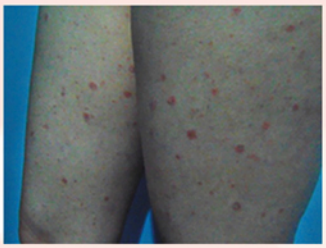
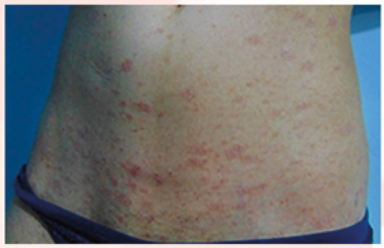
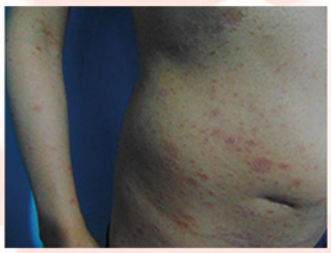
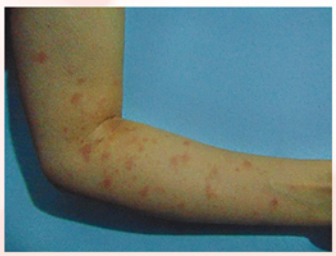
CASE REPORTS
REPORTES DE CASO

CASE REPORTS
VOL. 7 NUM. 2

ATYPICAL PITYRIASIS ROSEA

IN A YOUNG LATIN-AMERICAN WOMAN. CASE REPORT

Facultad de Medicina
Sede Bogotá

UNIVERSIDAD NACIONAL DE COLOMBIA

e-ISSN 2462-8522

Case reports (e-ISSN: 2462-8522) is a specialized official publication by the Universidad Nacional de Colombia, in digital versions, peer-reviewed, in open access, published since 2015, whose objective is the dissemination of case reports, reports of adverse events, case series, reviews and editorials; which are relevant for the advancement in education, reflection and action of the health sciences, social sciences and related. Is indexed/tracked/covered by: SciELO (Scientific Electronic Library Online), DOAJ (Directory of Open Access Journals), REDIB (Ibero-American Network of Innovation and Scientific Knowledge), OJS (Open Journal Systems), the Universidad Nacional de Colombia OJS website and Google Scholar. The journal is published biannual: an annual volume consisting of two issues (January-June, July-December). The purpose of the journal is to be a leader and model in the field of national and international case report.

CONTENTS

https://doi.org/10.15446/cr.v7n2.95527

PITYRIASIS ROSEA, AN EXANTHEMATOUS REACTION

Editorial

Michel Faizal-Geagea
Universidad Nacional de Colombia
- Bogotá Campus - Faculty of Medicine -
Department of Internal Medicine
- Bogotá, D.C. - Colombia.
Academia Nacional de Medicina de Colombia
- Bogotá, D.C. - Colombia.

Corresponding author
Michel Faizal Geagea.
Facultad de Medicina,
Universidad Nacional de Colombia.
Bogotá, D.C. Colombia.
Email: mfaizalg@unal.edu.co.

Received: 25/03/2021 **Accepted:** 05/04/2021

Dermatological emergencies are rare events that can be caused by acute medical conditions, with or without systemic involvement, or by chronic diseases when exacerbation is observed.

Exanthematous diseases are one of the leading causes of dermatological emergencies and may include a broad spectrum of diagnoses. Depending on their causes, they are classified as infectious (viral, bacterial, parasitic, and fungal), immunological, inflammatory, neoplastic, or caused by adverse drug reactions. The diagnosis of an exanthem is based on the patient's medical history; however, in some cases it is necessary to perform complementary laboratory tests and pathology studies to confirm it.

Pityriasis rosea (PR) was first described in 1860 by Dr. Camille Melchior Gibert, a renowned French dermatologist who opposed the iconography of the time by stressing that "to get to know things in depth, you must first see them. Nothing can replace direct observation, which can only be done by a professional physician" (1).

PR is an exanthematous disease of sudden onset that in some cases appears after experiencing mild symptoms similar to those of an upper respiratory infection. It usually begins with a small, fawn-colored, oval-shaped plaque with fine scales along the borders of the ring, which Louis-Anne-Jean Brocq named primitive or herald patch in 1897 (1). Then, 2 weeks after the onset of symptoms, multiple annular or rounded, reddish, scaling plaques, smaller than the initial lesion, appear in a linear pattern or in the shape of a "Christmas tree." Lesions caused by PR may be vesicular in nature and have hypopigmented macules during the involution phase.

This disease is more common in people between the ages of 15 and 40 and usually has a spontaneous resolution (2-4). Its diagnosis is based on clinical findings and laboratory tests, but syphilis serology (VDRL and FT-ABS) and mycology tests (2-4) should be requested for confirmation; a skin biopsy may also be necessary. The main differential diagnoses of this condition are syphilis, tinea, and other exanthematous diseases (5).

The main cause of PR is reactivation of human herpesviruses 6 and 7 (6), and its treatment is based on topical corticosteroids, UVB phototherapy, emollients, oral acyclovir (7-10) or erythromycin at a dose of 25-40 mg/kg/day or 250mg every 8 hours for 15 days in adults (9).

The current issue of Case Reports presents the case of a 28-year-old woman diagnosed with PR and treated with deflazacort 30mg for 21 days, who had a favorable evolution and complete improvement of symptoms after 2 months (11). With this article, the authors stress the relevance of performing an in-depth study of the medical history, the diagnostic difficulties of this condition, and the differential diagnoses to be considered. Likewise, this case report stands out as evidence of the importance of primary care physicians having adequate training in dermatology so that they can recognize and treat PR, since its diagnosis is eminently clinical, and it can have multiple atypical presentations. In this sense, it will surely be a reference text.

REFERENCES

1. **Wallach D, Tilles G.** La Dermatología en Francia. Ediciones Privat; 2002
2. **Chuang TY, Ilstrup DM, Perry HO, Kurland LT.** Pityriasis rosea in Rochester, Minnesota, 1969 to 1978: a 10-year epidemiologic study. *J Am Acad Dermatol.* 1982;7(1): 80-9. https://doi.org/cfw7kr.
3. **Hartley AH.** Pityriasis rosea. *Pediatr Rev.* 1999;20(8): 266-9. https://doi.org/cwrdmc.
4. **Allen RA, Janniger CK, Schwartz RA.** Pityriasis rosea. *Cutis.* 1995;56(4):198-202.

5. **Balci DD, Hakverdi S.** Vesicular pityriasis rosea: an atypical presentation. *Dermatol Online J.* 2008;14(3):6.
6. **Drago F, Broccolo F, Rebora A.** Pityriasis rosea: an update with a critical appraisal of its possible herpes viral etiology. *J Am Acad Dermatol.* 2009;61(2):303-18. https://doi.org/bf89nq.
7. **Drago F, Rebora A.** Treatment for pityriasis rosea. Skin Therapy Lett. *2009;14(3):6-7.*
8. **Leenutaphong V, Jiamton S.** UVB phototherapy for pityriasis rosea: a bilateral comparison study. *J Am Acad Dermatol.* 1995;33(6):996-9. https://doi.org/fqnmmg.
9. **Drago F, Vecchio F, Rebora A.** Use of high-dose acyclovir in pityriasis rosea. *J Am Acad Dermatol.* 2006;54(1):82-5. https://doi.org/b9sqbv.
10. **Sharma PK, Yadav TP, Gautam PK, Taneja N, Satyanarayana L.** Erythromycin in pityriasis rosea: a double-blind, placebo-controlled clinical trial. *J Am Acad Dermatol.* 2000;42(2 Pt 1):241-4. https://doi.org/fvbnmv.
11. **Porras-Villamil JF, Hinestroza AG, López-Moreno GA, Parra-Sepúlveda DJ.** Atypical pityriasis rosea in a young Colombian woman. Case report. *Case Reports.* 2021;7(2):8-21.

https://doi.org/10.15446/cr.v7n2.88809

ATYPICAL PITYRIASIS ROSEA IN A YOUNG COLOMBIAN WOMAN. CASE REPORT

Keywords: Pityriasis Rosea; Exanthema; Herpesviridae.
Palabras clave: Pitiriasis; Exantema; Herpesviridae.

Julián Felipe Porras-Villamil
Universidad Nacional de Colombia
- Bogotá Campus- Faculty of Medicine -
Master's degree in Infections and Health in the Tropics - Bogotá D.C. - Colombia.

Ángela Catalina Hinestroza
Gabriela Andrea López-Moreno
Doris Juliana Parra-Sepúlveda
Universidad Nacional de Colombia
- Bogotá Campus - Faculty of Medicine -
Medical program - Bogotá D.C. - Colombia.

Corresponding author
Julián Felipe Porras-Villamil,
Maestría en Infecciones y Salud en el trópico,
Facultad de Medicina, Universidad Nacional de Colombia.
Bogotá D.C. Colombia.
E-mail: jfporrasv@unal.edu.co

Received: 02/07/2020 **Accepted:** 03/12/2020

ABSTRACT

Introduction: Pityriasis rosea is an acute and self-limited exanthem first described by Gilbert in 1860. Its treatment is symptomatic, and although there is no conclusive evidence, it has been associated with the reactivation of the human herpesviruses 6 and 7 (HHV-6 and HHV-7).

Case presentation: A 28-year-old woman, from Bogotá, Colombia, a health worker, attended the emergency room due to the onset of symptoms that began 20 days earlier with the appearance of punctiform lesions in the left arm that later spread to the thorax, abdomen, opposite arm, and thighs. The patient reported a history of bipolar II disorder and retinal detachment. After ruling out several infectious diseases, and due to the evolution of the symptoms, pityriasis rosea was suspected. Therefore, treatment was started with deflazacort 30mg for 21 days, obtaining a favorable outcome and improvement of symptoms after 2 months. At the time of writing this case report, the patient had not consulted for recurrence.

Conclusion: Primary care physicians should have sufficient training in dermatology to recognize and treat dermatological diseases since many of them are diagnosed based on clinical findings. This is an atypical case, in which the patient did not present with some of the pathognomonic signs associated with pityriasis rosea.

RESUMEN

Introducción. La pitiriasis rosada es un exantema agudo y autolimitado que fue descrito formalmente por Gilbert en 1860. Su tratamiento es sintomático y, aunque faltan pruebas concluyentes, su aparición se ha asociado a la reactivación de los herpevirus humanos 7 y 6 (HHV6 y HHV7).

Presentación del caso. Mujer de 28 años procedente de Bogotá, Colombia, quien se desempeñaba como trabajadora de la salud y consultó al servicio de urgencias por un cuadro clínico de 20 días de evolución que inició con la aparición de lesiones punteadas en el brazo izquierdo que se expandieron posteriormente a tórax, abdomen, brazo contralateral y muslos. La paciente informó antecedente de trastorno bipolar tipo II y desprendimiento de retina. Después de descartar varias enfermedades infecciosas, y debido a la evolución del cuadro clínico, se sospechó pitiriasis rosada, por lo que se instauró tratamiento con 30mg de deflazacort por 21 días, con el cual se logró una evolución favorable y la mejoría total de los síntomas a los 2 meses. Hasta el momento de la elaboración del presente reporte de caso la joven no había consultado por recurrencia.

Conclusión. Es indispensable que los médicos de atención primaria tengan una educación adecuada en dermatología para poder reconocer y tratar la pitiriasis rosada, pues su diagnóstico es eminentemente clínico y puede tener múltiples presentaciones atípicas, como en el caso aquí reportado donde la paciente no tuvo algunos de los signos patognomónicos característicos.

INTRODUCTION

Pityriasis rosea is an acute and self-limited exanthem. It was first described by Gilbert in 1860, (1,2) but the initial report was done by Robert Willan as early as 1798. (3) It has also received other names, the first being *Roseola annulate*. (3) This condition has been associated with the reactivation of human herpesviruses 6 and 7 (HHV-6 and HHV-7) (4-7), as well as with infection with *Legionella micdadei*, *Mycoplasma pneumoniae*, enterovirus, COVID-19, and others, (8-10) although conclusive evidence is lacking.

Other theories, notably the one given by Burch and Rowell (11), have proposed that it has an auto-immune origin and are backed by some published research. (4,12) One of such studies reported that 28% of the patients included in their sample had anti-lymphocyte antibodies, suggesting an autoimmune role. Other theories are based on psychosomatic aspects of the disease, which has been sustained in the papers published by Grinspan-Bozza (13) and Mahajan *et al*. (14)

The disease affects people of any age and sex, although it is more common between the ages of 5 and 35 and, develops in two stages (15,16). The first occurs before the onset of dermatological signs and symptoms and is characterized by symptoms similar to respiratory infection in 70% of the cases, whereas the remaining 30% may present with malaise, low grade fever, headache and arthralgia, (15,16) which usually disappear after the appearance of dermatological manifestations.

The second stage of the disease typically begins with an oval spot or "herald patch" in the chest, abdomen or back in 80% of patients. (17) Afterwards, smaller erythematous plaques appear, which can be pruriginous and have internal desquamation (collaret desquamation). These plaques follow the distribution of the metameres and can produce a "Christmas-tree pattern" in the back.

Treatment is mainly symptomatic due to its benign course with little probabilities of transmission. Therapy involves the use of antihistamines or low-potency steroids, and corticotherapy in cases of severe pruritus. Moreover, erythromycin appears to shorten the duration of the natural history of the disease. (18) Another option is a seven-day course of acyclovir, which could be useful to shorten the days of eruption, and even though the disease can resolve spontaneously between 6 to 8 weeks with or without intervention, the effective dose seems to be between 400-800mg, (19-21) but evidence is contradictory. (22) Other type of therapy that could be useful is phototherapy, in which ultraviolet light type A or B are used multiple times a week (15,16,23), apparently reducing the severity and duration of the symptoms.

Nevertheless, evidence supporting these types of therapy is inconsistent or weak. Management with corticosteroids is based on consensus, opinions and case series, while the evidence for the use of acyclovir is inconsistent and macrolides seem to be ineffective (16). Many options have been explored, but clear evidence of an effective treatment is still missing (14,24). Table 1 describes some of the options and dosages recommended. Recurrence is relatively rare even without treatment. (20)

Table 1. Some treatments and therapies for Pityriasis rosea

Therapy	Dose
Erythromycin	Adults 200mg *per os* 4 times per day Children 40 mg/kg/day divided in 4 doses
Clarithromycin	Adults 250mg *per os* 2 per day for 2 weeks
Azithromycin	Children 12 mg/kg/day for 5 days, maximum 500 mg/day
Acyclovir	400mg *per os* every 4 hours for 5 days 800mg *per os* s 5 times per day
Phototherapy	UVB 5 times/week
Special cases	Children with severe pruritus Methylprednisolone 16mg/day Pregnant women: acyclovir may prevent miscarriage. The safety of acyclovir needs to be confirmed (level of safety B)

Source: Own elaboration based on Urbina *et al.,* (15) Villalon-Gomez (16) and Drago & Rebora. (24)

The following is a case report of an unusual case of pityriasis rosea in a female health worker.

CASE DESCRIPTION

This is the case of a 28-year-old health worker from Bogotá, Colombia, from a middle-class household. Her family history included the maternal grandmother with Alzheimer's disease, bipolar I disorder and hypertension; mother with breast cancer; and deceased father due to an acute myocardial infarction associated with a thoracic trauma one month after a car accident. She also reported a medical history of bipolar II disorder, retinal detachment, appendicectomy, Lasik and Yag laser, allergies to sulfa drugs, a sexual partner in the last 4 years, no previous pregnancies, and no tattoos. The timeline of her case is presented below.

14/10/2018: First appointment (symptoms for three days). The patient attended the emergency room due to punctiform skin lesions in the upper extremities, thorax, and neck. She also reported odynophagia, musculoskeletal pain, diarrhea without mucus or blood, fever (38°C) nausea and vomit. A general physician and a pediatrician considered a possible diagnosis of rubella, for which they prescribed acetaminophen, loratadine and rehydration salts. A nasopharyngeal swab for rubella and measles was performed, considering the presence of abnormal migration patterns in Colombia and her contact with patients in a clinical setting. An assessment from the internal medicine service was requested, which suspected secondary syphilis.

21/10/2018: The patient visited again the emergency room, this time in a tertiary care center. She reported the appearance of macular and punctiform lesions in the left arm 10 days earlier. The lesions, which showed a collaret desquamation, spread to the chest and abdomen, and three weeks later they appeared in the opposite arm and thighs (proximal third) (Figure 1). The palms, feet and scalp were spared and no adenopathy was observed.

She also presented with odynophagia, upper respiratory tract symptoms, and fever (38°C). Moreover, she referred moderate depression due to her underlying disease, which started weeks before the onset of the skin lesions. She denied dyspnea, or relatives with a similar condition. The heraldic plaque was neither described by the patient nor documented in the physical examination. IgM and IgG for rubella and measles were pending, and the emergency service also suspected HIV infection. She was finally referred to the dermatology service with a prescription of clemastine tablets 1mg every 8 hours for 5 days and loratadine 10mg every 12 hours for five days.

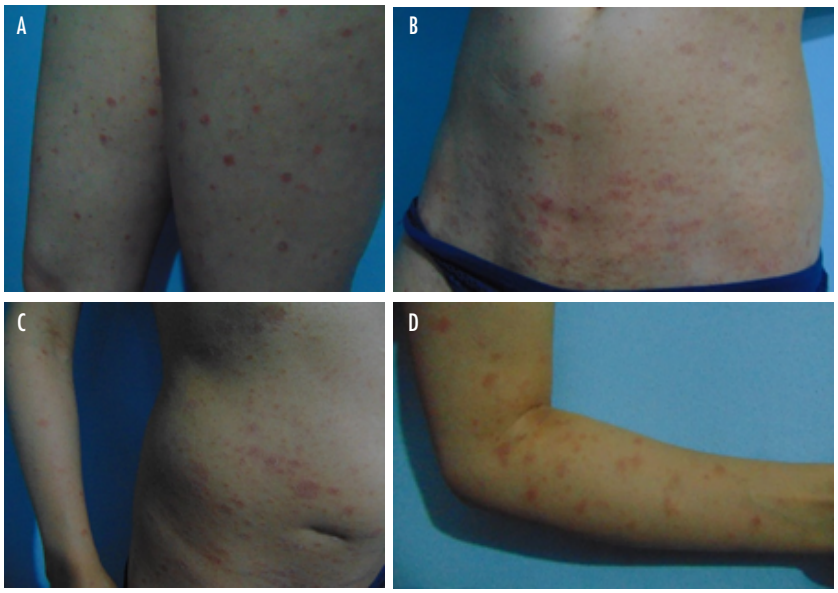


Figure 1. Aspect and distribution of the lesions. A) Lesions in the thighs of the patient; B) and C) Lesions in the abdomen; D) Lesions in the left upper limb.

Source: Document obtained during the study.

28/10/2018: Tests performed by both the health center and the surveillance institution (Bogotá's Health Department) reported negative results for measles and rubella (negative ELISA IgM). Electrochemiluminescence immunoassay on Cobas® platform yielded negative results for HIV, antigen p24, and antibodies anti-HIV I and II were negative (Table 2). The patient also manifested that she had been given a medical leave for 4 weeks due to the contagious aspect of the lesions and because they persisted.

Table 2. Blood tests performed to the patient

Test	Date	Result	Reference values
Varicella-Herpes zoster virus	18/01/2015	34.2	Neg <9.0 Borderline 9-11 Pos >11.0
Anti-HIV antibodies	25/10/2018	0.20	Neg <0.90 Borderline 0.90-1.00 Reactive >1.00
Rubella IgM - ELISA	16/10/2018	Negative	NA
Measles IgM - ELISA	16/10/2018	Negative	NA

Source: Own elaboration.

30/10/2018: The patient attended her first appointment with the dermatology service with these results. After analyzing them, pityriasis rosea and guttate psoriasis were suspected. Based on the course of the disease, pityriasis rosea was clinically diagnosed; however, a biopsy was requested to confirm this diagnosis. Oral steroids were

initiated (deflazacort 30mg for 21 days) with the following scheme:

1. Days 1 through 7: 1 tablet.
2. Days 8 through 14: ½ a tablet.
3. Days 15 through 21: ¼ of a tablet

Unfortunately, the patient did not have the biopsy taken.

15/11/2018: At her second appointment with the dermatology service, it was possible to observe that the lesions were resolving and further treatment with hydrocortisone cream 1% every 24 hours at night for 10 days was prescribed.

The skin lesions improved gradually until resolving 2 months later, without scarring. No recurrence has been reported to date and the patient reported that her psychiatric symptoms are under control.

DISCUSSION

This case exposes some of the difficulties regarding the diagnosis of diseases in dermatology. In this case, the lack of some pathognomonic signs, such as the initial primary lesion and its distribution, complicated the final diagnosis and differentiated it from other cases reported in the literature. (12,15,16) Another possible problem is the lack of biopsy, which, as previously stated, is not mandatory, bearing in mind that the diagnosis is mainly clinical but could have been used to provide stronger support for the final diagnosis.

The diagnosis of these types of cases is also hindered by the lack of dermatological education in medical schools. (25) The number of dermatologists is low, and they have been experiencing an increasing demand, treating over 2 000 medical conditions and approximately a quarter of the population that require dermatological care. (25)

Other relevant aspect of pityriasis rosea is its multiple forms with different clinical manifestations (Table 3), but there are two main variants. The most common is known as classic variant, which comprises 80-90% of the cases: one of the most important signs of this form is the heraldic plaque, which appears in all classic variant cases and earlier than any other dermatological sign. (14) The second form is atypical pityriasis rosea, which affects between 10-20% of the patients; in this variant, the heraldic plaque is absent and lesion distribution is different as well, being more frequent in arms, flexural areas, face, and mouth. Hypopigmentation or isolated papules may be observed in black patients. (14,26)

Table 3. Clinical presentation of pityriasis rosea.

Clinical presentation	Characteristics	Rate
Classic	Herald patch usually observed on the trunk. It is erythematous with slightly elevated scaly borders and a lighter depressed center, with 3cm in diameter. It can be the only dermatological manifestation for up to 2 weeks. Prodromal symptoms (~69% of the patients): malaise, fatigue, nausea, headache, joint pain, lymphadenitis, fever, sore throat. Rash: known as secondary eruption, it presents along the Langer lines on the trunk. It may extend to the upper arms and thighs and has a 'Christmas tree' pattern on the back and a V pattern on the chest. The mean duration of this exanthem is 45 days, but it can last up to 12 weeks. Pruritus occurs in 50% of the patients.	Up to 90% of the cases

Clinical presentation	Characteristics	Rate
Pediatric	Pityriasis rosea in children is similar to its presentation in adults. Black children may have more facial and scalp involvement and post-inflammatory pigmentary changes. The secondary rash tends to appear faster than in adults (4 days vs. 14 days on average). 50% have prodromal symptoms. Most cases have been described between 3 to 9 years of age.	
Atypical	The distribution, morphology, size, and number of lesions may vary as follows: 1. Pityriasis rosea of darier: Fewer but larger lesions. 2. Inversus pityriasis rosea: It involves face, axillae, and groin. 3. Pityriasis rosea of Vidal: Larger patches on axillae or inguinal lesions. 4. Herald patch on atypical locations: There are cases in which the herald patch has been found in unusual places, such as the sole. 5. Inversus pityriasis rosea: Lesions are located on flexural areas, face, neck and acral areas. Trunk is not affected. 6. Circinata and marginata pityriasis rosea: Seen mainly in adults, large lesions are located on limbs-girdle, hips, shoulders, axillae, or inguinal regions. 7. Pityriasis of extremities: Typical lesions confined to the extremities; trunk is not affected. 8. Acral pityriasis rosea: Lesions are exclusively located on palms, wrists, and soles. It does not involve the flexures. 9. Purpuric or hemorrhagic pityriasis rosea: Macular purpuric lesions and petechia may appear over different locations, including the palate. 10. Urticarial pityriasis rosea: Palpable itchy wheal-like lesions with peripheral collarette scaling following the lines of skin cleavage. 11. Erythema multiforme-like pityriasis rosea: Classical lesions of the disease can be accompanied by targetoid lesions resembling erythema multiforme. They are distributed on trunk, face, arms, or neck. There is no history of herpes simplex infection. 12. Papular pityriasis rosea: Multiple small papular lesions of 1-3mm in diameter. Lesions present with peripheral collarette and are distributed on the trunk and proximal extremities. It appears predominantly in young patients. 13. Follicular pityriasis rosea: It has been described in children. It can initiate with pruritic plaques on abdomen, thighs, and groins, followed by a follicular eruption with central clearing and peripheral collarette. Prodromal symptoms are observed. 14. Vesicular pityriasis rosea: It is characterized by a generalized itchy eruption of vesicles of 2-6mm in diameter with a rosette scaling. It has been described in young adults and children. 15. Hypopigmented pityriasis rosea: It is similar to the classic form. It initiates with the herald patch and a secondary eruption with hypopigmented lesions from the start. Hypopigmentation is not secondary and may appear after classical pityriasis rosea. 16. Irritated pityriasis rosea: Lesions with severe itch, pain, and burning sensation appear on contact with sweat.	Approximately 10% of the patients
Relapsing	The herald patch is absent and fewer and smaller lesions are observed. It can be seen in between 1.8-3.7% of the patients. It occurs within 5 to 18 months from initial episode. Multiple relapses are possible but rare. Duration is shorter and with less prodromal symptoms than the original episode.	
Persistent	It lasts more than 3 months and its incidence appears to be low (~2%). Most patients have a herald patch and prodromal symptoms (75%). The eruption persists for 12-24 weeks. Oral lesions are common (75%) and may include: strawberry tongue, erythematous macules, vesicular lesions, and petechia.	
Recurrent	Multiple episodes of pityriasis rosea may occur in a lifetime on rare occasions.	
Special populations	Pregnant women seem to be more susceptible to pityriasis rosea due to their altered immune response. This condition increases the risk of spontaneous abortion, especially if the infection occurs in the first 15 weeks of gestation.	

Source: Own elaboration based on Drago *et al.*, (5) Urbina *et al.*, (15) Villalón-Gómez, (16) Drago *et al.* (27) and Chuh *et al.* (28)

The diagnosis of pityriasis rosea is mainly clinical. Biopsy, although neither crucial nor necessary, may show the following pathological findings: epidermal hyperplasia, localized hyperkeratosis, absence or reduction of stratum granulosum, dermal spongiosis, extravascular erythrocytes, and perivascular lymphocytic infiltrates. (14) Several diagnostic criteria have been developed to achieve its diagnosis (Table 4). (28)

Table 4. Diagnostic criteria of atypical pityriasis rosea

Characteristics	Essential clinical features	Optional clinical features	Exclusion clinical features
ALL the essential clinical features are observed in the patient on at least one occasion, with **AT LEAST ONE** of the optional clinical features.	Discrete circular or oval lesions Scaling on most lesions Peripheral collarette scaling with central clearance	Truncal and proximal limb distribution with less than 10% of the lesions located distal to mid-upper-arms and mid-thighs. Orientation of most lesions along skin cleavage lines. A herald patch appearing at least 2 days before eruption	Multiple small vesicles at the center of two or more lesions Two or more lesions on plantar and palmar surfaces Clinical or serological evidence of secondary syphilis
NO exclusion clinical features are present on all occasions.			

Source: Own elaboration based on Chuh *et al.* (28)

Differential diagnosis includes secondary syphilis, toxicoderma, some types of psoriasis (the guttate variant), HIV infection, ringworm of the body, seborrheic dermatitis, among others. (14) More information regarding these and other differential diagnosis can be seen in Table 5.

Table 5. Differential diagnosis of pityriasis rosea.

Clinical condition	Characteristics
Gianotti-Crosti syndrome	Monomorphic, pink-brown papules. Involvement of at least three of the following sites: i) cheeks, ii) buttocks, iii) extensor aspect of forearms and iv) extensor surface of legs. Symmetrical Duration of more than 10 days. Absence of i) scaly lesions, ii) extensive trunk lesions
Lichen planus	Small violaceous papules (1-10mm in diameter). Lesions on wrists, lumbar region, shin, scalp, penis glans, and mouth. This disease may be asymptomatic.
Nummular eczema	Small vesicles and papules that group in small-coined lesions (4-5cm in diameter), with erythematous plaques and distinct borders, and intense pruritus, often in legs and back of hands.
Pityriasis lichenoides chronica	Red-brown papules with central mica-like scales, randomly arranged on trunk and extremities. It is a chronic and relapsing condition. Alteration of skin pigmentation may be observed.
Pityriasis rosea–like drug eruptions	Similar presentation to the classic form. Symptoms resolve after medication is suspended. Associated medications include adalimunab, allopurinol, arsenic compounds, aasenapine, atelonol, barbiturates, bismuth, bupropion, captopril, clonidine, clozapine, ergotamine, etanercept, hepatitis B vaccine, yellow fever vaccine, interferon α-2a, isotretinoin, ketotifen, lamotrigine, smallpox vaccine, omeprazole, among others.

Clinical condition	Characteristics
Seborrheic dermatitis	Orange-red or gray-white skin with greasy or white dry scaling. Diffuse scalp involvement. Condition worsens with dry conditions. Pruritus increases with perspiration.
Secondary syphilis	Round or oval brownish-red or pink macules of 0.5-1cm, affecting the trunk, palms, and soles. Patchy alopecia. Mucous membrane involvement with round or oval patches covered by hyperkeratotic white-to-gray membrane.
Ringworm of the body (tinea corporis)	Scaling, sharply marginated plaques with or without pustules or vesicles along margins. Lesions present with peripheral enlargement and central clearing. Annular configuration with concentric or arcuate lesions.
Viral exanthems	Diffuse maculopapular erythema. Mucosal involvement with microulcerative lesions, palatal petechiae or conjunctivitis. Associated with lymphadenopathy, hepatomegaly, and splenomegaly.

Source: Own elaboration based on Villalón-Gómez (16), Chuh *et al.*, (28) Stulberg & Wolfrey, (29) Chuh *et al.*, (30) Stratigos *et al.*, (31) Brzezinski & Chiriac, (32) Polat *et al.*, (33) Makdisi *et al.*, (34) Papadavid *et al.*, (35) Bangash *et al.*, (36) Sezer *et al.*, (37) Lai *et al.*, (38) Atzori *et al.*, (39) Chen *et al.*, (40) Guarneri *et al.*, (41) Rajpara *et al.*, (42) Güleç *et al.*, (43) Scheinfeld, (44) Brazzelli *et al.*, (45) Aydogan *et al.*, (46) Atzori *et al.*, (47) Gaertner *et al.*, (48) Sasmaz *et al.*, (49) Durusoy *et al.*, (50) Gupta *et al.*, (51) Buckley, (52) George *et al.* (53) and Gürel *et al.* (54)

Besides all aspects mentioned above, the number of patients may grow considering that general practitioners do not have sufficient information on this viral rash and refer many patients with benign conditions for assessment (for example, a dermatologist may expect to treat between 20-40 benign lesions for every melanoma diagnosed). (55) Moreover, there is a significant disparity between demand and available resources, as well as inadequate education in medical schools, a scarcity of dermatologists, and lack of standardized training. (25,56) For instance, on average, a medical student receives no more than six days of training in dermatology, even when skin disorders account for a quarter of all general practitioner appointments. (25,56,57) This care crisis may worsen as a result of changes in governmental policies, which can increase costs, lead to neglect of patients in need, and destroy medical education. (58) This is true for many health systems around the world, with health inequities potentially aggravating the situation. (56,58,59) Therefore, reinforcement and practices regarding dermatology, using new and old technologies, should be implemented in medical schools. (56,60,61)

Furthermore, there are similarities and differences with other cases published in the literature and with other cases of atypical pityriasis rosea since no herald patch was found anywhere in the body, although it was looked for even in atypical locations. (15,62)

The clinical characteristics observed in this patient, who is an adult, are incompatible with other types of atypical pityriasis rosea; for example, the form of the lesions and their localization are different from the form circinata and marginata, (63,64) and the distribution was not the one expected for the inversus, (65) extremities (15) or acral forms. (66) Moreover, the lesions resembled those of the classical form and were not compatible with the lesions found in other atypical cases such as purpuric,

(67) urticarial, (67) erythema multiforme-like, (68) papular, (67) follicular (69) vesicular or others. (58)

Finally, it is worth noting that the patient had moderate depression, which was diagnosed before developing the condition, and that it has been associated with the onset of pityriasis rosea. Such an association has been reported and presented in other cases and could be explained by immunological compromise. (62)

One of the strengths of this case were the early notification of the case to the surveillance system, the comprehensive assessment done on the patient, and the differential diagnosis that were considered and ruled out. It is worth noting that based on some of the results obtained in clinical tests, this case seems to be associated with infection and reactivation of herpesvirus, which coincides with other cases. (62) One of the weaknesses is the lack of a biopsy to confirm the diagnosis.

CONCLUSIONS

Pityriasis rosea is a self-limited disease possibly associated with stress periods and infection with HHV6 and HHV7. It can be difficult to diagnose because it has multiple forms, so physicians must have deep knowledge of dermatological diseases and a high suspicion of its presentation. This case is particularly relevant because the patient presented with atypical manifestations.

STATEMENT OF TRANSPARENCY

The authors state that all the information contained in these pages is true, honest and transparent, that no aspect of the case was omitted, and that all relevant characteristics or differences were exposed.

INFORMED CONSENT

Written informed consent was obtained from the patient for the publication of this case and the photographs contained therein.

PATIENT'S PERSPECTIVE

The patient understood the importance of follow-ups and treatment recommendations. Although some aspects of her life were affected, such as her working routine up to a certain extent, other aspects of her daily life did not change, including her relationships, her mood —which remained stable—, and her self-image —which suffered from a bit of frustration and some and alterations that did not last long.

CONFLICT OF INTERESTS

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGEMENTS

None stated by the authors.

REFERENCES

1. **Gibert CM.** Traité pratique des maladies de la peau et de la syphilis. Paris: Henri Plon; 1860.
2. **Petit A.** Pitiriasis rosada («pityriasis rosea»). *EMC-Dermatología*. 2015;49(4):1-7. https://doi.org/gd9q.
3. **González LM, Allen R, Janniger CK, Schwartz RA.** Pityriasis rosea: an important papulosquamous disorder. *Int J Dermatol.* 2005;44(9):757-64. https://doi.org/bmtpzb.

4. **Chuh AA, Chan HH, Zawar V.** Is human herpesvirus 7 the causative agent of pityriasis rosea?--A critical review. *Int J Dermatol.* 2004;43(12):870-5. *https://doi.org/dk83hq.*
5. **Drago F, Broccolo F, Javor S, Drago F, Rebora A, Parodi A.** Evidence of human herpesvirus-6 and-7 reactivation in miscarrying women with pityriasis rosea. *J Am Acad Dermatol.* 2014;71(1):198-9. https://doi.org/f2sfh7.
6. **Rebora A, Drago F, Broccolo F.** Pityriasis rosea and herpesviruses: facts and controversies. *Clin Dermatol.* 2010;28(5):497-501. https://doi.org/bzm72v.
7. **Drago F, Ciccarese G, Rebora A, Parodi A.** Human herpesvirus -6,-7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol.* 2021;93(4):1850-1. https://doi.org/gfbn.
8. **Chia JK, Shitabata P, Wu J, Chia AY.** Enterovirus infection as a possible cause of pityriasis rosea: demonstration by immunochemical staining. *Arch Dermatol.* 2006;142(7):927-47. https://doi.org/dp2dws.
9. **Ehsani AH, Nasimi M, Bigdelo Z.** Pityriasis rosea as a cutaneous manifestation of COVID-19 infection. *J Eur Acad Dermatol Venereol.* 2020;34(9):e436-7. https://doi.org/ggx33r.
10. **Dowling JN.** Clinical Features of Disease Due To Legionella Species. In: Katz SM, editor. Legionellosis. Volume I. New York: CRC Press; 1985.
11. **Burch PR, Rowell NR.** Pityriasis rosea—an autoaggressove disease? Statistical studies in relation to aetiology and pathogenesis. *Br J Dermatol.* 1970;82(6):549-60. *https://doi.org/btrnhd.*
12. **Singh M, Pawar M, Chuh A, Zawar V.** Pityriasis rosea: elucidation of environmental factors in modulated autoagressive etiology and dengue virus infection. *Acta Dermatovenerol Alp Pannonica Adriat.* 2019;28(1):15-20.
13. **Grinspan-Bozza N.** Pitiriasis rosada de Gibert: un nuevo enfoque sobre su etiopatogenia. *Arch argent dermatol.* 2008:58(3):121-3.
14. **Mahajan K, Relhan V, Relhan AK, Garg VK.** Pityriasis rosea: An update on etiopathogenesis and management of difficult aspects. *Indian J Dermatol.* 2016;61(4):375-84. https://doi.org/gfbq.
15. **Urbina F, Das A, Sudy E.** Clinical variants of pityriasis rosea. *World J Clin Cases.* 2017;5(6):203-11. https://doi.org/gcrh27.
16. **Villalon-Gomez JM.** Pityriasis rosea: diagnosis and treatment. *Am Fam Physician.* 2018;97(1):38-44.
17. **Gay JT, Gross GP.** Herald patch. Treasure Island: StatPearls Publishing; 2019.
18. **Sharma PK, Yadav TP, Gautam RK, Taneja N, Satyanarayana L.** Erythromycin in pityriasis rosea: A double-blind, placebo-controlled clinical trial. *J Am Acad Dermatol.* 2000;42(2 Pt 1):241-4. https://doi.org/fvbnmv.
19. **Drago F, Vecchio F, Rebora A.** Use of high-dose acyclovir in pityriasis rosea. *J Am Acad Dermatol.* 2006;54(1):82-5. https://doi.org/b9sqbv.
20. **Rassai S, Feily A, Sina N, Abtahian S.** Low dose of acyclovir may be an effective treatment against pityriasis rosea: a random investigator-blind clinical trial on 64 patients. *J Eur Acad Dermatol Venereol.* 2011;25(1):24-6. https://doi.org/dskth9.
21. **Das A, Sil A, Das NK, Roy K, Das AK, Bandyopadhyay D.** Acyclovir in pityriasis rosea: An observer-blind, randomized controlled trial of effectiveness, safety and tolerability. *Indian Dermatol Online J.* 2015;6(3):181-4. https://doi.org/gfbs.
22. **Rodriguez-Zuniga M, Torres N, Garcia-Perdomo H.** Effectiveness of acyclovir in the treatment of pityriasis rosea. A systematic review and meta-analysis. *Ans Bras Dermatol.* 2018;93(5):686-95. https://doi.org/gd49mc.
23. **Jairath V, Mohan M, Jindal N, Gogna P, Syrty C, Monnappa PM, *et al.*** Narrowband UVB phototherapy in pityriasis rosea. *Indian Dermatol Online J.* 2015;6(5):326-9. https://doi.org/gfbt.
24. **Drago F, Rebora A.** Treatments for pityriasis rosea. *Skin Therapy Lett.* 2009;14(3):6-7.

25. **Schofield J, Grindlay D, Williams H.** Skin conditions in the UK: a health care needs assessment. Hertfordshire: University of Hertfordshire Research Archive; 2009.
26. **Kilinc F, Akbas A, Sener S, Aktaş A.** Atypical pityriasis rosea: clinical evaluation of 27 patients. *Cutan Ocul Toxicol.* 2017;36(2):157-62. https://doi.org/gfbv.
27. **Drago F, Broccolo F, Zaccaria E, Malnati M, Cocuzza C, Lusso P, *et al.*** Pregnancy outcome in patients with pityriasis rosea. *J Am Acad Dermatol.* 2008;58(5 Suppl 1):S78-83. https://doi.org/c25d4k.
28. **Chuh A, Zawar V, Sciallis GF, Lee A.** The diagnostic criteria of pityriasis rosea and Gianotti-Crosti syndrome-a protocol to establish diagnostic criteria of skin diseases. *J R Coll Physicians Edinb.* 2015;45(3):218-25. https://doi.org/gfbw.
29. **Stulberg DL, Wolfrey J.** Pityriasis rosea. *Am Fam Physician.* 2004;69(1):87-91.
30. **Chuh AA, Dofitas BL, Comisel G, Reveiz L, Sharma V, Garner SE, *et al.*** Interventions for pityriasis rosea. *Cochrane Database Syst Rev.* 2007(2):CD005068. https://doi.org/ddhbsd.
31. **Kane KS-M, Lio PA, Stratigos AJ, Johnson RA.** Color atlas and synopsis of pediatric dermatology. 2nd ed. McGraw-Hill; 2009.
32. **Brzezinski P, Chiriac A.** Uncommon presentation of pityriasis rosea after yellow fever inoculation. *JAMA Dermatol.* 2014;150(9):1020-1. https://doi.org/gfbx.
33. **Polat M, Uzun Ö, Örs I, Boran C.** Pityriasis rosea-like drug eruption due to bupropion: a case report. *Hum Exp Toxicol.* 2014;33(12):1294-6. https://doi.org/f6r48p.
34. **Makdisi J, Amin B, Friedman A.** Pityriasis rosea-like drug reaction to asenapine. *J Drugs Dermatol.* 2013;12(9):1050-1.
35. **Papadavid E, Panayiotides I, Makris M, Giatrakou S, Dalamaga M, Stavrianeas N, *et al.*** Pityriasis rosea-like eruption associated with lamotrigine. *J Am Acad Dermatol.* 2013;68(6):e180-1. https://doi.org/f2kzzb.
36. **Bangash HK, Finch T, Petronic-Rosic V, Sethi A, Abramsohn E, Lindau ST.** Pityriasis rosea-like drug eruption due to nortriptyline in a patient with vulvodynia. *J Low Genit Tract Dis.* 2013;17(2):226-9. https://doi.org/f4srhq.
37. **Sezer E, Erkek E, Cetin E, Sahin S.** Pityriasis rosea-like drug eruption related to rituximab treatment. *J Dermatol.* 2013;40(6):495-6. https://doi.org/gfbz.
38. **Lai YW, Chou CY, Shen WW, Lu ML.** Pityriasis rosea-like eruption associated with clozapine: a case report. *Gen Hosp Psychiatry.* 2012;34(6):703.e5-7. https://doi.org/f2g72w.
39. **Atzori L, Pinna A, Mantovani L, Ferreli C, Pau M, Mulargia M, *et al.*** Cutaneous adverse drug reactions to allopurinol: 10 year observational survey of the dermatology department-Cagliari University (Italy). *J Eur Acad Dermatol Venereol.* 2012;26(11):1424-30. https://doi.org/b3v5n2.
40. **Chen JF, Chiang CP, Chen YF, Wang WM.** Pityriasis rosea following influenza (H1N1) vaccination. *J Chin Med Assoc.* 2011;74(6):280-2. https://doi.org/ctxdhf.
41. **Guarneri C, Polimeni G, Nunnari G.** Pityriasis rosea during etanercept therapy. *Eur Rev Med Pharmacol Sci.* 2009;13(5):383-7.
42. **Rajpara SN, Ormerod AD, Gallaway L.** Adalimumab-induced pityriasis rosea. *J Eur Acad Dermatol Venereol.* 2007;21(9):1294-6. https://doi.org/ckjq5t.
43. **Güleç Aİ, Albayrak H, Kayapinar O, Albayrak S.** Pityriasis rosea-like adverse reaction to atenolol. *Hum Exp Toxicol.* 2016;35(3):229-31. https://doi.org/gfb2.
44. **Scheinfeld N.** Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol.* 2006;5(3):228-31.
45. **Brazzelli V, Prestinari F, Roveda E, Barbagallo T, Bellani E, Vassallo C, *et al.*** Pityriasis rosea-like eruption during treatment with imatinib mesylate: Description of 3 cases. *J Am*

Acad Dermatol. 2005;53(5 Suppl 1):S240-S3. https://doi.org/dqhmdf.

46. **Aydogan K, Karadogan SK, Adim SB, Tunali S.** Pityriasis rosea-like eruption due to ergotamine: a case report. *J Dermatol.* 2005;32(5):407-9. https://doi.org/gfb3.
47. **Atzori L, Ferreli C, Pinna AL, Aste N.** 'Pityriasis rosea-like'adverse reaction to lisinopril. *J Eur Acad Dermatol Venereol.* 2004;18(6):743-5. https://doi.org/c4856w.
48. **Gaertner EM, Groo S, Kim J.** Papular spongiotic dermatitis of smallpox vaccination: report of 2 cases with review of the literature. *Arch Pathol Lab Med.* 2004;128(10):1173-5.
49. **Sasmaz S, Karabiber H, Boran C, Garipardic M, Balat A.** Pityriasis rosea-like eruption due to pneumococcal vaccine in a child with nephrotic syndrome. *J Dermatol.* 2003;30(3):245-7. https://doi.org/b3vb.
50. **Durusoy Ç, Alpsoy E, Yilmaz E.** Pityriasis rosea in a patient with Behçet's disease treated with interferon alpha 2A. *J Dermatol.* 1999;26(4):225-8. https://doi.org/gfb4.
51. **Gupta AK, Lynde CW, Lauzon GJ, Mehlmauer MA, Braddock SW, Miller CA, *et al.*** Cutaneous adverse effects associated with terbinafine therapy: 10 case reports and a review of the literature. *Br J Dermatol.* 1998;138(3):529-32. https://doi.org/fs66zh.
52. **Buckley C.** Pityriasis rosea-like eruption in a patient receiving omeprazole. *Br J Dermatol.* 1996;135(4):660-1. https://doi.org/fcrjmw.
53. **George A, Bhatia A, Kanish B, Williams A.** Terbinafine induced pityriasis rosea-like eruption. *Indian J Pharmacol.* 2015;47(6):680-1. https://doi.org/gfb5.
54. **Gürel G, Şahin S, Çölgeçen E.** Pityriasis rosea-like eruption induced by isotretinoin. *Cutan Ocul Toxicol.* 2018;37(1):100-2. https://doi.org/gfb6.
55. **Leigh IM.** Progress in skin cancer: the UK experience. *Br J Dermatol.* 2014;171(3):443-5. https://doi.org/gfb7.
56. **Ulman CA, Binder SB, Borges NJ.** Assessment of medical students' proficiency in dermatology: Are medical students adequately prepared to diagnose and treat common dermatologic conditions in the United States? *J Educ Eval Health Prof.* 2015;12:18. https://doi.org/gfb8.
57. **Murase JE.** Understanding the importance of dermatology training in undergraduate medical education. *Dermatol Pract Concept.* 2015;5(2):95-6.
58. **Clough C.** Final report: Independent review of Nottingham dermatology services. NHS Rushcliffe Clinical Commissioning Group; 2015.
59. **Buster KJ, Stevens EI, Elmets CA.** Dermatologic health disparities. *Dermatol Clin.* 2012;30(1):53-9. https://doi.org/d5867w.
60. **Karthikeyan K, Kumar A.** Integrated modular teaching in dermatology for undergraduate students: a novel approach. *Indian Dermatol Online J.* 2014;5(3):266-70. https://doi.org/gfb9.
61. **Silva CS, Souza MB, Silva Filho RS, Medeiros LMd, Criado PR.** E-learning program for medical students in dermatology. *Clinics.* 2011;66(4):619-22. https://doi.org/b3c27g.
62. **Drago F, Broccolo F, Rebora A.** Pityriasis rosea: an update with a critical appraisal of its possible herpesviral etiology. *J Am Acad Dermatol.* 2009;61(2):303-18. https://doi.org/bf89nq.
63. **Sarkany I, Hare PJ.** Pityriasis rotunda. (Pityrisis circinata). *Br J Dermatol.* 1964;76(5):223-8. https://doi.org/b8ww4f.
64. **Jacyk WK.** Pityriasis rosea in Nigerians. *Int J Dermatol.* 1980;19(7):397-9. https://doi.org/fk694h.
65. **Gibney MD, Leonardi CL.** Acute papulosquamous eruption of the extremities demonstrating an isomorphic response. Inverse pityriasis rosea (PR). *Arch Dermatol.* 1997;133(5):651-4. https://doi.org/ck8zw2.
66. **Zawar V.** Acral pityriasis rosea in an infant with palmoplantar lesions: A novel manifestation. *Indian Dermatol Online J.* 2010;1(1):21-3. https://doi.org/fgn5rt.

67. Chuh A, Zawar V, Lee A. Atypical presentations of pityriasis rosea: case presentations. *J Eur Acad Dermatol Venereol*. 2005;19(1):120-6. https://doi.org/dq36d7.

68. Das A, Sarkar TK, Chandra S, Ghosh A, Gharami RC. A case series of erythema multiforme-like pityriasis rosea. *Indian Dermatol Online J*. 2016;7(3):212-5. https://doi.org/gfcc.

69. Zawar V, Chuh A. Follicular pityriasis rosea. A case report and a new classification of clinical variants of the disease. *J Dermatol Case Rep.* 2012;6(2):36-9. *https://doi.org/gfcd.*

https://doi.org/10.15446/cr.v7n2.88306

ROSAI-DORFMAN DISEASE: A RARE PRESENTATION OF EXTRANODAL INVOLVEMENT OF ISOLATED BONE. CASE REPORT

Keywords: Histiocytosis, Sinus; Extranodal Extension; Methotrexate; Rosai-Dorfman Disease.
Palabras clave: Histiocitosis Sinusal; Extensión Extranodal; Metotrexato; Enfermedad de Rosai-Dorfman.

Camilo Andrés García-Prada
Tomás Rodríguez-Yanez
Universidad de Cartagena
- Faculty of Medicine -
Cartagena de Indias - Colombia.

Carlos Alberto Ferrer-Santos
Universidad de los Andes
- Faculty of Medicine -
Bogotá D.C. - Colombia.

Corresponding author
Camilo Andrés García-Prada.
Universidad de Cartagena de Indias.
Cartagena de Indias. Colombia.
Correo electrónico: cgarciap4@unicartagena.edu.co

Received: 15/06/2021 **Accepted:** 01/02/2021

RESUMEN

Introducción. La enfermedad de Rosai-Dorfman, también conocida como histiocitosis sinusal, es un trastorno poco frecuente caracterizado por la proliferación de histiocitos.

Presentación del caso. Hombre de 33 años quien consultó al servicio de urgencias de una institución de tercer nivel de Cartagena de Indias, Colombia, por una deformidad de progresión lenta que apareció 6 meses atrás en el costado frontal derecho de la cara y generaba dolor. Al examen físico no hubo hallazgos mayores y los estudios paraclínicos fueron normales o negativos. Se obtuvieron imágenes que evidenciaron extenso compromiso inflamatorio/infeccioso del hueso frontal, por lo que se sospechó de osteomielitis y se realizó biopsia de la lesión que permitió establecer diagnóstico de enfermedad de Rosai-Dorfman variante extranodal con compromiso óseo aislado. El paciente recibió tratamiento con corticoide sistémico sin obtener respuesta, por lo que se adicionó metotrexato, con lo cual se logró mejoría a los 2 meses.

Conclusiones. Las manifestaciones de la enfermedad de Rosai-Dorfman en población adulta son poco conocidas, además no hay mucha información sobre su tratamiento, por lo que el presente caso contribuye a ampliar la literatura sobre esta enfermedad que puede presentarse con sintomatología completamente inusual.

ABSTRACT

Introduction: Rosai-Dorfman disease (RDD), also known as sinus histiocytosis, is a rare disorder characterized by histiocyte proliferation.

Case presentation: A 33-year-old man consulted the emergency department of a tertiary care institution in Cartagena de Indias, Colombia, due to a 6-month history of progressive deformity in the frontal right side of the face, associated with pain of slow progression, without any other symptoms or dermatological involvement. There were no other major findings on physical examination and laboratory tests performed were negative. Imaging scans obtained showed extensive inflammatory involvement of the frontal bone, which led to suspect osteomyelitis as the first diagnostic possibility. A biopsy of the lesion was performed with negative cultures for bacteria, which allowed establishing a diagnosis of extranodal Rosai-Dorfman disease with isolated bone involvement. Treatment with systemic corticosteroids was indicated with poor response, so methotrexate was added, achieving an evident improvement after 2 months.

Conclusions: Little is known about the manifestations of Rosai-Dorfman disease and its treatment in the adult population. The present case report contributes to expanding the literature on this topic, which can present with rare symptoms that may pose challenges for its diagnosis.

INTRODUCTION

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease, was first described by Rosai and Dorfman in 1969. It is a rare histiocytic proliferative disorder of unknown etiology (1), and different cell populations and cytokines are involved in its pathogenesis. The participation of inflammatory cytokines such as macrophage colony stimulating factor, IL-1β, IL-6, and TNF-α is common (2).

This disease predominantly affects children and young adults in the first 2 decades of life, particularly males. Patients who present with extranodal disease may require systemic therapy, for which there is currently no standardized regimen to date. Systemic therapies include corticosteroids, mTOR inhibitors, radiation therapy, chemotherapy, and immunomodulatory therapy.

CASE DESCRIPTION

A 33-year-old mestizo man from Cartagena - Colombia, who works as a street vendor, of low economic status, without a relevant medical history, consulted due to the presence of a progressive deformity in the right frontal side of the face and pain of 6 months of evolution with slow progression and no other associated symptoms.

On physical examination, he presented with growth of the right frontal region, without the presence of dermatological lesions, lymphadenopathy or visceromegaly. Complementary laboratory tests (complete blood count, blood chemistry, sedimentation rate, C-reactive protein, proteinogram, immunoglobulins, complement, ANA, VDRL, hepatitis and HIV, beta-2-microglobulin and chest radiography) were performed, which were normal or negative. Initial imaging studies showed extensive inflammatory/infectious bone involvement, which led to suspect osteomyelitis as the first diagnostic possibility (Figure 1).

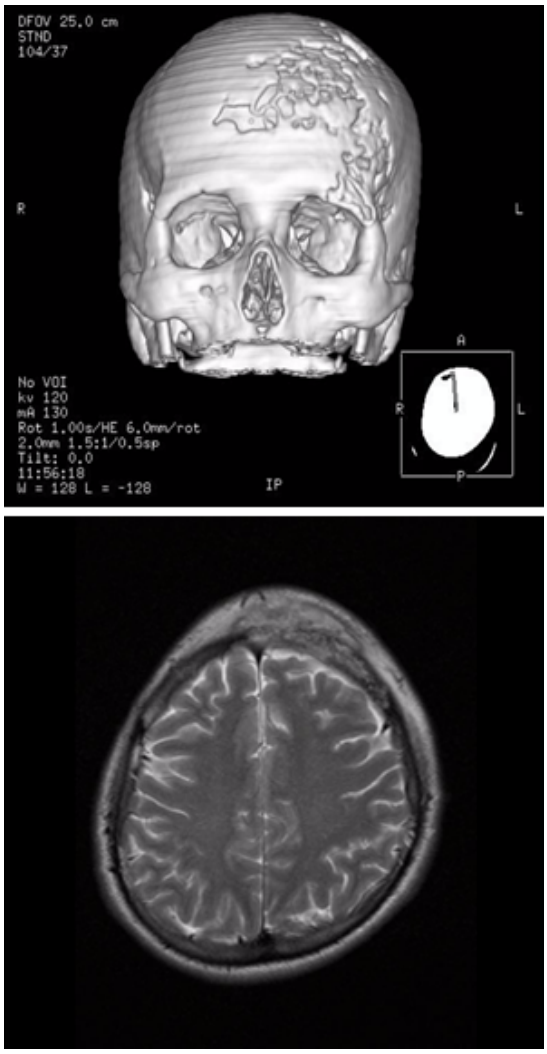


Figure 1. Initial imaging studies of the lesion showing extensive inflammatory bone involvement, with osteomyelitis as the first diagnostic possibility.
Source: Document obtained during the study.

The histopathological study revealed histiocyte sheets at the frontal bone level with clear cytoplasm and rounded nuclei, without significant atypia, lymphocyte and neutrophil emperipolesis, positivity for CD68 and S100, and negativity for CD1a in immunohistochemistry (Figure 2). The microbiological study was negative for fungi, *M. tuberculosis,* atypical mycobacteria and *Leishmania* sp. These findings led to the diagnosis of extranodal Rosai-Dorfman disease with isolated

bone involvement; an extension study was carried out, but no systemic affectation was detected.

Given the possibility of having a self-limited course (50% of cases), medical follow-up was provided for a period of 2 months without achieving improvement. As a consequence, treatment with prednisolone at 1 mg/kg/day was started for 2 months, without obtaining a positive response, so methotrexate 15 mg/week was initiated with evident improvement, from a clinical perspective, after 2 months due to the improvement of the deformity in the face and imaging scans showing partial resolution of the initial tomographic findings. Throughout the clinical follow-up, no adverse reactions to the use of steroids in conjunction with methotrexate were observed.

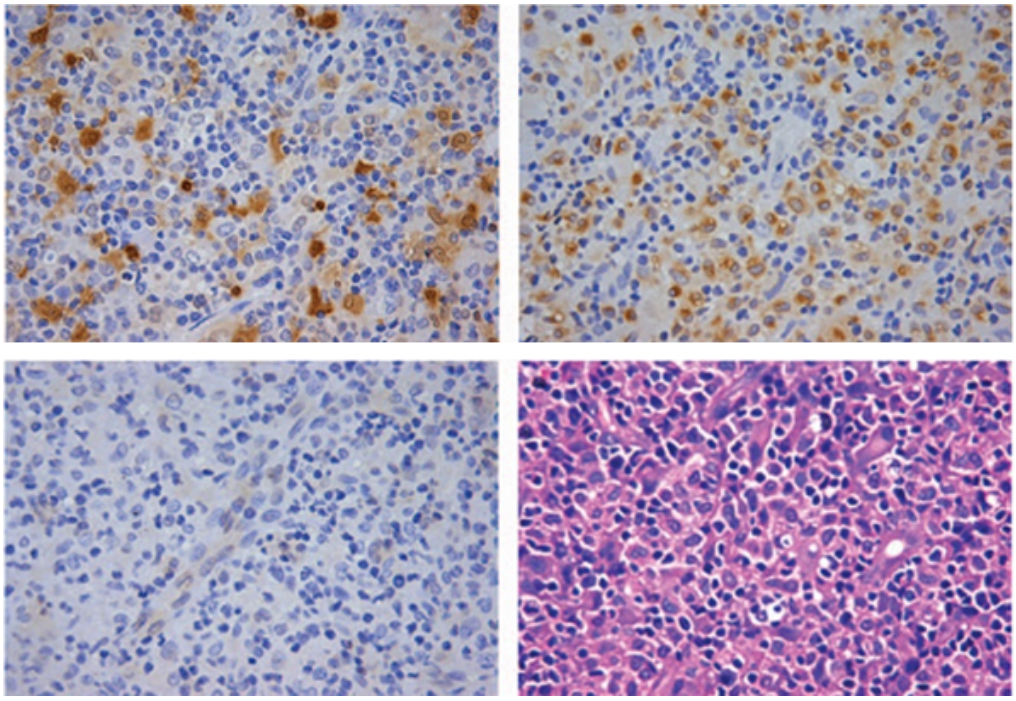


Figure 2. The histopathological study showed histiocyte sheets with clear cytoplasm and rounded nuclei, without significant atypia and lymphocyte and neutrophil emperipolesis. Positivity for CD68 and S100 and negativity for CD1a were found in immunohistochemistry stains.

Source: Document obtained during the study.

DISCUSSION

Rosai-Dorfman disease may occur in any age group; however, its occurrence predominates in children and young adults, particularly males. Its classic clinical presentation is characterized by the appearance of massive and indolent cervical lymphadenopathy with fever, hypergammaglobulinemia and increased erythrocyte sedimentation rate (3). The reported patient did not have these characteristics since local bone involvement predominated at the level of the cranial vault, being initially managed as an infectious process.

RDD is a benign histiocytic proliferative disorder, with a prevalence of 1:200 000 and an estimated 100 new cases per year in the United States. Its form may be nodal or extranodal. In cases of nodal disease, cervical lymphadenopathy is the most frequent, followed by axillary, inguinal and mediastinal location. On the

other hand, extranodal forms usually affect the central nervous system, skin, soft tissues, bone, oral cavity, and salivary glands (2). Extranodal involvement is frequent and occurs in 43% of patients, mainly in the head and neck. Isolated extranodal presentation may also occur, as in the case of our patient (1).

Isolated bone involvement is a rare manifestation of the disease, occurring in less than 10% of the cases (4). The most common symptoms in this scenario are pain and swelling. Data available in the reviewed literature states that the skull, face and long bones are the most affected areas, with lytic lesions predominantly (4). In contrast to the benign course of nodal manifestations, Rosai-Dorfman disease in the bones has a poorer prognostic factor, as it tends to have a chronic course with frequent relapses.

Imaging scans are useful for the identification, staging and monitoring of the clinical course of the disease with bone involvement. However, this disease may simulate other conditions, including neoplasms (lymphoma, Kaposi's sarcoma, metastasis and malignant histiocytosis) and inflammatory conditions (infections: tuberculosis and histiocytosis; non-infectious granulomatous conditions: Castleman disease, granulomatosis and sarcoidosis) (1). In the present case, scans were interpreted as initially associated with a local infectious process, for which the patient received a course of antibiotics that was suspended based on histological findings.

The course of this disease is usually benign, with frequent cases of spontaneous regression; less than 10% of patients suffer progressive disease associated with adverse outcomes, including death. In most cases documented in the literature, patients usually receive surgical or glucocorticoid-based management. Several treatments, such as systemic corticosteroids, surgery, chemotherapy and radiotherapy, or a combination of these, have been reported, all with variable efficacy (5). Vincristine and imatinib (6) have demonstrated it to be effective in refractory patients. There have also been reports of patients who responded well to low dosages of methotrexate (7).

Timely diagnosis and treatment based on the descriptions found in the literature allowed for the improvement of the patient's condition, who was previously isolated from his family and social group due to the lack of knowledge on his disease.

CONCLUSION

Extranodal Rosai-Dorfman disease is common; however, isolated bone involvement is rare, accounting for less than 10% of cases. This is an extremely rare disease that poses a diagnostic challenge considering that its clinical suspicion is based on its traditional form of presentation, which was not observed in our patient. In this case, histology and immunohistochemical studies were essential to reach the diagnosis.

ETHICAL APPROVAL

Informed consent was obtained from all participants included in the study.

CONFLICTS OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGEMENTS

None stated by the authors.

REFERENCES

1. **Mar WA, Yu JH, Knuttinen MG, Horowitz JM, David O, Wilbur A, *et al.*** Rosai-Dorfman Disease: Manifestations Outside of the Head and Neck. *AJR Am J Roentgenol*. 2017;208(4):721-32. https://doi.org/f93zbn.
2. **Piris MA, Aguirregoicoa E, Montes-Moreno S, Celeiro-Munoz C.** Castleman Disease and Rosai-Dorfman Disease. *Semin Diagn Pathol.* 2018;35(1):44-53. https://doi.org/gd53.
3. **Cai Y, Shi Z, Bai Y.** Review of Rosai-Dorfman Disease: New Insights into the Pathogenesis of This Rare Disorder. *Acta Haematol.* 2017;138(1):14-23. https://doi.org/gbhkdh.
4. **Mosheimer BA, Oppl B, Zandieh S, Fillitz M, Keil F, Klaushofer K, *et al.*** Bone Involvement in Rosai-Dorfman Disease (RDD): a Case Report and Systematic Literature Review. *Curr Rheumatol Rep.* 2017;19(5):29. https://doi.org/gd54.
5. **Paryani NN, Daugherty LC, O'Connor MI, Jiang L.** Extranodal rosai-dorfman disease of the bone treated with surgery and radiotherapy. *Rare tumors*. 2014;6(4):5531. https://doi.org/gd55.
6. **Utikal J, Ugurel S, Kurzen H, Erben P, Reiter A, Hochhaus A, *et al.*** Imatinib as a treatment option for systemic non-Langerhans cell histiocytosis. *Arch Dermatol.* 2007;143(6):736-40. https://doi.org/bv4b58.
7. **Inoue S, Onwuzurike N.** Venorelbine and methotrexate for the treatment of Rosai-Dorfman disease. *Pediatric Blood Cancer.* 2005;45(1):84-5. https://doi.org/dwz9tk.

https://doi.org/10.15446/cr.v7n2.86507

TUBAL HETEROTOPIC PREGNANCY. CASE REPORT

Keywords: Ectopic Pregnancy; Hemoperitoneum; Laparotomy; Ultrasonography.
Palabras clave: Embarazo ectópico; Hemoperitoneo; Laparotomía; Ultrasonografía.

Mayerli Catalina Díaz-Narváez
Fundación Universitaria San Martín - Pasto Campus - Faculty of Health Sciences - Medical Program - Pasto - Colombia.
Clínica Hispanoamérica - Gynecology and Obstetrics Service - Pasto Colombia.
Universidad Libre – Barranquilla Campus - School of Health Sciences - Specialty in Gynecology and Obstetrics - Barranquilla - Colombia.

Erika Cristina Enriquez-Enriquez
Fundación Universitaria San Martín - Pasto Campus - Faculty of Health Sciences - Medical Program - Pasto - Colombia.
Clínica Hispanoamérica - Gynecology and Obstetrics Service - Pasto Colombia.

Corresponding author
Mayerli Catalina Díaz-Narváez. Facultad de Ciencias de la salud, Fundación Universitaria San Martín. Pasto. Colombia. Email: catadiaz181@gmail.com

Received: 21/04/2020 **Accepted:** 26/08/2020

RESUMEN

Introducción. El embarazo heterotópico se considera una patología de interés debido a que, aunque su incidencia es baja, su tasa de mortalidad es elevada; además, esta es una entidad que representa un reto diagnostico por sus diversas presentaciones clínicas.

Presentación del caso. Mujer de 32 años, mestiza, procedente de Pasto (Colombia) y en estado de embarazo, quien asistió al servicio de urgencias de una institución de tercer nivel de atención por un dolor abdominal difuso asociado a sangrado vaginal. Teniendo en cuenta los hallazgos imagenológicos (ecografía) y los niveles de gonadotropina encontrados, la paciente fue diagnosticada con embarazo heterotópico de ubicación tubárica derecha que requirió tratamiento quirúrgico por laparotomía. A los 8 días del procedimiento la paciente asistió a control y mediante ecografía se evidenció continuidad de embarazo intrauterino.

Conclusiones. El pilar fundamental para el diagnóstico del embarazo heterotópico es la sospecha clínica, pero es necesario confirmarlo mediante ayudas diagnosticas como la ecografía y a través de la medición de los niveles de gonadotropina coriónica humana. Este evento se debe sospechar en pacientes con cuadro de dolor abdominal a pesar de que no tengan factores de riesgo para presentarlo. La elección de tratamiento (médico o quirúrgico) depende de la condición clínica y hemodinámica de cada paciente y de la ubicación y el tamaño del embarazo ectópico.

ABSTRACT

Introduction: Heterotopic pregnancy (HP) is an uncommon yet interesting condition with a high mortality rate despite its low incidence. It can be difficult to diagnose due to its diverse clinical manifestations.

Case presentation. A 32-year-old, mestizo, pregnant woman from Pasto (Colombia) attended the emergency department of a tertiary care institution due to diffuse abdominal pain associated with vaginal bleeding. Taking into account the imaging findings (ultrasound) and the gonadotropin levels found, the patient was diagnosed with heterotopic pregnancy in right fallopian tube that required surgical treatment by laparotomy. Eight days after the procedure, the patient attended a follow-up appointment during which an ultrasound showed continuity of intrauterine pregnancy.

Conclusions. The mainstay for the diagnosis of heterotopic pregnancy is clinical suspicion, but it is necessary to confirm it through diagnostic aids such as ultrasound and the measurement of human chorionic gonadotropin levels. A heterotopic pregnancy should be suspected in patients with abdominal pain, even if they do not have risk factors for this type of pregnancy. Choosing medical or surgical treatment will depend on the clinical and hemodynamic condition of the patient and the location and size of the ectopic pregnancy.

INTRODUCTION

Heterotopic pregnancy is defined as the coexistence of an intrauterine pregnancy and an ectopic pregnancy at any location, although most cases occur in the uterine tubes (1). According to Zatarain-Gulmar & Torres-Hernández (2), the first case of heterotopic pregnancy was described by Duberney in 1708 in the findings of an autopsy.

Even though this type of pregnancy is extremely rare, it is estimated to occur in 1 out of every 30 000 to 50 000 spontaneous pregnancies. In recent years, there has been an increase in cases related to the use of assisted reproductive technologies since the prevalence rate increases by up to 1% in pregnancies achieved using these techniques (3).

Determination of the human chorionic gonadotropin ß-core fragment and transvaginal ultrasound are the most useful options for diagnosing heterotopic pregnancy. Methotrexate, hypertonic injectables, expectant management, and laparoscopic surgery are all options for treating this illness (4) and the best option should be chosen based on the expertise of the treating physician and the patient's clinical and hemodynamic status (5).

Heterotopic pregnancy is associated with high maternal morbidity and mortality, so its diagnosis and timely care are crucial. The following is the case of a patient who presented with abdominal pain suggestive of the aforementioned condition.

CASE PRESENTATION

A 32-year-old mestizo patient from the city of Pasto, Colombia, who worked as a nursing assistant and came from a middle-income household, consulted the emergency department of a tertiary health care institution. For five hours, she presented with diffuse, abdominal, colicky pain with predominance in the hypogastrium and right iliac fossa of moderate intensity that progressed to intense, associated with moderate vaginal bleeding. At the time of consultation, the patient was 5.1 weeks pregnant. She stated that it was his first pregnancy and that it was not the result of fertilization techniques. Her medical history revealed that she had hypothyroidism treated with levothyroxine 50mcg and that she had no surgical or allergy history and no sexually transmitted diseases.

On physical examination, the following vital signs were found: blood pressure of 120/80 mmHg; heart rate of 62 bpm; respiratory rate of 19 rpm; and temperature of 36.2°C. She also presented painful expression and soft abdomen, depressible and tender to palpation at the level of hypogastrium and right iliac fossa. Vaginal examination showed a closed central cervix and scant red vaginal bleeding, although no signs of peritoneal irritation were found.

In view of the findings, complementary laboratory tests were performed, showing C-reactive protein level of 0.57 mg/L; blood count with leukocytes of 16.85 mg/L, neutrophils of 90.4%, hemoglobin of 14.8 mg/L, hematocrit of 43.2%, and platelets of 294 mg/L; normal urinalysis; negative gram stain of uncentrifuged urine; and quantitative human chorionic gonadotropin ß-subunit levels of 16 627.77 mIU/mL.

Because gonadotropin levels were elevated for gestational age and the patient had vaginal bleeding, it was decided to perform a transvaginal ultrasound that showed anteverted retroflexed uterus with a well implanted gestational sac in the uterine cavity and adequate decidual reaction. In the right adnexa, an echogenic yolk sac of 47x29mm was observed, which is characteristic of the "tubal ring sign" or "bagel sign." The ultrasound reading concluded intrauterine pregnancy of less than 6 weeks and the presence of a right adnexal mass that ruled

out a second extrauterine gestational sac with free fluid in the posterior sac fundus (Figure 1).

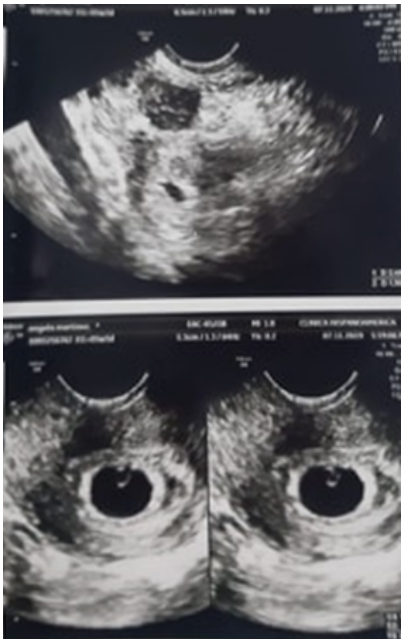


Figure 1. Transvaginal ultrasound with visualization of intrauterine pregnancy less than 6 weeks and right adnexal mass.

Source: Document obtained during the course of the study.

Due to the suspicion of heterotopic pregnancy, the patient was taken to laparotomy, a procedure in which there were no complications. A hemoperitoneum of 150cm^3 was found and an ectopic right tubal pregnancy was confirmed, leading to a total right salpingectomy (Figure 2).

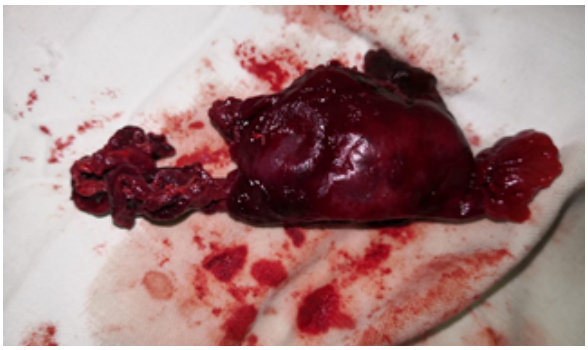


Figure 2. Sample removed during salpingectomy.

Source: Document obtained during the course of the study.

The patient progressed satisfactorily and was discharged with an indication for outpatient follow-up at 8 days, when a new transvaginal obstetric ultrasound was performed. It showed early pregnancy with retrochorial hematoma and a single live fetus that, according to fetal biometry, had a gestational age of 6.4 weeks.

At 12 weeks of gestation, the patient underwent a genetic screening ultrasound in which markers suggestive of chromosomopathy were detected, so she decided to request the voluntary interruption of her pregnancy.

DISCUSSION

Ectopic pregnancy is a serious public health concern in Colombia as it is one of the leading causes of maternal death. It is defined as the implantation of the blastocyst anywhere outside the uterine cavity (6,7), the most common location being the uterine tubes, with an incidence between 95 and 98%. Other less frequent locations are the cervix, ovaries, and abdomen (8-10).

Heterotopic pregnancy, on the other hand, is defined as the coexistence of a uterine and ectopic pregnancy (11). The literature reports that the main risk factors for this type of pregnancy are anatomical alterations of the uterine tubes, which in turn could be caused by infections; a history of pelvic inflammatory disease, tubal procedures, and ectopic pregnancy; use of intrauterine devices; and use of assisted reproductive techniques (12-16). However, in some cases, as in the case reported here, there is no associated risk factor.

The diagnosis of heterotopic pregnancy is based on clinical suspicion, but it should be confirmed with an ultrasound, preferably transvaginal, and the measurement of human chorionic gonadotropin levels. Ultrasound aids in the detection of significant findings such as an adnexal mass separated from the ovary, the

tubal ring sign (17), and the visualization of another intrauterine embryo. It also helps to determine whether there is embryonic cardiac activity outside the uterus (18).

The ability to detect a heterotopic pregnancy in a timely manner is critical because it allows for the early adoption of appropriate treatment and, in this way, reduce maternal morbidity and mortality associated with this cause (19).

Although the symptomatology of heterotopic pregnancies may vary greatly depending on the location and weeks of gestation, the most common symptoms and signs include abdominal pain (80%), vaginal bleeding (50%), and hypovolemic shock (13%) (20).

There are several therapeutic options for treating this condition, including expectant management, medical management, and surgical management. Treatment with methotrexate and injection of hypertonic solutions in the extrauterine embryo are two options that are not currently recommended because their effects on intrauterine pregnancy are still unclear (21,22), which is why these options were ruled out in this case.

With regard to surgical treatment, laparotomy or laparoscopy may be performed, but the latter is chosen if the patient is hemodynamically stable and if the size of the ectopic pregnancy is adequate, because it is a safe technique and less painful and costly than the open surgical approach (23-25). In the clinical case presented here, laparotomy was chosen due to the presence of free fluid in the cul-de-sac, suggesting hemoperitoneum secondary to ectopic pregnancy that was confirmed during the procedure.

CONCLUSIONS

Although heterotopic pregnancy is a rare condition, it is an important cause of maternal morbidity and mortality. For this reason, it is essential that physicians are aware of it so that they can make a timely diagnosis and implement appropriate treatment. It should also be noted that this condition can have various clinical presentations.

Moreover, clinical signs and symptoms, human chorionic gonadotropin levels and ultrasound findings should be correlated in order to confirm a case of heterotopic pregnancy; it should also be considered that the pathognomonic sign of ectopic pregnancy is the visualization of the tubal ring sign and heterotopic pregnancy on ultrasound, as well as the visualization of intrauterine and extrauterine embryonic cardiac activity at the same time.

Finally, in cases of tubal ectopic pregnancies, medical treatment is not recommended as there is no evidence that intrauterine pregnancy may or may not be affected. As for surgical management, laparoscopy is the treatment of choice, as long as the patient's condition allows it.

ETHICAL CONSIDERATIONS

The patient's informed consent was obtained for the preparation of this case report.

CONFLICTS OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors

ACKNOWLEDGMENTS

None stated by the authors

REFERENCES

1. **Álvarez-Bernabeu R, Reina-Paniagua M, Encinas-Pardilla MB, Serrano-González L, Sal-**

cedo-Mariña A, Tejerina-Gonzalez E, *et al.* Gestación heterotópica: dos casos con gestación intrauterina viable a término. *Rev. Chil. Obstet. ginecol.* 2016;81(2):117-21. https://doi.org/gcdp.

2. **Zatarain-Gulmar A, Torres-Hernández VE.** Embarazo heterotópico espontáneo en una mujer sin factores de riesgo: reporte de un caso. *Anales de Radiología México*. 2019;18:59-64. https://doi.org/gcdq.
3. **Luna Lugo G.** Embarazo heterotópico espontáneo en pacientes con antecedente de embarazo gemelar familiar: 2 casos. Servicio de Ginecología y Obstetricia, Hospital General de Pachuca, Servicios de Salud de Hidalgo, Hidalgo, México. *Progr Obstet Ginecol.* 2012;55 (3):141–5.
4. **Hernández-Cruz R, Tobón-Delgado SR, García-Rodríguez AM, Escobar-Ponce LF, Olguín-Ortega AA.** Embarazo heterotópico espontáneo. Reporte de un caso y revisión de la bibliografía. *Ginecol Obstet Mex. 2*017;85(6):403-8.
5. **Monzón-Castillo EP, Tejada-Martínez G, Oliva-García AB.** Embarazo heterotópico espontáneo. Presentación de dos casos. *Rev Peru Ginecol Obstet.* 2019;65(3):355. https://doi.org/gcdt.
6. **Stulberg DB, Cain LR, Dahlquist I, Lauderdale DS.** Ectopic pregnancy rates in the Medicaid population. *Am J Obstet Gynecol.* 2013;208(4):274-7. https://doi.org/f2hrmd.
7. **Escobar-Vidarte MF, Caicedo-Herrera G, Solarte-Erazo JD, Thomas-Pérez LS, Dávalos-Pérez DM, López-Tenorio J, *et al.*** Embarazo ectópico abdominal avanzado: reporte de casos y revisión de la literatura. *Rev. Colomb. Obstet. Ginecol.* 2017;68(1):71-2. https://doi.org/gcdv.
8. **Nkusu-Nunyalulendho D, Einterz EM.** Advanced abdominal pregnancy: Case report and review of 163 cases reported since 1946. Rural Remote Health. 2008;(8):1087.
9. **Govindarajan MJ, Rajan R.** Heterotopic pregnancy in natural conception. *J Hum Reprod Sci.* 2008;1(1):37-8. https://doi.org/cqf37w.
10. **Simsek T, Dogan A, Simsek M, Pestereli E.** Heterotopic triplet pregnancy (twin tubal) in a natural cycle with tubal rupture: case report and review of the literature. *J Obstet Gynecol Res.* 2008;34(4 Pt 2):759-62. https://doi.org/bp759s.
11. **Berek J.** Early pregnancy loss and ectopic pregnancy. In: Berek JS, Novak E, editors. Berek and Novak's Gynecology. 14th ed. Philadelphia, PA: Lippincott Williams y Wilkins; 2007. p. 533-4.
12. **Herrera E, Otero E, Hincapié LC, Camacho R, Gómez G, Quintero CH, *et al.*** Heterotopic pregnancy: Presentation of four cases. Colomb. Med. 2015;42(4):518-22.
13. **Giarenis I, Shenoy J, Morris E.** Cervical ectopic pregnancy after endometrial ablation: A case report. *Arch Gynecol Obstet.* 2008;277(6):567-9. https://doi.org/cwqts5.
14. **Ahmadi F, Irani S.** Cervical ectopic pregnancy following assisted reproductive technology: A case report. *Int J Fertil Steril.* 2012;6(3):201-4.
15. **Pantelis A, Daniilidis A, Dinas K.** Conservative treatment of a 7 weeks cervical ectopic pregnancy after intrauterine insemination. *Hippokratia.* 2013;17(1):95.
16. **Anev I, Wang J, Palep-Singh M, Seif MW.** Monochorionic diamniotic twin cervicalectopic pregnancy following assisted conception: a case report. *J Reprod Med.* 2013;58(9-10):445-7.
17. **Lin E, Bhatt S, Dogra VS.** Diagnostic clues to ectopic pregnancy. *Radiographics*. 2008;28(6):1661-71. https://doi.org/bjr4tf.
18. **Singhal M, Ahuja CK, Saxena AK, Dhaliwal L, Khandelwal N.** Sonographic appearance of heterotopic pregnancy with ruptured ectopic tubal pregnancy. *J Clin Ultrasound.* 2010;38(9):509-11. https://doi.org/b6v7tt.
19. **Paspulati RM, Bhatt S, Nour SG.** Sonographic evaluation of first-trimester bleeding. *Radiol Clin North Am.* 2004;42(2):297-314. https://doi.org/fdvqhk.
20. **López-Luque PR, Bergal-Mateo GJ, López-Olivares MC.** El embarazo ectópico: su interés en atención primaria de salud. *Semergen*. 2014;40(4):211-7. https://doi.org/f2p35s.

21. **Umranikar S, Umranikar A, Rafi J, Bawden P, Umranikar S, O'Sullivan B, *et al.*** Acute presentation of a heterotopic pregnancy following spontaneous conception: a case report. *Cases J.* 2009;2:9369. https://doi.org/fsg5xb.
22. **Stika CS.** Methotrexate: the pharmacology behind medical treatment for ectopic pregnancy. *Clin Obstet Gynecol.* 2012;55(2):433-9. https://doi.org/gcdx.
23. **Chetty M, Elson J.** Treating non-tubal ectopic pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2009;23(4):529-38. https://doi.org/cmgc7g.
24. **Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, Van der Veen F.** Interventions for tubal ectopic pregnancy. *Cochrane Database Syst Rev.* 2007;2007(1): :CD000324. https://doi.org/cgbkdv.
25. **León-Cid I, Rodríguez-Iglesias G, Segura-Fernández A, Atienza-Barzaga A.** Embarazo ectópico abdominal con implantación en el hígado. *Rev Cub Med Mil.* 2011:40(3-4).

https://doi.org/10.15446/cr.v7n2.87345

SPERMATIC VEIN THROMBOSIS. FIRST CLINICAL CASE REPORTED IN COLOMBIA

Keywords: Testis; Thrombosis; Spermatic cord; Ultrasonography; Doppler.
Palabras clave: Testículo; Trombosis; Cordón espermático; Ultrasonografía Doppler.

Fabián Danilo Rosero-Rosero
Juan Leonel Castro-Avendaño
Wilfredo Donoso-Donoso
José Edwin Cagua-Agudelo
Universidad Nacional de Colombia
- Bogotá Campus - Faculty of Medicine -
Department of Surgery - Urology Program -
Bogotá D.C. - Colombia.

Juan Felipe Rivillas-Reyes
Universidad Nacional de Colombia - Bogotá
Campus - Faculty of Medicine - Department of
Surgery - Bogotá D.C. - Colombia.

Daniela del Pilar Rey-Meléndez
Pontificia Universidad Javeriana -
School of Medicine - Program of Medicine -
Bogotá, D.C. - Colombia.

Corresponding author
Fabian Danilo Rosero-Rosero.
Departamento de Cirugía, Facultad de Medicina,
Universidad Nacional de Colombia.
Bogotá D.C. Colombia.
Email: fdroseror@unal.edu.co

Received: 16/05/2020 **Accepted:** 25/10/2020

RESUMEN

Introducción. La trombosis de la vena espermática (TVE) es una entidad muy poco frecuente de la cual no se tienen datos epidemiológicos específicos. Su presentación es de predominio izquierdo, en la mayoría de los casos su causa es desconocida y su diagnóstico suele realizarse por exclusión en el estudio del escroto agudo. A continuación, se presenta el primer caso documentado de TVE en Colombia y uno de los pocos de lateralidad derecha en el mundo.

Presentación del caso. Hombre de 21 años quien consultó al servicio de urgencias de una institución de tercer nivel de atención de Bogotá, Colombia, por un cuadro clínico de una semana de evolución consistente en dolor en región inguinoescrotal derecha que aumentó progresivamente de intensidad y estuvo acompañado de un pico febril no cuantificado; el paciente indicó como único antecedente médico un trauma craneoencefálico leve sin secuelas a los 20 años. Se realizó estudio con ecografía Doppler testicular en donde se observó trombosis del cordón espermático derecho. Se inició manejó con antibioticoterapia, heparinas de bajo peso molecular y cumarínicos, con lo cual se obtuvo una adecuada respuesta y la resolución del cuadro.

Conclusión. La TVE representa un reto diagnóstico, por lo que se requiere de una alta sospecha clínica, la cual se genera teniendo conocimiento de la entidad e incluyéndola en el diagnóstico diferencial del escroto agudo. La ecografía Doppler es una herramienta fundamental para diagnosticar TVE, además permite iniciar un tratamiento conservador oportuno, seguro y eficaz que evite desenlaces desfavorables para el paciente, lo que resulta ser costo-efectivo.

ABSTRACT

Introduction: Spermatic vein thrombosis (SVT) is a very rare event with no specific epidemiological data. Its presentation is predominantly on the left, and in most cases, its cause is unknown. Its diagnosis is usually made by exclusion when studying acute scrotum pain. The following is the first case of SVT reported in Colombia and one of the few cases of right laterality in the world.

Case presentation. A 21-year-old male patient consulted the emergency department of a tertiary care institution in Bogotá, Colombia, due to pain in the right inguinoscrotal region for a week that progressively increased in intensity and was accompanied by unquantified fever, without other associated symptoms. The patient reported only a medical history of a mild cranioencephalic trauma without sequelae at the age of 20 years. A testicular Doppler ultrasound was performed, revealing right spermatic cord thrombosis. He started antibiotic therapy, low molecular weight heparins and coumarin, which resulted in an adequate response and resolution of the condition.

Conclusion: SVT poses a diagnostic challenge that requires a high clinical suspicion, which is achieved by having knowledge of this condition and establishing it as a differential diagnosis of acute scrotum pain. Once suspected, Doppler ultrasound becomes a useful tool for diagnosis because, in addition to being cost-efficient, it allows the initiation of a timely, safe and effective conservative treatment, thus avoiding unfavorable outcomes for the patient.

INTRODUCTION

Spermatic vein thrombosis (SVT) is a rare condition with a low clinical prevalence and no specific epidemiological data available due to a lack of published studies. The bibliography on this condition consists mainly of case reports, of which roughly 25 can be found around the world. Among the cases reported, it is evident that left lateral presentation is more common, which is explained by the anatomical variation in the drainage of the pampiniform plexus (1).

Thrombosis of the pampiniform plexus was first described in 1935 by McGavin (2); then, in 1950, Mathis & Claret (3) described spontaneous phlebothrombosis of the spermatic plexus; in 1970, Delevett & Goodrich (4) made the first SVT report; and in 1980, Coolsaet & Weinberg (5) reported three cases of this condition in children.

The treatment of SVT is conservative and includes the administration of anticoagulants at therapeutic doses, analgesia, local therapy, testicular suspension, and rest (1). Since it is a rare condition, understanding its main characteristics is critical to suspect it and provide the patient with timely treatment to avoid unfavorable outcomes. The following is the first case of this kind reported in Colombia and one of the few of the right laterality in the world.

CASE DESCRIPTION

A 21-year-old man from Bogotá D.C., Colombia, a university student, from a middle-class household and a medical history of mild traumatic brain injury without sequelae at the age of 20, was admitted to the Emergency Department of the Hospital Universitario Nacional de Colombia (a tertiary care institution) referred from another tertiary care hospital due to pain in the right inguinoscrotal region for a week, which progressively increased in intensity and exacerbated reaching a value of 8/10 on the analog pain scale. The patient also reported unquantified fever on one occasion and denied associated urinary symptoms or recent trauma to the scrotal region.

On physical examination upon admission, he was stable, with a soft abdomen, no signs of systemic inflammatory response and vital signs within normal limits. It was possible to establish that he had pain on deep palpation in the right spermatic cord, without palpable or visible varicocele and no signs of local infection, inflammation, or peritoneal irritation in the right inguinal canal. No inguinal hernias were observed, and the penis and testes were normal. No additional relevant findings were found in the other systems.

Initially, a testicular Doppler ultrasound was requested, which reported a non-compressible hypoechoic venous structure with thickened walls, located in the spermatic cord, extending into the pelvic cavity and compatible with right SVT. Furthermore, the study revealed inflammatory changes in spermatic cord fat that did not form abscesses or hematomas. It was found that the testes had well-defined contours, the epididymides were symmetrical, and the pampiniform plexuses had normal diameters. There were no signs of a cystic or solid focal lesion inside the testes and epididymides, and both showed normal echogenicity (Figure 1).

Based on the ultrasound findings, laboratory tests were requested. The only relevant finding was a slightly positive C-reactive protein test (Table 1). With these results, and given the diagnostic impression, conservative treatment was immediately started with analgesia optimization (1g of intravenous dipyrone every 8 hours), full-dose anticoagulation with low molecular weight heparin (60 mg of subcutaneous enoxaparin every 12 hours), and local therapy.

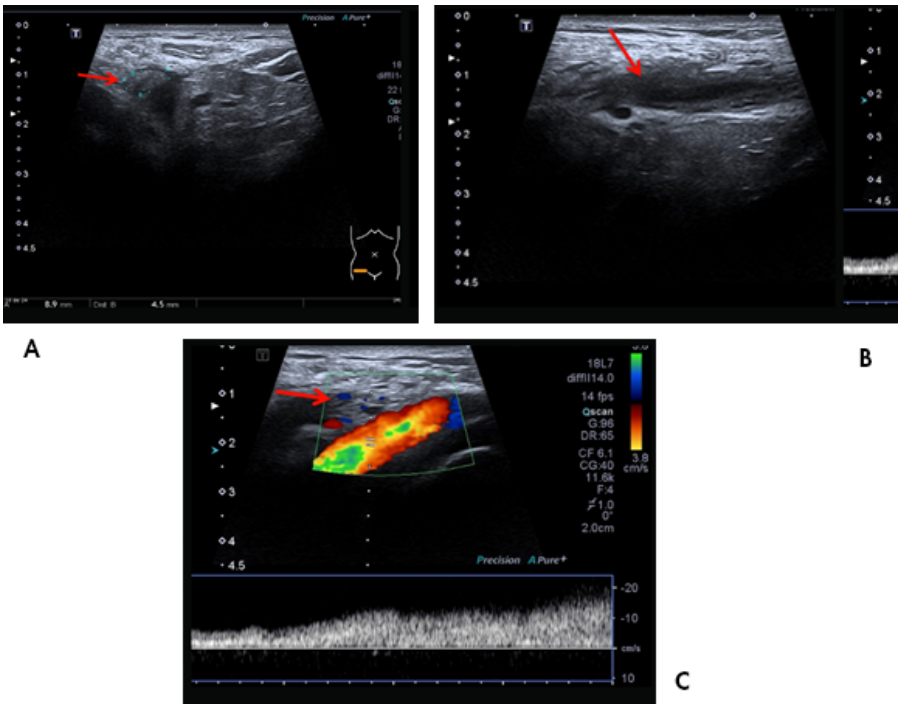


Figure 1. Ultrasound study. A) right spermatic vein thrombus (arrow); B) longitudinal view of right spermatic vein with intraluminal thrombus (arrow); C) Doppler analysis showing disturbance of venous flow at the thrombus site in the spermatic vein (arrow).
Source: Document obtained during the study.

Table 1. Laboratory tests.

Study	Upon admission	Follow-up at 96 hours
Blood count	Leukocytes 7920 mm^3 Neutrophils 49% Hemoglobin 16.4 mg/d Hematocrit 47.8% Platelets 211 000 mm^3	Leukocytes 7830 mm^3 Neutrophils 41.1% Hemoglobin 15.4 mg/d Hematocrit 44.8% Platelets 258 000 mm^3
Clotting times	PT: 15.6 s INR: 1.161 PTT: 29.9 s	PT: 15.6 s INR: 1.16 PTT: 33.8 s
Acute phase reactants	CRP 19.56	

PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; CRP: C-reactive protein.
Source: Own elaboration.

Furthermore, given the inflammatory findings at the right spermatic cord described in the ultrasound, the day after admission, it was decided to initiate an antibiotic regimen with norfloxacin 400mg orally every 12 hours and doxycycline 100mg orally every 12 hours for 10 days, after taking urine culture, which was negative.

On the second day of hospitalization, an assessment by the hematology service was requested, which ruled out systemic thrombotic disorders and considered that it was a right SVT possibly associated with deferentitis. Due to the risk of venous infarction, hematology also suggested starting anticoagulation with

60mg of subcutaneous enoxaparin every 12 hours until the international normalized ratio was therapeutic for 48 hours, and 5mg of oral warfarin every day until the ratio was maintained between 2 and 3 for three months.

The patient was discharged after five days and returned three months later for an outpatient follow-up appointment, during which a satisfactory clinical course was observed, with thrombus disappearance and complete relief of symptoms. No ultrasound follow-up images are available.

During hospitalization and discharge, the patient had a satisfactory evolution thanks to adequate tolerance and adherence to medical treatment, which did not generate adverse reactions. In addition, the man had no signs of systemic inflammatory response or infectious deterioration, and hemodynamic stability and pain resolution were achieved.

DISCUSSION

The etiology of SVT has not been determined because most cases occur spontaneously. Nonetheless, clinical conditions associated with the presentation of this disorder have been described, leading to the development of different theories about its possible origin. Authors such as Esmon (6), Grainge *et al.* (7) and Murthy *et al.* (8) have suggested that inflammatory bowel diseases, mainly ulcerative colitis and terminal ileitis, are possible causes of SVT since they are characterized by a prothrombotic state secondary to their inflammatory nature. Caño-Velasco *et al.* (1), Bolat *et al.* (9) and Diana *et al.* (10) have also stated that hematological disorders, such as Henoch-Schönlein purpura or heterozygous factor V Leiden mutation and the use of psychoactive substances, such as cocaine, produce hypercoagulability states that can trigger SVT.

Other risk factors for venous thromboembolism such as cancer, hospitalization, recent surgeries, infections, trauma, inflammatory diseases and personal or family history of venous thromboembolism may also influence the development of SVT (11). In the reported case, it is suspected that the thrombus formed as a result of an inflammatory process in the ductus deferens; however, the cause of the deferentitis observed in the ultrasound is unknown.

Among the mechanical causes, it has been hypothesized that vigorous physical exercise, weight-lifting and abdominal trauma generate an increase in intra-abdominal pressure, which, in turn, increases venous pressure and, in addition to a decreased blood flow in the gonadal system, predisposes to the formation of thrombi (8,12,13). Nutcracker syndrome (increased pressure of the left renal vein secondary to compression by the superior mesenteric artery and aorta) and having undergone laparoscopic inguinal herniorrhaphy have also been associated with the development of SVT (14-16).

In addition, it is important to note that the anatomical connection between the testicular vein and the left renal vein allows kidney disorders, including neoplasms, to spread to the left spermatic vein and cause thrombosis. SVT has also been linked to renal, testicular, adrenal, gastrointestinal, hematologic, and liposarcoma cancers in that order of occurrence (11,17).

The frequent involvement of the left spermatic vein in SVT has been attributed to predisposing anatomical factors similar to those of varicocele formation or thrombosis of the left pampiniform plexus: the right testicular vein drains into the vena cava obliquely, while the left testicular vein drains into the left renal vein perpendicularly, resulting in increased left vein pressure and reduced ipsilateral flow (11).

The symptoms of SVT are non-specific, with the main clinical manifestations being: testicular pain, groin pain with or without irradiation to the scrotum or lumbar region, abdominal pain

or discomfort, palpable masses in the inguinal canal or scrotum, edema or local erythema, fever, vegetative symptoms and macroscopic hematuria; all these symptoms exacerbate when patients are standing upright and perform Valsalva maneuvers and decrease with rest. Physical examination shows signs such as increased consistency and size of the spermatic cord, local inflammation, among others (1,18,19).

Due to the high variability and low specificity of symptoms, its clinical similarity with other conditions and its low incidence, a high suspicion rate is required to diagnose SVT. In this scenario, the occurrence of this event should be confirmed by radiological findings; however, it is important to keep in mind that surgical exploration is sometimes also necessary given the impossibility of distinguishing between incarcerated inguinal hernias or testicular thrombosis (19,20).

Doppler ultrasound is the gold standard test for the diagnosis of SVT due to its high sensitivity and specificity, compared to techniques such as angiography, its low cost and because it is a non-invasive method. However, CT angiography may sometimes be necessary to evaluate the extent of the thrombus (18,21). The findings of SVT on ultrasound include a hypoechoic image with absence of venous flow in the Doppler analysis at the level of the occlusion generated by the thrombus and a negative response to Valsalva maneuvers, which helps to differentiate it from varicocele (1,18).

The differential diagnosis of SVT includes testicular torsion, torsion of the appendix testis, epididymitis, orchitis, testicular trauma, idiopathic testicular infarction, incarcerated inguinal hernia, hydrocele, spermatocele, abscesses, thromboangiitis obliterans, and tumors (1,17,19).

There is insufficient information to provide evidence-based therapy recommendations for SVT because conservative management is recommended even though patients typically require surgery. However, Mallat *et al.* (14) state that when the lesion is located outside the external inguinal ring (pampiniform plexus), conservative treatment could be selected, including anticoagulation associated with non-steroidal anti-inflammatory drugs, local therapy (ice and testicular suspension), and rest.

Likewise, Caño-Velasco *et al.* (1) state that antibiotic therapy is recommended for patients with signs of local or systemic inflammatory response and/or adjacent or contiguous collections. On the other hand, indications for surgical treatment are inadequate response to conservative management, uncertain diagnosis despite complementary tests, onset of complications (pulmonary thromboembolism), extension of thrombus into the external inguinal ring, and patients at high risk for new episodes of venous thromboembolism (1,20).

Although rare, SVT complications include testicular infarction, complicated inguinal hernias (12), extension of the thrombus into the renal vein, and even secondary pulmonary thromboembolism (21). The course of this condition is often benign and usually controlled with medical treatment, even though its diagnosis is often post-surgical.

The present case is relevant because it is the third of its kind reported on the right side worldwide (1,9) and because a favorable outcome and an acceptable follow-up were achieved. The limitations of this report include the fact that no specific etiology was found to explain the onset of the disease.

CONCLUSIONS

SVT is rarely observed, and its etiology may be associated with multiple factors, which makes it a diagnostic challenge. This condition is one of

the differential diagnosis of acute scrotum pain and is, therefore, usually observed after surgical examination. Doppler ultrasound is the preferred method to confirm its presence due to its low cost; nevertheless, angiotomography may be required when thrombus extension is suspected.

SVT treatment is conservative in most cases and includes anticoagulant therapy, anti-inflammatory drugs, antibiotics (in case of inflammatory process), local therapy, and clinical follow-up. In the event of complications, diagnostic doubt and poor response to conservative treatment, surgical management with thrombus excision and/or vein ligation may be considered.

Knowledge of this disease allows medical personnel to suspect it and provide the patient with timely treatment to obtain good outcomes; in this sense, the publication of this case is relevant to know a little more about such a rare entity.

PATIENT PERSPECTIVE

At the time of the last check-up, the patient said he was pleased with the outcomes of his treatment and that he was willing to follow all the recommendations given to him. He also expressed his gratitude for the opportunity to contribute with his case to the scientific literature and thus broaden the knowledge about this disease.

ETHICAL CONSIDERATIONS

For the preparation and publication of this case report, the patient signed an informed consent form authorizing the use of the information in his medical records for academic purposes.

CONFLICT OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

To the Hospital Universitario Nacional de Colombia, the Urology Research and Innovation Group of the Universidad Nacional de Colombia and the Department of Surgery of the same institution.

REFERENCES

1. **Caño-Velasco J, Ramírez-Martín D, Lledó-García E, Hernández-Fernández C.** Trombosis de la vena espermática derecha. Revisión de la literatura a propósito de un caso. *Rev Int Androl.* 2018;16(1):38-41. https://doi.org/gdg9.
2. **McGavin D.** Thrombosis Of The Pampiniform Plexus. *Lancet*. 1935;226(5842):368-9. https://doi.org/bqmpt4.
3. **Mathis RI, Claret AJ.** Flebo-trombosis espontanea del plexo espermático. *Rev Argent Urol.* 1950;19(9-12):229-33.
4. **Delevett AF, Goodrich A.** Thrombophlebitis of left spermatic vein and pulmonary thromboembolism. Cure by ligation. *Johns Hopkins Med J.* 1970;126(1):15-8.
5. **Coolsaet B, Weinberg R.** Thrombosis of the spermatic vein in children. *J Urol.* 1980;124(2):290-1. https://doi.org/gdhf.
6. **Esmon CT.** Inflammation and thrombosis. *J Thromb Haemost.* 2003;1(7):1343-8. https://doi.org/bwgcs9.
7. **Grainge MJ, West J, Card TR.** Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet.* 2010;375(9715):657-63. https://doi.org/c6dwrt.
8. **Murthy PB, Gill BC, Khurana S, Nyame YA, Sabanegh ES, Kaouk JH.** Spermatic Vein Thrombosis. *Urology.* 2018;119:32-4. https://doi.org/gdh9.

9. **Bolat D, Gunlusoy B, Yarimoglu S, Ozsinan F, Solmaz S, Imamoglu FG.** Isolated thrombosis of right spermatic vein with underlying Factor v Leiden mutation. *Can Urol Assoc J.* 2016;10(9-10):E324-7. https://doi.org/gdjb.
10. **Diana A, Gaze H, Laubscher B, de Meuron G, Tschantz P.** A case of pediatric henoch-schönlein purpura and thrombosis of spermatic veins. *J Pediatr Surg.* 2000;35(12):1843. https://doi.org/fnr47w.
11. **Lenz CJ, McBane RD, Cohoon KP, Janczak DT, Simmons BS, Saadiq RA, *et al.*** Testicular vein thrombosis: Incidence of recurrent venous thromboembolism and survival. *Eur J Haematol.* 2018;100(1):83-7. https://doi.org/gdjc.
12. **Hashimoto L, Vibeto B.** Spontaneous thrombosis of the pampiniform plexus. *Scand J Urol Nephrol.* 2006;40(3):252-4. https://doi.org/fhd8sj.
13. **Kayes O, Patrick N, Sengupta A.** A peculiar case of bilateral, spontaneous thromboses of the pampiniform plexi. *Ann R Coll Surg Engl.* 2010;92(7):W22-3. https://doi.org/ck7g9p.
14. **Mallat F, Hmida W, Ahmed KB, Mestiri S, Mosbah F.** Spontaneous spermatic vein thrombosis as a circumstance of discovery of the nutcracker syndrome: An excepcional entity. *Int J Case Rep Images.* 2014;5(7):519-23. https://doi.org/gdjd.
15. **Moore JB, Hasenboehler EA.** Orchiectomy as a result of ischemic orchitis after laparoscopic inguinal hernia repair: case report of a rare complication. *Patient Saf Surg.* 2007;1(1):3. https://doi.org/d2hkmj.
16. **Elyamany G, Alzahrani AM, Bukhary E.** Cancer-associated thrombosis: An overview. *Clin Med Insights Oncol.* 2014;8:129-37. https://doi.org/gdjf.
17. **Girolami A, Treleani M, Bonamigo E, Tasinato V, Girolami B.** Venous thrombosis in rare or unusual sites: A diagnostic challenge. *Semin Thromb Hemost.* 2014;40(1):81-7. https://doi.org/gdjg.
18. **Raghavendran M, Venugopal A, Kiran-Kumar G.** Thrombosed varicocele - A rare cause for acute scrotal pain: A case report. *BMC Urol.* 2018;18(1):34. https://doi.org/gdjh.
19. **Hennawy HE, Abuzpur ME, Bedair S.** Surgical management of spontaneously thrombosed extratesticular varicocele presented with irreductible inguinal swelling: A case report. 2010.
20. **Mabjeesh NJ, Bar-Yosef Y, Schreiber-Bramante L, Kaver I, Matzkin H.** Spermatic Vein Tumor Thrombus In Renal Cell Carcinoma. *Scientific World Journal.* 2004;4(Suppl 1):192-4. https://doi.org/bdq6jg.
21. **Castillo OA, Diaz M, Vitagliano GJ, Metrebian E.** Pulmonary thromboembolism secondary to left spermatic vein thrombosis: A case report. *Urol Int.* 2008;80(2):217-8. https://doi.org/b3p8fx.

https://doi.org/10.15446/cr.v7n2.87728

AMYAND'S HERNIA, CASE REPORT AND REVIEW OF CURRENT LITERATURE

Keywords: Appendicitis; Appendix; Inguinal, Hernia; Amyand's, Hernia.
Palabras clave: Apendicitis; Hernia inguinal; Apéndice.

Cesar Arévalo-Wazhima
Hospital Teófilo Dávila - Emergency Service
- Machala - Ecuador.

Tamara Cristina Matute-Sánchez
Hospital UTPL Santa Inés - Hospitalization Service
- Loja - Ecuador.

Edison Fernando Angamarca-Angamarca
Hospital UTPL Santa Inés - Department of Surgery -
Trauma and Emergency Service
- Loja - Ecuador.

Corresponding author
Edison Fernando Angamarca-Angamarca.
Servicio de trauma y emergencias, Departamento de
Cirugía, Hospital, Hospital UTPL Santa Inés.
Loja. -Ecuador.
Email: edifer-711@hotmail.com.

Received: 28/05/2020 **Accepted:** 07/11/2020

RESUMEN

Introducción. La hernia de Amyand es una condición clínica infrecuente que agrupa a dos patologías quirúrgicas habituales: apendicitis aguda y hernia inguinal; en esta entidad el apéndice vermiforme se encuentra en el interior del saco de una hernia inguinal. Su diagnóstico preoperatorio es difícil, por lo que debe tenerse en cuenta en casos de hernia inguinal antes de que se presente un proceso inflamatorio, el cual puede traer más complicaciones; además, aunque no existe un consenso para el manejo según las clasificaciones actuales, estas sirven de guía para una resolución quirúrgica oportuna.

Presentación del caso. Hombre de 57 años procedente de la costa sur de Ecuador, quien consultó al servicio de emergencias de una institución de segundo nivel de atención por un cuadro clínico de 24 horas de evolución que inició con la aparición de una masa dolorosa e irreductible en la región inguinal derecha asociada a hiporexia. El paciente fue diagnosticado con hernia inguinal incarcerada y se le practicó una hernioplastia inguinal derecha en la que se encontró el apéndice y el ciego dentro del saco herniario; durante este procedimiento también se realizó apendicectomía y hernioplastia con técnica de Lichtenstein. El paciente fue dado de alta en buenas condiciones y en controles posteriores, a los 8 y 15 días de la cirugía, no presentó complicaciones.

Conclusiones. La hernia de Amyand es una entidad cada vez más frecuente que tiene un difícil diagnóstico preoperatorio debido a su cuadro clínico inespecífico. Ante la sospecha de esta patología se deben realizar estudios de imagenología que ayuden a su visualización y orienten, junto con las clasificaciones actuales de este tipo de hernias, un manejo individualizado y temprano.

ABSTRACT

Introduction: Amyand's hernia (appendix trapped within an inguinal hernia) is a rare clinical condition that groups two common surgical diseases: acute appendicitis and inguinal hernia. Its preoperative diagnosis is difficult, so it should be considered in cases of inguinal hernia before an inflammatory process occurs in the appendix to avoid complications. Although there is no consensus on its treatment, current classifications serve as a guide for a timely surgical resolution.

Case presentation: A 57-year-old male patient from the southern coast of Ecuador consulted the emergency department of a secondary level health care institution due to a 24-hour history of painful and irreducible mass in the right inguinal region associated with hyporexia. The patient was diagnosed with incarcerated inguinal hernia and underwent a right inguinal hernioplasty, during which the appendix and cecum were found inside the hernia sac. Hernioplasty and appendectomy were performed using the Lichtenstein technique. The patient was discharged in good conditions and did not have any complications at 8- and 15-day follow-up.

Conclusions: Amyand's hernia is increasingly reported. It is difficult to diagnose preoperatively due to its nonspecific symptoms. When suspected, imaging studies help its visualization and guide an individualized and early treatment, together with the current classifications of this type of hernias.

INTRODUCTION

Acute appendicitis and inguinal hernia are two very common conditions in the surgical field, both emergency and scheduled, with the lifetime risk of developing them being 7-8% (1-3) and 27% (4), respectively. However, it is a rare association that was first described in 1735 by Claudius Amyand in a 11-year-old boy, which is why this clinical condition is known as Amyand's hernia (AH).

AH is more common in children and men because of the persistence of processus vaginalis, and its incidence is higher on the right side of the inguinal hernia due to its location in the right lower quadrant. This condition is difficult to diagnose and is usually done intraoperatively, but its pre-surgical identification is becoming more frequent due to a better understanding of its pathophysiology and the fact that imaging studies are carried out to confirm its presence in the event of a diagnostic suspicion.

The treatment of AH is surgical and based on the Losanoff and Banson classification (Table 1) (5-10). One of the therapeutic options, according to these authors, is incidental appendectomy in young people, although its performance is controversial, and even contraindicated in adults, when no signs of appendiceal inflammation are observed.

Table 1. Classification and surgical management of Amyand's hernias according to Losanoff and Basson.

Type of hernia	1	2	3	4
Features	Normal Appendix	Acute appendicitis located within an inguinal hernia	Acute appendicitis with peritonitis or abdominal sepsis	Acute appendicitis associated with other intra-abdominal disease
Surgical management	Hernia reduction (appendectomy in young patients) and mesh repair	Appendectomy through hernia and hernia repair without mesh	Laparotomy, appendectomy, and hernia repair without mesh	Appendectomy and specific treatment of the associated disease as appropriate

Source: Own elaboration based on Servide-Staffolani *et al.* (8) and Losanoff & Basson (10).

The following is the case of a patient with AH in whom treatment was partially implemented using hernia repair with mesh according to the Losanoff and Basson classification and in whom no complications occurred during postoperative follow-up.

CASE PRESENTATION

A 57-year-old mestizo man from the southern coast of Ecuador, a longshoreman with a low socioeconomic status, consulted the emergency department of a secondary healthcare center due to a 24-hour history of painful and irreducible mass in the right inguinal region associated with general malaise and hyporexia. The patient did not report any known medical or surgical history.

Physical examination on admission revealed a 4x3cm inguinal mass with no color changes, painful on palpation and irreducible. Blood tests showed leukocytes of 10 000 with neutrophilia of 79%. Diagnostic imaging was not ordered because the symptoms were typical of an incarcerated right inguinal hernia and, consequently, therapeutic management would not change with or without an ultrasound or CT scan.

Based on the findings and on the resources available at the hospital, a conventional right inguinal hernioplasty was decided to avoid a major complication such as strangulation. During the procedure, a hernial ring of 1.5cm and a hernia sac of 6x7cm were found within the cecal appendix and cecum (Figure 1). An incidental appendectomy was performed and, since no contamination was found, a hernioplasty was performed using the Lichtenstein technique with a low-density polypropylene mesh. These procedures were performed on the same day of admission.

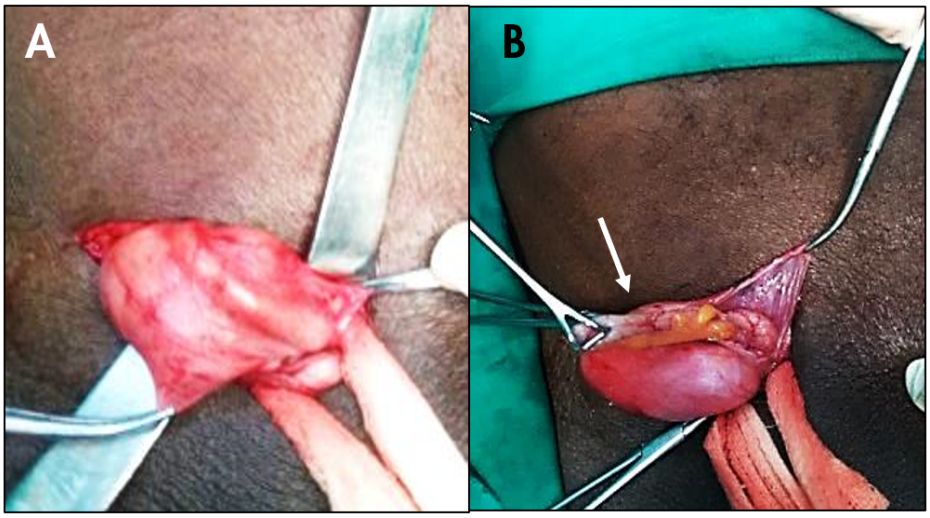


Figure 1. Amyand's hernia. A) Hernia sac; B) Appendix (arrow)
Source: Document obtained during the study.

The patient progressed favorably and was discharged 24 hours after surgery. Medical check-ups were performed 8 and 15 days after the procedure and an adequate healing process was observed without complications.

DISCUSSION

AH is defined as the presence of the cecal appendix within an inguinal hernia sac. This condition was first described in 1735 by the French surgeon Claudius Amyand after performing an appendectomy for perforated appendicitis in a 11-year-old patient with an incarcerated inguinal hernia (4,8,11-18). If the cecal appendix is located in a femoral hernia, it is called a De Garengeot's hernia (19).

This type of hernia is an apparently rare condition in which two very common symptoms are associated: acute appendicitis and inguinal hernia. AH occurs in 0.1-1% of all inguinal hernias and in up to 0.3% of cases the appendix is inflamed (4,6,7,16,18,20-24). The mortality rate of this disease rises between 15% and 30% in cases of perforation due to subsequent sepsis (8,9,19).

It should be noted that there is a rise in the reports and papers on AH, showing an increase in the number of publications per year from 1985 to May 2020 (25), as shown in Figure 2, which was created based on the results of a search made in PubMed by entering the terms "Amyand, hernia," regardless of the type of treatment and without a specific year range. Many of the publications found describe a pre-operative diagnosis established using imaging studies (5-9,14,17,19, 25-28).

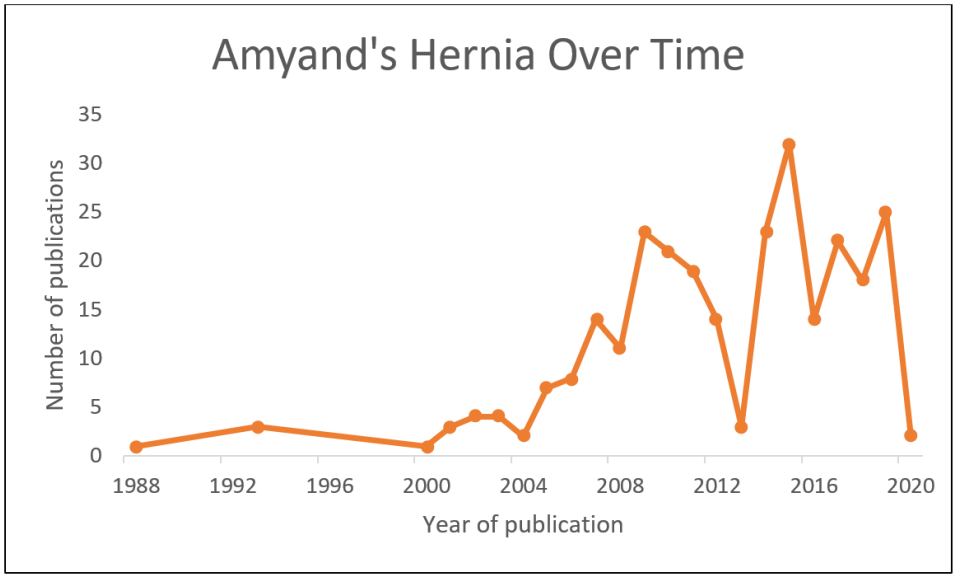


Figure 2. Number of publications on Amyand's hernia available in PubMed, from 1985 to May 2020.

Source: Own elaboration.

The significant increase in the number of AH cases, added to the lifetime risk of developing inguinal hernia and appendicitis (27% and 7-8%, respectively) (1-4), obliges health professionals to consider this condition for differential diagnosis when evaluating an inguinal hernia, especially on the right side. However, its diagnosis is usually intraoperative, as in the case reported here.

AH occurs most often in childhood due to persistent processus vaginalis and the incidence of inguinal hernia in men. These hernias are also more frequent on the right side, as found in the reported patient, although it is not ruled out that they can occur on the left side due to mobile cecum, situs inversus, or malrotation (8,9,11,27,29).

The most frequent post-surgical complications of AH are infection, ranging from 5% to 50% (6,19,26), and hernia recurrence, neither of which was observed in the reported case.

Regarding pathophysiology, two situations may occur in AH. In the first, the appendix migrates into the hernia sac, where some authors state that a fibrous connection between the appendix (retrocecal) and the testicles added to the persistence of processus vaginalis favor the passage of the appendix into the inguinal canal and this would be the reason for the higher incidence of this condition in children and premature infants. In the second situation, the appendix becomes inflamed inside the hernia, and this may be secondary to the vascular involvement caused by the pressure of the hernial neck, triggering the inflammatory process and the subsequent bacterial proliferation (11,17,25,30), without ruling out luminal obstruction by fecaliths, ganglionic hypertrophy, parasites, or other causes.

Due to the presence of the inguinal ring, the inflammatory process of the appendix in AH may not extend into the abdominal cavity and may be limited to the inguinal canal, affecting the cecum or the base of the ring if they are also within the hernia sac (27).

As mentioned above, the diagnosis of AH is usually incidental during surgery since the

symptoms are nonspecific and accompanied by lower abdominal tenderness and irreducible mass in the inguinal region, which are also symptoms of an incarcerated or strangulated inguinal hernia. Although laboratory findings are not specific, imaging studies, such as ultrasound and computed tomography (6,28), allow identifying the presence or absence of the appendix and deciding on the best approach.

Surgery is the treatment for AH and three conditions must be met before performing it: 1) it must be determined whether appendectomy is necessary, 2) the need to use prosthetic material to repair the continuity solution must be established, and 3) the best approach must be decided. Since there are so many variables, there is no general consensus on what the management of this disease should be, so Losanoff and Basson classified AH into four types with their corresponding treatment (Table 1).

When signs of inflammation are detected, an appendectomy is required; however, its use for prophylaxis is controversial when findings are incidental. Those in favor argue that if it is performed carefully avoiding contamination, morbidity and mortality, as well as the cost of future appendicitis, are reduced without increasing the anesthetic risk in young patients, although some experts do not recommend it in pediatric patients (31). On the other hand, those who oppose it claim that appendectomy transforms the procedure from a clean one to a contaminated one, which might result in infectious complications and recurrence (8,16,32).

The patient in the case reported here was diagnosed during hernioplasty with type 1 AH. Therefore, according to this classification, management included prophylactic appendectomy and hernia repair with a polypropylene mesh since there is a low probability of infection in these cases (11). The intervention was effective, and the patient's progress was favorable in follow-up.

The satisfactory evolution of the patient reported here, as well as that of other cases mentioned in the literature, seems to be related to the use of a clean surgical technique when correcting the wall defect with a mesh after incidental appendectomy (5,16) or during the inflammatory phase, preventing contamination of the surrounding tissues because the appendix is manipulated to a minimum, the remnant appendix is isolated from the hernia sac with a good closure, and the procedure is accompanied by adequate antibiotic prophylaxis. It is worth mentioning that this technique has also reported good results in more advanced stages of appendicitis (6,8,21,32), although its performance is not usually indicated due to the high risk of infection it entails.

There is a modification or complement to the Losanoff and Basson classification known as the Rikki's classification (33) (Table 2), in which incisional hernia is added and its management depends on the inflammatory status of the appendix.

Table 2. Modified Rikki's classification.

Classification	Features	Surgical treatment
1	Normal appendix	Hernia reduction (appendectomy in young patients) and mesh repair
2	Acute appendicitis within the sac	Appendectomy through hernia and repair of hernia, without mesh
3	Acute appendicitis with peritonitis or abdominal sepsis	Laparotomy, appendectomy, and hernia repair, without mesh

Classification	Features	Surgical treatment
4	Acute appendicitis associated with other intra-abdominal disease	Appendectomy and specific treatment of the associated disease as appropriate
5a	Normal appendix within an incisional hernia	Appendectomy plus mesh herniorrhaphy
5b	Acute appendicitis within incisional hernia, without abdominal sepsis	Appendectomy plus herniorrhaphy, without mesh
6c	Acute appendicitis within the incisional hernia, abdominal sepsis or secondary disease	Same management as type 4.

Source: Own elaboration based on Patoulias *et al.* (9), Villarreal *et al.* (11) and Desai *et al.* (29)

Both classifications mentioned above are an important guide to surgical management when AH is diagnosed intraoperatively, with herniotomy and laparotomy as access methods. However, due to clinical suspicion and the use of diagnostic imaging, pre-surgical diagnosis is becoming more common, allowing for intervention before complications with the appendix occur and even allowing a laparoscopic approach to the resolution of the hernia (9).

The first case of AH was described in 1999 by Vermillion *et al.* (34); since then, there has been an increase in the number of reported cases that have been resolved with this technique (17,30). For its part, the first preperitoneal mesh repair of a hernia of this type was carried out by Saggar *et al.* in 2004, as reported by Michalinos *et al.* (27)

CONCLUSIONS

AH is an apparently rare disease that is increasingly reported in the literature. It is difficult to diagnose preoperatively since it does not present with specific symptoms. Therefore, when it is suspected, imaging studies should be performed to help its visualization and guide, along with the current classifications, early individualized treatment of both appendicitis and hernia.

ETHICAL CONSIDERATIONS

The patient signed an informed consent to treat and disclose his medical record for scientific and academic purposes.

CONFLICT OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

None stated by the authors.

REFERENCES

1. **Bhangu A, Soreide K, Di Saverio S, Assarsson JH, Drake FT.** Acute appendicitis: Modern understanding of pathogenesis, diagnosis, and management. *Lancet.* 2015;386(10000):1278-87. https://doi.org/f3jcx8.
2. **Rafiq MS, Khan MM, Khan A, Jan H.** Evaluation of postoperative antibiotics after non-perforated appendectomy. *J Pak Med Assoc.* 2015;65(8):815-7.

3. **Daskalakis K, Juhlin C, Pahlman L.** The use of pre- or postoperative antibiotics in surgery for appendicitis: A systematic review. *Scand J Surg*. 2014;103(1):14-20. https://doi.org/f24gvh.
4. **Kromka W, Rau AS, Fox CJ.** Amyand's hernia with acute gangrenous appendicitis and cecal perforation: A case report and review of the literature. *Int J Surg Case Rep*. 2018;44:8-10. https://doi.org/gdw2.
5. **Holmes K, Guinn JE.** Amyand hernia repair with mesh and appendectomy. *Surg Case Rep* 2019;5(1):3-6.
6. **Gómez-Sánchez J, García-Rubio J, Garde-Lecumberri C, Mirón-Pozo B.** Hernia de Amyand. Reporte de un caso y revisión de la literatura. *Actual Medica*. 2018;103(804):95-7.
7. **Mohaidin N, Ong SCL.** Incidental discovery of Amyand's hernia. *BMJ Case Rep*. 2018;2018:1-2. https://doi.org/gdw6.
8. **Servide-Staffolani MJ, Perfecto-Valero A, Cervera-Aldama J, Anduaga-Peña MF, García-González J, Colina-Alonso A, *et al.*** Controversias en el tratamiento de la hernia de Amyand. *Rev Colomb Cirugía*. 2018;33(1):107-10. https://doi.org/gdw7.
9. **Patoulias D, Kalogirou M, Patoulias I.** Amyand's Hernia: an Up-to-Date Review of the Literature. *Acta medica (Hradec Kral.* 2017;60(3):131-4. https://doi.org/gdw8.
10. **Losanoff JE, Basson MD.** Amyand hernia: A classification to improve management. *Hernia*. 2008;12(3):325-6. https://doi.org/bfqdqs.
11. **Villarreal R, Luna-Jaspe C, Cabrera LF, Vinck E.** Hernia de Amyand encarcelada, revisión de la literatura y reporte de un caso en una institución de tercer nivel en Bogotá. *Rev Colomb Cirugía*. 2016;31(4):283-8.
12. **Córdova A, Viscido G, Picón-Molina H, Palencia R, Doniquian A.** Hernia de Amyand: comunicación de dos casos reparados con técnica de Rutkow-Robbins. *Rev Hispanoam Hernia*. 2014;2(3):111-4. https://doi.org/f2r9wb.
13. **Nicola M, Mora G, Stock R, Vallejos R, Robles M, Tapia C, *et al.*** Hernia de Amyand : presentación de un caso y revisión de la literatura. *Rev Chil Cirugía*. 2007;59(2):142-4. https://doi.org/fwrzb2.
14. **Tsang WK, Lee KL, Tam KF, Lee SF.** Acute appendicitis complicating amyand's hernia: Imaging features and literature review. *Hong Kong Med J.* 2014;20(3):255-7. https://doi.org/gdxc.
15. **Hiatt JR, Hiatt N.** Amyand´s Hernia. *N Engl J Med.* 1988;318(21):1402. https://doi.org/cv4bm7
16. **Benavides-de la Rosa DF, López-de Cenarruzabeitia Í, Moreno-Racionero F, Merino-Peñacoba LM, Beltrán-de Heredia J.** A propósito de un caso: hernia de Amyand, diagnóstico a considerar en un procedimiento de rutina. *Rev Esp. Enferm. Dig. 2015;107(11):708-9.*
17. **Ivashchuk G, Cesmebasi A, Sorenson EP, Tubbs SR, Loukas M.** Amyand's hernia: A review. *Med Sci Monit*. 2014;20:140-6. https://doi.org/f5rfhb.
18. **García-Cano E, Martínez-Gasperin J, Rosales-Pelaez C, Hernández-Zamora V, Montiel-Jarquín J, Franco-Cravio F.** Hernia de Amyand y apendicitis complicada; presentación de un caso y elección de tratamiento quirúrgico. *Cir Cir.* 2016;84(1):54-7. https://doi.org/f3hb8h.
19. **Agirre-Etxabe L, Prieto-Calvo M, García-Etxebarría A, García-Gomzález J, Sarriugarte-Lasarte A, Colina-Alonso A.** Hernia de Amyand (tipo 2 de Losanoff) diagnosticada preoperatoriamente y tratada mediante hernioplastia con malla biológica. *Rev Hispanoam Hernia.* 2014;2(4):169-72. https://doi.org/f2scff.
20. **Mebis W, Hoste P, Jager T.** Amyand's Hernia. *J Belgian Soc Radiol.* 2018;102(1):8. https://doi.org/gdxn.
21. **Chiang CC, Liu PH, Chou CP, Liu CH, Tsai MJ.** Incarcerated Amyand´s hernia. *Ci Ji Yi Xue Za Zhi.* 2017;29(2):129-30.
22. **Bhatti SI, Hashmi MU, Tariq U, Bhatti HI, Parkash J, Fatima Z.** Amyand's Hernia: A Rare Surgical Pathology of the Appendix. *Cureus.* 2018;10(6):e2827. https://doi.org/gdxp.
23. **Ortega-León LH, Ramírez-Tapia D, Dieguez-Jiménez CM, Cruz-Melgar LM, Gar-**

cía-Puig MA, Chávez-Gómez A, *et al.* Hernia de Amyand : Presentación de un caso y revisión de la bibliografía. *Rev Médica del Hosp Gen México.* 2011;74(2):98-100.

24. **Vidal-González P, Contreras R, Sánchez G, Flores LM, Kunz W, Menéndez AL, *et al.*** Hernia de Amyand. *Cir Gen.* 2005;27:328-9.
25. **Burgess PL, Brockmeyer JR, Johnson EK.** Amyand hernia repaired with Bio-A: A case report and review. *J Surg Educ*. 2011;68(1):62-6. https://doi.org/b3bwwm.
26. **Manzanares-Campillo M, Muñoz-Atienza V, Sánchez-García S, García-Santos E, Ruescas-García F, Martín Fernández J.** Hernia de Amyand: presentación de dos casos y revisión de la bibliografía. *Cir Cir.* 2014;84(2):195-9.
27. **Michalinos A, Moris D, Vernadakis S.** Amyand's hernia: A review. *Am J Surg.* 2014;207(6):989-95. https://doi.org/gdxs.
28. **Guler I, Alkan E, Nayman A, Tolu I.** Amyand's Hernia: Ultrasonography Findings. *J Emerg Med.* 2016;50(1):e15-7. https://doi.org/f747tf.
29. **Desai G, Suhani, Pande P, Thomas S.** Amyand´s Hernia: Our Experience and Review of Literature. *Arq Bras Cir Dig*. 2017;30(4):287-8. https://doi.org/gdxt.
30. **Angamarca E, Mendieta-Bermeo EG, Merchán-Peñafiel P, Matute-Sánchez T.** Caso Clínico: Hernia de Amyand, Resolución Laparoscópica. *Rev Médica Hosp del José Carrasco Arteaga*. 2016;8(2):205-8. https://doi.org/gdxv.
31. **Cigsar EB, Karadag CA, Dokucu AI.** Amyand's hernia: 11 years of experience. *J Pediatr Surg.* 2016;51(8):1327-9. https://doi.org/f839vr.
32. **Sancho-Muriel J, Torregrosa-Gallud A, García-Pastor P, López-Rubio M, Argüelles BG, Bueno-Lledó JA.** Hernia de Amyand: presentación de tres casos y revisión bibliográfica. *Rev Hispanoam Hernia.* 2015;4(3):2-6. https://doi.org/f3g34p.
33. **Singal R, Gupta S.** "Amyand's Hernia" Pathophysiology, Role of Investigations and Treatment. *Maedica (Buchar)*. 2011;6(4):321-7.
34. **Vermillion JM, Abernathy SW, Snyder SK.** Laparoscopic reduction of Amyand's hernia. *Hernia*. 1999;3(3):159-60. https://doi.org/bggw4p.

https://doi.org/10.15446/cr.v7n2.88563

MANDIBULAR DISTRACTION OF FREE ILIAC CREST BONE GRAFT AS TREATMENT IN A PATIENT WITH A HISTORY OF GUNSHOT WOUND. CASE REPORT

Keywords: Bone Transplantation; Distraction Histiogenesis; Iliac Crest.
Palabras clave: Injerto óseo; Distracción histiogénica; Cresta ilíaca.

Jaime Andrés Jiménez-Álvarez
Jesus Andrés Duque-Montealegre
Instituto de Ortopedia Infantil Roosevelt
- Department of Oral and Maxillofacial Surgery -
Bogotá D.C. - Colombia.

José Manuel Valdés-Reyes
Pontificia Universidad Javieriana – School of Dentistry - Department of Oral and Maxillofacial Surgery - Bogotá, D.C. - Colombia.

Corresponding author
José Manuel Valdés-Reyes.
Departamento de Cirugía Oral y Maxilofacial,
Facultad de Odontología,
Pontificia Universidad Javieriana.
Bogotá D.C. Colombia.
E-mail: jose_valdes@javeriana.edu.co.

Received: 24/06/2020 **Accepted:** 24/12/2020

ABSTRACT

Introduction: The combination of non-vascularized iliac crest bone graft and distraction osteogenesis in a second surgical intervention has only been described to achieve alveolar ridge augmentation. This technique is not recommended to treat bone defects of the jaws caused by firearm projectile.

Case presentation: 40-year-old woman with a segmental mandibular defect in the mandible body caused by the impact of a firearm projectile at the age of 1 year. The patient developed a severe Class II dentofacial anomaly that required a two-stage treatment; she underwent mandibular reconstruction with free iliac crest bone graft followed by a bilateral mandibular distraction at the level of the iliac crest bone graft. With these interventions, a remarkable improvement of the patient's malformation was achieved.

Conclusion: Horizontal distraction of the free iliac crest bone graft is a safe and predictable procedure to treat dentolabial anomalies requiring mandibular reconstruction. This procedure was performed in the patient without complications. Further studies on the effectiveness of this technique are required.

RESUMEN

Introducción. La combinación del injerto de la cresta ilíaca no vascularizado y la distracción osteogénica del injerto en una segunda intervención quirúrgica solo ha sido descrita para lograr un aumento del reborde alveolar. Esta técnica no se recomienda para tratar defectos óseos en la mandíbula causados por proyectil de arma de fuego.

Presentación del caso. Mujer de 40 años con un defecto mandibular segmentario en el cuerpo mandibular causado por el impacto de un proyectil de arma de fuego a la edad de 1 año. La paciente desarrolló una anomalía dentofacial grave Clase II que requirió dos tratamientos en diferentes momentos: en primer lugar, se le practicó una reconstrucción mandibular con injerto de cresta ilíaca libre y posteriormente, una distracción mandibular bilateral que incluyó un injerto libre de cresta ilíaca. Con estas intervenciones se logró una mejoría notable de la malformación de la paciente.

Conclusión. La distracción horizontal del injerto de cresta ilíaca libre es un procedimiento seguro y predecible para tratar anomalías dentolabiales que requieran reconstrucción de la mandíbula; no obstante, es necesario realizar más estudios sobre la efectividad de la técnica frente este tipo de malformaciones.

INTRODUCTION

Although dentofacial anomalies are usually congenital, they may also be acquired by trauma, surgery, or during growth. In turn, segmental mandibular defects can be caused by gunshot wounds or as a result of ablative surgery of malignant or benign tumors. (1) These mandibular bone continuity defects have a major psychological and social impact on patients since they are associated with aesthetic and functional alterations that affect the patient's health status.

Mandibular reconstruction is essential in patients with mandibular defects because it improves or restores mandibular function and allows the placement of dental implants for the rehabilitation of masticatory function, thus improving the patient's health and quality of life. Several types of bone graft are used for mandibular reconstruction, including autologous non-vascular, allogenic, and xenogeneic bone grafts, as well as free tissue transfer via vascularized flap. (2) The most widely used donor sites for mandibular reconstruction are the radial forearm, scapula, iliac crest, and fibula. Each donor site differs in the amount of bone and soft tissue needed. (3)

Literature or studies explaining or evaluating horizontal distraction of free iliac crest bone grafts, especially to solve problems such as micrognathia caused by firearm injury in children, is scarce. The combination of non-vascularized iliac crest bone graft and two-stage maxillary distraction osteogenesis has only been described to achieve alveolar ridge augmentation and subsequent dental implant placement and rehabilitation of masticatory function in the maxillary bones. Currently, there are no case reports of mandibular distraction using free iliac crest bone graft for the management of mandibular hypoplasia.

In the absence of reports evaluating horizontal distraction of free iliac crest bone grafts used specially to solve problems such as micrognathia as a consequence of childhood gunshot wound, we present the case of a patient with a gun-related injury, who required a free anterior iliac crest bone graft for mandibular reconstruction and horizontal graft distraction for correction of skeletal dentofacial anomaly.

CASE PRESENTATION

The present case is a 44-year-old black woman from Cartagena, Colombia, who was shot in the jaw when she was 1 year old. The patient did not receive reconstructive treatment until she was 40 years old, when she entered the Maxillofacial Surgery Service of the Instituto Roosevelt, in Bogotá, Colombia (Figure 1). Although the patient is currently employed as a merchant, she has limited resources due to her low socioeconomic status. The patient's treatment approach focused on mandibular reconstruction and not on having an adequate facial balance. The patient was explained that there were treatment options to achieve a better profile and she accepted the treatment proposed.

Panoramic radiography and computed tomography were utilized as diagnostic aids. The intervention began in 2016 after performing a standard mandibular reconstruction with a non-vascularized iliac crest bone graft, integrating the graft without complications. Then, in 2018, bilateral mandibular distraction was started, including the free iliac crest bone graft. For mandibular distraction, distractors were placed, and mandibular osteotomy was performed in the center of the iliac crest graft. Latency was maintained for 7 days and distracted 1 mm daily thereafter. A distraction of approximately 28mm was carried out. In 2019, consolidation ended, and distractors were removed. As of August 2020, the patient had adequate mandibular function and there was no evidence of complications.

Adequate reconstruction of the arch shape and facial contour was achieved, but the patient presented a deficient masticatory function and, because of the affectation of mandibular growth due to the history of gunshot wound, she had a severe class II dentofacial anomaly with a dental discrepancy of 28mm (Figure 2).

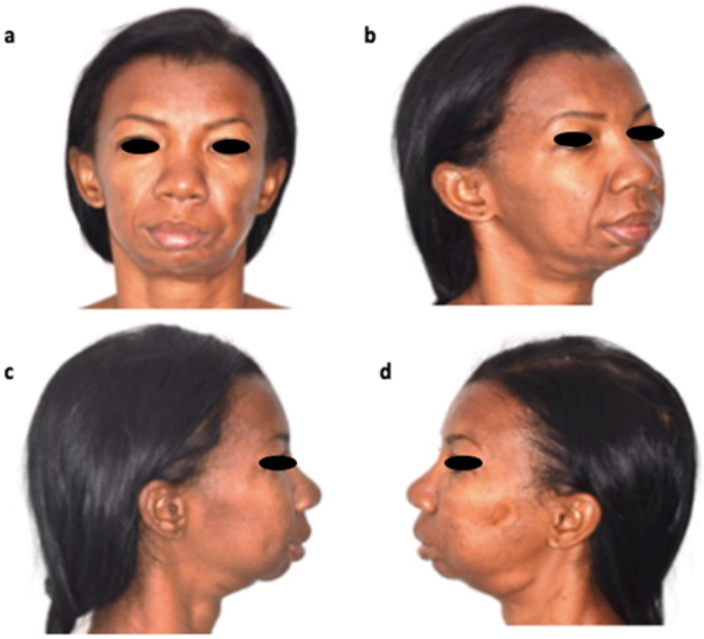


Figure 1. First photo of the patient when she was admitted in 2016. An extremely convex profile is observed. a) Frontal photography, b) ¾ photography, c-d) Profile photography. Severe mandibular micrognathia is observed.

Source: Document obtained during the study.

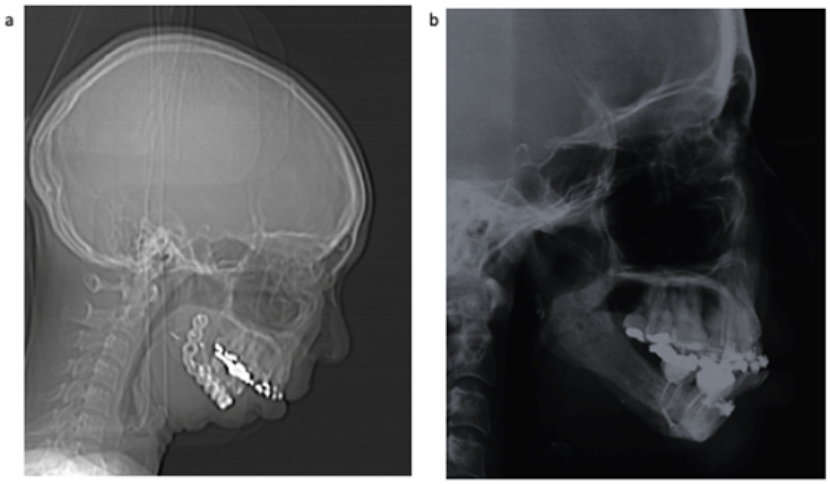


Figure 2. Free bone graft in position and patient with severe class II anomaly with a dental discrepancy of 28mm (a). Figure (b) shows the final discrepancy after distraction.

Source: Document obtained during the study.

In 2018, the patient underwent a bilateral mandibular distraction, where the free iliac crest bone graft was distracted without complications (Figure 3).

The patient currently has an adequate profile, favorable facial harmony and adequate maxillomandibular relationship (Figures 4 and 5). Moreover, the patient is on a plan to rehabilitate masticatory function using implant-supported fixed dental prostheses. The patient has been attending follow-up appointments every 6 months since the last intervention, and no complication has been observed after two years.

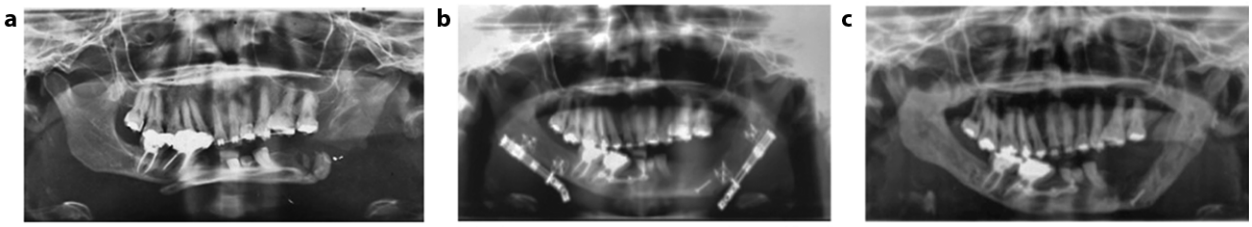


Figure 3: Panoramic radiographs (a) Initial radiography taken in 2012; (b) Radiography with bilateral mandibular distractors; (c) radiography taken at the end of the mandibular free graft bone distraction.
Source: Document obtained during the study.

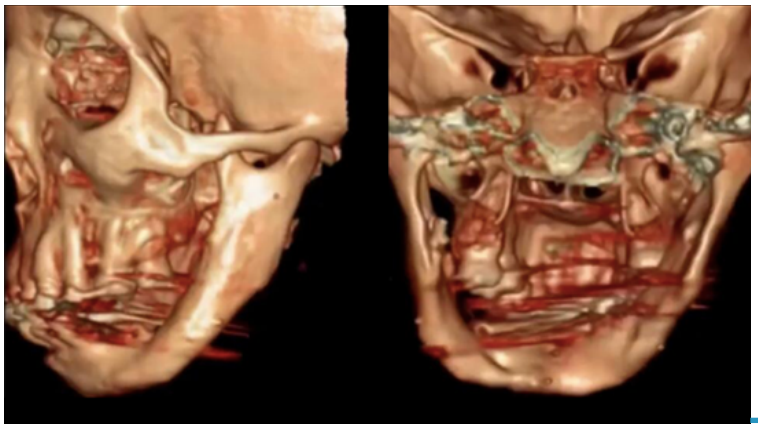


Figure 4. Three-dimensional facial reconstruction after free iliac crest bone graft distraction. Adequate maxillomandibular relationship and mandibular contour.
Source: Document obtained during the study.

Figure 5. Photograph taken in 2019 at the end of the distraction and bone consolidation. (a) patient profile before distraction; (b) patient profile after distraction.
Source: Document obtained during the study.

DISCUSSION

Segmental bone loss in the craniofacial region can result from blast injuries, gunshot wounds, blunt trauma, tumor removal, or repeated surgical debridement for the treatment of tumor or infectious diseases. (4)

Multiple techniques are used for mandibular reconstruction, including microvascular free flap, bone grafts, and bone distraction, which are widely used depending on the defect. Throughout history, the iliac crest bone graft has been used for both maxillary and mandibular reconstruction. This technique is indicated in non-irradiated jaws with mandibular defects of up to 5cm reconstructed with an anterior iliac crest bone and up to 10cm if reconstructed with posterior iliac crest bone. (2,3)

Another technique for mandibular reconstruction is osteogenic distraction bone neoformation, a process in which the formation of new bone is gradually induced by a device that is placed between two bone surfaces. This technique was initially described by Codivilla in 1904, (5) but Ilizarov popularized it by creating a device for the surgical lengthening of long bones in 1951. (3)

Osteogenic distraction is a slow, progressive, and continuous biological process that involves the formation of new bone between bony segments that are gradually separated by incremental traction. Regarding this process, it has been documented that there is not only bone formation, but also tissue formation under tension stress, including mucosa, skin, muscles, tendons, cartilage, blood vessels and peripheral nerves, which explains why it is currently called distraction histiogenesis. (5-8)

The combination of non-vascularized iliac crest bone and distraction osteogenesis of the graft in a second surgical intervention has been described for alveolar ridge augmentation and subsequent implant placement and rehabilitation of masticatory function. (9)

However, horizontal distraction of a free iliac crest bone graft for treating dentofacial anomalies and gunshot injuries has not been described to date. The clinical case presented here aims to propose this technique as a safe alternative in the management of similar cases, as it is considered to be a safe procedure, with similar behavior to the native jaw of the patient.

CONCLUSIONS

Iliac crest bone graft distraction as a treatment for dentofacial deformities is a safe and predictable procedure that can be performed in patients that require reconstructive treatment with horizontal mandibular distraction. The authors consider that it is a safe procedure, although more cases and studies are needed to acquire scientific evidence.

COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

None stated by the authors.

INFORMED CONSENT

Informed consent was obtained from the patient.

FUNDING

None stated by the authors.

REFERENCES

1. **Bobinskas AM, Subramaniam SS, Vujcich NJ, Nastri AL.** Bilateral Distraction Osteogenesis of Vascularized Iliac Crest Free Flaps Used in Mandibular Reconstruction. *Plast Reconstr Surg Glob Open.* 2016;4(3):e635. https://doi.org/gd6g.

2. **Kademani D, Keller E.** Iliac crest grafting for mandibular reconstruction. *Atlas Oral Maxillofac Surg Clin North Am.* 2006;14(2):161-170. https://doi.org/fswmcv.
3. **Goh BT, Lee S, Tideman H, Stoelinga PJ.** Mandibular reconstruction in adults: a review. *Int J Oral Maxillofac Surg.* 2008;37(7):597-605. https://doi.org/br25n6.
4. **Gülses A, Sencimen M, Ayna M, Gierloff M, Açil Y.** Distraction histogenesis of the maxillofacial region. *Oral Maxillofac Surg.* 2015;19(3):221!8. https://doi.org/gd6j.
5. **Codivilla A.** On the means of lengthening, in the lower limbs, the muscles and tissues which are shortened through deformity. 1904. *Clin Orthop Relat Res.* 1994;(301):4-9.
6. **Trento GDS, Reis JMDSN, Hochuli-Vieira E, Pereira-Filho VA.** Mandibular Reconstruction by Osteogenic Distraction Due to Two Different Injuries. *J Craniofac Surg.* 2018;29(2):e133-5. https://doi.org/gd6n.
7. **Shen W, Tang C, Yang J, Kong L, Zhang X.** Evaluating Loading Deflection of Distraction Osteogenic Rib in a Rabbit Model. *Plast Reconstr Surg Glob Open.* 2016;4(10):e1008. https://doi.org/gd6q.
8. **Tosun E, Bilgiç M, Yildirim B, Tüz HH, Özer T.** Effects of Piezoelectric Surgery on Bone Regeneration Following Distraction Osteogenesis of Mandible. *J Craniofac Surg.* 2017;28(1):74-8. https://doi.org/f9mjdc.
9. **Nocini PF, Albanese M, Buttura da Prato E, D'Agostino A.** Vertical distraction osteogenesis of the mandible applied to an iliac crest graft: report of a case. *Clin Oral Implants Res.* 2004;15(3):366-70. https://doi.org/b2kxf5.

https://doi.org/10.15446/cr.v7n2.89300

CLEAR CELL CHONDROSARCOMA OF THE PROXIMAL TIBIA - CASE REPORT

Keywords: Chondrosarcoma; Clear Cell; Knee; Tibia; Surgery.
Palabras clave: Condrosarcoma de células claras; Rodilla; Tibia; Cirugía.

Daniela Gutiérrez-Zúñiga
Helbert Martín
Jerónimo Sotomayor
Francisco Linares
Pontificia Universidad Javeriana
- School of Medicine -
Department of Orthopedics and Traumatology -
Bogotá, D.C. - Colombia.
Hospital Universitario San Ignacio
- Orthopedics Service -
Bogotá D.C. - Colombia

Oscar Messa-Botero
Pontificia Universidad Javeriana
- School of Medicine -
Department of Pathology -
Bogotá, D.C. - Colombia.
Hospital Universitario San Ignacio
- Pathology Service -
Bogotá, D.C. - Colombia

Corresponding author
Helbert Martín. Servicio Ortopedia,
Hospital Universitario San Ignacio.
Bogotá D.C. Colombia.
Email: hmartin@javeriana.edu.co

Received: 21/07/2020 **Accepted:** 19/02/2021

RESUMEN

Introducción. El condrosarcoma de células claras es un subtipo de tumor poco frecuente del grupo de los condrosarcomas de bajo grado. A diferencia de los condrosarcomas convencionales, estos tumores se presentan principalmente en epífisis de huesos largos. Dadas sus características líticas de aspecto quístico, pueden confundirse con quistes óseos, por lo que su diagnóstico debe hacerse por histopatología e inmunohistoquímica mediante biopsia. Igualmente, la negatividad para citoqueratinas y anticuerpos antiendomisio es una herramienta para descartar el diagnóstico diferencial de metástasis. Su tratamiento es quirúrgico, bien sea con manejo intralesional o resección completa con márgenes libres.

Presentación del caso. Mujer de 46 años quien consultó al servicio de ortopedia oncológica de una institución de IV nivel de atención por un cuadro clínico de 8 meses de evolución consistente en dolor en la cara medial de la rodilla izquierda a nivel de la tibia proximaluna. Se practicaron imágenes diagnósticas que mostraron una lesión quística en el platillo tibial lateral; se ordenó biopsia de la lesión, y mediante histopatología e inmunohistoquímica se diagnosticó condrosarcoma de células claras. Se realizó un manejo quirúrgico con resección de la lesión con márgenes libres y una reconstrucción del defecto óseo con un aloinjerto estructural de tibia proximal, con lo cual se obtuvo una evolución satisfactoria.

Conclusiones. Se presenta el caso de una paciente con un subtipo de condrosarcoma de bajo grado infrecuente en su presentación y localización, quien fue diagnosticada mediante inmunohistoquímica y tratada quirúrgicamente para lograr un salvamento exitoso de su extremidad.

ABSTRACT

Introduction: Clear cell chondrosarcomas are a rare type of low-grade chondrosarcoma. Unlike conventional chondrosarcomas, these tumors occur mainly in the epiphyses of long bones, especially in the proximal femur and proximal humerus. Given their lytic characteristics with a cystic appearance, they can be mistaken for bone cysts and diagnosed late. Diagnosis must be made based on histopathology and immunohistochemistry. Likewise, negativity for cytokeratins and anti-endomysial antibodies are tools to rule out the differential diagnosis of metastasis. The treatment of this low-grade chondral lesion is surgical, either with intralesional management or complete resection.

Case presentation: This is the case of a 46-year-old woman who consulted the orthopedic oncology service of a quaternary care institution due to medial knee pain at the level of the proximal tibia for 8 months. Diagnostic imaging studies showed a cystic lesion in the lateral tibial plateau; a biopsy of the lesion was performed, and clear cell chondrosarcoma was diagnosed based on histopathology and immunohistochemistry. Surgical management included tumor-free resection margins and reconstruction of the bone defect with a structural allograft of the proximal tibia. The patient progressed satisfactorily.

Conclusions: This was the case of a patient with a subtype of low-grade chondrosarcoma that is rare in incidence and location, who was diagnosed based on immunohistochemistry and treated surgically to achieve a successful limb salvage.

INTRODUCTION

Clear cell chondrosarcoma is a rare subtype of benign tumor (2% of all chondrosarcoma cases) (1) that predominantly affects young adults and involves the epiphyses of long bones, especially the femur and proximal humerus (2-4). This type of neoplasm can be mistaken for other cystic lesions due to its imaging characteristics; moreover, there are no clear guidelines for its treatment and outcomes to date.

The following is the case of a patient with clear cell chondrosarcoma in the proximal tibia at the level of the medial tibial plateau who was successfully treated with *en bloc* excision with tumor-free margins, structural allograft, and stabilization with tibia proximal plate.

CASE PRESENTATION

A 46-year-old Caucasian woman from Bogotá (Colombia), a civil engineer with no significant medical or surgical history, consulted the oncology orthopedic department of a quaternary care institution in November 2019 due to chronic pain in the medial left knee at the level of the proximal tibia for 8 months that woke her up at night and forced her to use a cane as an external support while walking. The patient reported having attended physical therapy sessions and using oral analgesia without improvement.

On physical examination, the only finding was tenderness to palpation at the medial tibial plateau of the left knee associated with edema; the range of motion at the joint was normal and there were no clinical signs that suggested ligamentous or meniscal lesions. Considering these findings, diagnostic imaging studies (X-ray and MRI) were performed.

Conventional knee radiographs (Figure 1) showed a small round epiphyseal lytic lesion with well-limited borders at the medial tibial plateau, although no periosteal reaction or other associated changes suggesting local aggressiveness were observed.

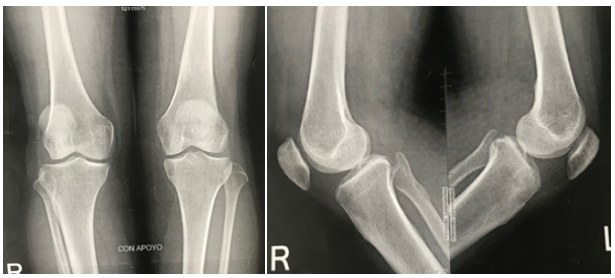


Figure 1. Anteroposterior and lateral knee radiographs showing a lytic lesion at the medial level of the proximal epiphysis of the left tibia.

Source: Document obtained during the study.

On the other hand, magnetic resonance imaging (MRI) (Figure 2) showed a prominent and confluent bone and subchondral cysts of 18mm in diameter in the medial tibial plateau, as well as a diffuse increase in bone marrow signal intensity and changes associated with disuse osteopenia.

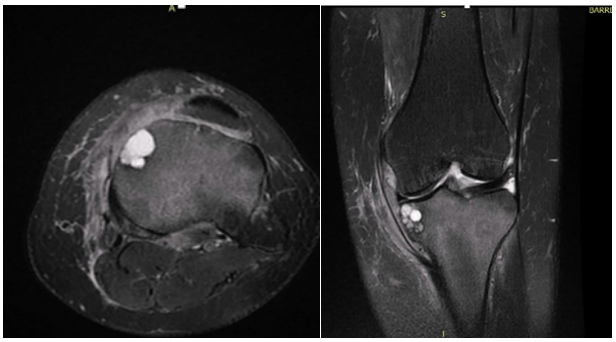


Figure 2. MRI of the left knee in T2 mapping sequence in axial and coronal view showing a cystic lesion in the medial tibial plateau and a diffuse increase in the signal intensity of the tibia.

Source: Document obtained during the study.

Taking into account the clinical and imaging findings, an epiphyseal chondroblastoma or giant cell tumor were initially suspected as the main differential diagnosis. Consequently, an open biopsy was performed, which macroscopically showed a chondral lesion with sclerotic edges and no involvement of the articular cartilage of

the tibia. Microscopically, it showed nests of epithelial clear cells that led to suspect between metastases or clear cell chondrosarcoma.

Immunohistochemistry of the lesion proved positive for vimentin, S100 and D2-40 proteins and negative for antibodies AE1/AE3, CK7, CK20, PAX8, PAX2, NAPSIN-A, RCC, which supported the diagnosis of clear cell chondrosarcoma. Further tests were performed, including thoracic and abdominopelvic tomography, which were negative for distant metastasis.

Based on these findings and the rare occurrence of clear cell chondrosarcoma, the following month the case was brought to a multidisciplinary board (orthopedic oncology, musculoskeletal radiology, oncology, surgical oncology, radiotherapy, and pathology services), in which, by consensus, complete surgical resection of the lesion was decided upon.

The surgery was performed on January 7, 2020, using an anteromedial approach to the proximal tibia. During this procedure, the biopsy trajectory and the described lesion were removed, with tumor-margins of approximately 2cm. The medial tibial plateau was resected, and the ligamentous and meniscal structures of the knee were preserved (Figure 3). The bone defect was also managed by applying a structural corticocancellous allograft (Figure 4) that was stabilized with a proximal tibia plate, thus achieving recovery of the joint surface and the anatomy of the proximal tibia (Figure 5). There were no complications during the procedure.

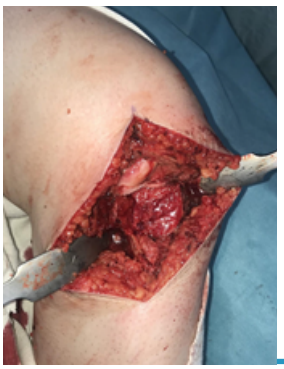


Figure 3. Picture taken during the procedure showing oncologic resection of the chondral lesion at the level of the medial tibial plateau.
Source: Document obtained during the study.

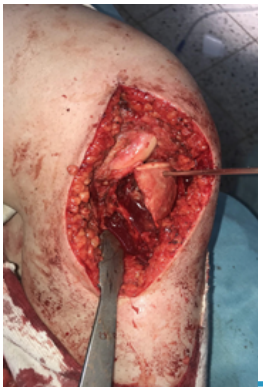


Figure 4. Allograft of corticocancellous bone at the level of the proximal tibia.
Source: Document obtained during the study.

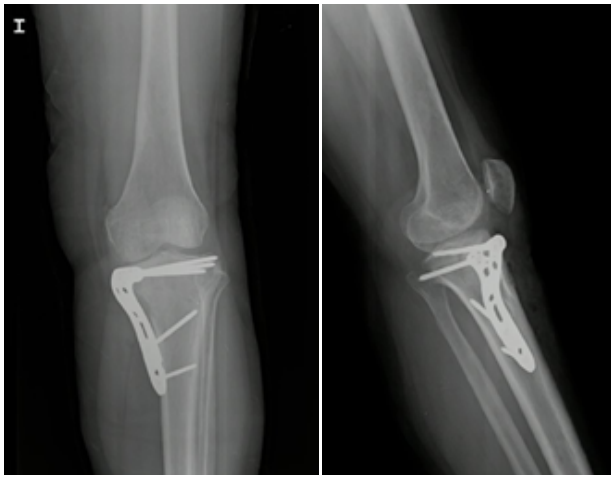


Figure 5. Postoperative x-ray showing recovery of the joint surface and proximal tibia anatomy.
Source: Document obtained during the study.

Histopathological analysis revealed a lesion composed of nests of clear cell (Figure 6) surrounded by mixed inflammatory infiltrate without clear chondroid differentiation, findings that raised suspicion of metastatic carcinoma, melanoma, and clear cell chondrosarcoma. Clinically, there were no lesions at other sites where metastasis was suspected. An immunohistochemistry study was performed, finding reactivity for S100 (Figures 7 and 8) with negativity for cytokeratins (AE1AE3), anti-endomysial antibodies (EMA), and melanocytic markers HMB45, Melan A, and SOX10. These findings were consistent with clear cell chondrosarcoma with negative tumor margins.

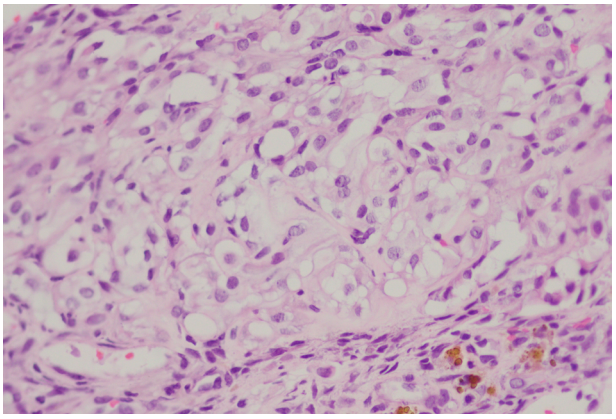


Figure 6. Histopathological analysis showing nests of clear cells.
Source: Document obtained during the study.

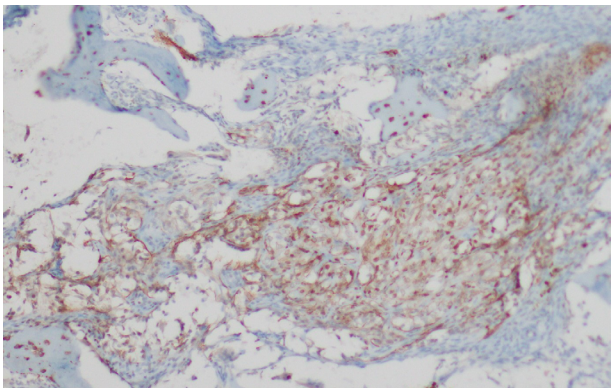


Figure 7. Histopathological analysis showing positivity for S100 in tumor nests and negativity for melanocytic markers.
Source: Document obtained during the study.

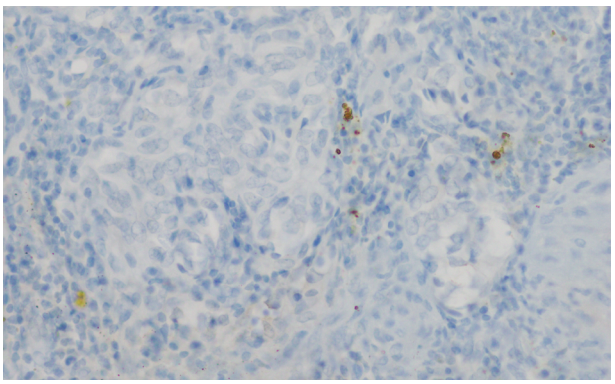


Figure 8: Histopathological analysis showing negative cytokeratin cocktail in tumor cells.
Source: Document obtained during the study.

After the procedure, the patient began a rehabilitation process with initial non-weight bearing. Five months after the procedure, she no longer felt pain and was able to achieve full mobility of the knee and walk without limping and using only one crutch. Likewise, her clinical condition continued to be followed up using diagnostic imaging. At the time of writing this report, she had not presented any tumor recurrence and had an adequate integration of the allograft observed during radiographic follow-up.

Figure 9 presents the case timeline.

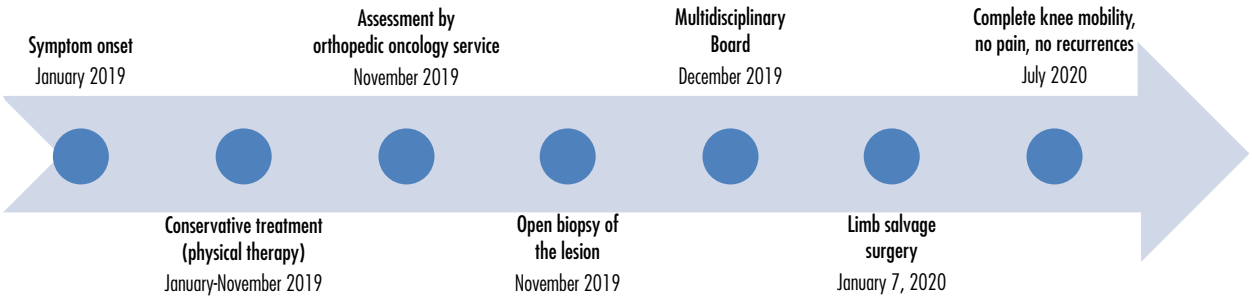


Figure 9. Case timeline.
Source: Own elaboration.

DISCUSSION

Chondrosarcoma is the third most common type of bone tumor after myeloma and osteosarcoma, with conventional central chondrosarcoma being the most frequent (85% of all cases) (5). Clear cell chondrosarcoma, which was first described by Unni *et al.* in 1976 (6), is a rare variant of low-grade chondrosarcoma (2-4% of all cases) (2,7) mostly observed in men aged 20 to 40 years. Together with mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma, it is one of the rare subtypes due to its histological and clinical characteristics (1).

Conventional chondrosarcomas originate mainly in the pelvis, shoulders, and ribs, while clear cell chondrosarcomas usually occur in the epiphyses of long bones, being more common in the femur and proximal humerus (2-4). Even though there are reports of dedifferentiated clear cell tumors, they are usually low grade, so cases of metastasis are rare and, if they occur, mainly affect the lung and brain (4).

Since it is a slow-growing, low-grade lesion, clear cell chondrosarcoma can be mistaken for bone cysts on diagnostic imaging and therefore diagnosed late. In conventional x-rays, they are seen as expansive radiolucent lesions of cystic or lobulated appearance with reactive cortical thickening, without destruction of the cortical layer nor periosteal or soft tissue involvement. (3,4) In computed tomography, they can be identified as calcifications of the chondroid matrix with sclerotic contour and cortical involvement (3).

Given these findings, differential imaging diagnoses are usually simple or aneurysmal bone cysts, giant cell tumor, chondroblastoma, enchondroma, and chondromyxoid fibroma. No imaging findings are specific to this type of tumor, so biopsy with histopathological and immunohistochemistry analysis is decisive to confirming the diagnosis (4).

On histopathological analysis, clear cell chondrosarcomas appear macroscopically as gray or whitish masses with areas of mineralization, and not as hyaline areas typical of chondrosarcomas (8). On the other hand, on microscopic analysis, characteristic clear cells are observed in lobules or sheets infiltrating the trabecular bone and have centralized, round or oval nuclei with clear cytoplasm and well-defined borders. In addition, some

areas of the tumor usually show characteristics of a conventional chondrosarcoma with hyaline areas (4,8,9). It is worth noting that although these are low-grade tumors, an increase in metalloproteinases 2 (MMP-2) may be associated with the behavior of a tumor with a high risk of metastasis (10,11).

Both clear cell chondrosarcoma and chondroblastoma show epithelioid and chondrogenic cell characteristics. Immunohistochemistry is a useful tool for confirming the diagnosis of the former since this procedure is positive for type II collagen, vimentin and S100, and negative for EMA and cytokeratin (9,12,13). In this regard, it should be noted that the most important differential diagnoses in epiphyseal lesions are chondroblastomas, which are usually more frequent in adolescents and present individual calcifications and pink cartilage nests on diagnostic imaging and are positive for DOG-1 in immunohistochemistry. Other differential diagnoses are giant cell tumor, carcinoma, and melanoma. In immunohistochemistry, carcinoma is positive for epithelial markers such as cytokeratins and epithelial membrane antigen, while melanoma is reactive for melanocytic markers such as Melan A, HMB-45, and SOX10 (14-16).

The mainstay of treatment for clear cell chondrosarcoma is surgery, in which a wide excision with free of tumor at the margins of at least 5mm (2,4,8) should be performed. Long-term follow-up is essential in the management of these tumors because, as Kang *et al.* (9) stated in their case report, simple excision or intralesional curettage can cause recurrence and metastasis in more than 80% of cases. However, Klein *et al.* (12) state that these values are lower (30% and 15%, respectively) in follow-ups at less than 10 years. The latter authors also found a correlation between shorter survival and previously identified risk factors for chondrosarcoma: positive margins and metastases. (12)

Chemotherapy and radiation therapy are ineffective to treat clear cell chondrosarcomas; however, they may be indicated as adjuvant or palliative treatments when metastases occur and in inoperable cases (4).

There is no clear evidence in the literature regarding the prognosis of clear cell chondrosarcomas due to the low incidence of these tumors. However, Itälä *et al.* (17) reported that, in their study, the overall 10-year survival of patients with these tumors was 89% and disease-free survival was 68%.

The case presented here is noteworthy because clear cell chondrosarcoma was found in an unusual location (tibial plateau) that is little described in the literature, and because the diagnosis was delayed due to subtle changes in radiographic images, with immunohistochemistry being the primary tool for confirmation. Surgical therapy was chosen for this patient, including free-margin resection and allograft reconstruction of the proximal tibia. Even though the results obtained with this management were satisfactory, and there was no evidence of tumor recurrence at the time of writing this report (medium term), prognosis may change in the long term and the patient may present with arthroscopic changes of the knee and require new interventions.

CONCLUSIONS

This is the case of a patient with a very rare subtype of chondrosarcoma found in an unusual location, who presented chronic knee pain and subtle changes on imaging studies. Given the nonspecific nature of the symptoms, the diagnosis of clear cell chondrosarcoma was made 8 months after their onset, and immunohistochemistry was the key tool to rule out more frequent differential diagnoses. Resection with free margins of neoplastic infiltration and reconstruction with proximal tibial allograft were performed, with which the functionality of the knee was restored, and the pain disappeared.

CONFLICT OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

None stated by the authors.

REFERENCES

1. **van Oosterwijk JG, Meijer D, van Ruler MA, van den Akker BE, Oosting J, Krenács T, *et al.*** Screening for Potential Targets for Therapy in Mesenchymal, Clear Cell, and Dedifferentiated Chondrosarcoma Reveals Bcl-2 Family Members and TGFb as Potential Targets. *Am J Pathol.* 2013;182(4):1347-56. https://doi.org/gfg6.
2. **Datt NS, Mounika CNS, Kiran KR, Rao DR, Sandeepc V.** Clear cell chondrosarcoma proximal femur with secondary aneurysmal component - A rarity. *J Clin Orthop Trauma.* 2017;8(1):93-5. https://doi.org/gfg7.
3. **Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP.** Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. *J Bone Joint Surg Am.* 2009;91(5):1063-72: https://doi.org/c7q58w.
4. **Kumar V, Abbas AK, Fausto N, Aster JC.** Robbins y Cotran. Patología Estructural y Funcional. 8th ed. Barcelona: Elsevier; 2010.
5. **Qian X.** Updates in Primary Bone Tumors Current Challenges and New Opportunities in Cytopathology. *Surg Pathol Clin.* 2018;11(3):657-68. https://doi.org/gfg8.
6. **Unni KK, Dahlin DC, Beabout JW, Sim FH.** Chondrosarcoma: clear-cell variant. A report of sixteen cases. *J Bone Joint Surg Am.* 1976;58(5):676-83.
7. **Bjornsson J, Unni KK, Dahlin DC, Beabout JW, Sim FH.** Clear cell chondrosarcoma of bone. Observations in 47 cases. *Am J Surg Pathol.* 1984;8(3):223-30. https://doi.org/c77p8q.
8. **Kilpatrick SE.** Chondrosarcoma Variants. Surg Pathol Clin. 2012;5(1):163-81 https://doi.org/fxsnz5.
9. **Kang CM, Han CS, Jung GY, Jeong HY, Kim YJ.** Clear Cell Chondrosarcoma of the Tibia Diaphysis: A Case Report. *J Korean Bone Joint Tumor Soc.* 2014;20:89-93. https://doi.org/gfgz.
10. **Elojeimy S, Ahrens WA, Howard B, Patt JC, Stone T, Kneisl JS, *et al.*** Clear-cell chondrosarcoma of the humerus. *Radiol Case Rep.* 2015;8(2):848. https://doi.org/gfhf.
11. **Kalil RK, Inwards CY, Unni KK, Bertoni F, Bacchini P, Wenger DE, *et al.*** Dedifferentiated clear cell chondrosarcoma. *Am J Surg Pathol.* 2000;24(8):1079-86. https://doi.org/bt8s7k.
12. **Klein A, Tauscher F, Birkenmaier C, Baur-Melnyk A, Knösel T, Jansson V,** *et al.* Clear cell chondrosarcoma is an underestimated tumor: Report of 7 cases and meta-analysis of the literature. J Bone Oncol. 2019;19:100267. https://doi.org/gjkmfj.
13. **Doyle LA, Hornick JL.** Immunohistology of Neoplasms of Soft Tissue and Bone. In: Dabbs DJ. *Diagnostic Immunohistochemistry. Theranostic and Genomic Applications. 5th ed.* Philadelphia: Elsevier; 2019. p. 82.
14. **Chebib I, Hornicek FJ, Bredella MA, Deshpande V, Nielsen GP.** Histologic variants of chondrosarcoma. *Diagnostic Histopathology.* 214;20(5):172 80. https://doi.org/gfhg.
15. **Matsuura S, Ishii T, Endo M, Takahashi Y, Setsu N, Yamamoto H, *et al.*** Epithelial and cartilaginous differentiation in clear cell chondrosarcoma. *Hum Pathol.* 2013;44(2):237-43. https://doi.org/gfhh.
16. **Söder S, Oliveira AM, Inwards CY, Müller S, Aigner T.** Type II collagen, but not aggrecan expression, distinguishes clear cell chondrosarcoma and chondroblastoma. *Pathology.* 2006;38(1):35-8. https://doi.org/fnnd37.

17. **Itälä A, Leerapun T, Inwards C, Collins M, Scully SP.** An Institutional Review of Clear Cell Chondrosarcoma. Clin Orthop Relat Res. 2005;440:209-12. https://doi.org/d84438.

https://doi.org/10.15446/cr.v7n2.89388

CONSTITUTIONAL SYMPTOMS AND ANEMIA AS THE INITIAL MANIFESTATION OF VASCULITIS IN AN OLDER ADULT. CASE REPORT

Keywords: Aged; Anemia; Renal Insufficiency; Systemic Vasculitis.
Palabras clave: Adulto mayor; Anemia; Insuficiencia renal; Vasculitis sistémica.

Virginia Naranjo-Velasco
Patricia Rubio-Marín
Juan Carlos Anglada-Pintado
Hospital Universitario de Jerez de la Frontera
- Internal Medicine Service -
Cadiz - Spain.

Marta Pastor-Mena
Hospital Universitario de Jerez de la Frontera
- Rheumatology Service -
Cadiz - Spain.

Corresponding author
Patricia Rubio-Marín. Servicio de Medicina Interna,
Hospital Universitario de Jerez de la Frontera.
Cádiz. España.
Email: prubiomarin@gmail.com.

Received: 24/07/2020 **Accepted:** 20/04/2021

RESUMEN

Introducción. Las vasculitis son enfermedades graves que suelen tener un debut muy inespecífico y un diagnóstico tardío, lo que implica una alta tasa de fracaso terapéutico. Se presenta un caso de vasculitis que puede contribuir a considerar esta enfermedad como parte del diagnóstico diferencial desde las primeras etapas del proceso de atención para garantizar un abordaje integral y un inicio temprano del tratamiento, lo que reduciría la morbimortalidad asociada a estas entidades y mejoraría la tasa de éxito de los tratamientos.

Presentación del caso. Mujer caucásica de 77 años que como único antecedente presentaba hipertensión arterial de dos años de evolución y quien consultó al servicio de urgencias de una institución de segundo nivel por cuadro clínico de un mes de evolución consistente en astenia, febrícula, hiporexia y pérdida de peso. La paciente fue hospitalizada para completar la historia clínica y dados los hallazgos se sospechó de una posible translocación bacteriana secundaria a una neoplasia intestinal y se inició cobertura antibiótica empírica, pero su condición seguía empeorando. Se realizaron pruebas complementarias que no arrojaron resultados concluyentes; ante la persistencia de la fiebre, la insuficiencia renal y la anemia, se realizó una biopsia de riñón que mostró vaso arterial con necrosis fibrinoide e infiltrados de polimorfonucleares asociados, claros signos de una vasculitis activa del tipo poliangeítis microscópica. Se instauró el tratamiento indicado pero la paciente tuvo una evolución desfavorable y falleció.

Conclusiones. La exposición de este caso inusual contribuye a que los profesionales de la salud consideren el diagnóstico de vasculitis desde el inicio de la atención, aun cuando la sintomatología sugiere otras patologías o incluso cuando se presentan síntomas tan inespecíficos como anemia y pérdida de peso, ya que esto ayudará a establecer un diagnóstico temprano.

ABSTRACT

Introduction: Vasculitis comprises a group of often serious diseases that have an unspecific onset and a late diagnosis. The following report describes a case of vasculitis that may lead to considering this disorder as a differential diagnosis from the beginning of the care process to ensure a comprehensive approach and early treatment initiation that reduce associated morbidity and mortality and improve the success rate of treatments.

Case presentation: A 77-year-old female, with a 2-year history of arterial hypertension was admitted to the emergency department of a secondary care center for having experienced symptoms of asthenia, fever, hyporexia and weight loss for a month. The patient was hospitalized for further testing and, given the findings, a possible bacterial translocation secondary to intestinal neoplasm was suspected. Empirical antibiotic treatment was started, but her condition continued to worsen. Complementary tests were performed, although they were not conclusive. Due to the persistence of fever, kidney failure and anemia, a kidney biopsy was performed, revealing arterial vessel with fibrinoid necrosis and associated polymorphonuclear infiltrates, clear signs of an active vasculitis of the microscopic polyangiitis type. Several lines of treatment were used, but the patient evolved unfavorably and died.

Conclusions: The presentation of this unusual case intends to contribute to the early diagnosis of this disorder by making medical staff aware of the possibility of considering it when symptoms suggest other diseases, or even when nonspecific symptoms such as anemia and weight loss occur.

INTRODUCTION

Primary systemic vasculitis is a heterogeneous group of highly complex and severe clinical processes characterized by inflammation and necrosis of blood vessels. The location and size of those vessels, as well as the severity of the damage and the histological pattern of involvement, are the features that differentiate each type of vasculitis and allow for their individualization (1).

A proper clinical assessment includes the preparation of a detailed medical history, doing a comprehensive physical examination, and requesting certain complementary tests. However, vasculitis is not usually considered as part of the differential diagnosis since the first moments of care because it has nonspecific symptoms, thus delaying diagnosis and implementation of appropriate treatment (2).

The following is the case of a patient with a rare type of vasculitis, which may prompt health staff to consider this diagnosis from the beginning.

CASE PRESENTATION

A 77-year-old middle-class woman of Spanish origin, retired, and with a good quality of life, attended the emergency department of a secondary care center in the city of Jerez de la Frontera, Spain, on July 1, 2019. She reported symptoms consisting of asthenia, fever, hyporexia and weight loss of 7kg for a month (Figure 1). The patient claimed that she had no relevant family history but a personal history of arterial hypertension for two years treated with angiotensin II receptor blockers; she also stated that she was neither a smoker nor a habitual alcohol user.

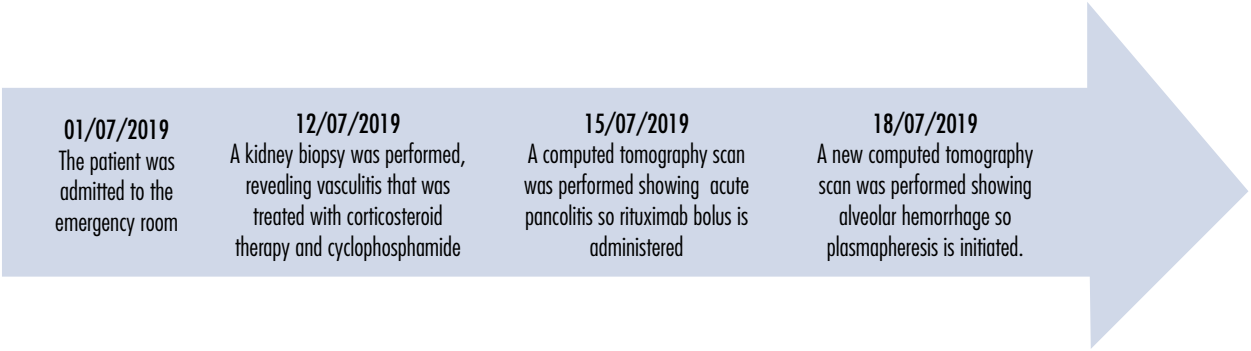


Figure 1. Timeline showing the dates of the most important procedures and interventions performed on the patient.
Source: Own elaboration.

Laboratory tests performed on the day of hospital admission showed hemoglobin of 7.4 g/dL with mean corpuscular volume (MCV) of 75fL and creatinine of 1.6 g/dL. Since previous values (one year earlier) were normal, she was admitted to the hospital in the internal medicine unit at 17:54 on the same day to complete the clinical assessment.

During the interview, the patient reported experiencing melena without alteration of the intestinal transit, as well as weight loss (7kg) and asthenia. On physical examination, her blood pressure was normal. She was awake and alert, with adequate skin and mucous membrane hydration, and no adenopathies, neurological alterations or dermal lesions, or organomegaly. Her temperature was 37.5°C and her body mass index was 23 kg/m^2. Cardiac auscultation revealed that the heart was rhythmic, with normal pulse rate and no murmurs,

while respiratory auscultation showed normal breath sounds. The abdomen was normal and bilateral kidney percussion was negative. No edema was evident, and all four limbs maintained their usual strength.

At 24 hours after admission, the patient had fever over 38°C and a possible bacterial translocation secondary to intestinal neoplasm was suspected. Therefore, serial blood cultures were taken, and empirical antibiotic treatment was initiated with ceftriaxone 1g IV every 24 hours for 7 days. Despite the treatment provided, the fever did not go down and the overall condition of the woman did not improve; in fact, blood tests taken 10 days after admission (July 10, 2019) showed a deterioration in her condition (Table 1).

Table 1. Timeline of the patient's blood tests.

Blood test	01/07/2019 First day of hospitalization	10/07/2019 Tenth day of hospitalization	Reference values
Glucose (mg/dL)	89	69	80-110
Creatinine (mg/dL)	2.25	6.19	0.5-1.11
Urea (mg/dL)	86	216	21-43
GF (mL/min)	20.44	6.01	90-100
Uric acid (mg/dL)	6.1	11	2.6-6
Proteins (g/dL)	6.2	5.4	6.4-8.3
Albumin (g/dl)	3	2.6	3.2-4.6
Total bilirubin(mg/dL)	0.6	3.1	0.30-1.20
AST (U/L)	20	22	5-37
ALT (U/L)	16	20	5-33
GGT (U/L)	27	89	9-36
ALP (U/L)	100	149	40-150
LDH (U/L)	186	300	120-225
CK (U/L)	15	43	29-169
TROP (ng/L)	13	433	2.0-15.6
Sodium (mEq/L)	135	125	135-145
Potassium (mEq/L)	3.6	4.2	3.5-5.1
Phosphorus (mg/dL)	3	6.1	2.3-4.7
Calcium (mg/dL)	8	7	8.8-10.2
NT-proBNP (pg/mL)	10.000	>35.000	0-300
C-reactive protein (mg/L)	180	196	0.0-5.0
Procalcitonin	1	9.5	0.02-0.5
ESR (mm/h)	90	100	0.0-30.1
Hemoglobin (g/dL)	10	7.4	11.8-15.8
Leukocytes (x10^3)	12.10	19.89	3.6-10.5
Neutrophils (x10^3)	10.82	15.45	1.5-7.5
Platelets (x10^3)	348	489	130-400
Sediment in urine			
Proteins (mg/dL)	0	50	0
Red blood cells (UL)	30	300	0

GF: glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; CK: creatine kinase; TROP: troponin I; NT-ProBNP: N-terminal pro-b-type natriuretic peptide; ESR: erythrocyte sedimentation rate.

Source: Own elaboration.

As the patient's condition continued to worsen, within 10 days of admission, antibiotic coverage was extended for 7 days to piperacillin 4g and tazobactam 500mg every 8 hours in extended perfusion adjusted for kidney function and linezolid 600mg every 12 hours for adequate coverage of gram-positive bacteria. Similarly, an echocardiographic study was requested to assess the existence of a possible hematogenous infectious endocarditis originated in an abdominal focus that could explain the persistence of the fever.

Both serial blood cultures and echocardiography were negative, and microbiological tests showed serology without acute infection. Tests for human immunodeficiency virus, hepatitis C virus, Coxiella burnetii, urine smear, mantoux and quantiFERON were also negative, while immunoglobulin G was positive for both cytomegalovirus and parvovirus B19. An additional finding was previous hepatitis B virus infection.

On the other hand, due to the constitutional symptoms and the anemia presented by the patient, a digestive neoplasm was suspected. A study of anemia was requested, showing saturation index of 8%; ferritin and iron levels of 421 ng/mL and 3 3mcg/dL, respectively; normal vitamin B12, folic acid and haptoglobin levels; and reticulocytes at 2%. Similarly, a fecal occult blood test (FOBT) was performed, which was positive in all 3 samples, and endoscopic studies (gastroscopy without findings and colonoscopy with uncomplicated diverticula without other findings) were performed for *Helicobacter pylori*, which was negative.

Given the lack of conclusive findings, chest and abdominal CT scans were performed, showing hiatal hernia, bilateral pleural effusion, fluid in the pelvis and a subcentimeter space-occupying liver lesion. The patient was also screened for chronic diseases that could explain the anemia and the onset of acute kidney failure by proteinogram, immunoglobulin chain quantification and immunofixation, tests that ruled out a monoclonal gammopathy.

Immunoglobulins A, G, and M were normal; hematuria (150 erythrocytes/field) and proteinuria (750mg proteins in 24 hours) were found in urine, although proteinuria in the 24-hour urine for Bence Jones was negative. The albumin-to-creatinine ratio was 160 mg/g, and the protein-to-creatinine ratio was 760 mg/dL, and renal echo-Doppler showed an increase in resistance rates of intraparenchymal arteries (Figures 2 and 3).

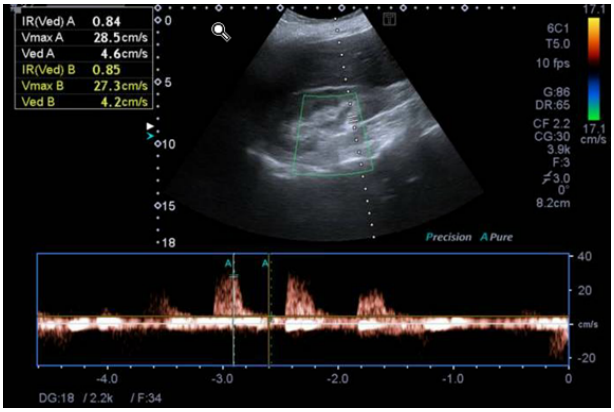


Figure 2. Renal Doppler ultrasound of the right kidney.
Source: Document obtained during the course of the study.

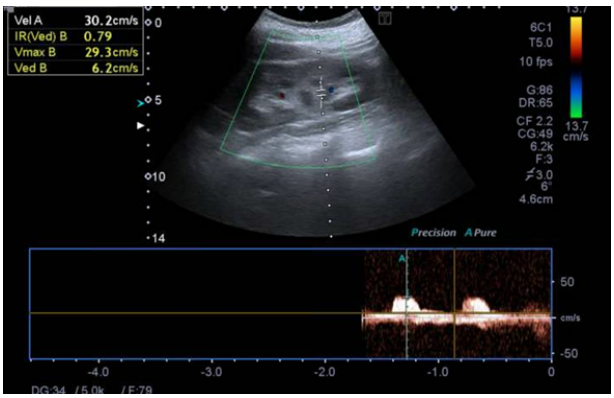


Figure 3. Renal Doppler ultrasound of the left kidney.
Source: Document obtained during the course of the study.

Although renal dysfunction was initially attributed to a prerenal kidney failure due to hyporexia, poor water intake and decreased blood flow due to anemia, it was necessary to look for other causes considering the progressive deterioration of the patient despite having implemented management with serum therapy and red blood cell concentrates.

Finally, due to the inconclusive results of the complementary tests and the persistence of fever, kidney failure and progressive anemia without externalization of bleeding despite the treatments given, the hypothesis that the patient suffered from an autoimmune disease of the vasculitis type was reinforced.

After expanding the spectrum of diagnostic tests to confirm the clinical suspicion, an autoimmunity study was performed. It was positive for perinuclear myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA), with a 1/80 dilution. A Doppler ultrasound of temporal arteries was also performed and was normal (Figure 4). However, in view of the existing involvement, and since the confirmatory diagnosis of vasculitis is anatomopathological, a kidney biopsy was performed in which the presence of an arterial vessel with fibrinoid necrosis and associated infiltration of polymorphonuclear cells was observed. These are clear signs of active microscopic polyangiitis (MPA) vasculitis (Figure 5).

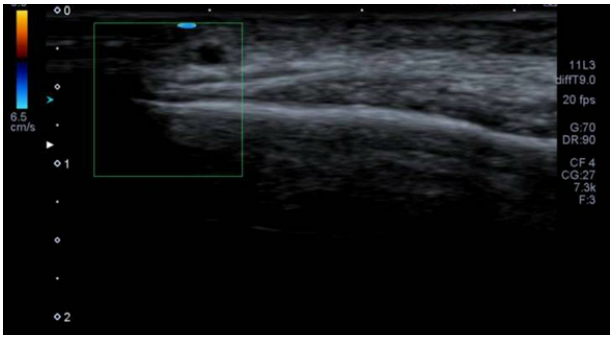


Figure 4. Doppler ultrasound of temporal arteries without alterations in temporal artery flow.

Source: Document obtained during the course of the study.

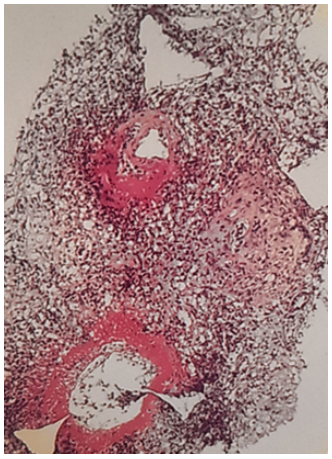


Figure 5. Kidney biopsy showing an arterial vessel with fibrinoid necrosis and associated polymorphonuclear infiltrates suggestive of microscopic polyangiitis.

Source: Document obtained during the course of the study.

After establishing the diagnosis of MAP, treatment was started with methylprednisolone 500mg per day for five days; however, the patient's condition did not improve and she had complications in different target organs, requiring combination therapy as follows: acute renal failure with the need for replacement therapy prompted the initiation of management with cyclophosphamide 15 mg/kg IV every two weeks; the development of ischemic pancolitis required the administration of a single dose of rituximab 1g IV; and acute respiratory failure caused by alveolar hemorrhage (Figure 6) made it necessary to perform 5 sessions of plasmapheresis. Despite all efforts, the patient had an unfavorable course and died.

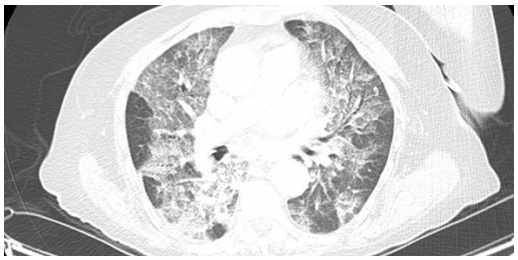


Figure 6. Computed tomography of the chest showing alveolar hemorrhage.

Source: Document obtained during the course of the study.

DISCUSSION

According to the World Health Organization, anemia in older adults is defined as hemoglobin concentration <13g/dL in men and <12g/dL in women (3). This condition has a global prevalence ranging from 10% to 24% (4-5) and its origin is usually multifactorial: one third of cases are caused by nutritional deficiencies (iron, vitamin B12 or folic acid); another third is caused by chronic diseases (neoplastic, inflammatory and/or infectious processes), with or without associated kidney disease; and the causes of the other third are not clear (6).

When anemia occurs due to iron, folic acid, or vitamin B12 deficiency, it may be explained by bleeding lesions (benign or malignant), gastritis, polytherapy, *H. pylori* infection, malnutrition, intestinal malabsorption or inflammatory processes such as chronic kidney disease, cancer, autoimmune diseases or chronic infections (5).

In cases of microcytic or normocytic anemia, which are part of ferropenic anemias, a pattern with a transferrin saturation (TS) index <20% and ferritin level <30µg/L is usually observed; in these cases, FOBT tests and endoscopic studies are recommended. However, if TS<20% and ferritin levels >100µg/L are present, chronic inflammatory anemia caused by neoplasms, infections, or even autoimmune diseases should be considered (7). On the other hand, IS>20% suggests a renal or medullary origin, or deficiencies of vitamin B12 and folic acid (4).

The present case suggested a mixed pattern: microcytic anemia and occult blood in feces with elevated ferritin. Therefore, screening was performed for establishing gastrointestinal disorders, while other chronic conditions such as solid tumor, monoclonal gammopathy, infections (tuberculosis, infectious endocarditis, etc.) and viral and/or autoimmune diseases were subsequently ruled out.

The main causes of progressive kidney failure in the elderly include vascular nephropathy and diabetic nephropathy. However, ANCA vasculitis and vasculitis associated with monoclonal gammopathies are commonly developed by the elderly and may cause kidney damage (8).

In the present case, the patient had mild kidney damage with creatinine levels of 1.6 mg/dL, so it was considered that low food intake secondary to hyporexia and renal hypoperfusion had led to prerenal failure. Nevertheless, both the lack of response to serum therapy and red blood cell transfusion, as well as the progressive kidney failure led to search for other etiologies, including renal stenosis, monoclonal gammopathy, or vasculitis.

After ruling out a solid tumor, infectious causes, monoclonal gammopathy, and gastrointestinal bleeding, it was established that symptoms could be explained by the presence of an autoimmune disease, which led to request a kidney biopsy.

Vasculitis, defined as the presence of inflammatory leukocytes in the walls of blood vessels, comprises a group of conditions that cause both hemorrhagic and ischemic processes that can be primary or secondary to another underlying disease (infectious diseases, paraneoplastic syndromes, etc.) (9), and are classified according to the size of the vessel they affect and their location.

It is worth noting that the classification of vasculitis has generated great controversy for decades. Therefore, the 2012 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides established a classification based mainly on the size of the affected vessel (9), bearing in mind that certain forms do not involve a single size. This classification indicated that vasculitis affecting small vessels include those that express ANCA and those that do not (10). However, ANCAs are not a criterion despite their potential value for clinical guidance.

Similarly, the 2012 Chapel Hill Consensus Conference included MPA, eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis (GPA) within vasculitis with positive ANCA. These are usually associated with specific markers such as myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) (9). Moreover, PR3-ANCA vasculitis is the most frequent subgroup in the West and appears to be associated with greater multiorgan involvement (1).

Microscopic polyangiitis, on the other hand, is a necrotizing vasculitis that mainly affects the capillaries, venules or arterioles and it manifests more frequently as necrotizing glomerulonephritis and/or pulmonary capillaritis, with rare involvement at the digestive level. Medium and small arteries may also be involved in polyangiitis and early diagnosis is important to initiate adequate therapy and prevent organ failure, so a kidney biopsy should be performed for confirmation, although it should not delay the start of treatment (11).

Some limitations of the present case were the delay in diagnosis and the start of treatment; however, its main strength was diagnostic confirmation by anatomopathological study.

CONCLUSIONS

This case demonstrates the importance of a broad differential diagnosis in patients with constitutional symptoms of unknown etiology, in whom the most common causes should be ruled out, without forgetting other conditions that could explain their origin.

The information presented above, combined with the proper use of complementary tests, helps to confirm the diagnosis of disorders that can cause a variety of symptoms, such as the vasculitis described here, and to determine the most accurate therapeutic approach, which required a kidney biopsy in this case. Furthermore, early diagnosis allows for earlier initiation of treatment, which aids in obtaining a better response and avoiding consequences associated with a more severe disease.

ETHICAL CONSIDERATIONS

This case report was approved by the Research Ethics Committee of the Hospital Universitario Puerto del Mar de Cadiz, belonging to the Andalusian Health Service of the Andalusian Regional Government, Spain, according to the minutes of October 30, 2020. Personal details were processed in accordance with the regulations in force in Spain (12).

CONFLICTS OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

None stated by the authors.

REFERENCES

1. **Zazueta-Montiel B, Flores-Suárez LF.** Ruta y retos diagnósticos en vasculitis primarias. *Reumatol Clin.* 2011;7(S3):S1-S6. https://doi.org/bjhttv.
2. **Tenorio-Cañamás MT, Galeano-Álvarez C, Rodríguez-Mendiola N, Liaño-García F.** Diagnóstico diferencial de la insuficiencia renal aguda. *NefroPlus.* 2010;3(2):16-32. https://doi.org/f25sp3.
3. **WHO Scientific Group on Nutritional Anaemias & World Health Organization.** Anemias nutricionales: informe de un Grupo Científico de

la OMS [se reunió en Ginebra del 13 al 17 de marzo de 1967]. Ginebra: World Health Organization; 1968 [cited 2021 Jun 23]. Available from: https://bit.ly/3zPSr53.

4. **Gómez Ramírez S, Remacha Sevilla AF y Muñoz Gómez M.** Anemia en el anciano. *Med Clin (Barc).* 2017;149(11):496-503. https://doi.org/gj66.
5. **Stauder R, Thein SL.** Anemia in the elderly: clinical implications and new therapeutic concepts. *Haematologica*. 2014;99(7):1127-30. https://doi.org/gj7f.
6. **Robalo-Nunes A, Fonseca C, Marques F, Belo A, Brilhante D, Cortez J.** Prevalence of anemia and iron deficiency in older Portuguese adults: An EMPIRE substudy. *Geriatr Gerontol Int*. 2017;17(11):1814-22. https://doi.org/gj7g.
7. **Muñoz M, Gómez-Ramírez S, Kozek-Langeneker S, Shander A, Richards T, Pavía J, *et al.*** «Fit to fly»: overcoming barriers to preoperative haemoglobin optimization in surgical patients. *Br J Anaesth.* 2015;115(1):15-24. https://doi.org/gj7h.
8. **Hamroun A, Frimat M, Beuscart JB, Buob D, Lionet A, Lebas C, *et al.*** Spécificités des néphropathies du sujet âgé. *Nephro Ther.* 2019;15(7):533-52. https://doi.org/ghb43w.
9. **Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, *et al.*** 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013;65(1):1-11. https://doi.org/b7cw.
10. **Guchelaar NAD, Waling MM, Adhin AA, van Daele PLA, Schreurs MWJ, Rombach SM..** The value of anti-neutrophil cytoplasmic antibodies (ANCA) testing for the diagnosis of ANCA-associated vasculitis, a systematic review and meta-analysis. *Autoimmun Rev.* 2021;20(1):102716. https://doi.org/gj7j.
11. **Jayne D.** The diagnosis of vasculitis. *Best Pract Res Clin Rheumatol*. 2009;23(3):445-53. https://doi.org/bxrdzm.
12. España. Jefatura del Estado. Ley Orgánica 3 de 2018 (diciembre 5): de Protección de Datos Personales y garantía de los derechos digitales. Madrid: Boletín Oficial del Estado 294; diciembre 6 de 2018.

https://doi.org/10.15446/cr.v7n2.90576

THYROID STORM AND THERAPEUTIC PLASMA EXCHANGE. CASE REPORT

Keywords: Thyrotoxicosis; Plasmapheresis; Thyroid Storm.
Palabras clave: Tirotoxicosis; Plasmaféresis; Crisis tiroidea.

Adrián Bolívar-Mejía
Universidad Pontificia Bolivariana - School of Health Sciences - Department of Cardiology - Medellín - Colombia.

Oriana Qasem-Gómez
Clínica Nueva - Emergency Department - Bogotá D.C. - Colombia.

Santiago Sánchez-Pardo
Clínica Colsanitas - Department of Internal Medicine - Bogotá D.C. - Colombia.

José García-Habeych
Universidad del Rosario - School of Medicine and Health Sciences - Department of Nephrology - Bogotá - Colombia.

Susana Echavarria-García
Universidad Pontificia Bolivariana - School of Health Sciences - Department of Anesthesiology - Medellín - Colombia.

Corresponding author
Santiago Sánchez-Pardo.
Departamento de Medicina Interna,
Clínica Colsanitas. Bogotá D. C. Colombia.
E-mail: sasanchez21@hotmail.com.

Received: 16/09/2020 **Accepted:** 11/03/2021

RESUMEN

Introducción. La tormenta tiroidea es una afectación orgánica severa que se produce por la liberación de triyodotironina (T3) y tiroxina (T4). Su incidencia es de 0.20 casos por cada 100 000 habitantes y puede conllevar a una mortalidad de hasta el 30%. Esta es una entidad refractaria para la cual existen pocas opciones terapéuticas, siendo la terapia de intercambio plasmático una estrategia potencialmente útil para su manejo.

Presentación del caso. Paciente femenina de 17 años quien ingresó al servicio de urgencias de una institución de tercer nivel de atención por un cuadro clínico de aproximadamente 25 días de evolución consistente en palpitaciones, disnea en reposo, ortopnea, dolor torácico y abdominal, astenia, adinamia, mareo, cefalea y deposiciones líquidas; como antecedentes presentaba hipertiroidismo en manejo ambulatorio. Dada la sintomatología y gracias a que se obtuvo un puntaje de 65 en la escala de Burch-Wartofsky, se diagnosticó tormenta tiroidea, se dio orden de hospitalización y se inició manejo farmacológico, con el cual no se logró una mejoría. Al tercer día de hospitalización la joven presentó deterioro clínico continuo y un episodio convulsivo, por lo que se consideró tormenta tiroidea refractaria que fue tratada satisfactoriamente con terapia de intercambio plasmático como terapia puente previo a tiroidectomía total de urgencia.

Conclusión. La terapia de intercambio plasmático permite una rápida remoción de las hormonas tiroideas y, aunque su implementación no es ampliamente difundida por las guías de práctica clínica, existe evidencia que demuestra una disminución en el riesgo de complicaciones perioperatorias y una evolución exitosa tras su uso como terapia puente previo a tiroidectomía en pacientes con tormenta tiroidea refractaria.

ABSTRACT

Introduction: Thyroid storm is a life-threatening condition caused by an elevated release of T3 and T4. Its incidence is 0.20/100 000 inhabitants, with reported mortality rates of up to 30%. Due to its refractory nature, few therapeutic options are available, but plasma exchange is considered a potentially useful strategy for its treatment.

Case presentation: A 17-year-old female patient was admitted to the emergency department of a tertiary care institution due to the onset of symptoms approximately 25 days before consultation, consisting of palpitations, dyspnea at rest, orthopnea, chest and abdominal pain, asthenia, adynamia, dizziness, headache, and liquid stools. In addition, the patient had a history of hyperthyroidism treated on an outpatient basis. Thyroid storm was diagnosed considering the symptoms and a score of 65 on the Burch-Wartofsky scale. As a result, the patient was admitted to the hospital, and pharmacological management was initiated, although no improvement was achieved. On the third day of hospitalization, her condition deteriorated and she had a seizure, which led to consider a refractory thyroid storm. This condition was satisfactorily treated with plasma exchange as a bridge therapy prior to emergency thyroidectomy.

Conclusion: Plasma exchange therapy allows a rapid removal of thyroid hormones. Although its implementation is not widely disseminated in clinical practice guidelines, there is evidence of a decrease in the risk of perioperative complications and a successful evolution after its use as a bridge therapy before performing thyroidectomy in patients with refractory thyroid storm.

INTRODUCTION

Thyroid storm is a rare clinical condition characterized by the excessive release of the thyroid hormones triiodothyronine (T3) and thyroxine (T4), which affects the functioning of different body systems, generating severe clinical manifestations such as seizures, cardiac arrhythmias, etc. (1,2) Its incidence is 0.2 cases per 100 000 inhabitants and is considered the most severe manifestation of hyperthyroidism based on its associated mortality rates, which can reach up to 30% if it is not recognized and treated immediately (3).

Therapeutic plasma exchange (TPE), also known as plasmapheresis, was first implemented nearly five decades ago to treat hyperthyroidism. At present, however, not all clinical practice guidelines for this disease include it as an alternative for patients in whom thyrotoxicosis has not been treated with other therapeutic measures because there are no high-quality studies evaluating its effectiveness (1,2). Still, there are reports (1-4) that show that using TPE as a rescue measure can produce good results and that it can be considered as a strategy in patients with severe clinical conditions refractory to conventional management.

The following is the case of a patient successfully treated with TPE as a bridge therapy prior to definitive surgical management with emergency thyroidectomy in the context of a thyroid storm refractory to conventional pharmacological treatment.

CASE PRESENTATION

A 17-year-old female student of low socioeconomic status from Magdalena, Colombia, was admitted to the emergency department of a tertiary care institution due to symptoms consisting of palpitations, dyspnea at rest, orthopnea, chest and abdominal pain, asthenia, adynamia, dizziness, headache, and liquid stools for 15 days. The patient did not have a significant family history but reported hyperthyroidism that was being treated on an outpatient basis with 80mg propranolol every 12 hours and 30mg methimazole, 5mg prednisolone and 1mg folic acid daily.

On admission, physical examination revealed tachycardia (heart rate: 142 bpm), third heart sound (S3), exophthalmos (Figure 1), class III enlarged thyroid gland with a painful goiter and grade 3 edema in lower limbs; no fever was reported, and blood pressure was 110/60 mmHg. An electrocardiogram showed sinus tachycardia.

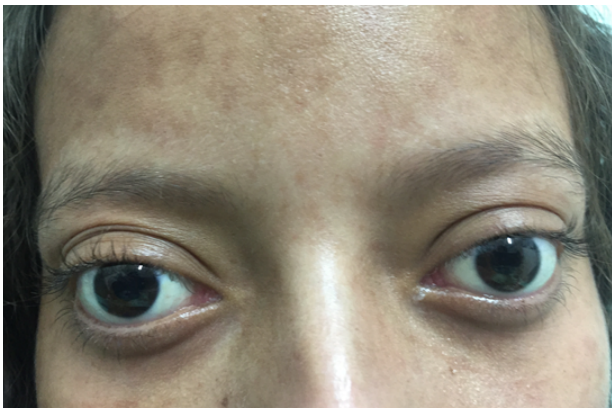


Figure 1. Exophthalmos, a common characteristic of Graves' disease.

Source: Document obtained during the study.

Based on the symptoms and a score of 65 obtained on the Burch-Wartofsky scale, her clinical condition was considered compatible with thyroid storm. Treatment was started with 7 drops of Lugol's iodine every 8 hours during the first 24 hours and then 7 drops daily plus 20mg methimazole every 8 hours, 80mg of propranolol every 8 hours, 100mg cholestyramine IV every 8 hours and 100mg hydrocortisone IV every 8 hours. No clinical improvement was observed for 48 hours. On

the third day of admission, the patient had decreased consciousness and severely elevated blood pressure. Propranolol was discontinued and 1mg/min intravenous labetalol was administered for 24 hours. Also, on the third day of hospital stay, the patient's condition deteriorated and had a convulsive episode that was controlled with intravenous benzodiazepine; no additional electrolyte or metabolic alterations were reported at that time.

Considering that the patient had a thyroid storm refractory to medical treatment, on the fourth day of hospitalization it was decided to initiate TPE as a bridge therapy prior to total emergency thyroidectomy. Following the first and only plasmapheresis session, a significant decrease in thyroid hormone levels was achieved and no associated complications were observed (Table 1). The results achieved allowed for the discontinuation of labetalol, the reduction of blood pressure, and the improvement of her neurological status. Consequently, the patient underwent total thyroidectomy the next day with no complications. The young woman progressed satisfactorily and was discharged on day 16 of hospitalization with an indication of outpatient treatment with 100mcg levothyroxine daily and 600mg calcium carbonate every 6 hours.

Table 1. Free thyroxine levels during hospitalization and therapeutic plasma exchange and thyroidectomy.

Days of hospital stay	1	2	3 *	4	5 †	6	7	8	9	10	11
Free thyroxine (reference value: 0.9-2.3 ng/dL)		320	100	100	85	85	79.67	37.4	19.94	12.6	9.56

* First day of therapeutic plasma exchange.
† Day of emergency thyroidectomy.
Source: Own elaboration.

Pathology results showed multinodular goiter associated with thyroiditis without malignancy. The patient was monitored by telephone one month after discharge and she reported a reduction in symptoms and adequate adherence to the proposed pharmacological therapy.

DISCUSSION

Thyroid storm can be triggered by stressful conditions including surgical procedures, infections, trauma, Graves' disease, Hashimoto's thyroiditis, molar pregnancy, use of drugs such as amiodarone, or discontinuation of antithyroid treatment in patients with hyperthyroidism (4,5); none of these conditions was identified as a trigger in the case described.

When blood concentrations of thyroid hormones increase, they are more bound to specific receptors (T3 and T4) and interact with segments of nucleic acid that stimulate genetic expression on various tissues and the appearance of multiple clinical manifestations, particularly fever, cardiovascular dysfunction due to tachycardia, atrial fibrillation, and supraventricular arrhythmia. This condition may also cause neurological manifestations such as insomnia, psychosis, confusion, delirium, or seizures; gastrointestinal disorders such as vomiting, diarrhea, or abdominal pain; and other systemic disorders such as liver failure, kidney failure, and disseminated intravascular coagulation (4,5). Although the patient described here presented with many of these manifestations, it is noteworthy that

her neurological symptoms were severe and persisted after implementing and exhausting the available therapeutic options.

As described by Baena *et al.* (6), in 1993 Burch and Wartofsky developed a scale to estimate the probability of developing a thyroid storm according to some clinical features. This tool was successfully implemented in the reported case. Once diagnosed, the management of thyroid storm refractory to pharmacological treatment consists of the administration of propylthiouracil, methimazole, propranolol, radioactive iodine, or emergency thyroidectomy (7). It is important to keep in mind that even though surgical management is an option, the patient should be in the best possible condition before undergoing thyroidectomy, which means considering non-pharmacological interventions to control persistent symptoms and reduce circulating levels of thyroid hormones to the lowest possible concentrations to also reduce the risk of perioperative complications.

In response, TPE was proposed as an adjuvant treatment for refractory thyroid storm in 1970. This strategy helps to control thyrotoxicosis and significantly reduces the risk of perioperative complications, favoring its use as a bridge therapy for emergency thyroidectomy (2). The mechanism of action of TPE acts by removing T3 and T4 hormones that are bound to albumin, plasma proteins and transthyretin, thus balancing the amounts of the hormone in the extravascular and intravascular space. This technique also reduces the number of antibodies that stimulate thyroid hormone release in cases of Graves' disease and the concentration of catecholamines and cytokine 3.

Several studies have shown that TPE can decrease plasma thyroid hormone concentrations by up to 85% in 24 hours, demonstrating that this is an excellent alternative for patients who have been refractory to other conventional therapies, including those with subacute thyroiditis in whom antithyroid drugs are not useful and require corticosteroids (3,7-9).

Although refractory thyroid storm has not been described in the literature, TPE is a viable option to consider when all first-line treatment options fail and progressive clinical deterioration, characterized by heart failure, uncontrolled arrhythmia and/or neurological involvement, occurs, as was the case of the reported patient (8,9). According to authors such as Padmanabhan *et al.* (9), Yamamoto *et al.* (10) and Simsir *et al.* (11), since TPE was introduced as an adjuvant treatment for thyroid storm, more than 300 cases in which TPE was implemented have been reported worldwide. Moreover, in 41.3% of those patients, the use of this therapy was supported by the lack of response to pharmacological management, while in 87% of them, the therapy served as a bridge for total thyroidectomy (11-12).

This information has been the basis of the American Society for Apheresis (ASFA) for considering the use of TPE in the treatment of thyroid storm refractory to pharmacological management, establishing it as a grade 3 recommendation (7-9). Padmanabhan *et al.* (9) recommended 3 to 6 sessions based on the response observed. However, it is worth highlighting that in the case described here, a single session was required to stabilize the patient sufficiently to be taken to emergency thyroidectomy, obtaining a good postoperative course. This is relevant because additional sessions at a cost of approximately 204 USD each were avoided (2016). Potential associated risks such as hypocalcemia, air embolism or allergy to the implemented components were also avoided.

Consequently, the present case highlights the importance of considering TPE as part of the treatments available for patients with thyroid storm associated with severe symptoms that are refractory to pharmacological management

according to current clinical practice guidelines (12). It also describes a successful experience in which a single plasmapheresis session managed to clinically stabilize the patients, so that she could undergo emergency thyroidectomy and have an adequate postoperative course. Thus, it is evident that this is a field of research that requires further studies to consolidate with better evidence the benefits of TPE as a rescue measure in patients with thyroid storm.

CONCLUSION

This is the case of a patient with severe thyroid storm who was successfully treated with TPE as bridge therapy prior to total thyroidectomy. Given the results, it is concluded that this therapy could be considered in patients refractory to pharmacological management in order to rapidly decrease circulating levels of thyroid hormones prior to surgery.

ETHICAL CONSIDERATIONS

For the preparation of this case report, the patient signed an informed consent form, authorizing the publication of her pictures and clinical information.

CONFLICT OF INTEREST

None stated by the authors.

FUNDING

None stated by the authors.

ACKNOWLEDGMENTS

To the patients because they are the purpose of our study and to hospital staff for taking care of them.

REFERENCES

1. **Haley PA, Zabaneh ID, Bandak DN, Iskapalli S.** The Resolution of thyroid storm using plasma exchange and continuous renal replacement therapy. JABB. 2018;20(1):1-4. https://doi.org/gfm3.
2. **Zhu L, Zainudin SB, Kaushik M, Khor LY, chng CL.** Plasma exchange in the treatment of thyroid storm secondary to type II amiodarone-induced thyrotoxicosis. *Endocrinol Diabetes Metab Case Rep.* 2016;2016:160039. https://doi.org/gfms.
3. **Cheat JM, Ng D, Low MY, Foo SH.** Weathering the crisis: a case of thyroid crisis with propranolol-induced circulatory collapse successfully treated with therapeutic plasma exchange. *J ASEAN Fed Endocr Soc.* 2019;34(2):206-9. https://doi.org/gfk3.
4. **Bolaños-Rodríguez H, Alvarado-Vega A, Salas-Segura D.** Plasma separación en el manejo de la tormenta tiroidea: reporte de un caso. Acta méd. *Costarric. 2016;58(1):41-3.*
5. **Devereaux D, Tewelde SZ.** Hyperthyroidism and thyrotoxicosis. *Emerg Med Clin North Am.* 2014;32(2):277-92. https://doi.org/f53stw.
6. **Baena JC, Padilla J, Guzmán G.** Tormenta tiroidea asociada a disfunción multiorgánica. *Medicina* (B. *Aires).* 2017;77(4):337-40.
7. **Keklik M, Kaynar L, Yilmaz M, Sivgin S, Solmaz M, Pala C, *et al.*** The results of therapeutic plasma exchange in patients with severe hyperthyroidism: a retrospective multicenter study. *Transfus Apher Sci.* 2013;48(3):327-30. https://doi.org/f44fnt.
8. **Muller C, Perrin P, Faller B, Richter S, Chantrel F.** Role of plasma exchange in the thyroid storm. *Ther Apher Dial.* 2011;15(6):522-31. https://doi.org/d7pz4k.
9. **Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, *et al.*** Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. *J Clin Apher.* 2019;34(3):171-354. https://doi.org/gj3qgn.

10. **Yamamoto J, Dostmohamed H, Schacter I, Ariano RE, Houston DS, Lewis B, *et al.*** Preoperative therapeutic apheresis for severe medically refractory amiodarone-induced thyrotoxicosis: a case report. *J Clin Apher.* 2014;29(3):168-70. https://doi.org/f56528.
11. **Simsir IY, Ozdemir M, Duman S, Erdogan M, Donmez A, Ozgen AG.** Therapeutic plasmapheresis in thyrotoxic patients. *Endocrine.* 2018;62(1):144-8. https://doi.org/gfcmns.
12. **Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH.** 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. *Eur Thyroid J.* 2018;7(4):167-86. https://doi.org/gfch6h.

Universidad Nacional de Colombia
Bogotá Campus ~ Bogotá D. C., Colombia
Faculty of Medicine • Building 471 • Office 219
Telephone numbers: 3165000 Ext. 15161 • Bogotá, D.C., Colombia
http://unal.edu.co/
email: casereport_fmbog@unal.edu.co
Web: https://revistas.unal.edu.co/index.php/care/index