactyly; hypoplasia of the right side of the thoracic cage; gastroschisis; ventral hernia with liver content; equinovarus foot deformity; scoliosis with curvature of the spine to the right; and left ovary agenesis (Figures 1, 2, 3). The morphological detail of the images highlights the midline deviation in the face (Figure 1).

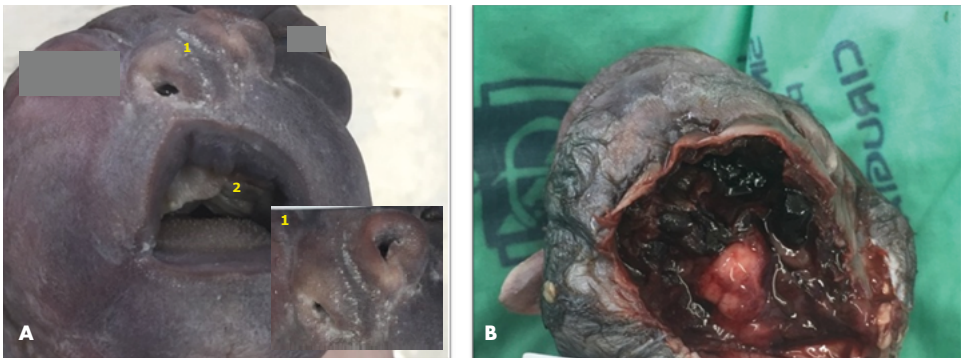


Figure 1. Photographic record of the head of the stillbirth. A) face (1. asymmetric and separated nostrils with ipsilateral hypoplasia of the nostril and nasal wings; and 2. cleft palate); B) medial parieto-occipital region (amniotic band).

Source: Photographs obtained during the study.

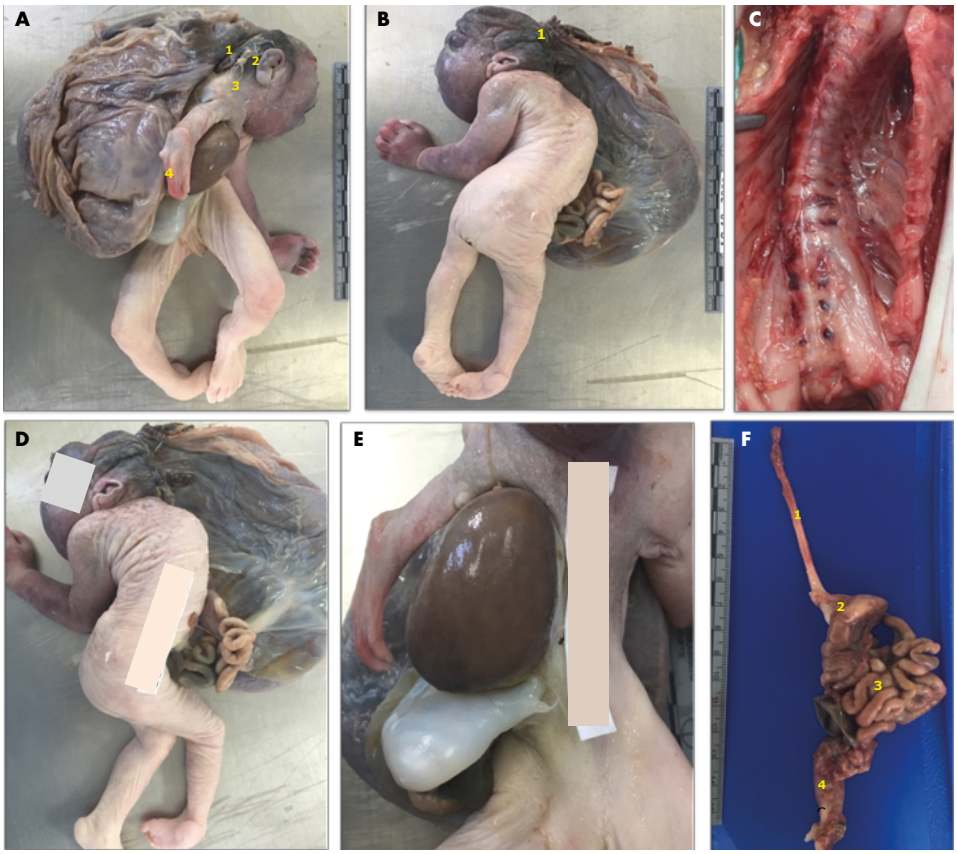


Figure 2. Photographic record of body defects of the stillbirth. A) right lateral view (1. amniotic bands attached to occiput and placenta, 2. low-set ears, 3. short neck, and 4. hypoplasia of the right upper limb ); B) left posterolateral view; C) anterior spinal dissection; D) right lateral view (gastroschisis); E) anterior view (liver outside the body and gastroschisis); F) dissection of the intestinal tract (1. esophagus, 2. stomach, 3. small intestine, and 4. rectum).

Source: Photographs obtained during the study.

During the internal examination of the fetus, it was noted that hypoplasia of the thoracic cage was predominant with asymmetry on the right side and that the diaphragm separated the thoracoabdominal region, although it was displaced to the right and attached to the Glisson's capsule in the right lobe. It was also found that the liver protruded from the abdominal wall and that the area below the thoracic cage was adjacent to the psoas muscles, which were fused. The lungs weighed 3.5g and their overall size was reduced. The short inferior vena cava showed no intracardiac defects (Figures 3, 4, 5 and 6).

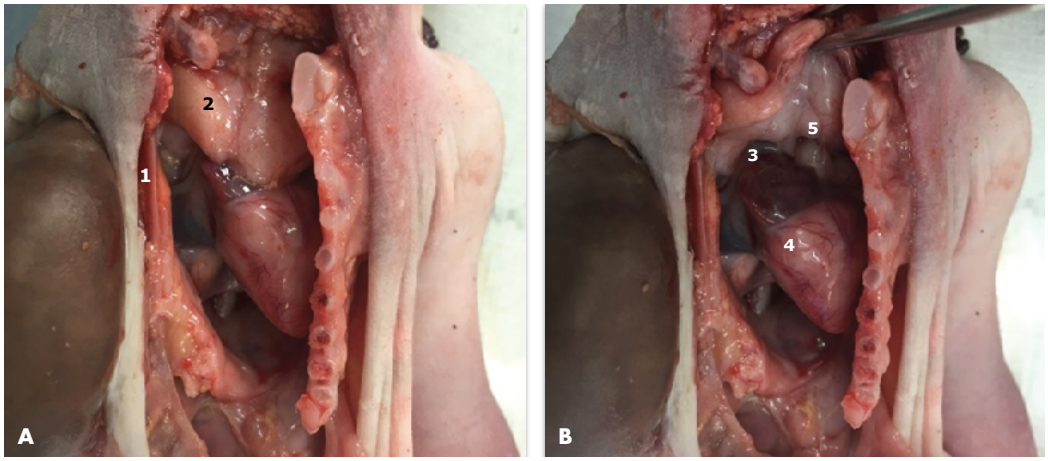


Figure 3. Thoracic cavity dissection. 1) hypoplasia on the right side of the thoracic cage; 2) thymus; 3) right atrium; 4) right ventricle; 5) normal arrangement of the main vessels.
Source: Photographs obtained during the study.

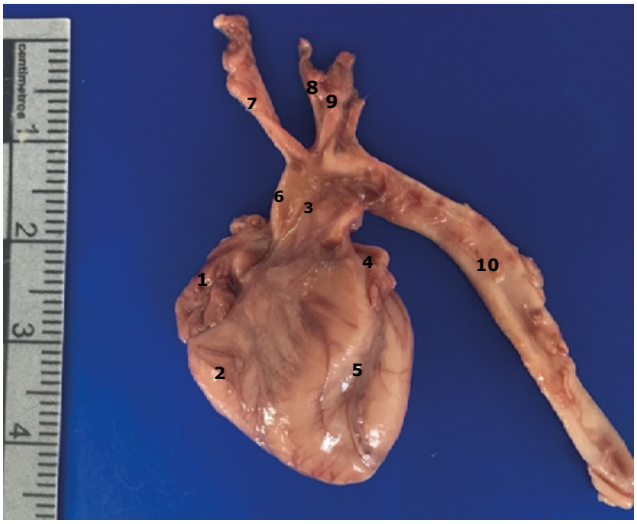


Figure 4. Heart and great vessels. 1) right atrium; 2) right ventricle; 3) pulmonary artery; 4) left atrium; 5) left ventricle; 6) ascending aorta; 7) brachiocephalic trunk; 8) left common carotid artery; 9) left subclavian artery; 10) descending aorta.
Source: Photographs obtained during the study.

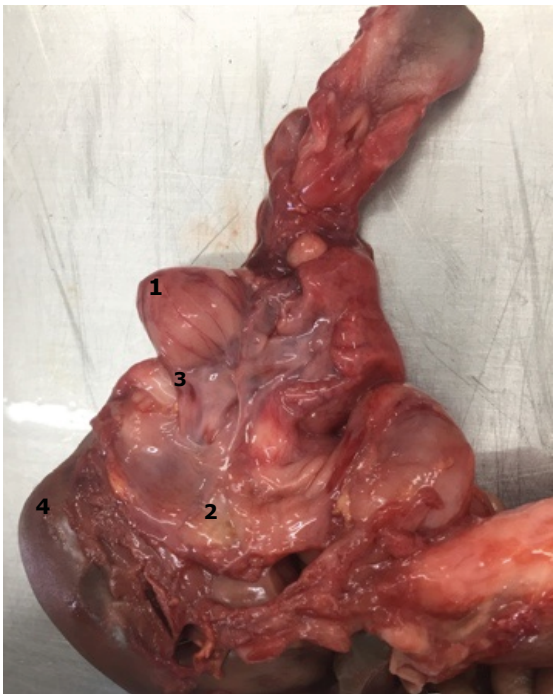


Figure 5. Viscera. 1) posterior aspect of the heart; 2) diaphragm; 3) inferior vena cava; 4) left liver lobe.
Source: Photographs obtained during the study.

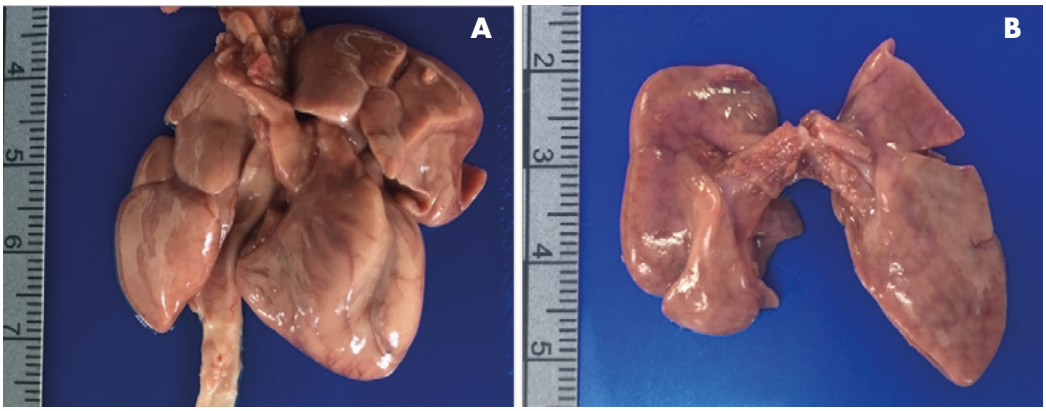


Figure 6. A) Right and left lungs, heart and great vessels; B) lungs.
Source: Photographs obtained during the study.

It was also evident that the reproductive system of the fetus was not fully formed and consisted of a uterus, right ovary and fallopian tubes hypoplasia, and agenesis of the left ovary (Figure 7).

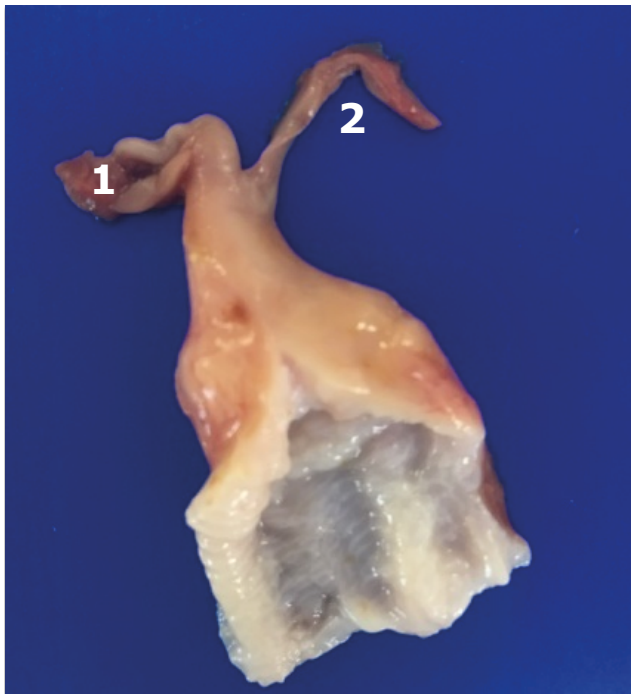


Figure 7. Uterus. 1) right ovary; 2) left fallopian tube.
Source: Photographs obtained during the study.

The histology of the organs showed that in the lung parenchyma there was a bilateral, but predominantly right, decrease in the alveolar surface area, with hypertrophy of the tunica media (Figure 8).

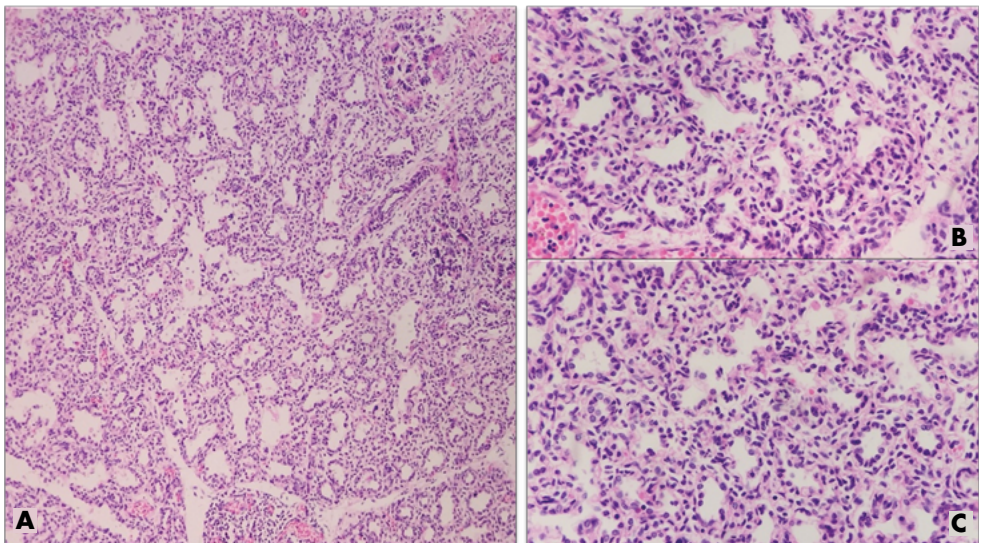


Figure 8. Hematoxylin and eosin staining of the right lung. A) 10X view; B) and C) 40X views.
Source: Photographs obtained during the study.

Microscopic examination of the placenta revealed 30% of tertiary chorionic villi with hyalinization, amniotic bands, chronic villitis, chorioamnionitis, and chronic deciduitis with microabscesses.

All the findings described here are part of the spectrum of partial expression or class 2 presentation of pentalogy of Cantrell (9,10), a syndrome suspected based on ultrasound findings and confirmed *postmortem.* The presence of craniofacial, musculoskeletal and reproductive system defects in the fetus also confirms the diagnosis, as they are described in the literature as additional and rare manifestations of this genetic anomaly (9,18,19).

## DISCUSSION

Pentalogy of Cantrell is a poorly described syndrome, but it has characteristic findings that allow to establish its diagnosis. Such findings comprise five basic defects: a midline supraumbilical abdominal wall, defect of the lower sternum, defect of the anterior diaphragm, defect in the pericardium, and intra-cardiac defects (19,20).

Embryological mechanisms involved in the development of pentalogy of Cantrell include abnormal mesoderm development (diaphragmatic, pericardial, and cardiac defects) and failure of fusion of lateral folds (sternal and abdominal wall defect) with changes in the development of a segment of the lateral plate mesoderm between 14 and 18 days of gestation. This leads to failure of the *septum transversum* to develop and failure of the somatic layer of the lateral plate mesoderm to migrate toward the midline, leaving the thoracoabdominal organs exposed (21).

Pentalogy of Cantrell is also characterized by damage to the amnion that may produce fiber-like bands that limit the development of the fetus, causing constriction on already formed structures (16,17). In the present case, a sternal defect with hypoplasia of the right side of the thoracic cage and thoracoabdominal midline defects, such as gastroschisis and liver eventration, were observed. Likewise, it was established that the fetus had ectopia cordis, although no pericardium defects or intracardiac anomalies were found, which does not rule out the diagnosis of pentalogy of Cantrell (10) because it has been proposed that this disorder has a wide spectrum of presentation, and its characteristics depend on the stage of development in which the defects occur (4).

Some of the causes described for pentalogy of Cantrell include aneuploidies such as trisomies 13 and 18; viral infections; mother's intake of teratogenic agents such as thalidomide, warfarin, and quinidine; vitamin A deficiency in the mother during pregnancy; and some type of familial tendency, with an X-linked dominant inheritance pattern and alteration of the region Xq25-Xq26,1, which is a characteristic of thoracoabdominal syndrome (8,15). However, no association with factors predisposing to malformations was evident in the present case. It should be noted that the patient did not undergo karyotype testing because the mother was young and reported no medical, pharmacological or intoxication history.

Pentalogy of Cantrell is more prevalent in men, with a 1.35:1 ratio (22,23), so this case is of great interest.

One of the described causes of pentalogy of Cantrell is amniotic rupture in cases of ectopia cordis (9), which was evidenced in the case reported here.

Routine ultrasounds performed during antenatal checkups (between 12 and 14 weeks and 19 to 24 weeks of gestation) are extremely helpful in diagnosing pentalogy of Cantrell (19,24). When this disease is suspected in the first trimester of gestation, it may be necessary to carry out complementary studies such as fetal echocardiogram, magnetic resonance imaging and biopsy of the chorial villi, which allows for G- or Q-banding karyotype testing. Such studies are essential, as they allow the identification of the full spectrum of disease presentation and offer the best advice regarding prognosis and follow-up (25). Moreover, early detection of congenital defects allows to offer interdisciplinary support from the beginning of pregnancy, as well as assistance in decision-making about anomalies incompatible with life.

Finally, it is important to mention that during autopsies it is essential to make a detailed macroscopic and microscopic documentation of the findings, that is, a complete record of the malformations of the body must be made so that this, together with the pathologist's report, allows to establish the diagnosis that caused the death. In the present case, the findings corroborated at the autopsy highlight the importance of performing this procedure in cases of multiple congenital anomalies, as it allows the family and even the scientific community to learn about the complications that led to the termination of a pregnancy (26-28).

## CONCLUSIONS

Adequate antenatal care, including strict ultrasound follow-up, is essential to detect future complications in the fetus, as well as to provide advice on possible malformations incompatible with life, such as pentalogy of Cantrell, and to determine the best therapeutic approach. Furthermore, autopsies on fetuses with multiple congenital anomalies are indispensable because, as in this case, they allow for the identification of alterations not detected on ultrasound or external physical examination.

## ETHICAL CONSIDERATIONS

The informed consent of the legal guardian of the 14-year-old girl who gave birth to the stillborn that is the subject of this report was obtained.

## CONFLICT OF INTEREST

None stated by the authors.

## FUNDING

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# SUCCESSFUL LAPAROSCOPIC APPROACH TO INTRAPERITONEAL BLADDER INJURY CAUSED DURING GYNECOLOGIC SURGERY. A CASE REPORT

**Keywords:** Wounds and injuries; Urinary bladder; Laparoscopy.
**Palabras clave:** Heridas y traumatismos; Vejiga urinaria; Laparoscopia.

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## RESUMEN

**Introducción.** Las lesiones del tracto urinario son frecuentes en el contexto de la cirugía pélvica; sin embargo, existe poca información sobre su manejo por vía laparoscópica. Se presenta el caso de una paciente con una lesión vesical intraperitoneal secundaria a cirugía pélvica ginecológica, quien recibió manejo por abordaje laparoscópico, y se propone un algoritmo de tratamiento.

**Presentación del caso.** Mujer de 39 años quién, luego de tres días de practicársele una salpingectomía izquierda y una resección del dispositivo intrauterino migrado mediante abordaje laparoscópico, consultó al servicio de urgencias por dolor abdominal generalizado y oligoanuria. Los exámenes de laboratorio evidenciaron microhematuria, creatinina sérica de 4.35mg/dl y nitrógeno ureico de 35,2mg/dl. En cistografía por tomografía computarizada (cisto-TC) se observó una solución de continuidad de la pared vesical posterolateral izquierda intraperitoneal. A la paciente se le trató la lesión vesical de forma exitosa por vía laparoscópica, y dos semanas después, también mediante cistografía retrógrada se confirmó una adecuada resolución de la misma.

**Conclusión.** Dados los resultados satisfactorios del manejo laparoscópico en la paciente y los beneficios de esta técnica, se puede concluir que el abordaje laparoscópico de las lesiones quirúrgicas de la vejiga es una opción terapéutica factible.

## ABSTRACT

**Introduction:** Urinary tract injuries are common in the context of pelvic surgery; however, there is little information in the medical literature on the management of these injuries using a laparoscopic approach. The following is the clinical case of a patient with intraperitoneal bladder injury secondary to gynecological pelvic surgery that was successfully treated using a laparoscopic approach. Moreover, a management algorithm is proposed based on the scientific data available.

**Case report.** A 39-year-old female patient was admitted to the hospital with generalized abdominal pain and anuria three days after undergoing a left laparoscopic salpingectomy and resection of a migrated intrauterine device. Laboratory tests showed microhematuria, serum creatinine of 4.35mg/dL, and urea nitrogen of 35.2mg/dL. Computed tomography cystography showed a solution of continuity on the left posterolateral intraperitoneal bladder. The patient underwent successful laparoscopic treatment for the bladder injury, and two weeks later, retrograde cystography confirmed its adequate resolution.

**Conclusions.** Based on the benefits of the laparoscopic approach and after extrapolating the outcomes of the laparoscopic management of bladder trauma, it can be concluded that the laparoscopic approach to surgical injuries of the bladder is a feasible therapeutic option.

## INTRODUCTION

Urinary tract injuries are the most common serious complication of laparoscopic pelvic surgery (1), and although their frequency varies depending on the gynecological surgery performed, Findleya & Solnik (2) found that between 0.2 and 15 cases occur per 1 000 procedures. Factors such as peritoneal adhesions, previous surgeries, and the presence of pelvic masses increase the risk of this type of injury.

Urinary tract injuries can be identified in the early or late postoperative period, and signs and symptoms include ileus, fever, anorexia, urinary ascites as a sign of cystotomy, and renal colic when there is ureteral obstruction (2).

The intrauterine device (IUD) is a small T-shaped plastic device used as a contraceptive method and can sometimes cause perforation of the uterus and migrate to pelvic or abdominal organs. The incidence of IUD migration and uterine perforation is reported in 1.9-3.6 cases per 1 000 insertions. It is worth mentioning that bladder perforation due to a displaced IUD is rare and is believed to occur primarily at the time of insertion. An IUD that migrated to the lower urinary tract, according to the literature, can be removed by three different methods: cystoscopy, laparoscopy, or open surgery (3).

In a 5-year retrospective cross-sectional analysis (January 2013 to December 2017) performed on 4 557 patients with IUD, Sharma & Suneja (4) found 71 cases of women (1.6%) requiring surgery for removing migrated devices, of which 63 (88.7%) were incomplete or embedded perforations and 8 (11%) were complete perforations or IUDs that migrated to omentum, vesicouterine pouch fundus, mesentery, or bladder.

Intraperitoneal bladder injuries require surgical repair (5), which is traditionally performed by laparotomy; however, little information is available on minimally invasive treatments in this clinical setting. The laparoscopic approach has demonstrated clear benefits, such as decreased bleeding, postoperative pain, intra-abdominal adhesions, risk of incisional hernias, and length of hospital stay and disability; improved visualization of pelvic organs; and early return to daily activities (1,5-7).

The following is the case of a patient who was successfully treated for intraperitoneal bladder injury secondary to gynecological pelvic surgery using a laparoscopic approach.

## CASE PRESENTATION

A 39-year-old, mestizo, single woman from a low-income household and living in Bogotá (Colombia), was treated by the outpatient gynecology and obstetrics service of a tertiary care university hospital in Bogotá due to a 1-year history of moderate, intermittent, pressure-type abdominal pain predominantly in the left hypogastrium and iliac fossa. No other associated symptoms or significant medical or surgical history were reported, besides two pregnancies with vaginal birth.

Physical examination found that the patient had deep and superficial tenderness of the hypogastrium and right iliac fossa, although no signs of peritoneal irritation were observed. There was also pain on vaginal palpation of the anterior wall of the vagina and the left adnexa, with a sensation of mass and enlargement of the posterior cul-de-sac. During the consultation, the patient reported that an IUD that she had been using as a contraceptive method for the last five years had been removed seven months earlier in another hospital.

Based on the findings, she underwent an outpatient enhanced CT of the abdomen and pelvis, which revealed the presence of a hyperdense foreign body compatible with the presence of an IUD migrated to the left vesicouterine pouch, located outside the uterus, and in close contact with the posterior wall of the bladder. This indicated that the first attempt to withdraw the IUD was not successful.

Given the patient's symptoms, a left salpingectomy was performed via laparoscopic approach, resecting the migrated IUD. During this procedure, performed one month after the gynecological consultation, the presence of a copper IUD migrated and inserted into the left uterine horn and into the left round ligament with surrounding inflammatory changes was confirmed. No lesions were reported under direct vision in other abdominal or pelvic organs. The patient progressed satisfactorily and was discharged one day after surgery. It should be noted that during her hospital stay, she received postoperative analgesic management and no alarming signs were present.

Three days after surgery, the patient visited again the emergency department of the same hospital due to anuria and generalized abdominal pain. On physical examination, vital signs were found within the normal ranges, and distension and moderate abdominal pain with no signs of peritoneal irritation were the only findings of relevance. Laboratory tests were performed, obtaining the following results: urinalysis with microhematuria, serum creatinine of 4.35mg/dL, and urea nitrogen of 35.2 mg/dL. Due to the suspicion of bladder injury, a urinary diversion with urethral catheter was passed to drain urine, and computed tomography (CT) cystography was requested. The procedure was performed on the day after readmission and showed a solution of continuity on the left posterolateral intraperitoneal bladder with approximate dimensions of 14x13mm, through which the contrast medium was leaked into the peritoneal cavity (uroperitoneum) (Figure 1).

Based on the imaging findings, the patient was taken to emergency surgery two days after hospital readmission for transurethral cystoscopy and placement of 6Fr open-end bilateral ureteral catheter (bilateral endoscopic renoatmospheric stent), in addition to laparoscopic repair of the bladder injury. During these procedures, a fistula with irregular borders and approximately 2cm in diameter along its major axis was observed on the left posterolateral side of the bladder (Figure 2).

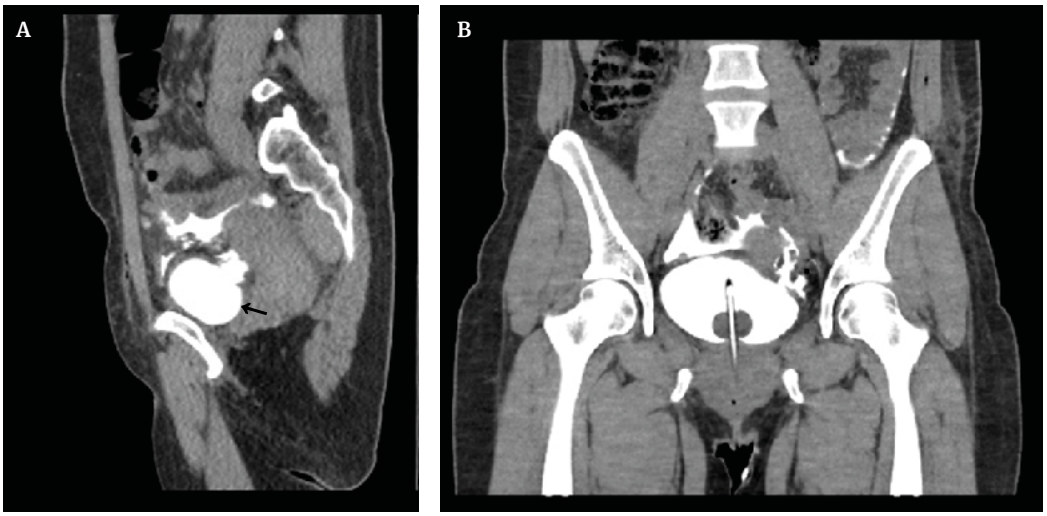


Figure 1 A) Sagittal view - CT cystography (arrow pointing to lesion site). B) Coronal-view - CT cystography (star indicating the presence of contrast medium in the peritoneal cavity).
Source: Document obtained during the course of the study.

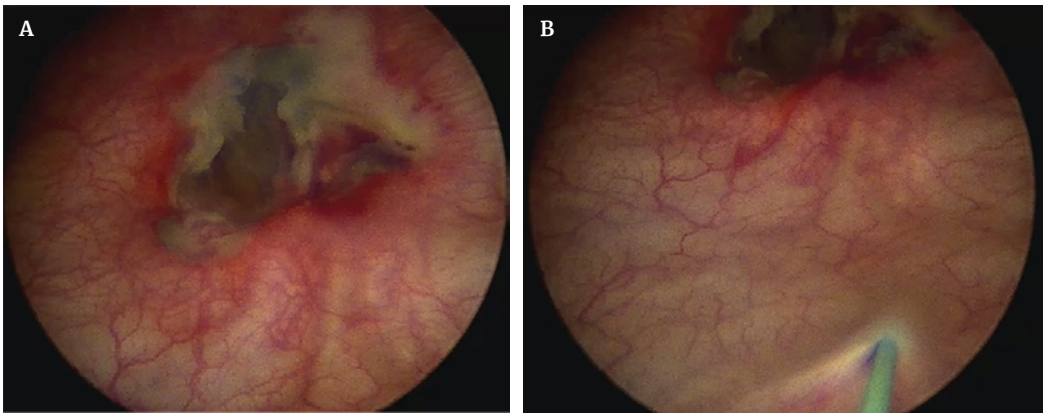


Figure 2 Endoscopic findings of transurethral cystoscopy. A) defect in the left posterolateral bladder wall; B) hydrophilic guidewire emerging from the left ureteral meatus.
Source: Document obtained during the course of the study.

For the laparoscopic approach, four trocars were used and distributed as follows: a 12mm umbilical trocar, two 12mm trocars in both iliac fossa at the midclavicular line crossing, and a 5mm accessory trocar in the right iliac fossa. This approach allowed finding urine in the peritoneal cavity and confirming the presence of a defect with irregular borders on the left posterolateral side of the bladder (Figure 3).

During this procedure, the devitalized edges of the bladder defect were also removed, and suturing was done in two planes with a 3-0 barbed suture, achieving an adequate and hermetic closure thanks to endoscopic and laparoscopic vision (Figure 4). Cystoscopy confirmed that the bladder defect had been properly closed and that the left urethral meatus was not involved. The 6Fr open end ureteral catheters were then threaded to the 16Fr Foley catheter and secured with

2-0 silk suture. The bilateral endoscopic renoatmospheric stent was maintained for one week and the urethral catheter for two weeks.

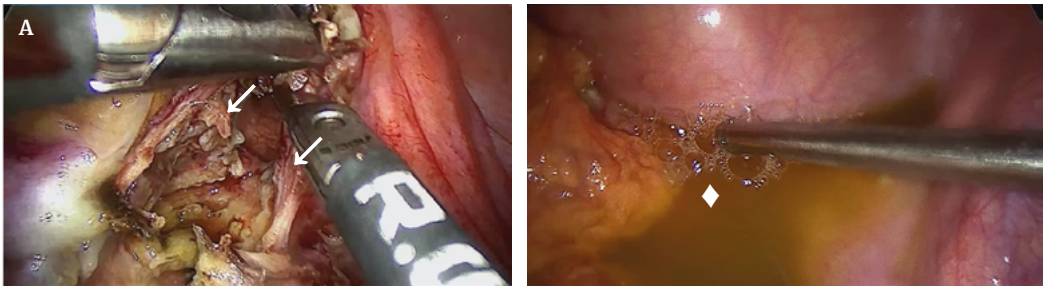


Figure 3 Laparoscopic findings. A) defect in the posterior wall of the bladder (arrows show the lateral edges of the bladder injury); B) uroperitoneum (star points to urine in the peritoneal cavity).
Source: Document obtained during the course of the study.

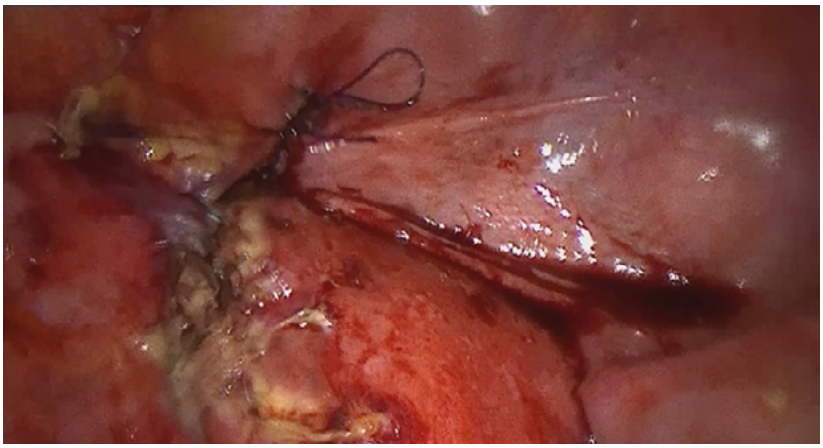

Figure 4 Laparoscopic view after closure of the bladder defect.
Source: Document obtained during the course of the study.

The patient had a satisfactory postoperative course and her blood creatinine levels improved, reaching values of 0.6mg/dL. Two days after the procedure, she was discharged and two weeks later a follow-up retrograde cystography was performed, confirming adequate resolution of the bladder injury (Figure 5) and the Foley catheter was removed without complications. After two months of outpatient follow-up, the patient was discharged by the urology service due to her good clinical course and the absence of urinary symptoms.

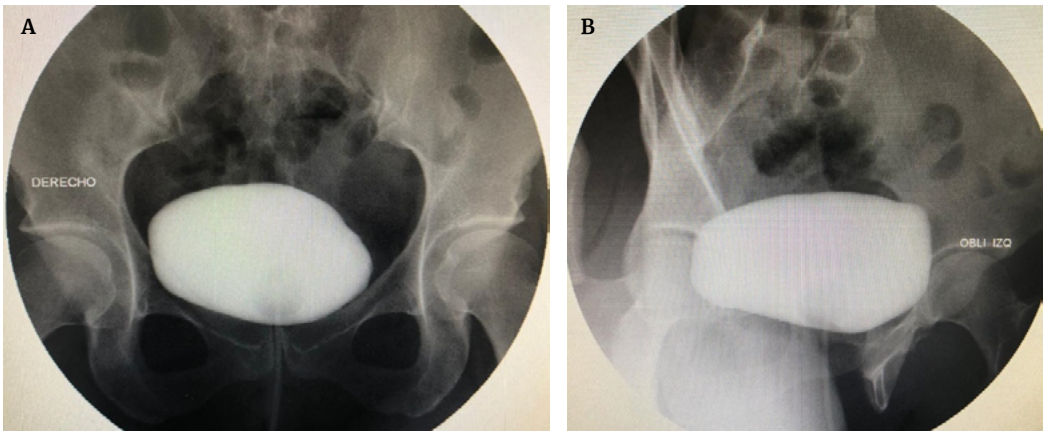


Figure 5 Post-operative retrograde cystography. A) anteroposterior projection; B) left oblique projection.

Source: Document obtained during the course of the study.

## DISCUSSION

Since its introduction in the 1970s, the laparoscopic approach has proven to be one of the most significant advances in surgery (1), allowing for the completion of various procedures. For example, as stated by Aydin & Mercimek (7), in 1994, Parra reported the first laparoscopic repair of an intraperitoneal bladder perforation after iatrogenic bladder trauma.

Laparoscopy has demonstrated clear benefits, including reduced hospital stay, bleeding, postoperative pain, disability time, intra-abdominal adhesions, and risk of incisional hernias; early return to daily activities; and improved visualization of the pelvic organs (5-7).

When grouped, urinary tract injuries represent the most common type of major complications in laparoscopic pelvic surgery (1). Bladder injuries are caused by obstetric and gynecologic surgery, general surgery, and urological surgery in 65%, 22%, and 13% of cases, respectively (8).

The bladder is at risk of injury during gynecologic laparoscopic surgery for two reasons: the trocar insertion process, for example during suprapubic port placement, or its close relationship with the surgical field, such as during hysterectomy (1). Regarding laparoscopic pelvic surgery, the reported incidence of bladder perforation varies widely, with injury rates ranging from 0.02% to 8.3%, placing this injury at the top of the list of visceral complications (1).

Some of the risk factors for urinary tract injury during gynecological surgeries include a history of radiation or pelvic surgery, endometriosis, urinary tract anomalies, peritoneal adhesions, pelvic masses, obesity, and uterine fibroids, as well as the surgeon's lack of experience, specifically a low volume of laparoscopic gynecological surgical procedures performed (7).

Although not supported by evidence, performing bladder catheterization prior to peritoneal insufflation and trocar insertion is recommended as good

clinical practice to avoid injury to a distended bladder (1,9). Preoperative prophylactic ureteral catheterization is debatable, as a beneficial effect on reducing the risk of ureteral injury during gynecological surgery has not been demonstrated consistently (7). Thus, to reduce the risk of urinary injury during gynecologic laparoscopic surgery, it is critical to understand and follow electrosurgery safety precautions, as bladder injuries may be difficult to detect because they can occur at a site distant from the surgeon's view and/or present as a late tissue rupture several days after the primary injury (1).

The following are some of the safety measures to consider for preventing potential complications related to electrosurgery in laparoscopy (1):

- Carefully inspect instrument insulation with the anatomical structures of interest before using electrical power.
- Use the lowest power setting possible to achieve the desired effect from the instruments.
- Use a low-voltage waveform for monopolar diathermy.
- Use bipolar energy when appropriate.
- Use brief intermittent activation during surgery.
- Do not activate instruments during laparoscopic surgery near or in direct contact with another instrument.
- Make sure that forceps are always in sight of the surgeon when activating power instruments.

Signs and symptoms of bladder injury include macroscopic hematuria, abdominal or suprapubic tenderness, inability to urinate, and oliguria (1,6,8). These symptoms usually appear within the first 48 postoperative hours after sustaining a thermal injury or up to 10-14 days after the procedure (1). Biochemical profiles help diagnose this type of injury because serum creatinine levels rise abnormally due to its reabsorption into the urine through the peritoneal membrane (1), as was the case of the patient reported here.

When evaluating patients with suspected bladder injury, imaging studies, such as retrograde cystography or CT cystography, are necessary, since they have sensitivity and specificity of 95% and 100%, respectively (5,6).

Extraperitoneal bladder injuries can be treated conservatively with a bladder catheterization (1); however, intraperitoneal injuries require surgical repair (10) because, if untreated, they can lead to complications such as peritonitis and sepsis (5).

Traditionally, intraperitoneal bladder injuries have been treated with laparotomy (11), but current literature also describes cases of laparoscopic bladder repair, for example, following blunt abdominal trauma (6,12). Matsui *et al.* (13), in a case report of a 61-year-old patient with acute abdomen secondary to intra- and extraperitoneal bladder injury, showed that laparoscopic repair may be indicated even in emergency situations involving bladder rupture.

An injury involving or near the bladder trigone carries the risk of urethral injury that can be assessed endoscopically (1). In most cases of bladder injury during laparoscopic surgery, repair should be performed by a urologist or gynecologist with advanced laparoscopic skills to avoid additional morbidity beyond that caused by laparotomy (1).

Cystotomy repair, i.e., surgical suture used to close a bladder injury, should be performed with absorbable suture to avoid creating a nidus that promotes the formation of urinary stones. It can also be performed with single-layer or two-layer technique, either continuous or interrupted (6). Urinary diversion with a Foley catheter for continuous drainage should be maintained for two weeks (1).

The case presented here describes the successful laparoscopic management of a bladder injury caused by gynecologic laparoscopic surgery in a tertiary care university hospital. Although the literature describing the laparoscopic management of post-surgical bladder injuries is scarce, the available evidence shows that the laparoscopic approach to injuries of this type, even those caused by blunt abdominal trauma, is feasible, has satisfactory outcomes, and is the current recommendation (6,14,15). Therefore, if the necessary resources (infrastructure, technology, human resources trained in laparoscopy, etc.) are available, the laparoscopic approach should be considered as the route of choice for the early management of iatrogenic bladder injuries in clinically stable patients (Figure 6).

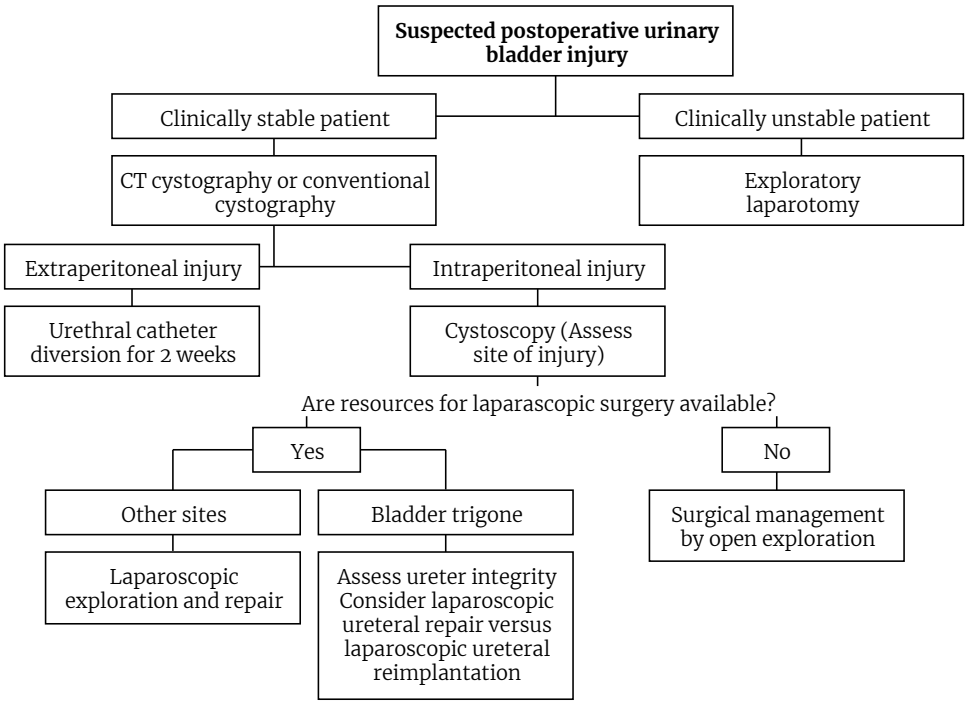


Figure 6 Algorithm for the management of postoperative bladder injuries.
Source: Own elaboration.

## CONCLUSION

This is the case report of a patient who had a bladder injury during the laparoscopic removal of an IUD that migrated to the uterine horn and vesicouterine pouch, which was diagnosed in the postoperative period and corrected via laparoscopy. Considering the advantages of laparoscopy over open surgery, and extrapolating the positive outcomes obtained with the laparoscopic management of traumatic bladder injuries in this patient, it is possible to conclude that the laparoscopic approach to surgical injuries in this organ should be regarded as a viable treatment option. Nevertheless, it is essential to keep in mind that this procedure requires assistance personnel with advanced laparoscopic training, as well as interdisciplinary support to provide comprehensive care to the patient.

## ETHICAL CONSIDERATIONS

This case report was prepared after obtaining the patient's informed consent for the use of the clinical data and the anonymous publication of this article.

## CONFLICTS OF INTEREST

None stated by the authors.

## FUNDING

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None stated by the authors.

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CASE REPORTS
REPORTES DE CASO

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# METHOTREXATE NEPHROTOXICITY IN A PATIENT WITH PRESERVED RENAL FUNCTION. CASE REPORT

**Keywords:** Methotrexate; Drug Toxicity; Acute Kidney Injury; Lymphoma non-Hodgkin.
**Palabras clave:** Metotrexato; Toxicidad; Insuficiencia renal; Linfoma no Hodgkin.

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## RESUMEN

**Introducción.** El metotrexato es un fármaco con propiedades quimioterapéuticas usado de forma frecuente para el tratamiento de ciertos tipos de cáncer. A continuación, se presenta un caso clínico que, a conocimiento de los autores, es el primer reporte en Colombia sobre nefrotoxicidad por este medicamento, así como sus consecuencias y el manejo que se le dio en un hospital de cuarto nivel.

**Presentación del caso.** Hombre de 71 años con diagnóstico de linfoma no Hodgkin y función renal normal, quien se sometió a tratamiento quimioterapéutico (metotrexato a altas dosis por vía endovenosa) y desarrolló insuficiencia renal aguda estadio 3 según las guías KDIGO, la cual muy probablemente se relacionaba al consumo de metotrexato. El paciente recibió manejo con líquidos endovenosos y bicarbonato de sodio como promotores de la eliminación renal del tóxico, así como folinato cálcico oral, según el protocolo institucional, con lo cual se logró la recuperación de su función renal y que los niveles de niveles de creatinina y nitrógeno ureico mejoraran.

**Conclusiones.** El manejo del paciente reportado demuestra que aunque la nefrotoxicidad por metotrexato es una entidad potencialmente grave, puede tener un buen pronóstico si se maneja oportunamente.



## ABSTRACT

**Introduction:** Methotrexate is a drug with chemotherapeutic properties frequently used for the treatment of certain types of cancer. The following is a clinical case which, to the best of the authors' knowledge, is the first report in Colombia on nephrotoxicity caused by this drug and describes the consequences as well as the treatment provided at a quaternary care hospital.

**Case report:** A 71-year-old patient with a diagnosis of non-Hodgkin's lymphoma with normal renal function underwent chemotherapy (high-dose methotrexate intravenously) and developed stage 3 acute renal failure according to the KDIGO guidelines, which was most likely related to methotrexate intake. The patient received treatment with intravenous fluids and sodium bicarbonate as promoters of urine excretion of the toxin, and oral calcium folinate following the institutional protocol. The patient was discharged with recovery of kidney function and improved creatinine and urea nitrogen levels.

**Conclusion:** The treatment given to the patient in this case report shows that although methotrexate nephrotoxicity is a potentially serious entity, it can have a good prognosis if treated promptly.

## INTRODUCTION

Methotrexate (MTX) is an essential drug for the treatment of certain oncological diseases since it increases survival in cancer patients. While it may have cytotoxic effects, they may be partially antagonized by the administration of folic acid, allowing for its usage at high doses. Even though manifestations of MTX toxicity are rare, they occur in 2-12% of treatment cycles and lead to clinical condition scenarios with high morbidity and mortality, such as hepatotoxicity, gastrointestinal mucositis, bone marrow suppression, neurotoxicity, and nephrotoxicity (1,2).

Although several population pharmacokinetic models of high-dose MTX for children have been developed to predict adverse events during chemotherapy, they are complicated and of little use in clinical practice, so serum drug concentration monitoring remains the gold standard for identifying patients at high risk of developing toxicity. It is important to note that there are specific drug concentration values depending on the time of administration (2).

As has been demonstrated in various case series, the management of MTX toxicity, in addition to controlling drug levels to achieve therapeutic goals, aims to a) promote renal perfusion to facilitate clearance of the drug, b) look for effective urine alkalinization levels that avoid precipitation, and c) block unfavorable effects through competitive inhibition or enzymatic cleavage (3,4).

The following is the case of an oncologic patient with preserved renal function who developed nephrotoxicity secondary to the use of MTX. A description of the diagnosis and treatment options is provided below.

## CASE PRESENTATION

This is the case of a 71-year-old man from Boyacá, Colombia, with high blood pressure, hearing loss in the right ear, and activated stage IV large B cell non-Hodgkin's lymphoma (central nervous system involvement due to bone marrow mass at the right petroclival junction) diagnosed in February 2020.

The patient, who was admitted in July 2020 to a quaternary care hospital for the administration of a second cycle of scheduled polychemotherapy, had already received a first cycle of this treatment in April 2020, which included rituximab, methotrexate, cytarabine, prednisolone, and filgrastim (5).

During the clinical assessment on admission for his second chemotherapy cycle, the patient presented the following vital signs: blood pressure of 130/80 mmHg, heart rate of 80 bpm, respiratory rate of 16 rpm, temperature of 36.5°C, oxygen saturation of 95% with $FiO_2$ 0.21, weight of 64kg, height of 163cm, body mass index of 24 kg/m$^2$, and body surface area 1.68m$^2$ using the DuBois formula. According to the Eastern Cooperative Oncology Group (ECOG) Performance Status scale, the patient rated as PS 1, indicating functional independence. As a relevant finding, the man was found to have right external strabismus as a sign of involvement of the sixth cranial nerve.

It should be noted that the second chemotherapy cycle was initiated in July 2020, one month later than initially scheduled, because the patient presented with left ear pinna perichondritis 15 days after the first chemotherapy cycle started. The infection was treated with antibiotic therapy for 21 days and he had an adequate response.

On the third day after starting the second chemotherapy cycle, the patient developed stage 3 acute renal failure (ARF) according to the KDIGO guidelines due to an increase in creatinine levels: a change from 1.05 mg/dL on admission to 3.25 mg/dL at 48 hours (Table 1). This chemotherapy treatment included the administration of 3 500 mg/m2 of MTX intravenously.

Table 1 Evolution of laboratory tests during hospital stay.

| Laboratory tests | Day 1 | Day 3 | Day 5 | Day 7 | Day 10 |
|---|---|---|---|---|---|
| Creatinine (mg/dL) | .- | 3.25 | 3.71 | 2.0 | 1.16 |
| Urea nitrogen (mg/dL) | 23 | 38 | 42 | 25 | 20 |
| Methotrexate levels (umol/L) | | 10.48 | 2.06 | 0.42 | 0.04 |
| Urinary pH | | 7.0 | 8.0 | 8.0 | |
| Sodium (mEq/L) | 140 | 144 | 148 | | |
| Potassium (mEq/L) | 4.2 | 3.5 | 3.0 | 3.5 | |
| Calcium (mEq/L) | 9.2 | 7.4 | 7.2 | 8.2 | |

Note: the following are the methotrexate levels that increase the risk of adverse effects: >10 umol/L at 24 hours, >1 umol/L at 48 hours, and >0.1 umol/L at 72 hours.
Source: Own elaboration.

In the partial urine samples, there were no striking findings or crystals typical of drug precipitation. Other causes of ARF were ruled out on the third day of treatment due to the transient relationship between MTX administration and renal function impairment, as well as the absence of intercurrent infectious, hemodynamic, or toxic phenomena and the adequate response to the treatment established, as creatinine and urea nitrogen levels improved from day 7 with the decrease of MTX in serum levels after suspension and the application of the treatment pillars for MTX toxicity (Table 1).

According to Naranjo *et al.* (6), all of the above is classified as a probable toxicity event associated with MTX because the patient obtained a score of 6 points (5-8 points: probable) after applying the adverse drug reaction algorithm published by them. No toxicity was observed in other organs.

Intravenous crystalloid fluids were optimized on the third day at 3-4 liters/day after starting the second chemotherapy cycle and given the patient's condition. Similarly, 50mg of calcium folinate were administered orally every 4 hours, as well as intravenous sodium bicarbonate at a rate of 40 mEq per liter of intravenous

crystalloid fluids, with the goal of achieving a urinary pH >7. It should be noted that during the administration of this infusion, there were changes in the levels of water electrolytes, such as hypernatremia and hypocalcemia, which were expected during the treatment; however, those changes did not have an impact on the clinical condition of the patient but were followed up until they were normalized.

The patient's progress was satisfactory, achieving a progressive decrease in creatinine and urea nitrogen levels and reaching baseline levels at 10 days. He also had adequate serum MTX clearance. Considering his favorable progress, it was not necessary to initiate renal replacement therapy.

Taking into account the patient's situation, the hematology oncology service decided to suspend the chemotherapy protocol after one month due to the high risk of renal complications and indicated treatment with external beam radiation therapy using 3D-CRT planning technique with computerized simulation at doses of 300-3000 cGy in PTV-CTV (right petroclival mass plus margin).

## DISCUSSION

According to Perazella & Moeckel (7), the overall incidence rate of ARF is approximately 1.8% (range: 0%-12%) and, in general, this type of injury is reversible.

The theory that more consistently explains the mechanism by which MTX-induced nephrotoxicity occurs indicates that it is mediated by the precipitation of this substance and its metabolites in the renal tubules, as well as by direct toxicity in these structures (4). In cases of MTX nephrotoxicity, urinalysis may often show tubular epithelial cells, granular casts and, to a lesser extent, drug crystals if urine is acidic (7).

Regarding factors that increase the risk of nephrotoxicity, Amitai *et al.* (8), in a retrospective single-center cohort study that included patients treated with high-dose MTX in the hematology ward of an Israeli hematology institute between January 2012 and February 2017 (n=160), found that lactate dehydrogenase levels >380 U/L and albumin levels <3.6 g/dL were the factors associated with the development of ARF with the greatest statistical significance.

High doses of MTX (>500 mg/m$^2$ in children and >1000 mg/m$^2$ in adults) used in various oncological diseases, including lymphomas and sarcomas, predictably increase the development of nephropathy, in part because chemotherapy doses used in solid tumors are higher than those used in hematologic malignancies (9).

On the other hand, SKärby *et al.* (10), in a study aimed at determining the relationship between MTX clearance time and various aspects of renal function, established that an increase in serum creatinine by more than 50% is a better predictor of delayed clearance than serum MTX at the end of the infusion, especially if information on previous creatinine measurements is used to reduce the impact of an occasionally low serum creatinine value prior to the start of the

infusion. Likewise, according to Iqbal *et al*. (11) in their case report, significant genetic variants affecting MTX disposition and effects have been described in pediatric patients with acute lymphoblastic leukemia, with the strongest variant residing in the reasonable candidate gene *SLCO1B1*, which is associated with the clearance of this medication.

In addition, it is critical to keep in mind that cancer patients generally receive adjunctive therapies, either because of the oncological disease or because of their underlying comorbidities, and thus some drugs may impair MTX clearance. These drugs include non-steroidal anti-inflammatory drugs, penicillin and its derivatives, salicylates, gemfibrozil, trimethoprim with sulfamethoxazole, amphotericin B, aminoglycosides, proton pump inhibitors, levetiracetam, among others (12).

MTX nephrotoxicity perpetuates ARF caused by this drug; as a result, this failure reduces drug clearance, prolongs toxic serum values over time, and, thus, generates adverse effects such as myelosuppression, mucositis, hepatotoxicity, conjunctival involvement, pulmonary toxicity, among others (12).

Regarding the treatment of MTX nephrotoxicity, it is important to point out that definitive discontinuation of the drug is not completely necessary. In fact, there are several pillars for the prevention and management of this condition, which include urine alkalinization, maintenance of urine output by means of intravenous crystalloid fluids, monitoring of serum creatinine and MTX levels, as well as pharmacological rescue with leucovorin (5-formyltetrahydrofolate) (4).

With regard to urinary alkalinization, a therapeutic possibility to consider is the use of intravenous sodium bicarbonate, which must be adjusted to maintain urine pH levels ≥7.0 and can be added to the perfusion in punctual boluses; this alkalinization can be verified later in the urinalysis (12,13). There is evidence that acetazolamide can be used to treat metabolic alkalosis in patients who do not have adequate urinary alkalinization (14).

Surprisingly, enteral alkalinization protocols have been studied as well. One of them is the one proposed by Kramer *et al.* (15), which supports the ability to conserve intravenous sodium bicarbonate by using an enteral-based urine alkalization regimen of high-dose MTX (no differences in outcomes or toxicity). However, individuals who received enteral-based urine alkalinization experienced more frequent diarrhea, lower serum bicarbonate levels, and urine pH readings that were slightly below target.

Concerning the maintenance of urinary output, it is expected that adequate administration of intravenous crystalloid fluids prior to and up to two hours after the MTX infusion will facilitate its clearance since 90% of the drug is eliminated by this route (4,8). It is worth noting that studies such as Kinoshita *et al.* (16) associate high sodium concentrations in MTX infusion (70 mEq/L versus 100 mEq/L) with better drug clearance when serum concentrations are monitored during chemotherapy.

About the use of medicinal products, Widemann *et al.* (17) state that pharmacological interventions to treat MTX nephrotoxicity include high-dose leucovorin,

glucarpidase, or thymidine. Leucovorin is a folate derivative (5-formyltetrahydrofolate) that enters the cell in the same way that MTX does and is extensively converted to its active metabolite 5-methyltetrahydrofolate. This medication has been used to prevent and treat this condition for over thirty years (18). It should be kept in mind that each high-dose MTX chemotherapy schedule includes the leucovorin dosing schedule to be administered during treatment cycles. The patient in this case was given 50mg of calcium folinate orally every six hours, but he still developed MTX nephrotoxicity.

Finally, as for glucarpidase, its efficacy in the management of MTX nephrotoxicity has been widely demonstrated (3,9,10,15,16) at doses of 50 U/kg body weight in a 5-minute intravenous infusion, as it reduces the serum concentration of this drug by 97% after 15 minutes of administration. However, it is important to note that it has no effect on intracellular MTX (7,18-20), so management with glucarpidase should include leucovorin, which should never be administered within two hours before or after glucarpidase because it can also cleave leucovorin.

Renal support therapy has also been included in the therapeutic options for MTX nephrotoxicity when other treatment measures are unsuccessful. From a physiological perspective, MTX has a volume of distribution of 0.4-0.8 L/kg, a molecular weight of 454 Daltons and a plasma protein binding of 50%, so extracorporeal renal support therapy has a favorable profile for MTX elimination. However, its use is subject to debate since there is a high level of MTX binding to plasma proteins; therefore, hemoperfusion (21), hemodialysis with high cut-off filters (22), or continuous renal support by means of continuous veno-venous hemofiltration have been proposed (23). These therapeutic options can be considered in addition to the previously mentioned medical management and in cases of persistently high MTX concentrations and multisystem involvement. In the reported case, the patient did not require any extracorporeal renal support therapy because the involvement was limited to the kidney, and the measures implemented resulted in a rapid decrease in MTX levels.

## CONCLUSIONS

The use of high-dose MTX is common in chemotherapy regimens. The present case illustrates the usual clinical scenario of nephrotoxicity induced by this drug. It also emphasizes the importance of understanding the mechanisms that cause it and describes the various therapeutic options available for treating it with the aim of improving the overall prognosis of patients.

## ETHICAL CONSIDERATIONS

For the preparation of this case report, we obtained the patient's informed consent and the approval of the Institutional Ethics Committee of the Hospital Universitario San Ignacio de Bogotá in accordance with Minutes No. FM-CIE-1286-20 of December 21, 2020.

## CONFLICTS OF INTEREST

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# TREATMENT APPROACH TO A PATIENT WITH CATAMENIAL EPILEPSY. CASE REPORT

**Keywords:** Menstrual Cycle; Drug Resistant Epilepsy; Neurosteroids; Progesterone; Estrogens.
**Palabras clave:** Ciclo menstrual; Epilepsia refractaria; Neuroesteroides; Progesterona; Estrógeno.

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## RESUMEN

**Introducción.** La epilepsia catamenial se define como un empeoramiento o la exacerbación de las crisis epilépticas en relación con el cambio hormonal durante el ciclo menstrual femenino. Se cree que esta se produce por las propiedades neuroactivas de las hormonas esteroides endógenas y la variación cíclica natural en sus niveles séricos a lo largo de dicho ciclo.

**Presentación del caso.** Mujer de 31 años de Bogotá (Colombia), quien fue llevada al servicio de urgencias por un episodio de crisis epiléptica con convulsiones tonicoclónicas asociado al período menstrual. Debido a que la aparición de las crisis epilépticas se asociaba con la menstruación (cada 28 días), se estableció que la paciente presentaba epilepsia focal estructural de características catameniales. En junta médica multidisciplinar se discutieron las ventajas del manejo médico y el manejo quirúrgico, y se decidió instaurar tratamiento farmacológico con progestágenos, el cual, tras seguimiento, evidenció supresión total de las crisis.

**Conclusiones.** La epilepsia catamenial debe considerarse como una causa de epilepsia refractaria al tratamiento antiepiléptico. Además, su abordaje debe ser multidisciplinario y su tratamiento debe ir enfocado a mejorar la calidad de vida de los pacientes.



## ABSTRACT

**Introduction:** Catamenial epilepsy refers to the worsening or exacerbation of seizures due to hormonal changes during the menstrual cycle. It is thought to be secondary to the neuroactive properties of endogenous steroid hormones and the natural cyclic variation in their serum levels throughout the menstrual cycle.

**Case presentation:** A 31-year-old female patient from Bogotá (Colombia) was admitted to the emergency department due to an episode of tonic-clonic seizure associated with the menstrual period. Since the onset of the seizures was related to menstruation (every 28 days), it was established that the patient had structural focal epilepsy with catamenial features. Advantages of medical vs. surgical treatment were discussed during a multidisciplinary medical board and it was decided to start pharmacological treatment with progestogens, which resulted in complete remission of the seizures as established during a follow-up visit.

**Conclusions:** Catamenial epilepsy should be considered as a cause of epilepsy refractory to antiepileptic medications. Furthermore, it should be approached from a multidisciplinary perspective and its management should be focused on improving the patients' quality of life.

## INTRODUCTION

In ancient times, the cyclical occurrence of epileptic seizures, just like menstrual cycles, was attributed to lunar phases, but in 1857, Sir Charles Locock, at a meeting of the Royal Medical and Chirurgical Society, first described the relationship between epileptic seizures and the menstrual cycle. Since then, multiple studies on what is known as catamenial epilepsy, a condition that refers to the exacerbation of seizures in association with the menstrual cycle, have been conducted. It is worth mentioning that the term "catamenial" is derived from the Greek word *katamenios*, which means monthly (1).

Worldwide, it is estimated that 2.4 million people are diagnosed with epilepsy each year and, in high-income countries, new cases per year vary between 30 and 50 per 100 000 inhabitants of the general population, while this figure can be up to 2 times higher in low- and middle-income countries (2). In Colombia, specifically, Velez & Eslava-Cobos (3) reported in 2006 that the overall prevalence rate of epilepsy was 11.3 cases per 1 000 people.

Herzog *et al.* (4), in a study of 184 women with intractable complex partial seizures, found that about one third of the participants may have catamenial epilepsy. In turn, Ducan *et al.* (5), in a study that aimed to establish the incidence of catamenial epilepsy in 40 young women with refractory epilepsy, found that only 5 participants (15.5%) met the criteria established by the authors for defining catamenial epilepsy (occurrence of at least 75% of seizures within 4 days before and 6 days after the onset of menstruation).

Currently, there are multiple therapeutic approaches available, both hormonal and non-hormonal, for the treatment of catamenial epilepsy; however, there is no consensus or specific recommendations regarding its management (6,7). The following is the case of a patient diagnosed with this disorder, who was treated with progestogens and had a satisfactory outcome.

## CASE PRESENTATION

A 31-year-old woman of mixed racial descent, from a middle-class household, and born in Bogotá, D.C. (Colombia), was taken to the emergency department of the Hospital Universitario Clínica San Rafael in Bogotá by a relative due to an episode of tonic-clonic seizures directly associated with her menstrual period and the subsequent onset of generalized headache. The patient's relative stated that she experienced the same symptoms every 28 days and that she had a history of refractory structural epilepsy, visual impairment due to meningitis at 9 months of age, autism spectrum, schizophrenia under pharmacological treatment, and surgical sterilization performed for family planning purposes.

On admission to the hospital, management was started with 5mg of intravenous midazolam; however, due to refractoriness to this treatment, the medication

was switched to levetiracetam 1g administered intravenously. 36 hours after admission, the patient had a new seizure, which was considered to be refractory status epilepticus. Therapy propofol was initiated at an infusion rate of 100mg every hour, which was maintained for 3 hours until a new episode occurred. Due to this new seizure, rapid sequence intubation was performed and 3mg of midazolam were administered intravenously every hour. She was transferred to the intensive care unit (ICU) where she was assessed by the neurology service to monitor and stabilize her condition, on the one hand, and to determine the advisability of starting treatment with antiepileptic drugs, on the other hand.

On the fifth day of her stay in the ICU, the patient presented with sepsis of urinary origin, for which she received treatment with 4.5g of piperacillin-tazobactam every 8 hours for 7 days; after 4 days she was stabilized and extubated. After 15 days in the ICU, she was transferred to the floor under the care of the internal medicine service, and a consultation with the gynecology and obstetrics department was requested to determine the need for hormone therapy.

Prior to being admitted to the emergency room, the patient was receiving outpatient care from psychiatry, neurology, and gynecology specialists. She was taking 250mg of valproic acid every 12 hours; 200mg, 100mg, and 200mg of lacosamide in the morning, afternoon, and evening, respectively; 5, 5, and 25 drops of clonazepam in the morning, afternoon, and evening, respectively; 250mg of acetazolamide per day; and 5mg of olanzapine per day.

On the same day of admission, the patient underwent a computed tomography scan of the skull (Figure 1) that revealed cortical laminar necrosis in the occipital region, a possible sequela of childhood meningitis, and an electroencephalogram in which no epileptogenic foci were observed.

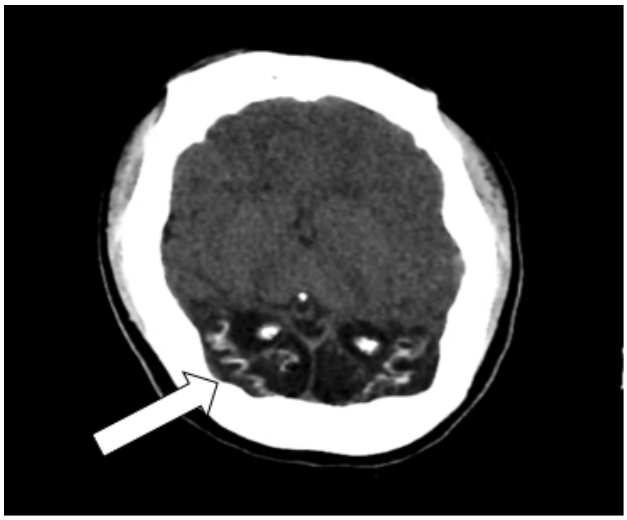

Figure 1. Computed tomography scan of the skull with evidence of cortical laminar necrosis in the occipital region.

Source: Document obtained during the study.

Since the seizures exacerbated every 28 days and were associated with menstruation, the clinical diagnosis of structural focal epilepsy with catamenial features was established.

The patient's case was presented to a multidisciplinary medical board (internal medicine, neurology and gynecology and obstetrics departments) on February 27, 2020. At this meeting, the advantages and disadvantages of medical pharmacological management versus surgery (bilateral oophorectomy) were discussed and it was decided to start pharmacological treatment with oral progestogens (2mg of dienogest orally daily for 3 months) and to monitor the patient's clinical response, considering that surgery in a young woman would imply early menopause with the associated risks of increased cardiovascular risk and early osteoporosis

Due to the patient's adequate clinical progress and the fact that she did not have any new seizures, she was discharged 21 days after her admission. Three months after starting treatment, she attended a follow-up appointment and was found to have adequate adherence to the treatment and complete remission of epileptic seizures had been achieved. Her relative reported no adverse effects.

## DISCUSSION

Catamenial epilepsy refers to the worsening or exacerbation of epileptic seizures related to hormonal changes during the menstrual cycle (1). This type of epilepsy develops because certain times during the menstrual cycle increase the likelihood of having epileptic seizures, a phenomenon known as seizure patterns. The patterns of catamenial epilepsy, which were described by Herzog *et al.* (4) in 1997, are related to hormonal variations, as shown in Table 1.

Table 1 Catamenial epilepsy patterns.

| Type | Characteristics |
|---|---|
| C1. Perimenstrual | More seizures during menstrual phase compared with follicular and luteal phases |
| C2. Periovulatory | More seizures during ovulatory days compared with follicular and luteal phases |
| C3. Inadequate luteal phase | More seizures during ovulatory, mid-luteal, and menstrual days compared with mid-follicular phase in women with inadequate luteal phase cycles (progesterone <5 ng/dL) |

Source: Own elaboration.

Catamenial epilepsy is not a distinct type of epilepsy, but rather a catamenial exacerbation of epileptic seizures that occurs frequently in multiple types of epilepsy (8) and is difficult to diagnose. In the case presented here, the main obstacle to determining the cause of the epileptic seizures was the difficulty in communicating with the patient and her multiple comorbidities; however, the refractoriness to treatment with antiepileptic medication (9) and the cyclical

onset of epileptic seizures associated with her menstrual period were useful to establish the diagnosis because increased seizure frequency associated with some phase of the menstrual cycle is considered a diagnostic criterion of catamenial epilepsy (10).

Catamenial epileptic seizures can occur in patients with any type of epilepsy but are more frequently seen in those with temporal lobe epilepsy (2). It is important to bear in mind that catamenial epilepsy is a common form of epilepsy refractory to drug therapy in women and it may have a significant impact on the quality of life of these patients (6,11).

The pathophysiology of the influence of sex hormones on epileptogenesis is poorly understood; however, catamenial epilepsy is thought to occur due to the neuroactive properties of endogenous steroid hormones and the natural cyclic variation in their serum levels throughout the menstrual cycle (7).

The onset of epileptic seizures has been correlated with changes in progesterone, estrogen, and neurosteroid levels: estrogen levels increase in the follicular phase, with a peak at the time of ovulation, while progesterone levels increase after ovulation and decrease before the end of the menstrual cycle (6,11). These two hormones modulate neuronal excitability through their derivatives, which are known as neurosteroids, via gamma-aminobutyric acid (GABA) receptors (11).

There is strong evidence in animal models that the physiological actions of progesterone are mediated by receptors belonging to the nuclear receptor superfamily that act as transcription factors. Thus, Reddy *et al*. (12) and Reddy & Rogawski (13) found that the anticonvulsant effects of progesterone are associated with the reduced 5α metabolites in this hormone; however, these decreased levels also affect susceptibility to epileptic seizures.

Progesterone reduces neuronal excitability by intervening in different processes: it enhances the action of adenosine, which exerts a powerful inhibitory function on neuronal activity; it decreases cytoplasmic estrogen receptors, altering the plasticity and excitatory capacity of neurones; and reduces the conductance of the nicotinic acetylcholine receptor, altering plasma membrane depolarization (10). Nevertheless, the antiepileptic effect of this hormone is mainly attributed to its conversion to 3a-5a-tetrahydroprogesterone (3a-5a-THP), which increases the chloride current to the intracellular space induced by GABA. Furthermore, in addition to influencing the responses of this acid, progesterone and its metabolites also impact its excitatory mechanisms and, therefore, alter the composition of GABA-A receptor subunits by dynamically changing the GABA receptor subunit composition in situations of progesterone withdrawal, which occurs during the premenstrual stage. Seizure threshold and sensitivity to anticonvulsant drug therapy also vary cyclically (14).

On the other hand, the role of estrogens is complex but possibly neuroexcitatory in certain circumstances (15). Estradiol, for example, may affect neuronal excitability by cytosolic neuronal estrogen receptor-mediated, genomically dependent mechanisms; moreover, because they regulate the expression of genes

that affect the activity, release, and postsynaptic action of different neurotransmitters and neuromodulators, estrogens may increase the excitability of neurons that concentrate estradiol (16). Evidence has also been found that estradiol increases the sensitivity of the N-methyl-D-aspartate (NMDA) receptor to glutamate and that this increased sensitivity positively correlates with increased dendritic spine density in hippocampal CA1 pyramidal cells (17).

It has been established that 5α-reduced neurosteroids (progesterone metabolites) are responsible for protection against epileptic seizures caused by progesterone. Therefore, susceptibility to epileptic seizures is very low during physiological conditions associated with high progesterone levels (11).

Progesterone is metabolized by glial cells in the brain, where it is converted to neurosteroids, which can alter both inhibitory and excitatory neurotransmitters (11). It is worth noting that the most studied neurosteroids are allopregnanolone, allotetrahydrocorticosterone and androstanediol (10). Neurosteroid levels in the brain depend on the amount of circulating steroid hormones since the enzymes involved in their synthesis are expressed in much of the brain, mainly in the cortex, hippocampus, thalamus, amygdala, and hypothalamus; however, GABAergic interneurons do not possess these enzymes. It is also believed that endogenous neurosteroids can regulate GABA activity and release (11) and that the activation of the GABA-A receptor by several ligands leads to an influx of chloride ions and to a hyperpolarization of the membrane that dampens neuronal excitability (9).

Catamenial epilepsy is diagnosed based on a detailed medical history, hence the importance of recording the anticonvulsant drugs used by patients and, in addition, asking them to keep a "seizure diary" under specific instructions from the treating physician (18) because it allows to identify the patterns of epileptic seizure occurrence. Nevertheless, there are different ways to determine whether patients are ovulating or not, for example by measuring basal body temperature in the morning (upon awakening), where an increase of at least 0.021°C is an indicator of ovulation.

Another way to determine whether patients are ovulating is through a kit to measure luteinizing hormone (LH) in urine, which helps detect the surge in luteinizing hormone 32 to 36 hours before ovulation. These tests should be performed depending on the length of the menstrual cycle: if the cycle is 28 days long, they should be done on day 12 and for 10 consecutive days until the LH peak occurs.

More sophisticated measures to confirm ovulation include documentation of a mean serum progesterone concentration >3ng/mL and a decrease in dominant follicle volume ≥90% as measured by transvaginal ultrasound or secretory endometrial biopsy (1).

According to Kandeepan & Shaaban (19), the treatment of catamenial epilepsy is mainly directed toward hormonal therapy, as it has been found that this type of epilepsy does not usually improve with antiepileptic drugs alone, as evidenced

in the present case. Similarly, it has been hypothesized that progesterone, progesterone metabolites, or estrogen antagonists can be used in combination with current antiepileptic drugs to treat patients with inadequate luteal phase or with anovulatory cycles (7).

Specifically, two approaches to progesterone therapy have been proposed: cyclic progesterone therapy, which involves supplementing progesterone during the luteal phase and gradually withdrawing it during the premenstrual phase; and suppressive therapy, which involves suppressing the menstrual cycle through the use of injectable progestins or gonadotropin-releasing hormone analogues (16).

Najafi *et al*. (20) conducted a double-blind randomized controlled trial in 38 women with intractable catamenial epilepsy, in which patients were divided into two groups, a case group that, in addition to antiepileptic drugs, received two 40mg of progesterone tablets (megestrol) in the second half of the 15 to 25-day cycle, and a control group that, in addition to the antiepileptics, received two placebo tablets daily. In this study, the authors found that the degree of reduction in the number of seizures in the case group was greater than in the control group, being statistically significant ($p<0.05$).

Regarding progestin therapy, Mattso *et al*. (21) reported in their study that the use of parenteral medroxyprogesterone acetate may reduce the frequency of seizures when administered in sufficient doses to induce amenorrhea. However, as indicated by Herzog (16), it is not clear whether the effect is related to the direct anticonvulsant activity of medroxyprogesterone or to the hormonal consequences of induced amenorrhea. Likewise, treatment with synthetic gonadotropin-releasing hormone (GnRH) analogs has been shown to have anticonvulsant effects in patients with intractable catamenial epilepsy (6).

In the management of catamenial epilepsy, triptorelin therapy has been shown to be more effective for the treatment of patients whose seizures are limited to the perimenstrual period (22). Furthermore, the use of clomiphene, an ovulation stimulant used to treat infertility in women with oligoanovulation or anovulation, (7) has shown a reduction in the frequency of epileptic seizures in this type of patient (23). In turn, ganaxolone, a neurosteroid analog whose mechanism of action modulates GABA-A receptor activity and has proven anticonvulsant properties, has been shown to be the most reliable therapy and the one that least exposes patients to the risk of hormonal side effects (24).

Another therapeutic approach is non-hormonal therapy, which was initially based on acetazolamide. Its mechanism of action is not well known; however, it is clear that its use develops tolerance, resulting in a decrease in efficacy over time. Therefore, this drug can only be administered intermittently, which, although appropriate for catamenial epilepsy, is not ideal for prophylaxis of ordinary epileptic seizures (7).

The overall effectiveness of benzodiazepines for seizure clusters has led to accept its intermittent use as an approach to catamenial seizure management;

however, the only benzodiazepine studied for this purpose to date is clobazam (25).

Surgical management in the treatment of catamenial epilepsy is not common, but it has been used as a menstrual cycle suppression strategy that favors the decrease of sex hormones and, consequently, decreases epileptic seizures with catamenial features. In this regard, Vilos *et al*. (26) reported the case of a woman with abnormal uterine bleeding who developed catamenial neurological signs and symptoms (including seizures) and in whom computed tomography scans and magnetic resonance imaging demonstrated a circumscribed lesion in the left centrum semiovale of the brain. The patient was treated with a GnRH agonist (goserelin) for 3 months and a subsequent laparoscopic bilateral oophorectomy, which resolved the neurological symptoms completely.

## CONCLUSIONS

Catamenial epilepsy is a disorder of clinical importance that should be considered as a cause of epilepsy refractory to antiepileptic therapy. Its approach should be multidisciplinary, and its treatment should focus on improving the quality of life of patients. Therefore, the importance of obtaining an adequate medical history that compiles relevant information for the management of patients suffering from this disease cannot be overstated.

With regard to treatment, it is important to bear in mind that each patient must be individualized since studies have supported certain combinations of hormonal and non-hormonal treatments, along with anticonvulsants, so it is essential to identify the specific pattern of catamenial epilepsy; however, surgery is an option that can be considered if there is no improvement with pharmacological treatment.

## ETHICAL CONSIDERATIONS

The Ethics Committee of the Hospital Universitario Clínica San Rafael approved the present case report according to Minutes No. CEI-084-2020 of July 7, 2020.

## CONFLICTS OF INTEREST

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CASE REPORTS
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# METANEPHRIC ADENOMA: DIFFERENTIAL DIAGNOSIS OF UPPER TRACT UROTHELIAL CARCINOMA. A CASE REPORT

**Keywords:** Kidney Neoplasms; Nephrectomy; Adenoma.
**Palabras clave:** Neoplasias renales; Nefrectomía; Adenoma.

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## ABSTRACT

**Introduction:** Metanephric adenoma is a rare benign kidney tumor. Patients with these tumors are usually asymptomatic, although polycythemia occurs in up 12% of cases. These masses are often described on diagnostic imaging as solid, single, well-defined, oval-shaped, unilateral lesions, located primarily in the renal medulla and without extrarenal involvement. These neoplasms are difficult to differentiate from malignant neoplasms of the upper urinary tract, so the definitive diagnosis is achieved by histopathology. Currently, the treatment of choice is radical nephrectomy.

**Case presentation:** A 51-year-old woman from Bogotá (Colombia) was referred to the urology service of a tertiary care hospital due to bilateral lumbar pain of non-specific characteristics. At the time of consultation, the patient was asymptomatic. Renal and urinary tract ultrasound showed hydronephrosis and right renal mass. Computed tomography urography was requested, which revealed a lesion in the right renal pelvis with parenchymal invasion highly suggestive of high-risk upper urinary tract urothelial carcinoma, as well as adenopathies in the para-aortic lymph nodes. The patient underwent a radical nephroureterectomy with bladder cuff, which allowed establishing a final diagnosis of metanephric adenoma according to the histopathological study.

**Conclusions:** Metanephric adenoma is a rare tumor that is difficult to diagnose through imaging, so it is necessary to explore additional tools to establish an accurate pre-surgical diagnosis that allows preserving the affected renal unit. Also, given their non-specificity, these tumors should be included in the differential diagnosis of lesions suggestive of upper tract urothelial carcinoma.



## RESUMEN

**Introducción.** El adenoma metanéfrico es un tumor renal benigno poco frecuente. Los pacientes con estos tumores no suelen presentar síntomas, aunque en el 12% de los casos se presenta policitemia. En las imágenes diagnósticas, los adenomas metanéfricos se observan como lesiones sólidas, únicas y bien definidas que, por lo general, comprometen la medula renal pero no ocasionan compromiso extrarenal. Estas neoplasias son difíciles de diferenciar imagenológicamente de neoplasias malignas del tracto urinario superior, por lo que el diagnóstico definitivo se logra mediante estudios histopatológicos. El tratamiento de elección es la nefrectomía radical.

**Presentación del caso.** Mujer de 51 años procedente de Bogotá (Colombia), quien fue remitida al servicio de urología de un hospital de tercer nivel de atención por dolor lumbar bilateral de características inespecíficas. Al momento de la consulta la paciente se encontraba asintomática. Mediante ecografía renal y de vías urinarias se evidenció hidronefrosis y una masa renal derecha. Se ordenó urografía por tomografía

axial computarizada que documentó una lesión en la pelvis renal derecha con invasión al parénquima renal altamente sugestiva de carcinoma urotelial de tracto urinario superior de alto riesgo, así como adenopatías en los ganglios paraaórticos, por lo que se le realizó una nefroureterectomía radical derecha con cuña vesical que permitió establecer un diagnóstico final de adenoma metanéfrico según el estudio histopatológico. La paciente tuvo una evolución satisfactoria.

**Conclusiones.** El adenoma metanéfrico es un tumor poco frecuente y de difícil diagnóstico imagenológico, por lo que se requiere explorar herramientas adicionales para establecer un diagnóstico certero prequirúrgico que permita preservar la unidad renal afectada. Asimismo, dada su inespecificidad, estos tumores deben incluirse dentro de los diagnósticos diferenciales de las lesiones sugestivas de carcinoma urotelial de tracto urinario superior.

## INTRODUCTION

Metanephric adenoma (MA) is a rare benign tumor that originates in renal epithelial cells and is usually detected as an incidental finding (1). This neoplasm is difficult to differentiate from malignant tumors affecting the upper urinary tract in the pre-surgical stage.

The definitive diagnosis of MA is established based on immunohistochemistry and histopathological findings. However, it has been proposed that the presence of solid, single, well-defined, oval-shaped, unilateral lesions predominantly in the renal medulla and without extrarenal involvement in imaging studies is a useful finding to differentiate it from other tumors. This finding also allows considering MA as a differential diagnosis in patients with upper urinary tract masses and thus avoid ablative treatment in the affected kidney and ureter (2).

The following is the case of a patient who underwent right radical nephro-ureterectomy due to clinical suspicion of high-risk upper urinary tract urothelial carcinoma, whose final diagnosis was MA according to the histopathological study.

## CASE PRESENTATION

A 51-year-old mixed-race woman from Bogotá D.C. (Colombia), housewife, from a lower-middle income household and without a relevant medical history, presented to the outpatient clinic of the urology service of a public tertiary healthcare center in Bogotá with mild to moderate bilateral lumbar pain of non-specific characteristics that lasted three months. The patient was referred by the general medicine service, which had previously requested a renal/urinary tract ultrasound that showed a right renal mass with ipsilateral  grade I hydronephrosis.

During the history-taking process, the patient was asymptomatic, and no relevant findings were found on the physical examination. Consequently, a

computed tomography (CT) urography was ordered, and the results were analyzed at the follow-up appointment 2 weeks after the initial assessment. CT showed a 44x44x28mm lesion in the right renal pelvis with invasion of the renal parenchyma at the lower pole and adenopathies in the para-aortic nodes that measured up to 17mm (Figures 1 and 2). Given this finding, a CT scan of the chest (assessed in a second follow-up appointment) was requested, finding no metastatic involvement, as well as a serial urinary cytology with findings consistent with a type II category lesion according to the Paris classification (negative for high-grade urothelial carcinoma) (3). In addition, the glomerular filtration rate (GFR) estimated with the CKD-EPI equation at that time was 101 mL/min/1.73 $m^2$.

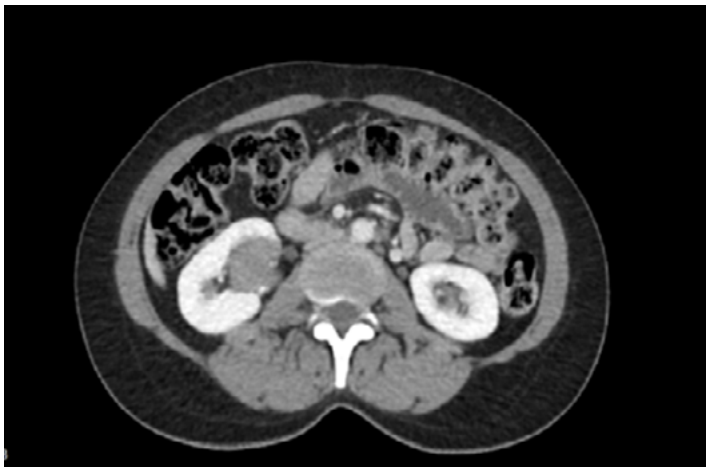

Figure 1 Computed tomography (CT) urography. Nephrogenic phase; axial plane.
Source: Document obtained during the study.

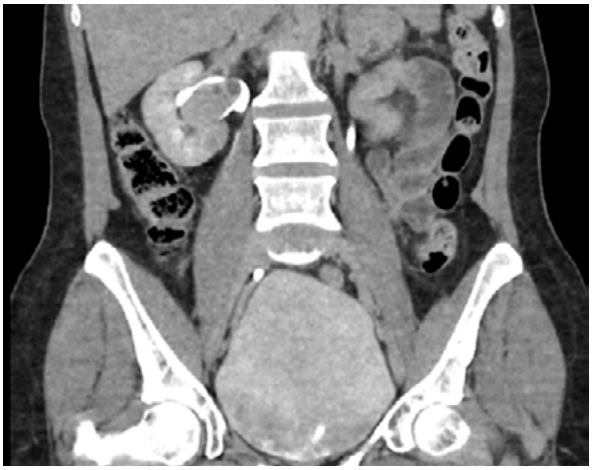

Figure 2 Computed tomography (CT) urography. Excretory phase; coronal plane.
Source: Document obtained during the study.

Due to the high suspicion of high-risk upper tract urothelial carcinoma (staging: cT3N1M0 according to the 2017 TNM classification), the presence of hydronephrosis, and the detection of adenopathies on the CT scan, during the second follow-up appointment, the patient was considered a candidate for a transurethral cystoscopy and then right radical nephroureterectomy with bladder cuff and right retroperitoneal lymph node dissection with curative intent. The surgery was scheduled to be conducted in an outpatient clinic with the urology department one month following the initial assessment.

Transurethral cystoscopy revealed no endoluminal bladder lesions, however during surgery, a tumor of approximately 5cm in diameter was discovered in the right renal pelvis with no macroscopic involvement of adjacent tissues; no retroperitoneal adenopathies were observed on macroscopic examination (Figures 3 and 4). It should be noted that nephroureterectomy with bladder cuff was performed using the intravesical approach.

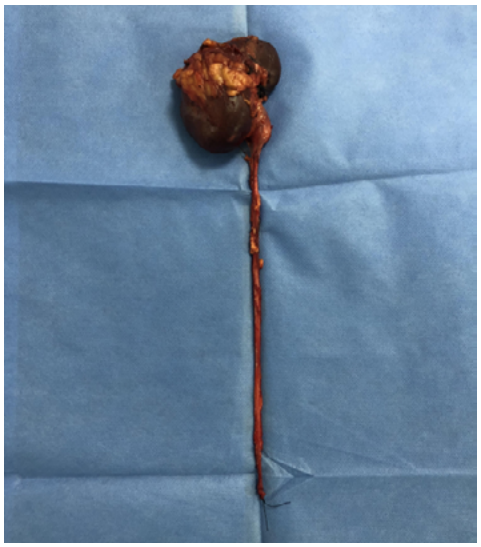

Figure 3 Surgical specimen.
Source: Photographs obtained during the study.

The patient presented no postoperative complications, her course was satisfactory, and she was discharged three days after the procedure. The pathology report showed a mixed epithelial and stromal tumor of the kidney with free borders, and immunohistochemistry confirmed the presence of a MA (positive for CD57, vimentin, and WT1; negative for CK7 and CD10).

During the first postoperative follow-up, 3 weeks after the procedure, the patient was asymptomatic and had a GFR according to the CKD-EPI formula of 85 mL/min/1.73m$^2$. In the second follow-up, 6 months after surgery, the patient was still asymptomatic, and no tumor relapse was observed in the CT of the abdomen and pelvis.

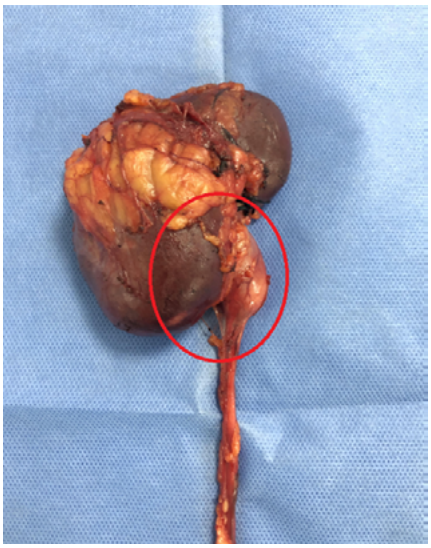

Figure 4 Approach to the area of interest (in red). Projection of the mass contained in the right renal pelvis.
Source: Photographs obtained during the study.

## DISCUSSION

MA is a rare renal neoplasm that accounts for 0.2% of adult renal epithelial tumors and has less than 200 cases reported in the literature (1,4). This type of tumor, according to Jiang *et al.* (1), was classified by the World Health Organization in 2016 as a subtype of metanephric neoplasm, which also includes adenofibroma and stromal tumors.

MAs can occur at any age, but they are most common in patients aged 50 to 60 years, with a female-to-male ratio of 2-2.6:1 (1,4). Genetic analyzes have revealed, as reported by Ding *et al.* (5), that the missense mutation of BRAF V600E could be detected in approximately 90% of these types of neoplasms.

Patients with MA usually have no symptoms, although lower back pain, gross hematuria, and fever occur in 10-50% of cases (2,6). In addition, polycythemia has been reported in about 12% of MA patients with hematuria (1).

MAs have a low rate of diagnostic certainty using imaging and the diagnosis is usually incidental, which may be explained by the low suspicion and prevalence (2). Similarly, these tumors are difficult to differentiate in the pre-surgical stage from other malignancies such as Wilms' tumor, metastatic papillary thyroid carcinoma, and papillary renal cell carcinoma (7).

The imaging characteristics described for MAs in small case series, such as Zhu *et al.* (2) in 8 patients with MA who were hospitalized at the Subei People's Hospital (China) between 2006 and 2011, refer to solid, single, well-defined, oval-shaped, unilateral lesions predominantly in the renal medulla and without extrarenal involvement. Ultrasound can detect hypo- or hyperechoic lesions with

lower Doppler flow compared to other tumors (1). On nuclear magnetic resonance imaging, these neoplasms are hypointense with delayed enhancement of contrast material in T1W1 sequence and hyperintense in DWI sequence (1). Finally, the predominant findings on CT scan are lesions with well-defined boundaries with enhancement, calcifications (20% of cases), and homogeneous enhancement that is lower compared to that of renal parenchyma in all enhanced phases (1,8).

The origin of MAs in epithelial cells of the renal collecting duct explains the imaging finding of invasion or displacement of the collecting system and suggests a differential diagnosis with urothelial carcinoma of the upper urinary tract (1,2). However, Li and collaborators, cited by Yan *et al.* (9), found that 83.3% of tumors of this type were located in the periphery of the renal cortex without involvement of the collecting system.

The characteristics of MAs have not been widely studied, but Jiménez-Heffernan *et al.* (10), in their letter to the editor, established that cytology, either as fine-needle aspirates or during intraoperative procedures, can be quite useful in identifying these tumors. Thus, the characteristic cytology findings are generally small, clustered cells, oval or round, with uniform basophilic nuclei and without nucleoli and scant cytoplasm; the absence of nuclear atypia, necrosis, and mitosis are also common findings in patients with MA (7,11). Taking into account these histopathological findings in cytological studies, it is necessary to consider Wilms' tumor and papillary renal cell carcinoma as differential diagnoses (7,10,11).

On the other hand, as reported by Le Nué *et al.* (12), MA diagnosis may be supported by core-needle renal biopsy. If biopsy is performed hemostasis must be double checked, as there is a possible association with acquired von Willebrand disease, as described in two pediatric cases.

MAs usually have a good prognosis, and the treatment of choice is complete surgical resection by partial or radical nephrectomy, depending on size; definitive diagnosis is established based on histopathological studies and immunohistochemistry (13-15).

Macroscopically, MA is described as a well-circumscribed brownish-yellow mass and with the presence of pseudocapsule (4,7,8). Microscopically, these neoplasms are comprised of tubules of different sizes and shapes, divided into lobes with fine fibrovascular septa; in addition, their cells are characterized by small cell nuclei and very low mitotic activity (2,5). These tumors have the following immunohistochemical pattern: positive for vimentin, pancytokeratin, WT1 and CD57; negative for CK7, AMACR, and CD10 (2,5).

Li *et al.* (16) conducted a cohort study of 18 patients with MA in which, through pathological examination, they found that 6 (33.3%) tumors had other carcinoma components concomitantly and 2 (11.1%) were malignant MA, a surprisingly high proportion of malignant cases. In the same study, the authors suggested a subclassification of these neoplasms into classic MA, malignant MA,

and MA with concomitant malignant component, concluding that their biological behavior is not yet well defined (16).

As reported in the literature and with the experience of the case described here, it can be said that MA is a rare pathology that is within the differential diagnosis of upper urinary tract masses. Pre-surgical diagnosis is difficult and treatment in general does not differ from the standard for renal carcinoma or urothelial carcinoma of the upper urinary tract, depending on the case. The diagnostic suspicion of this type of tumor may increase in patients in whom endoscopic assessment with biopsy is possible along with magnetic resonance imaging to complement imaging studies. The surgical treatment implemented in the case reported here is based on the recommendations of the 2020 European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma (staging: cT3N1M0) (17,18).

## CONCLUSION

MA is a very rare benign tumor that affects the upper urinary tract and is difficult to differentiate from other tumors with imaging studies. Its diagnosis is usually made by histopathological study and immunohistochemistry, although some research suggests the usefulness of pre-surgical fine-needle aspiration cytology. Given the low prevalence of this disease, reports and case series are of great importance as they allow to broaden the knowledge on the subject and to propose possible pre-surgical diagnostic strategies that, in turn, allow to implement treatment strategies that preserve the renal unit involved.

## ETHICAL CONSIDERATIONS

In accordance with Resolution 8430 of 1993 of the Ministry of Health of Colombia (19), this case report is a risk-free investigation. The patient completed an informed consent form, and the principles outlined in the Declaration of Helsinki (20) were adhered to.

## CONFLICTS OF INTEREST

None stated by the authors.

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