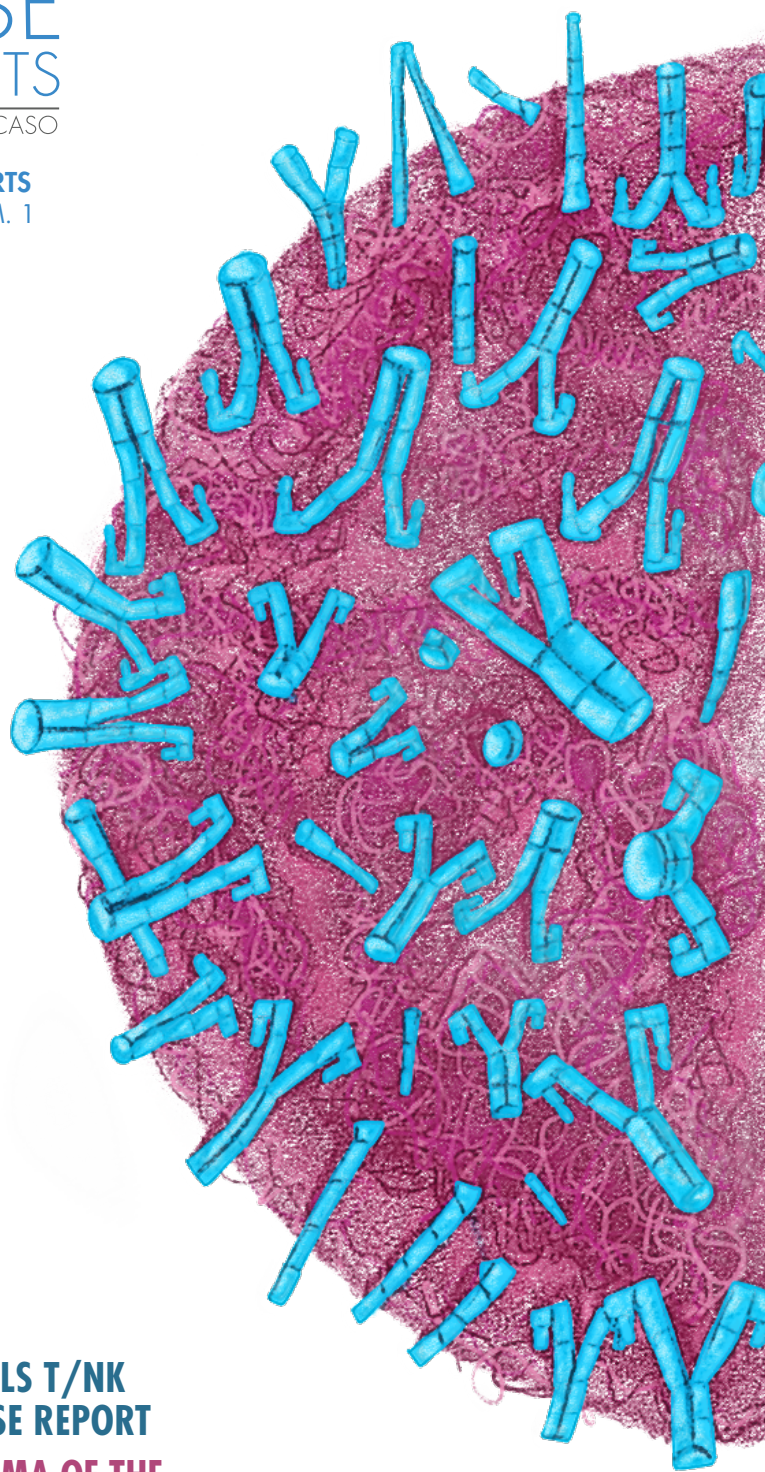
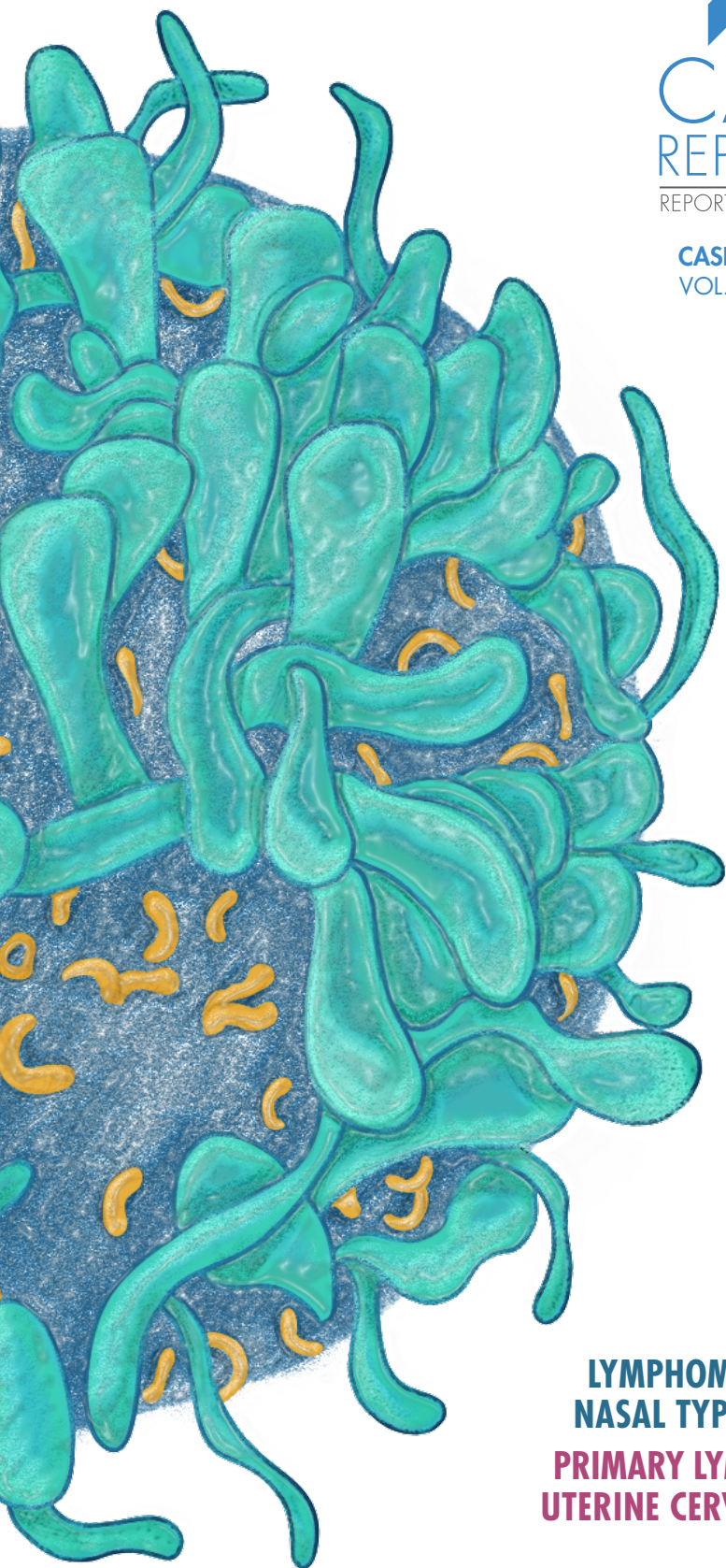




CASE
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REPORTES DE CASO

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VOL. 7 NUM. 1



**LYMPHOMA CELLS T/NK
NASAL TYPE: CASE REPORT**
**PRIMARY LYMPHOMA OF THE
UTERINE CERVIX: CASE REPORT**



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LYMPHOMAS IN DAILY PRACTICE. A DIFFERENTIAL DIAGNOSIS THAT SHOULD BE CONSIDERED

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In this issue of Case Reports, two papers describe the cases of middle-aged patients with lymphomas in different locations. Thus, this editorial is a good opportunity to draw the medical community's attention to the relevance of this disease.

Lymphomas are a type of cancer characterized by the proliferation of malignant cells in lymphoid tissues; they may have different locations, ranging from the lymph nodes (which increase in volume) to any organ with lymphatic cells, such as the kidney, gastrointestinal system, and even, as in the cases described here, the cervix, (1) nose, and sinuses (2).

The low specificity of symptoms in extranodal lymphomas hinders timely patient consultation, making the diagnostic process difficult and, as a result, delaying disease detection. This forces the first contact physician and the specialists who provide more complex care to be constantly alert to diagnose these entities. It should be noted that, according to the National Cancer Institute, the annual rate of new cases of non-Hodgkin lymphoma is 19.6 per 100 000 inhabitants (3).

Although symptoms such as fever, night sweats, weight loss, and fatigue are rather nonspecific, they should alert physicians to the possibility of lymphoma. Therefore, the diagnostic effort should involve a comprehensive medical history, complete blood count, and diagnostic imaging to explore possible organ involvement. This initial approach defines whether patients require biopsy, either lymph node, solid organ, or bone marrow biopsy.

The classification system for lymphomas is complex and has changed throughout history. For that reason, pathologists are very committed to reading and analyzing the specimens provided to them.

Although all the above seems obvious, tertiary and quaternary care hospitals often receive patients with advanced cancer making it difficult to explain the delay in diagnosis.

On the other hand, in recent decades, the research and development of new treatment schemes have markedly improved the prognosis of this group of malignancies, with five-year survival rates of between 70% and 80%, which could increase if the diagnosis is achieved early.

In summary, high suspicion, clinical effectiveness for early diagnosis, and timely initiation of therapies should be the medical community's goal to treating not only lymphomas, but any disease.

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EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE: CASE REPORT

Keywords: Lymphoma; Cellulitis; Sinusitis; Herpesvirus 4, Human; T lymphocytes.

Palabras clave: Linfoma; Celulitis; Sinusitis; Herpesvirus Humano 4; Linfocitos T.

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RESUMEN

Introducción. El linfoma extranodal nasal de células T/natural killer (ENKL) es un linfoma no Hodgkin altamente agresivo y de etiología desconocida. Sus manifestaciones clínicas suelen ser obstrucción nasal, epistaxis y signos inflamatorios; sin embargo, el diagnóstico puede llegar a ser difícil, requiriendo histopatología e inmunohistoquímica para su detección. Como tratamiento se han propuesto radioterapia y quimioterapia, según el estadio de la enfermedad.

Presentación del caso. Paciente masculino de 44 años de edad, previamente sano, quien asistió al servicio de consulta externa por cuadro clínico de 2 meses de evolución consistente en síntomas de obstrucción y secreción nasal, edema y eritema facial. Se realizó diagnóstico inicial de celulitis facial, pero dado que no hubo mejoría con el tratamiento antibiótico, el sujeto fue remitido al servicio de urgencias de una institución de mayor complejidad, donde se le practicaron imágenes complementarias que mostraron una masa en la cavidad nasal derecha; mediante análisis histopatológico se estableció que se trataba de un ENKL, por lo que se indicó radioterapia; sin embargo, a consecuencia del estadio avanzado de dicha patología, el paciente falleció.

Conclusión. El diagnóstico oportuno de ENKL es crucial para mejorar la expectativa de vida de quienes lo padecen; sin embargo, puede representar un reto clínico debido a su presentación inespecífica.

ABSTRACT

Introduction: Extranodal NK/T-cell lymphoma, nasal type (ENKL), is a highly aggressive non-Hodgkin's lymphoma of unknown etiology. Clinical manifestations are usually nasal obstruction, epistaxis, and inflammatory signs. Diagnosis can be difficult to achieve and requires histopathology and immunohistochemistry studies. Radiotherapy and chemotherapy have been proposed as treatment, depending on the stage of the disease.

Case presentation: A 44-year-old male patient, previously healthy, attended the outpatient service due to clinical nasal obstruction, secretion, edema, and facial erythema for 2 months. Facial cellulitis was initially diagnosed, but since there was no improvement with antibiotic treatment, the patient was referred to the emergency department of a higher complexity center, where complementary imaging showed a mass in the right nasal cavity. A histopathological analysis established that it was an ENKL, so radiotherapy was indicated; however, as a result of the advanced stage of this neoplasm, the patient died.

Conclusion: Timely diagnosis of ENKL is crucial to improve life expectancy. Nevertheless, it may represent a clinical challenge due to its nonspecific presentation.

INTRODUCTION

Lymphomas account for 3-5% of malignant tumors, and non-Hodgkin's lymphomas (NHL) account for 60% of all lymphomas (1). Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKL), is a type of non-Hodgkin lymphoma that accounts for about 75% of nasal lymphomas. It is commonly found in immunocompetent people and is considered a rare neoplasm (2).

Its prevalence in the US is about 1.5%, while in Asia and Latin America, it reaches up to 8%. Mexico, Guatemala, and Peru are the countries with the most reports of this disease in Latin America. However, it should be noted that there are still no statistical data to establish a relationship between the geographical location of patients and the development of this type of tumor (1,3).

In Colombia, between 12 and 15 new cases of ENKL occur every year, with a male-to-female ratio ranging from 2:1 to 3:1 and predominance in the regions of Antioquia, Bogotá, and Valle del Cauca. It has an aggressive course, and its prognosis is severe, with an average survival rate between 6 and 25 months (4).

Although the etiology of this disease is unknown, some authors consider Epstein-Barr virus as an oncogenic factor because this infection causes neoplastic transformation of natural killer (NK) cells. Moreover, this herpesvirus has been found in almost all patients with ENKL and persists in studies in people with poor response to treatment (3-5).

The standard technique for identifying tissues with lesions containing Epstein-Barr virus is molecular detection of ribonucleic acid (RNA) by in situ hybridization, which identifies the non-coding nuclear RNA produced by the virus in the latent phase of its infection cycle. In addition, immunohistochemistry techniques are available to identify virus proteins such as LMP1 and LMP2A (6).

80% of ENKL present in the nostrils, paranasal sinuses, and upper aerodigestive tract, but sometimes it may occur in the skin, gastrointestinal tract, testicles, kidney, and, to a lesser extent, in the eyes or orbital cavities (1). Batra *et al.* (7) state that regional lymph nodes are only involved until the tumor spreads.

The initial signs and symptoms of ENKL are usually localized in the nasal region and include nasal obstruction and chronic rhinorrhoea, with nasal septum perforation (up to 40% of cases) and edema of the soft or hard palate caused by the formation of a deep necrotic ulceration in this area, which destroys the tissues of the palate and, occasionally, may generate oronasal communication (1,8). B symptoms (fever, weight loss, night sweats, and anemia) are occasionally reported and are usually detected in advanced stages (9).

NK cells are a lineage of lymphocytes that are part of the innate immune response mediated by molecules of the major histocompatibility complex class I. They have cytolytic functions in settings such as viral diseases or neoplasms (10,11).

Histopathological diagnosis of ENKL may be difficult to achieve due to extensive tissue necrosis. Thus, multiple biopsies are often required (4), showing large pleomorphic cell imaging with angiocentric distribution of tumor cells and angiodestruction. It is worth mentioning that the latter simulates a vascular inflammatory process with histiocytic proliferation and that it is induced by neoplastic cells that invade the vascular walls of normal tissue with generalized necrosis due to the resulting thrombosis (12).

CASE PRESENTATION

A 44-year-old male patient, mestizo, resident in the municipality of San Joaquín, Santander (Colombia), from a lower-income household and a farmer, attended consultation due to a 2-month

history of mucinous nasal secretion associated with edema around the eyes and on the right side of the face, feeling of fullness in the right ear, nasal tamponade, and odynophagia. The patient, who stated that he had no previous respiratory infection events or relevant exposures or history, was initially assessed by the outpatient service and prescribed with two antibiotic regimens (amoxicillin and amoxicillin-clavulanate) without

improvement. For this reason, he was referred to the emergency department of a tertiary care center in Bucaramanga, Colombia.

Physical examination on admission to the emergency department revealed periorbital edema and right hemiface edema, preserved eye movements and erythema associated with posterior pharyngeal drip. Lab test results showed pancytopenia (Table 1).

Table 1. Blood count on admission and on the fifth day of antimicrobial treatment.

Test	21/05/2018	26/05/2018
Hemoglobin	10.3 g/dL (12-16 g/dL)	9.2 g/dL (12-16 g/dL)
Hematocrit	30.8% (37-47%)	26.6% (37-47%)
Complete white blood cell count	1.5 10^3 /ul (5.10 10^3 /ul)	1.560 10^3 /ul (5.10 10^3 /ul)
Neutrophils	75.6% (50-62%)	77.9% (50-62%)
Absolute neutrophil count	1.130	1.215
Lymphocytes (%)	18.3% (25-40%)	8.16% (25-40%)
Monocytes %	5.12% (3-7%)	11.6% (3-7%)
Mean corpuscular hemoglobin	27.1 pg (26-34pg)	27.1 pg (26-34pg)
Mean corpuscular volume	81.3fL (82-98fL)	80.1fL (82-98fL)
Platelets	59.000 10^3 /uL (150-500 10^3 /uL)	55.800 10^3 /uL (150-500 10^3 /uL)

Source: Own elaboration.

The first diagnosis was facial and periorbital cellulitis, which were treated with an in-hospital antibiotics: ampicillin/intravenous sulbactam 3g (IV) every 6 hours plus clindamycin 600mg IV every 6 hours. Due to the persistence of the symptoms, a computed tomography (CT) scan of paranasal sinuses was performed, finding a soft

tissue mass in the right nasal cavity with extension to nasopharynx and ethmoidal air cells. Based on the results of the CT scan, benign neoplasm and polyposis were suspected (Figure 1). The patient was assessed by the Otolaryngology Service, which ordered a fiberoptic nasolaryngoscopy, finding a polypoidal lesion in the right nasal fossa.

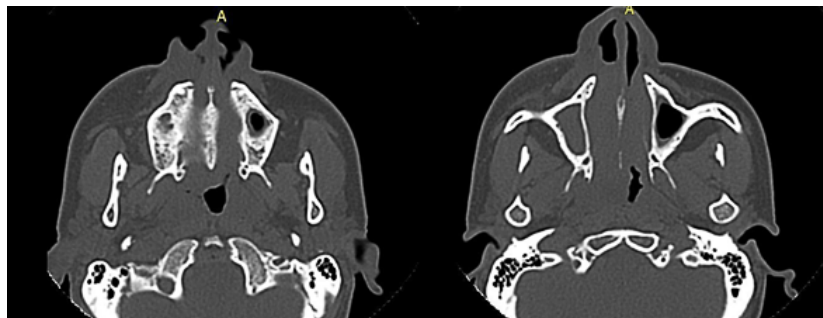


Figure 1. Computed tomography scan, axial plane, of paranasal sinuses, showing the nasopharynx and maxillary sinus, with evidence of mass in the right nasal cavity and areas of bone erosion into the nasal septum.

Source: Document obtained during the course of the study.

On the fifth day of in-hospital antibiotic treatment, the patient reported exacerbation of odynophagia and persistence of inflammatory signs on the right side of the face and subsequent purulent discharge. A new blood count was performed, revealing persistence of pancytopenia (Table 1). Therefore, it was decided to escalate antibiotic therapy to 4.5g piperacillin/tazobactam IV every six hours and perform a CT scan of the neck that reported thickening of the pharyngeal mucosa with inflammatory changes and possible tumor lesion. The patient was again assessed by the Otolaryngology Service, which found a partially necrotizing polypoid lesion with abundant secretions. At this point, the proposed treatment was posterior-to-anterior

ethmoidectomy plus maxillectomy to eradicate the infectious focus.

Once the antibiotic therapy was completed, the patient was taken to surgery. Tissue samples were obtained for histopathological study. While awaiting the pathology report, the patient presented ophthalmoplegia, so a possible orbital cellulitis was considered. Consequently, the antibiotic regimen was switched to ceftriaxone plus vancomycin. Furthermore, a CT scan of the orbital cavities was requested (Figure 2), which showed preseptal cellulitis of the right orbit with displacement and compression of ocular structures that led to suspect a highly malignant neoplasm (nasal adenocarcinoma versus lymphoma).

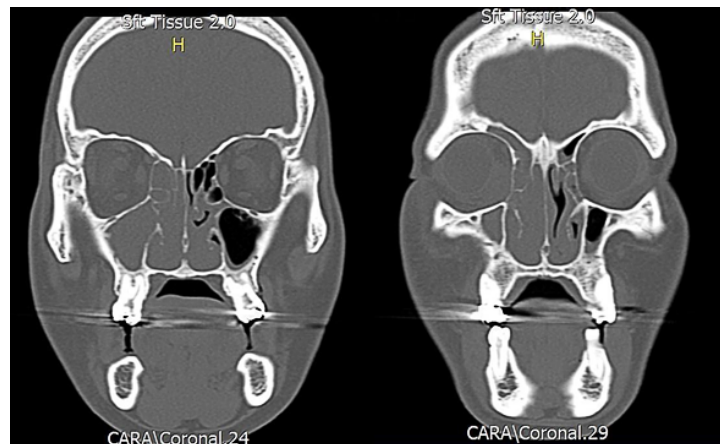


Figure 2. Computed tomography, axial plane, of orbital cavities showing infiltrative lesion of the right orbit.

Source: Document obtained during the course of the study.

Finally, the pathology report concluded that the patient had a high-grade lymphoproliferative syndrome. Immunohistochemistry, morphology and immunophenotype studies were compatible with ENKL, CD3, CD4, CD5, CD7 and CD8 were positive, and aberrant expression was established in *BCL2*, *CD56* and *CD30*. The patient was referred to the radiation oncology department, which started radiation therapy on the affected area (only 22 of the 25 sessions

prescribed were completed). The progression of the disease in the parapharyngeal space during treatment caused severe mechanical dysphagia that required a gastrostomy to ensure the patient's feeding route.

Due to the advanced stage of his disease, the outpatient hematology and oncology service indicated initiation of chemotherapy. However, the patient was unable to receive such treatment due to significant body weight loss and

icteric syndrome associated with signs of systemic inflammatory response with suspected abdominal sepsis secondary to non-obstructive intrahepatic cholestasis and pseudomembranous colitis. Despite antibiotic coverage (4.5g piperacillin-tazobactam IV every 6 hours and 500mg metronidazole every 8 hours due to gastrostomy), the patient had a torpid course and died.

DISCUSSION

T/NK cell lymphomas, formerly known as lethal midline granulomas, are neoplasms derived from mature T and NK cells; of these, ENKL is more common in Asian and Latin American populations (3).

The first clinical manifestations of ENKL are usually local and the most common symptoms include epistaxis, mass sensation, nasal obstruction, and face pain and swelling (5); the latter two were observed in the reported patient. Soft or hard palate edema may also occur, which occasionally progress to deep necrotic ulceration, as in this case.

Since the clinical course of ENKL varies depending on the stage of the disease, it is common that differential diagnoses, such as acute or chronic sinusitis, are considered early in the disease, as well as infectious processes of fungal etiology (fungal rhinosinusitis) with multiple treatments without improvement. Regarding disease progression, other differential diagnoses to consider in the presence of B symptoms include squamous cell carcinoma and nasopharyngeal non-keratinizing carcinoma, which are clinically similar to ENKL (only in immunohistochemistry), lymphomatoid granulomatosis, which is caused by B cells, and diffuse B-cell lymphoma in elderly patients, which has no regular involvement in the sinus or nasal area (3,5,12).

ENKL diagnosis is usually histological. Studies reveal angiodestruction with zonal

necrosis, cell biomarkers such as CD2 and expression of CD3 and CD56 in the cytoplasm and cytotoxic proteins in the azurophilic granules of tumor cells (13-15), as in the present case, where the pathology service reported the presence of a high-grade lymphoproliferative syndrome and immunohistochemistry with morphology and immunophenotype compatible with ENKL, in addition to positive CD3, CD4, CD5, CD7 and CD8.

The prognosis of ENKL is based on different parameters, but the International Prognostic Index is used to determine the probability of therapeutic success and survival of patients (16). Factors such as being older than 60 years, having T-cell phenotype lymphoma, having B symptoms, and identifying a high-grade tumor contribute to patients' worse prognosis. Survival rates at 5 years are reported in 25% of tumors that predominate in the nasal cavity; this time is shorter than in patients with tumors that only involve the paranasal sinuses (1).

Treatment of ENKL should include radiation therapy, especially in early stages, and should be supplemented with advanced-stage chemotherapy, as together they offer better disease-free survival rates. Recent evidence shows that NK cells express high concentrations of P-glycoprotein, which confers resistance to anthracycline-based chemotherapy. This has led to propose new regimens based on the use of L-asparaginase (17,18).

New problems have arisen as a result of this change in the treatment of ENKL patients. Other indices have been proposed in addition to the use of L-asparaginase-based treatments, such as the Prognostic Index of Natural Killer Lymphoma, which is intended specifically for patients treated with non-anthracycline chemotherapy regimens (19,20).

Although the clinical signs in this case are consistent with the literature, one of the

most significant limitations was the lack of an early diagnosis to determine a treatment that improved the disease's prognosis. Furthermore, due to the patient's progressive clinical deterioration, it was not possible to supplement radiation therapy with chemotherapy sessions, which could have slowed the lymphoma's progression.

CONCLUSION

ENKL is an aggressive, rapidly progressive infiltrative neoplasm that usually appears in the nasal cavity and perinasal regions but may also appear anywhere in the body. Its timely diagnosis is crucial to improving life expectancy; however, it may pose a clinical challenge due to its nonspecific presentation, often mistaken for multiple diseases. The presentation of this case aims to encourage health care professionals to consider this entity as a differential diagnosis in similar cases.

ETHICAL CONSIDERATIONS

The patient's authorization was obtained by means of an informed consent form for the preparation of this case report.

CONFLICTS OF INTEREST

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PRIMARY LYMPHOMA OF THE UTERINE CERVIX: CASE REPORT

Keywords: Cervix Uteri; Lymphoma; Neoplasms.
Palabras clave: Cuello uterino; Linfoma; Neoplasias.

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RESUMEN

Introducción. El linfoma primario del cuello uterino es una patología infrecuente, de síntomas inespecíficos y que pocas veces altera el examen de citología del cuello uterino dado que se desarrolla en el estroma cervical. Para su tratamiento existen varias opciones, incluyendo quimioterapia, radioterapia y cirugía, así como combinaciones de estas. La localización única del linfoma en el cuello uterino se considera un factor de buen pronóstico.

Presentación del caso. Paciente femenina de 49 años, quien consultó por dolor pélvico y flujo y sangrado genital. Se ordenó colposcopia por reporte de ASC-H (células escamosas atípicas que no excluyen lesiones intraepiteliales de alto grado) en citología vaginal. La biopsia reportó linfoma difuso de células B grandes, el cual se trató con rituximab, ciclofosfamida, doxorubicina, vincristina y prednisolona por tres ciclos, y con rituximab, ifosfamida, carboplatino y etopósido por dos ciclos; este cambio se hizo debido a una mala respuesta con el primer esquema. Se realizó nueva biopsia después del último ciclo de quimioterapia con reporte de pólipo de tipo endocervical y abundantes grupos de células glandulares con atipia focal. Los estudios de imágenes diagnósticas posteriores al tratamiento reportaron engrosamiento concéntrico de la unión entre cuello uterino y vagina. A los 7 años del diagnóstico del linfoma se realizó otra biopsia que resultó negativa para displasia o malignidad. Al momento de la elaboración del presente reporte, 10 años después del diagnóstico, la paciente se encontraba asintomática y libre de enfermedad.

Conclusiones. El linfoma primario del cuello uterino es una patología rara que en pocas oportunidades se evidencia con anormalidad en la citología vaginal como en el caso reseñado. Dado

este hallazgo se realizó una colposcopia mediante la cual se confirmó el diagnóstico de linfoma difuso de células B grandes. Se presenta un caso con evolución satisfactoria y supervivencia libre de enfermedad después de 10 años.

ABSTRACT

Introduction: Primary lymphoma of the uterine cervix is a rare disease, with nonspecific symptoms, that seldom alters Pap smear results since it develops in the cervical stroma. Chemotherapy, radiation therapy, and surgery, as well as their combination, are some of the medical options available for treatment. The unique location of the lymphoma in the cervix is considered a good prognostic factor.

Case presentation: A 49-year-old female patient consulted due to pelvic pain and vaginal discharge and bleeding. She underwent a colposcopy due to cytology findings of ASC-H (atypical squamous cells that do not exclude high-grade squamous intraepithelial lesions). The biopsy reported diffuse large B-cell lymphoma, which was initially treated with three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, and was then switched to two cycles with rituximab, ifosfamide, carboplatin and etoposide due to a poor response with the first scheme. A new biopsy was performed after the last cycle of chemotherapy with a report of endocervical polyp and abundant clusters of glandular cells with focal atypia. Post-treatment diagnostic imaging studies reported concentric thickening of the cervix-vagina junction. Seven years after being diagnosed with lymphoma, another biopsy was performed. The result was negative for dysplasia or malignancy. At the time of writing this case report, 10 years after diagnosis, the patient is asymptomatic and disease-free.

Conclusions: Primary lymphoma of the uterine cervix is an unusual condition that is rarely detected through an abnormal Pap smear result, as in this case. A colposcopy was done because of this finding, confirming the diagnosis of diffuse large B-cell lymphoma. This case report describes the satisfactory evolution of the patient and disease-free survival after 10 years.

INTRODUCTION

Lymphomas are hematologic malignancies that are subdivided into Hodgkin's lymphomas and non-Hodgkin's lymphomas. The latter are the most frequent (1) and, depending on their primary location, are further subdivided into nodal and extranodal (2).

Lymphomas usually grow in the lymphoid organs and can cause systemic symptoms such as fever, night sweats, and weight loss (3). However, non-Hodgkin's lymphomas affect extranodal regions, including the female genital tract, in about a third of patients (4).

Primary lymphoma of the uterine cervix is a rare disease that accounts for only 0.008% of cervical tumors and 2% of female extranodal lymphomas (5,6). Symptoms are usually non-specific and include vaginal bleeding (70%), perineal discomfort (40%) and persistent vaginal discharge (20%) (7).

The diagnosis of primary lymphoma of the cervix can be made when there is no nodal involvement and no other site of extranodal involvement is established at the time of presentation. Mandate *et al.* (8) suggest that these conditions may occur three months before and three months after diagnosis. The most common histological subtype of female genital lymphomas is diffuse large B-cell lymphoma, which is difficult to diagnose. Its detection may be delayed due to the rarity of the disease and the lack of clear clinical symptoms (8).

Most cases are presented in the literature as individual reports and no standard treatment for its management has been established (9).

CASE PRESENTATION

A 49-year-old female patient, Hispanic, from Bogotá, retired from the Colombian Armed Forces, with no relevant medical history other than two full-term pregnancies (one by vaginal delivery and one by cesarean section), consulted due to clinical symptoms consisting of pelvic pain and genital discharge and bleeding that she associated with a Pap smear. Given these symptoms, a transvaginal ultrasound was requested, showing normal findings. No cervical abnormality was found during the gynecological examination.

Due to the persistence of symptoms and a cytology report that indicated ASC-H (atypical squamous cells that do not exclude high-grade intraepithelial lesions), a colposcopy was requested, yielding unsatisfactory results due to incomplete visualization of the transformation zone. However, it was possible to identify a prominent lesion on the anterior lip of the cervix that was described as a dense acetowhite lesion with raised borders.

The biopsy reported diffuse large B-cell lymphoma, and the microscopic report noted: "The sections show endocervical fragments with benign-looking epithelium with focal atypical repair and a diffuse stroma extensively compromised by an intermediate and large size lymphoproliferative lymphocytic neoplasm with small nucleoli and irregular nuclear membrane." The tissue was positive for immunohistochemistry markers CD20, ACL (diffusely), and BCL6 (focally). Furthermore, CD3, CD43, and BCL2 were positive in the accompanying lymphocytes; CD22, KAPPA and Lambda were non-contributory; CD10 and cyclins were negative; and Ki-67 showed a cell proliferation index of approximately 60%.

In the general clinical examination, the patient was in good condition (ECOG 0 scale) and no adenopathies were reported, whereas the gynecological examination revealed a cervix with easy and abundant bleeding and the presence of a raised lesion on the anterior lip. Vaginal examination revealed a 4x4cm diameter lesion in the cervix and pelvic examination showed no alterations or masses in the body of the uterus, nor nodules in the parametria. Liver and kidney function tests were normal.

A computed axial tomography (CAT) scan was requested, which reported a retrouterine, pararectal and left lower retrovesical soft tissue lesion of homogeneous appearance measuring 5.7x7.5x5cm. The bladder did not show any alterations and no other findings of masses, adenopathies or fluid collection were reported. No changes were observed on chest x-ray.

The patient was diagnosed with primary lymphoma of the uterine cervix and was treated with three cycles of rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), which was switched to salvage chemotherapy with two cycles of RICE (rituximab, etoposide, carboplatin, ifosfamide) after obtaining an inadequate response with the first scheme, considering that the CAT scan showed that the size of the lesion had not changed since the previous study. Adverse events to these treatments were mild.

Eight days after completing the second cycle with RICE, a new colposcopy was performed. The biopsy reported acute, chronic, and ulcerated exocervix cervicitis, while the endocervix biopsy showed endocervical polyp and abundant clusters of glandular cells with focal atypia. The patient did not return for consultation with hemato-oncology.

CAT scan images in the following three years reported concentric thickening of the cervicovaginal junction. Seven years after the

diagnosis of primary lymphoma of the cervix, a biopsy was performed, reporting endocervix with muco-hemorrhagic material with loose endocervical glands without atypia, exocervix with mild chronic cervicitis, and negative results for dysplasia or malignancy. The endocervical polyp biopsy was also negative for malignancy.

At the time of writing this report (10 years after diagnosis), the patient was still undergoing gynecologic oncology follow-ups and was asymptomatic and disease-free. Gynecological assessment, Pap smear and ultrasound of the abdomen were normal at her last check-up.

DISCUSSION

Although the reported patient consulted for pelvic pain accompanied by genital bleeding and discharge, which are symptoms of primary lymphomas of the uterine cervix (bleeding is the most common symptom) (7,9), initial assessments showed no abnormality in the cervix. The Pap smear report prompted to perform colposcopy and biopsy and request additional diagnostic imaging scans.

Finding cytological anomalies in this condition is extremely uncommon since diffuse large B-cell lymphoma of the cervix is a stromal disease, and a cytological diagnosis would only be expected when there is ulceration of epithelial cells (5,10).

Primary lymphomas of the uterine cervix are most common in women between the ages of 40 and 59 (11), which is the age range of the reported patient. The correct diagnosis of this condition is often delayed, so the disease is detected in advanced stages mainly due to its low prevalence and the absence of specific clinical symptoms (8).

The most common finding in gynecologic examination of patients with primary lymphomas of the uterine cervix is diffuse thickening of the cervix wall without mucosal abnormality, which

is voluminous and shaped like a “champagne cork” (>4cm in diameter in 50% of cases) and without vegetations or necrosis. It is worth mentioning that squamous carcinoma does present with vegetations and necrosis (12).

The differential diagnosis, besides squamous carcinoma (especially in barrel-shaped presentations), may include cervical myomas, cervical sarcomas, and small-cell carcinomas (13). A biopsy is needed to confirm the diagnosis (14), but it is important to consider that, on occasions, a reactive lymphoma-like lesion can distort the diagnosis (15-17).

Primary lymphomas of the uterine cervix are treated in a variety of ways, and there is no established standard approach (3,8). However, depending on the situation, they have been treated with radiotherapy alone or in combination with surgery and/or chemotherapy, following the general principles of treatment for non-Hodgkin's lymphomas (1,18-20). They have also been effectively treated with combination chemotherapy in regimens such as CHOP, which has two additional advantages: it prevents micrometastases and can preserve fertility in young women (9,21). Rituximab, a chimeric monoclonal antibody that targets the B-cell CD20 antigen, is added to this chemotherapy. It is a human immunoglobulin G1 with a CD20 binding region derived from a mouse monoclonal antibody through genetic engineering (22,23). This addition to the CHOP scheme improves overall survival (24,25).

Approximately 40-60% of patients with low-grade non-Hodgkin lymphoma treated with anthracycline regimens fail to achieve a complete response or relapse after achieving a complete response (26,27), but the addition of RICE has proven to be successful in these cases (28).

Female genital lymphomas, in general, and cervical lymphomas, in particular, have a

worse prognosis than the most common nodal lymphomas (8,29-31). This is explained by inaccurate initial diagnoses and late-onset or failed therapies. However, the prognosis of primary lymphoma of the uterine cervix, when diagnosed early and treated properly, tends to be excellent (24,32,33), with overall five-year survival between 73-86% (31,34).

CONCLUSIONS

Abnormal findings on Pap smear in the reported case led to the diagnosis of cervical neoplasm, allowing for an early diagnosis of primary lymphoma of the uterine cervix. Two chemotherapy regimens were used to treat what appeared to be a stable disease based on medical imaging, but biopsies revealed a full pathological response, and the patient exceeded 10 years of disease-free survival.

ETHICAL CONSIDERATIONS

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

CONFLICTS OF INTEREST

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SPONTANEOUS LUNG HERNIATION: A CASE REPORT

Keywords: Hernia; Lung; Cough; Lung diseases; Lung injury; Thoracic wall.
Palabras clave: Hernia; Pulmón; Tos; Enfermedades pulmonares; Lesión pulmonar; Pared torácica.

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RESUMEN

Introducción. La hernia pulmonar espontánea (HPE) es una protrusión del pulmón en una abertura anormal a través de la pleura parietal que se presenta a nivel de la pared torácica, el diafragma o el mediastino. Esta es una entidad infrecuente de la que solo se han reportado algo más de 300 casos a nivel internacional. A continuación, se presenta el primer caso de HPE reportado en Ecuador.

Presentación del caso. Paciente masculino de 59 años sin antecedentes de trauma, ni patologías respiratorias crónicas, quien asistió al servicio de urgencias por cuadro clínico de 3 días de evolución consistente en hemoptisis, dolor en hemitórax derecho de moderada intensidad, edema, hematoma a nivel submamario y defecto herniario de la pared torácica que se evidenciaba durante los movimientos respiratorios y la maniobra de Valsalva. La tomografía simple de tórax mostró líquido libre en cavidad pleural derecha, infiltrado alveolar en parche, protrusión del segmento medial del lóbulo medio y fracturas desplazadas en la 2°, 3°, 4° y 5° costilla del hemitórax derecho. Se diagnosticó neumonía, derrame pleural y HPE con fracturas costales derechas. Se decidió dar manejo quirúrgico con toracotomía derecha con incisión paraesternal. Luego de 3 meses de postoperatorio, los controles de imagen mostraron correcta disposición de material de osteosíntesis. El paciente no presentó molestias y continuó en seguimiento y con manejo médico multidisciplinario.

Conclusiones. La HPE es una patología infrecuente de diagnóstico principalmente clínico que se caracteriza por dolor torácico, presencia del defecto herniario y en algunas ocasiones antecedente de tos. El diagnóstico actualmente es muy preciso; sin embargo, su tratamiento aún se encuentra en discusión, pero sin dudas la intervención quirúrgica es la opción que aporta mejores resultados debido a la rápida mejoría de los síntomas y a que previene recidivas.

ABSTRACT

Introduction: Spontaneous lung herniation (SLH) refers to a protrusion of the lung into an irregular opening through the parietal pleura occurring at the level of the chest wall, diaphragm, or mediastinum. This is a rare entity, and only about 300 cases have been reported worldwide. The following is the first case of SLH reported in Ecuador.

Case presentation: This is a 59-year-old male patient with no history of trauma or chronic respiratory diseases. He attended the emergency department due to a 3-day history of hemoptysis, moderate pain in the right hemithorax, edema, submammary hematoma, and a chest wall hernia that was evident during respiratory movements and the Valsalva maneuver. A non-contrast chest CT scan showed free fluid in the right pleural cavity, alveolar patchy infiltrate, protrusion of the medial segment of the middle lobe, and displaced fractures in the 2nd, 3rd, 4th and 5th ribs of the right hemithorax. Pneumonia, pleural effusion, and SLH with right rib fractures were diagnosed. Due to the patient's symptoms, surgical management with right thoracotomy with parasternal incision was decided to reduce the herniated lung parenchyma. Three months after surgery, follow-up imaging scans showed correct disposition of the osteosynthesis material. The patient did not present any discomfort, so follow-up and multidisciplinary medical management were continued.

Conclusions: SLH is a very rare condition. Its diagnosis is mainly clinical, characterized by chest pain, presence of the hernial defect and sometimes a history of cough, as in this patient. The diagnosis is currently very precise, but treatment options are still under debate. However, surgical intervention is unquestionably the safest choice for achieving the best outcomes due to the rapid improvement of symptoms and the prevention of recurrences.

INTRODUCTION

Spontaneous pulmonary herniation (SPH) is a protrusion of the lung into an abnormal opening through the parietal pleura that occurs at the level of the chest wall, diaphragm, or mediastinum (1). It can be caused by costal arch fractures without a history of trauma. It has also been reported in cases of chronic coughing patients (2). SPH is a rare entity and only about 300 cases have been reported worldwide (3).

According to its etiology, Morel-Lavallée (4) classified pulmonary hernias as congenital or acquired; in turn, the latter are classified into spontaneous or caused by local and traumatic diseases.

SPHs are usually located at the intercostal space and associated with previous thoracic surgeries, particularly thoracotomies (5,6), or chest trauma (7). SPHs are the least common form of pulmonary hernia, and there are few records of them presenting during a coughing or sneezing episode (8).

SPH is diagnosed primarily based on clinical symptoms such as chest pain and dyspnea, as well as a hernia defect that can be large and mobilized with Valsalva maneuvers and respiratory movements (9). The diagnosis is usually confirmed by an oblique chest x-ray or a non-contrast chest computed tomography (CT) scan in its different planes (10).

While surgery is the most common treatment for SPH, conservative management is still

under debate. It should be noted that there is no standard surgical technique to treat this type of protrusion. However, surgery (11) is indicated to treat the defect with primary closure either by using autologous tissue; synthetic materials such as Teflon, dacron, ivalon, GoreTex® (12) or Marlex®; or osteosynthesis materials designed specifically for the chest wall, such as wire and transcostal sutures, Kirschner wires or pins, metal plates (Judet struts) and titanium plates (7-13). Jheon S *et al.* (14) reported correction by means of videothoracoscopy.

The following is the first case of SLH reported in Ecuador.

CASE PRESENTATION

A 59-year-old male patient, Hispanic, from Guayaquil (Ecuador), an office worker, from a middle-income family, hypertensive, with diabetes under control and no history of surgery, trauma or inherited disease, attended the emergency department of the Hospital Clínica San Francisco of Guayaquil due to a 3-day history of hemoptysis, moderate pain in the right hemithorax, and subsequent appearance of edema and a small hematoma at the right submammary level. He also presented with a hernial defect of the thoracic wall that was noticeable during respiratory movements and the Valsalva maneuver (Figure 1). The patient was able to breathe without supplemental oxygen and his vital signs were stable.

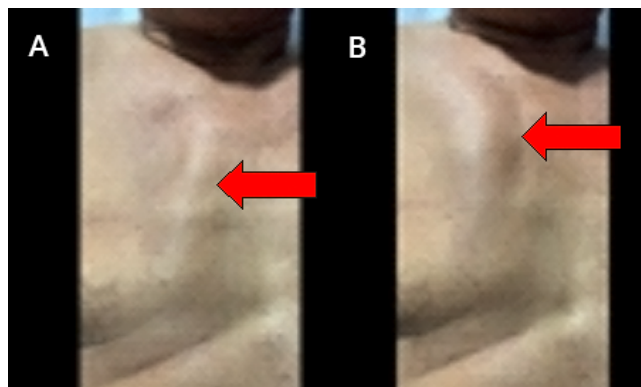


Figure 1. Patient morphology. A) Right parasternal depression during inspiration; B) Pulmonary hernia during Valsalva maneuver.

Source: Document obtained during the course of the study.

On admission, laboratory tests showed leukocytosis of $15.55 \times 10^3/\mu\text{L}$ with 75.4% neutrophilia; all other tests were within normal values. Anteroposterior chest x-ray showed accentuation of bilateral pulmonary interstitium, pleural effusion, and obliteration of right costophrenic and cardiophrenic angles. Pleural ultrasound revealed right pleural cavity with fluid (approximate volume: 1 061 cc with no septa or sediment) and collapse of lower segments with air bronchogram in the right lower lobe.

Moreover, a non-contrast CT of the chest showed free fluid in the right pleural cavity of the aortopulmonary window (Figure 2), alveolar infiltrate in a diffuse distribution patch in the anterior segment of the right upper lobe, protrusion

of the medial segment of the middle lobe and alveolar infiltrate in posterior segments of the right lower lobe, thus indicating the presence of pulmonary parenchyma outside the right pleuropulmonary cavity. On the other hand, a three-dimensional computed tomography reconstruction showed displaced ribs fracture (2nd to 5th rib) in the right hemithorax with collapse next to the median plane in the bony window (Figure 3). Based on these findings, a middle lobe pulmonary herniation with an alveolar pattern was suspected, with possible association with the area of pulmonary contusion, right pleural effusion, multiple costal fractures in right hemithorax and community-acquired pneumonia (CAP).

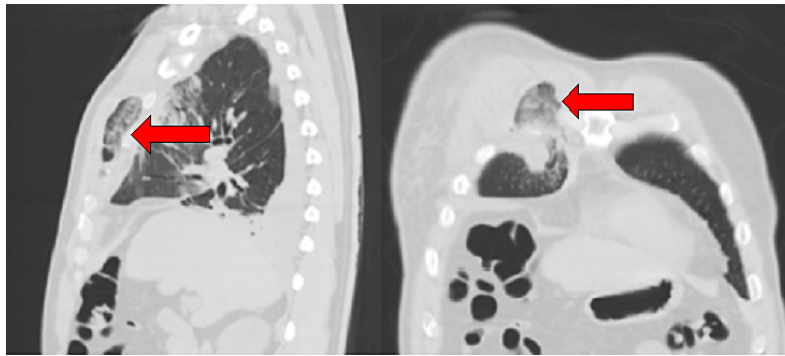


Figure 2. Non-contrast CT of the chest, sagittal and coronal planes.

Source: Document obtained during the course of the study.

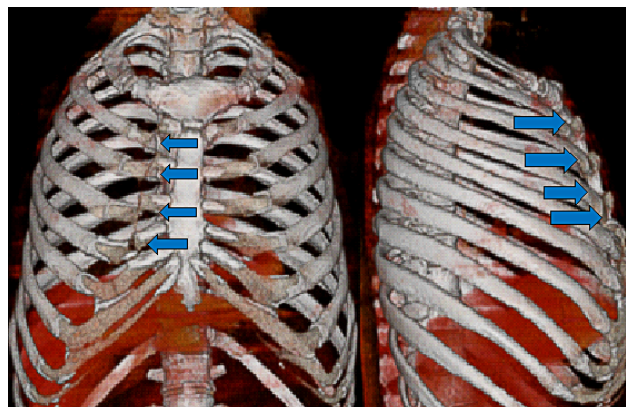


Figure 3. 3D computed tomography reconstruction of the chest, coronal, and sagittal planes.

Source: Document obtained during the course of the study.

Blunt chest trauma and costochondritis were suggested as potential differential diagnoses for this case; however, the patient did not experience any current or previous trauma or chronic pain at the fracture site, so these diagnoses were ruled out.

When the patient was admitted to the emergency department, thoracentesis was also performed placing a 28Fr chest tube on the right side connected to the chest drainage system (Thorametric™). During this procedure, a culture of the fluid was taken, which showed no evidence of bacterial growth and the biochemical study showed exudate according to Light's criteria.

The patient was admitted to the intensive care unit (ICU) after a few hours and was treated for CAP with 1.5g of ampicillin/sulbactam IV every 6 hours for 4 days and 500mg of clarithromycin IV every 12 hours for 7 days. The pulmonology service in the hospital ward decided to switch to intravenous meropenem 1g every 8 hours for 7 days due to the occurrence of fever no higher than 38°C and leukocytosis with no apparent focus other than pulmonary.

After 11 days of hospital stay, due to clinical improvement, the hernial defect was repaired by right thoracotomy with a parasternal incision of ± 10 cm. A hernial defect was found with protruding pulmonary parenchyma (Figure 4) through displaced fractures in the 2nd, 3rd, 4th, and 5th ribs of the right hemithorax. Similarly, reduction of herniated pulmonary parenchyma was performed and deperiostization and osteosynthesis were performed with miniplates and titanium screws between the 3rd and 5th ribs, fixing them to the costochondral junction (Figure 5). Thorametric™ chest drainage was not removed. This surgery, which lasted 120 minutes, ended without complications and the drainage was removed at 48 hours.

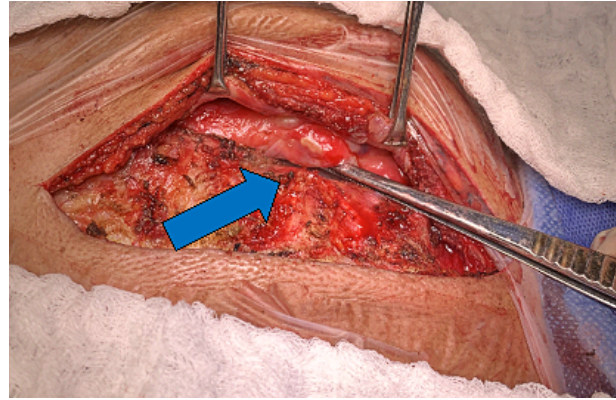


Figure 4. Hernial defect with protruded lung parenchyma.

Source: Document obtained during the course of the study.

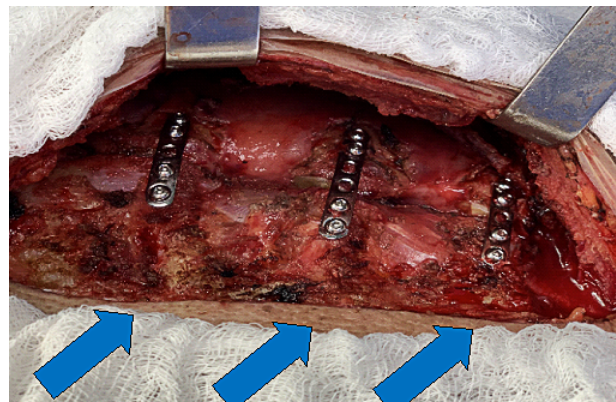


Figure 5. Osteosynthesis material placed at the level of fractures in the 3rd, 4th, and 5th right ribs.

Source: Document obtained during the course of the study.

The patient remained hospitalized for 32 days (4 days in the ICU) and his stay was prolonged due to CAP and persistent leukocytosis. Five days after the surgery, he was discharged from the hospital and follow-up in the outpatient clinic was ordered.

At the time of writing this report, and three months after the surgery, the patient had a satisfactory recovery and was asymptomatic. Follow-up imaging showed correct placement of osteosynthesis material, but he was still monitored by a multidisciplinary team on a regular basis.

DISCUSSION

In Latin America, only one case of SHP was reported in Colombia in 2015, which was solved by video-assisted thoracic surgery (VATS) using a polypropylene mesh (14). Other publications have only reported intercostal or transdiaphragmatic hernias involving abdominal cavity structures (15,16), which are normally the result of thoracoabdominal trauma (17) and are treated with open surgery and prosthetic materials.

Worldwide, reports on SHP are also scarce: Nielsen & Nielsen (18) published a single case in 1971 and Cantó *et al.* (19) presented 7 cases of costal fractures in 1985, of which only 4 had pulmonary herniation, indicating their rarity.

Other authors, such as Mitchell (20), Derbes & Haran (21), Wynn-Williams (22) and Pearson (2), identified pulmonary herniations in tuberculous or chronic bronchitis patients and reported that they were caused by the patients' effort due to repeated coughing. Kronenberger (23), on the other hand, addressed some costal fractures that he referred to as spontaneous, but he did not specify their etiology.

As mentioned above, pulmonary hernias may be congenital or acquired. The former are caused by the weakness of the suprapleural membrane are located in the cervical thorax between the scalene and sternocleidomastoid muscles, and can be seen with Valsalva maneuvers; they are also asymptomatic and disappear with growth. On the other hand, the latter are usually post-traumatic (7) or postoperative due to failure of surgical closure of the thoracic wall, most often after thoracotomies (5-6), but they may also be attributed to malignant neoplasms (metastasis) and, less commonly, cough (24).

It is worth noting that attempts have been made on multiple occasions to link cough to rib fractures as a result of prior conditions such as osteoporosis and senility, which is highly debatable considering that cases have also been reported

in young patients (25). According to Pearson (2), the key factor for determining chest wall weakness is anterior serratus muscle tension for the first 8 ribs and external oblique tension for ribs 6 through 12. Additionally, and under this same concept, Jacka & Luison (11) state that rib fractures may be related to 3 factors: physical constitution, abdominal plethora, and cough in chronic bronchial patients.

SPH was found in the right hemithorax between the 2nd and 5th ribs in this case; however, several authors (7,10-11) claim that they occur more frequently in the left hemithorax and between the 8th and 9th ribs. The involvement of the liver, an organ that prevents the ipsilateral hemidiaphragm from abruptly shifting, is an anatomical reason for the rarity of this form of hernia on the right side. In the case series of Cantó *et al.* (19), of the 7 patients reported, 6 had costal fractures in the anterior hemithorax, as in the patient reported here, and only 1 in the posterior hemithorax.

As in the present case, rib fractures and/or pulmonary hernias are usually accompanied by large hematomas in the thorax that extend to the abdomen. In some patients, pulmonary hernias are the consequence of a previous thoracotomy after receiving mechanical ventilation since the intercostal muscle is weakened by increased intrathoracic pressure with positive pressure (26). It should be noted that lung protrusion is more common in less extensive surgical procedures such as VATS because the form of closure is less meticulous (9).

An anteroposterior chest x-ray usually shows subtle, non-confirmatory changes such as radiopaque lesions similar to an alveolar infiltrate or areas of apparent lung contusion. If SPH is suspected, a non-contrast 3D CT scan reconstruction of the chest should be requested to confirm and identify the anatomy of herniation and determine whether herniation depends on a hernial sac or if it is accompanied by costal

fractures. Likewise, it is important to establish early if there are findings of strangulation that require urgent intervention. Moreover, according to Clark *et al.* (27), some herniations show up very clearly on coronal and sagittal CT planes, giving an overview of the area and extent of the disease and aiding surgical planning.

Regarding the treatment of SPH, there is still debate between conservative and surgical management. In the first case, immobilizing bandages are placed expecting the spontaneous closure of the hernia, provided that it is a minor lesion with mild symptoms; however, some of these patients have COPD and are unable to withstand the bandage.

The decision to opt for surgical treatment is related to clinical findings, recurrence of symptoms (particularly pain), and the presence of chest wall infection or incarceration (10). Surgery is thus indicated to treat the chest wall defect, and sometimes the hernial sac and non-viable tissue must be removed from the herniated lung (11,28).

Other authors report that SPHs can be corrected by video-thoracoscopy (14), although this is not a well-established technique. In the case presented here, there was no need to remove any part of the lung, as there were no drawbacks at the time of reducing the hernia manually and the chest wall defect was corrected without any further problem. Reduction of the pulmonary parenchyma should be considered if there is a possibility of any complication due to pulmonary hypertension or its recurrence. In the present case, since there was a chest wall defect with fractures at the costochondral junction, it was decided to place osteosynthesis material that had both ends of the bone and the sternum as support planes.

CONCLUSIONS

SPH is a rare disorder with a mostly clinical diagnosis that includes pain, involvement of a hernial defect, and a history of cough, although

the latter is unusual. Currently, the diagnosis can be made with great accuracy, and the extent of the hernia and pulmonary involvement can be determined, allowing for surgical care.

Although the treatment for SPH has not been yet established, surgery is the most effective treatment choice due to the rapid improvement of the patient's symptoms and the prevention of recurrence. According to the few studies available on this condition, surgery may be done using an open or a video-assisted approach (none of which is yet protocolized), or even a combination of both approaches, especially if there are rib fractures.

The case presented here is relevant because it demonstrates that the surgical method using miniplate osteosynthesis and titanium screws can achieve optimal results, prevent recurrences, and fully alleviate symptoms. Therefore, this approach may be considered a viable option for the surgical treatment of SPH.

ETHICAL CONSIDERATIONS

The patient provided an informed consent to publish this case report.

CONFLICTS OF INTEREST

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MYXEDEMA COMA AS A CAUSE ASSOCIATED WITH MULTIPLE ETIOLOGIES OF HEART FAILURE

Keywords: Myxedema; Heart Failure; Pulmonary Embolism; Atrial Fibrillation.
Palabras clave: Mixedema; Insuficiencia cardíaca; Embolia pulmonar; Fibrilación atrial.

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RESUMEN

Introducción. El coma mixedematoso representa la máxima y más rara expresión del hipotiroidismo en los adultos. Esta complicación es más frecuente en mujeres ancianas y tiene diversas formas clínicas asociadas como enfermedades con compromiso sistémico, entre ellas la falla cardíaca, el tromboembolismo pulmonar y la fibrilación auricular en pacientes inestables.

Presentación del caso. Paciente femenina de 73 años con antecedentes de insuficiencia cardíaca, hipertensión arterial y sobrepeso, quien presentó deterioro funcional, disnea en reposo, taquipnea, taquicardia, desaturación, edemas generalizados, cianosis distal e ingurgitación yugular. Los exámenes paraclínicos mostraron anemia leve, glucemia y electrolitos normales, azoados con deterioro de la función renal, TSH: 100 μ UI/mL, T4 libre: 0.21 ng/dL, ritmo de fibrilación auricular con respuesta ventricular rápida e hiperlactatemia. A partir de los hallazgos se diagnosticó falla cardíaca asociada a coma mixedematoso de novo, que requirió soporte inotrópico y vasopresor, y tromboembolismo pulmonar asociado a signos de disfunción sistólica derecha. Finalmente, la paciente tuvo evolución lenta hacia la mejoría con la suplencia hormonal, optimización de falla cardíaca y anticoagulación.

Conclusión. El coma mixedematoso es una forma extrema e infrecuente de hipotiroidismo que se asocia con altos niveles de morbilidad dado que implica manifestaciones sistémicas graves. El diagnóstico oportuno y la implementación temprana de un tratamiento de soporte y específico, sobre todo con suplencia agresiva de hormonas tiroideas y vigilancia en unidad de cuidados intensivos, ayudan a mejorar el pronóstico de los pacientes con esta complicación.

ABSTRACT

Introduction: Myxedema coma is the rarest and most extreme manifestation of hypothyroidism in adults. It is more frequent in older women and is associated with various clinical manifestations including diseases with systemic involvement, such as heart failure, pulmonary thromboembolism, and atrial fibrillation in unstable patients.

Case presentation: A 73-year-old female patient with a history of heart failure, hypertension and overweight, presented functional deterioration, dyspnea at rest, tachypnea, tachycardia, desaturation, generalized edema, distal cyanosis, and jugular venous pressure. Laboratory tests showed mild anemia, normal blood glucose and electrolytes, azotemia with impaired renal function, TSH: 100 μ UI/ml, free T4: 0.21 ng/dL, atrial fibrillation with accelerated ventricular rhythm and high lactate level in blood. Based on the findings, heart failure associated with de novo myxedema coma was diagnosed, as well as pulmonary thromboembolism associated with signs of right systolic dysfunction. The patient's condition gradually improved with hormone replacement therapy, heart failure treatment, and anticoagulation.

Conclusion: Myxedema coma is a rare and extreme form of hypothyroidism. It is associated with high mortality and morbidity rates because it has severe systemic manifestations. Timely diagnosis and early implementation of supportive and specific treatment, especially with aggressive thyroid hormone replacement therapy and intensive care unit monitoring, help improve the prognosis of patients.

INTRODUCTION

Myxedema coma is the most extreme expression of hypothyroidism (1). It is now a rare pathology due to universal iodine supplementation, which started in Colombia around the 1950s and has significantly reduced the number of cases of endemic goiter, hypothyroidism, and cognitive retardation, as well as infant mortality in areas with low economic and social development (2).

The pathophysiology of myxedema coma is caused by severe and prolonged thyroid hormone depletion —thyroxine (T4) and triiodothyronine (T3) (3). It is an endocrinological emergency, more frequently observed in women and the elderly and is characterized by a compromised state of consciousness that can lead to coma (3,4). It is associated with exposure to extremely low temperatures and the development of acute conditions such as sepsis secondary to pneumonia, urinary tract infection and cellulitis, which in the case of developed countries are the most frequently reported (1,5). However, other factors have been identified in Latin American countries such as stroke, acute myocardial infarction, polytrauma (3,6,7), or decompensation of chronic diseases such as heart failure (8).

Surprisingly, myxedema coma still occurs despite the widespread availability of tests to assess thyroid function and the regular presentation of changes in these hormones, especially hypothyroidism (5). This condition requires a high degree of diagnostic suspicion, but because of its rarity, it is not commonly regarded as a probable diagnosis in the emergency room, so identification and care are delayed, particularly when it presents with atypical symptoms; this lack of diagnostic suspicion overshadows the prognosis (5,7).

Treatment for myxedema coma is based on intense hormonal replacement with levothyroxine, preferably intravenous (IV), with loading doses up to 400mcg. During the implementation of

this treatment, patients with a history of coronary disease or arrhythmias should be treated with special care since it could be harmful, and the necessary support measures should be provided, including physical means to avoid hypothermia, maintenance of hemodynamic stability with vasopressors and inotropic agents (if applicable), and ventilatory support. Other specific measures include starting broad-spectrum antibiotic treatment early if associated infection is suspected, correcting electrolyte imbalance, mainly hyponatremia, and treating other specific triggers discovered (1,3,5,9).

CASE PRESENTATION

A 73-year-old female patient, Hispanic, from the urban area of Manizales (Colombia), with elementary schooling, housewife and with a history of unstratified chronic heart failure, hypothyroidism, high blood pressure and atrial fibrillation without any anticoagulation, and apparent poor adherence to treatment, consulted the emergency department due to a 2-month history of bilateral edema of the lower limbs, predominantly in the evening, non-painful generalized cyanosis, dyspnea on exertion associated with functional class deterioration, orthopnea, paroxysmal nocturnal dyspnea and episodes of lipothymia. The patient reported no chest pain, fever, hemorrhagic manifestations, nor digestive or urinary symptoms.

The patient attended the hospital due to a pronounced physical and functional limitation. On admission, she was medicated with furosemide 40mg every 24 hours, losartan 50mg every 24 hours, metoprolol 25 mg every 12 hours, hydrochlorothiazide 25mg every 24 hours and atorvastatin 40mg every 24 hours. She also reported a long history of toxic exposure to biomass combustion and a surgical history of left inguinal herniorrhaphy and umbilical herniorrhaphy.

Physical examination on admission revealed: respiratory rate: 24 brpm, heart rate: 119 bpm, blood pressure: 140/80 mm/Hg, pulse pressure: 60 mm/Hg, mean arterial pressure: 100 mm/Hg, oxygen saturation: 87% on room air and 93% with low-flow oxygen, axillary temperature: 36°C, weight: 64kg, height: 1.47m and body mass index: 29kg/m². The patient was anxious and had mild respiratory distress, signs of moderate dehydration and cyanosis, anasarca and moon facies, jugular vein distention at 45°, and positive hepatojugular reflux. On inspection and palpation of the neck, there was no evidence of goiter or masses.

The chest was symmetrical, with normal expansion and subcostal retractions, hypoven-tilated lung fields, and bilateral basal stertor. Heart sounds were arrhythmic, but no cardiac murmurs or carotid bruits were auscultated. The abdomen was globose as a consequence of ascites without collateral circulation, audible peristaltic sounds, and enlarged liver at 4cm from the costal margin, but there was no pain on palpation. Grade 3 edema was found in the lower limbs with fovea, capillary refill for 5 seconds, low-intensity posterior dorsalis pedis artery and tibial artery pulses, and acrocyanosis (Figure 1).



Figure 1. Lower limb edema and acrocyanosis.

Source: Document obtained during the course of the study.

During the neurological examination, the patient was alert, attentive, oriented to place, time and event, and did not present alterations in cranial nerves, strength or sensation. No prior laboratory tests were provided at the time of assessment.

An initial diagnosis of acute chronic heart failure of probable hypertensive etiology was made with the Stevenson B hemodynamic

pattern and incipient signs of tissue hypoperfusion. Therefore, treatment was started with supplemental oxygen therapy by low-flow nasal cannula, loop diuretics and prophylaxis for venous thrombosis with low molecular weight heparin (LMWH). Initial examinations included a 12-lead electrocardiogram that showed atrial fibrillation with triplets of wide QRS complex extrasystoles and (Figure 2).

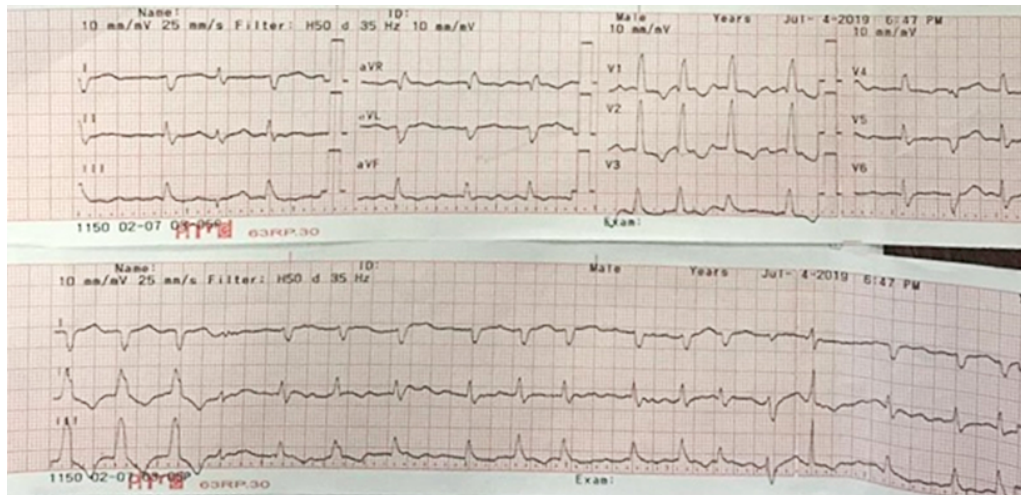


Figure 2. Electrocardiogram.

Source: Document obtained during the course of the study.

Lab tests results yielded blood arterial gases without oxygenation disorder, compensated respiratory alkalosis, lactate: 2.5 mmol/L, blood count with mild heterogeneous normocytic hypochromic anemia, hemoglobin: 11.2 g/dL, mean corpuscular volume: 81 fL, mean corpuscular hemoglobin: 25.5 pg, red cell distribution width: 17.7% and platelets, leukocytes, sodium, and potassium within normal ranges. Chest

x-ray showed an increased cardiothoracic ratio and angiosclerotic changes with calcified plaques and signs of precapillary pulmonary hypertension. Furthermore, mixed involvement of the parenchyma was found with a greater predominance of parahilar alveolar and lower lobe involvement, with a moderate amount of bilateral free fluid predominantly in the left hemithorax (Figure 3).

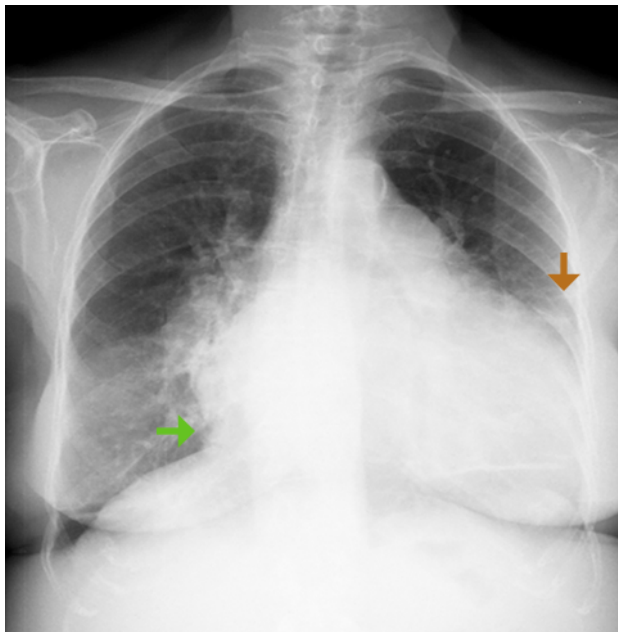


Figure 3. Chest x-ray.

Green arrow: overall cardiomegaly with cardiothoracic ratio of 0.7;

Orange arrow: left pleural effusion.

Source: Document obtained during the course of the study.

Other tests showed: TSH: 100 μ IU/mL (normal 0.27-4.2 mIU/mL), free T4: 0.21 ng/dL (normal 0.9-1.7 ng/dL), free T3: 1.61 pmol/L (normal 3.1-6.4 pmol/L), BUN: 18.5mg, creatinine: 1.53 mg/dL, glomerular filtration rate: 33.4 mL/min/1.73 m² estimated by MDRD, blood glucose: 106 mg/dL, and hs troponin T: 0.031 ng/mL (normal <0.014 ng/mL).

The internal medicine department examined the patient on the next day of admission and diagnosed myxedema coma as a result of acute chronic heart failure with Stevenson C hemodynamic pattern and atrial fibrillation (CHADS₂-VAsc score of 4). Therefore, an increase in the LMWH dosage to anticoagulation dose was requested. To rule out acute myocardial infarction, a control troponin test was taken for delta measurement, which was negative (0.034 ng/mL) and corresponded to myocardial injury due to exacerbation of heart failure.

Hormone replacement was initiated with a loading dose of 200mcg of oral levothyroxine and continued at 100mcg/day. Continuous monitoring was also undertaken to determine the need to initiate inotropic support with low dose milrinone (0.375mcg/kg/min) and transfer to the intermediate care unit (IMCU).

A transthoracic echocardiogram showed left ventricular ejection fraction of 57%, moderate right ventricular systolic dysfunction, functional tricuspid regurgitation grade 2/4 with moderate increase in pulmonary systolic pressure, grade 2/4 mitral regurgitation with sclerotic changes, severe dilatation of both atria, and mild pericardial effusion with no hemodynamic effect. A renal ultrasonography showed decreased cortex-medulla ratio as a sign of chronic kidney disease.

Since the patient's condition did not improve, a D-dimer test was requested, finding elevated levels (1 727 ng/mL). Then, to confirm sus-

picion of pulmonary thromboembolism as an additional cause of decompensation, a chest CT scan with intravenous contrast was performed with previous nephroprotection due to the high risk of nephropathy. Adequate opacity of the vascular structures of the mediastinum was observed, without filling defects or other findings suggestive of acute or chronic thrombotic phenomena. There was an increase in the diameter of the main pulmonary artery of approximately 36mm, global cardiomegaly and scarce fluid in the pericardial sac. Pulmonary parenchymal assessment showed areas of hypoattenuation with mosaic perfusion pattern due to precapillary pulmonary hypertension with moderate amount of free pleural fluid in the right hemithorax and scarce fluid in the contralateral hemithorax with passive atelectasis.

After two days of stay at the IMCU, the patient's condition improved with marked reduction of edema, improvement in dyspnea and gradual recovery of kidney function. However, cyanosis and inotropic support requirement persisted, so hydrocortisone was started at a dose of 50mg every 12 hours. Subsequently, the patient became hypotensive, diaphoretic, desaturated, and bradycardic, so vasopressor support was initiated with norepinephrine. Milrinone was suspended, and an electrocardiogram was taken with no significant new findings.

On the third day at the IMCU, noninvasive mechanical ventilation was initiated because the patient persisted with congestive signs and had respiratory acidosis associated with oxygenation disorder. On the fourth day, vasopressor support was withdrawn, and a follow-up chest x-ray was performed, showing bilateral pleural effusion that was drained the following day without measuring cholesterol, albumin or other markers for the categorization of a probable associated transudate. Improvement in respiratory pattern and acid-base balance in

arterial gases was observed, as well as regulation of free T4 on the rise (0.61 ng/dL). 24-hour Holter monitoring was requested.

Due to clinical improvement, the patient was transferred to the general ward on the sixth day of her stay at the IMCU. Holter monitoring showed atrial fibrillation with a maximum ventricular response of 177 beats per minute in wakefulness and a minimum ventricular response of 58 beats per minute in sleep hours, with a mean heart rate of 97 beats per minute.

During hospitalization in the general ward, hydrocortisone was discontinued, and bridging anticoagulation therapy was started with warfa-

rin; the patient persisted with lower limb edema and dyspnea episodes, even with diuretic dose adjustment. Given the slow and torpid evolution, the suspicion of pulmonary thromboembolism persisted, so pulmonary perfusion and ventilation (V/Q) scans were requested, which showed multiple segmental perfusion defects that involved the posterior basal and anterior basal faces in the right lower lobe and the lateral surface in the middle lobe. There was also an involvement of the apical segment of the left upper lobe and segments of the lingula. The findings were highly suggestive of bilateral multiple pulmonary thromboembolism (Figures 4 and 5).

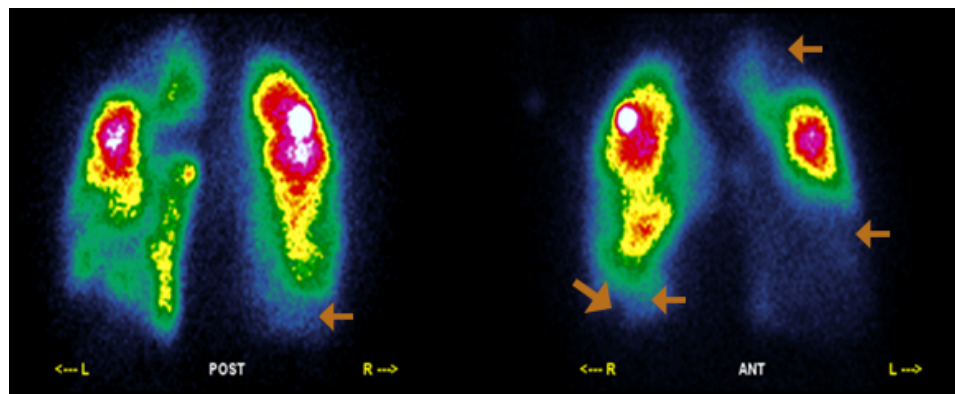


Figure 4. Perfusion scintigraphy.

Orange arrows: perfusion deficits in the basal anterior, lateral and posterior segments of the right lower lobe, in the apical segment of the left upper lobe, and in segments of the lingula.

Source: Document obtained during the course of the study.

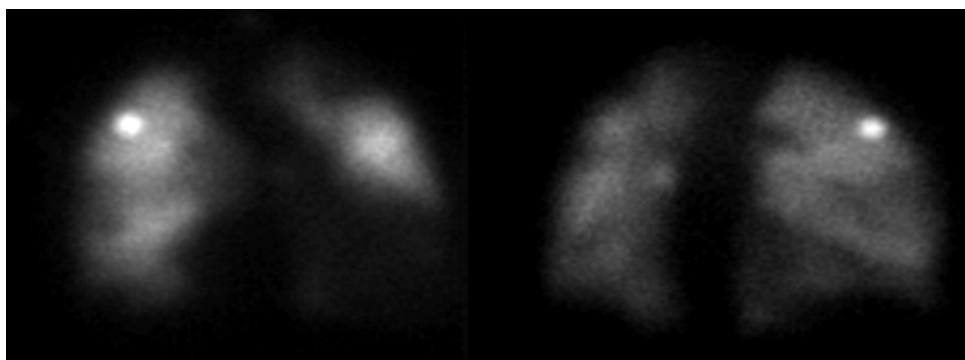


Figure 5. Ventilation lung scan.

Note: The study could not be performed due to the patient's inability to properly inhale the radiopharmaceutical agent.

Source: Document obtained during the course of the study.

The anticoagulation therapy allowed achieving the target international normalized ratio by increasing the coumarin dose and improving the free T4 levels (0.8 ng/dL), although without achieving a normal range (lower limit 0.9 ng/dL). A BNP of 19.791 pg/mL was also obtained, which will be useful as a reference in future outpatient monitoring. The patient was

discharged 12 days after her stay in the general ward and after 20 days of her admission, when she had an evident improvement in her clinical condition. However, due to her comorbidities and persistent hypoxemia, home oxygen was ordered.

Figure 6 presents the case timeline. No follow-up diagnostic tests are available.

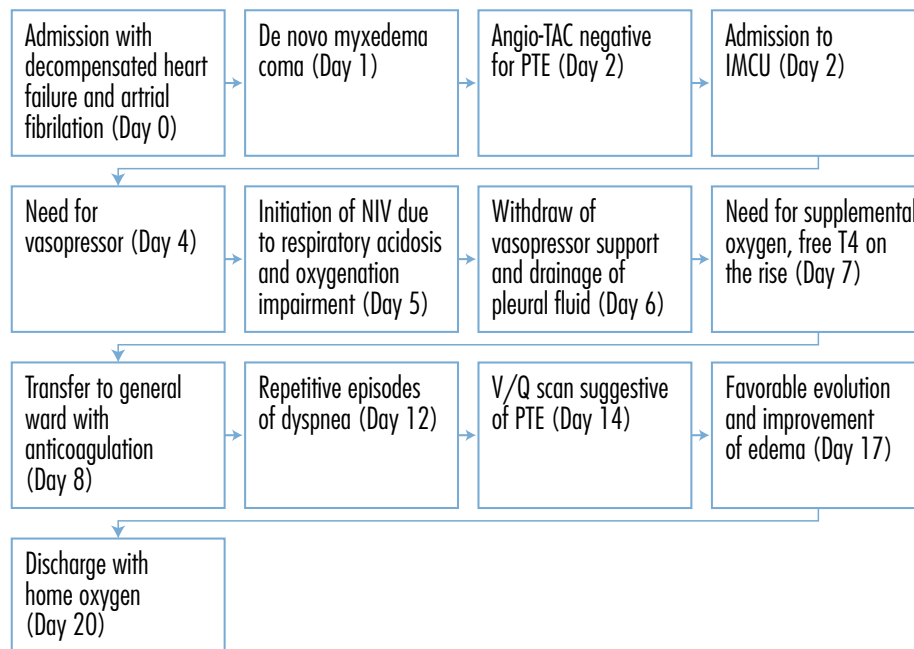


Figure 6. Timeline. The number of days is counted from the date of admission to the emergency department.

PTE: Pulmonary thromboembolism; IMCU: Intermediate care unit; NIV: noninvasive mechanical ventilation.

Source: Own elaboration.

DISCUSSION

Thyroid hormones (T4 and T3) play a key role in human health, mainly in cell growth, differentiation, and metabolism (10). Therefore, it is not surprising that its deficiency is one of the most common endocrine disorders in clinical practice (5,10).

Myxedema coma is the most extreme expression of thyroid hormone deficiency, and its presentation is rare nowadays. This clinical

condition, which, contrary to what its name indicates, does not involve the alteration of the state of consciousness in most cases, is characterized by being more usual in the female sex and causing alterations in the thermoregulation and hemodynamic status (the latter is a major clinical finding accompanied by hypotension and other signs of hypoperfusion). It is also associated with glomerular and tubular alterations that reduce the homeostatic capacity to respond to triggering disorders such as pulmonary thromboembolism

and heart failure, which should be recognized early to establish specific treatment (3,8).

Hyponatremia is one of the most frequent electrolytic alterations associated with myxedema coma (11); however, in the present case, it did not occur. On the other hand, the most common electrocardiographic alteration in hypothyroidism is bradycardia, although other arrhythmias that are detected in electrocardiography are also described (3,12), as in the case of the reported patient. This could be explained, among other things, by myxedema accumulation due to mucopolysaccharides, particularly atrial fibrillation possibly caused by dilatation of the right atrium associated with the chronic increase of the afterload.

Sequential electrocardiograms should be performed in the emergency department when ischemia is suspected (12). In the reported patient, there was no clinical or electrocardiographic suspicion since no waves of injury, ischemia or necrosis were shown on the electrocardiogram upon admission.

An assessment scale developed in Washington D.C., USA, allows for an objective review of the clinical findings reported for myxedema coma and, as a result, a prompt and accurate diagnosis (13).

The specific treatment of the myxedema coma is based on hormone replacement therapy, preferably by IV route, as well as on the treatment of precipitating entities, general support measures and the prevention of the multiple complications, among which glucocorticoid supplementation stands out. In this way, it is possible to prevent adrenal insufficiency, as indicated in the American Thyroid Association's hypothyroidism management guidelines (9). The ideal place for the treatment of this complication is the intensive care unit (ICU) (13) since patients may need vasopressor, inotropic, and ventilatory support. Response is assessed

based on clinical improvement (hemodynamic, neurological, and metabolic), which in turn improves cardiac and pulmonary function (1,9).

Poor prognostic factors in myxedema coma include hypotension, hypothermia, sepsis, altered consciousness (low Glasgow score), and a high APACHE II score, the latter two being the main factors related to mortality (14).

Some strengths of this case report include a detailed description of clinical manifestations, laboratory findings and diagnostic imaging, as well as the patient's evolution and treatment. This is valuable in order not to lose sight of the fact that this type of severe disease is still present today. It also helps to illustrate that, despite the negative result of chest angiotomography, the clinical hypothesis of associated pulmonary thromboembolism persisted, leading to the use of V/Q scintigraphy as a secondary diagnostic method that made it possible to confirm the clinical suspicion. Furthermore, the use of clinimetric instruments allowed for a more objective definition of the condition's onset and severity. One of the study's drawbacks is that there was no adequate outpatient follow-up of the signs and symptoms.

CONCLUSIONS

Myxedema coma is a condition that most often occurs in women, the elderly, and patients with comorbidities. Although in most cases it is not associated with a true coma, it can cause high levels of morbidity and mortality because it involves serious systemic manifestations.

Arterial hypertension, heart failure, pulmonary thromboembolism and atrial fibrillation are conditions associated with the presence of myxedema coma.

Timely diagnosis and early implementation of supportive and specific treatment, especially with aggressive thyroid hormone replacement therapy and intensive care unit monitoring, help

to improve the prognosis of patients with this complication.

ETHICAL CONSIDERATIONS

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

CONFLICTS OF INTEREST

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OEIS COMPLEX (OMPHALOCELE-EXSTROPHY-IMPERFORATE ANUS-SPINAL DEFECTS): A CONFUSING SYNDROME. CASE REPORT

Keywords: Meningomyelocele; Anus, Imperforate; Neural Tube Defects; Bladder Exstrophy.

Palabras clave: Meningomielocelo; Ano imperforado; Defectos del tubo neural; Extrofia de la vejiga.

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RESUMEN

Introducción. El complejo OEIS es un conjunto de defectos polimalformativos con baja incidencia y prevalencia mundial que suele estar asociado a causas epigenéticas y genéticas que ocasionan alteración al final de la blastogénesis, dando como resultado la asociación de cuatro malformaciones clásicas: onfalocele, extrofia vesical, ano imperforado y lesiones de la médula espinal. En ocasiones también se presenta espina bífida, diástasis de la sínfisis púbica y anomalías en las extremidades.

Presentación del caso. Paciente femenina de 7 meses de edad (al momento de la elaboración del presente reporte), procedente de un área rural colombiana, producto de una tercera gestación con alto riesgo obstétrico y diagnosticada prenatalmente con un defecto en el plegamiento caudal de la pared abdominal y un lipomeningocele. Durante el nacimiento se evidenció extrofia vesical, ano imperforado y disrafismo espinal, lo que permitió plantear el diagnóstico de complejo OEIS e iniciar manejo interdisciplinario pertinente.

Conclusiones. El complejo OEIS es una polimalformación fetal con signos y anomalías características, en donde los conocimientos sobre la etiopatogenia, el diagnóstico pre y postnatal, el asesoramiento genético y las propuestas terapéuticas son primordiales para favorecer el manejo precoz de las diferentes comorbilidades, aliviar la sintomatología aguda, reducir múltiples comorbilidades y mejorar la calidad de vida del paciente.

ABSTRACT

Introduction: The OEIS complex is a group of polymorphic defects with low incidence and prevalence worldwide. It is associated with epigenetic and genetic causes that occur in early blastogenesis, resulting in 4 classic malformations consisting of omphalocele, bladder/cloaca exstrophy, imperforate anus, and spinal cord injuries. Spina bifida, symphysis pubis diastasis and limb abnormalities may also be observed.

Case presentation: 7-month-old female patient (at the time of writing this report). The mother was from a rural region of Colombia, and this was her third pregnancy, which was at high risk of obstetric complications. The infant was prenatally diagnosed with a caudal folding defect in the abdominal wall and a lipomeningocele. During birth, bladder exstrophy, imperforate anus and spinal dysraphism were observed, leading to a diagnosis of OEIS complex. Relevant interdisciplinary management was initiated.

Conclusions: The OEIS complex is a fetal polymorphic malformation with characteristic signs and defects. Knowledge on its etiopathogenesis, pre- and postnatal diagnosis, genetic counseling and therapeutic approaches are essential to favor the early treatment of different comorbidities, alleviate acute symptoms, reduce multiple comorbidities and improve the patient's quality of life.

INTRODUCTION

The OEIS complex is a rare polymorphic malformation. Its worldwide prevalence has been estimated between 0.04 and 0.05% in live newborns or 1 case per 200 000-400 000 pregnancies, with a male-to-female ratio of 1:2 (1,2). According to Mallikarjunappa & Ghosh (3), the first case of this syndrome was reported in 1709 by Littre. However, as stated by Keppler-Noireuil (4), it was not until 1978 that Carey *et al.* described a congenital syndrome with multiple abdominal wall malformations, including omphalocele, cloacal exstrophy, imperforate anus, and spinal defects, which was called the "OEIS complex" (3,4). Other conditions associated with this disorder have also been discovered over time, including spina bifida, congenital urological anomalies, renal anomalies, pubic symphysis diastasis and limb abnormalities (5).

The spinal anomaly associated with the OEIS complex is occult spinal dysrafism (6), which is defined as a group of congenital malformations of the spine and spinal cord characterized by failure of fusion (total or partial) of neural structures, bone, and midline mesenchymal fields (7).

OEIS is considered a complex as it comprises morphological defects that share a common or adjacent embryological region. Its etiology is not yet clear, but it is believed to involve genetic and epigenetic factors (8). The degree of malformation depends on the prenatal period in which the primary defect occurs (9). Its prognosis is unfavorable, so early family management and counseling is always necessary.

The present article describes the case of an infant diagnosed with OEIS complex in order to emphasize the scarcity of information on this entity, especially in Latin America, and to inform about the treatment options available to date.

CASE PRESENTATION

This is the case of a 7-month-old female patient (at the time of writing this report). The mother came from a rural region of Colombia and this was her third pregnancy. Her parents were not related by blood and were low-income farmers. The pregnancy was at high obstetric risk due to advanced maternal age and prolonged intergenetic period (> 11 years). The mother did not report exposure to toxics or psychoactive substances during pregnancy and had adequate prenatal check-ups. Her TORCHS profile was negative. A prenatal ultrasound scan (at 20 weeks) allowed diagnosing omphalocele associated with abdominal wall malformations. Fetal karyotyping revealed 46XX.

The patient was delivered through a cesarean section at 34 weeks gestation due to preterm labor caused by pre-eclampsia with severity criteria: APGAR 5/10 per minute, 7/10 at 5 minutes, and 8/10 at 10 minutes. At birth, her weight was 2 215g; head circumference was 32cm; height was 43.5cm. Induration in the lumbosacral region, bladder exstrophy due to a defect in the midline of the abdominal wall, bilateral talipes equinovarus and cloacal malformation were observed. Therefore, a possible OEIS complex was considered and other differential diagnoses such as gastroschisis, limb-body wall complex and pentalogy of Cantrell were ruled out.

On the third day of life, the baby was taken to skin vesicostomy, omphalocele closure, tubularization of the colonic pouch and intestinal bypass, with favorable postoperative evolution. During her hospital stay, a cranial ultrasound was performed, finding no alterations. A urinary tract ultrasound also showed grade 4 hydronephrosis, necessitating a right nephrostomy. Two days later, the infant was assessed by the

pediatric neurology and neurosurgery services, which established that she presented with hypotonia and a lumbosacral mass of approximately 4x4cm, paraparesis, and hyporeflexia of lower limbs and talipes equinovarus. As a result, MRI of the neuraxis was performed, revealing lumbosacral lipomeningocele, type II diastematomyelia (Figure 1), and sacral agenesis. Occult spinal dysrafism was considered that did not require immediate intervention was considered. However, this condition had to be followed up on an outpatient basis and treated through rehabilitation with physical and occupational therapy.



Figure 1. Magnetic resonance imaging. Axial plane. T2 sequence with evidence of type II diastematomyelia, single dural sac, and spinal cord with no bony septum/spur.

Source: Document obtained during the course of the study.

At 6 months, the patient was taken back to surgery for a bilateral pelvic osteotomy and colostomy remodeling by the pediatric orthopedic and pediatric surgery services. These procedures allowed for proper positioning and bone consolidation in the pelvis and did not cause further complications.

At the time of writing the present case report, the patient, aged 7 months, did not present any significant clinical deterioration, had adequate response to the treatment provided to alleviate her symptoms, and did not develop any postop-

erative complications despite the uncertainty of her prognosis. Furthermore, she was awaiting spinal anchoring and interdisciplinary follow-up by the pediatric neurology, neurosurgery, urology, pediatric surgery, interventional radiology, and physical and occupational therapy services. Clinical genetics requested genomic hybridization + microarray to identify any pathogenic variant, deletion or copy number variation that could explain the etiology, but no report has yet been received.

DISCUSSION

The first case of a patient with an OEIS complex was reported in 1709. However, Carey *et al.* characterized this entity for the first time in 1978 (4,9,10) after identifying 175 children with one or more of the following malformations after reviewing the medical records from a California hospital: omphalocele, cloacal exstrophy, imperforated anus, and spinal defects. According to Austin *et al.* (11), Meizner was the first to perform an ultrasound diagnosis of the OEIS complex in 1985.

OEIS is defined as a complex since it comprises a group of defects that share an embryological region and stage. It occurs at the end of blastogenesis (fourth gestational week) (12), when important embryological processes occur, such as closure of the neural tube, transverse and longitudinal folding of the embryo (formation of the anterior chest and abdominal wall), development of the midline and laterality, disappearance of the chorionic cavity due to the expansion of the amniotic cavity, formation of the umbilical cord and the cardiovascular system, onset of kidney development and initial growth and patterning of the limbs (13,14), explaining the characteristic polymorphic malformations of the entity.

Concerning pathogenesis, there are several theories that postulate four major defects: 1) failure in the formation of the urorectal septum,

which prevents the separation of the urogenital and anorectal tract; 2) total rupture of the cloacal membrane and failed junction of genital tubercles and pubis branches; 3) alteration of ventral abdominal wall closure secondary to abnormal lateral folding, and 4) incomplete development of the lumbosacral vertebrae and failure of cranial neural tube closure (15,16). The reported patient showed phenotypic effects associated with the above-mentioned mechanisms. The first caused persistent cloaca, imperforate anus and genitourinary alterations such as hydronephrosis; the second caused cloacal exstrophy; the third led to an abdominal wall defect, and the fourth led to occult spinal dysraphism with diastematomyelia and tethered cord syndrome, as well as sacral agenesis.

Most OEIS complex cases are isolated and caused by a multifactorial alteration involving environmental factors such as smoking and exposure to benzodiazepines during pregnancy (17) and genetic factors such as deletion of 9q 34.1-q, 1p36 and 3q12.2-3q11.2, trisomy 18,

mosaic Turner syndrome, mutations in mitochondrial 12S rRNA and mutations in homeobox genes such as *HLXB9* since recurrence has been reported in some families with monozygotic conjoined twins (2,18-20). Almost all cases are premature with low birth weight; however, there are reports of patients with an average gestational age of 37.5 weeks and proper weight, height, and head circumference for age (21).

Cohen (22) suggests that the proximity of the neural tube to the cloaca during embryonic development may explain cloacal abnormalities related to occult spinal dysraphism, an entity that includes a broad spectrum of congenital fusion abnormalities of one or more dorsal midline structures. These abnormalities can affect the skin, subcutaneous tissue, vertebral bodies, meninges, and neural tissue.

There are two categories of occult spinal dysraphism: open spinal dysraphism, associated with skin defects and exposed neural tissue, and the closed spinal dysraphism, characterized by subcutaneous masses (Figure 2).

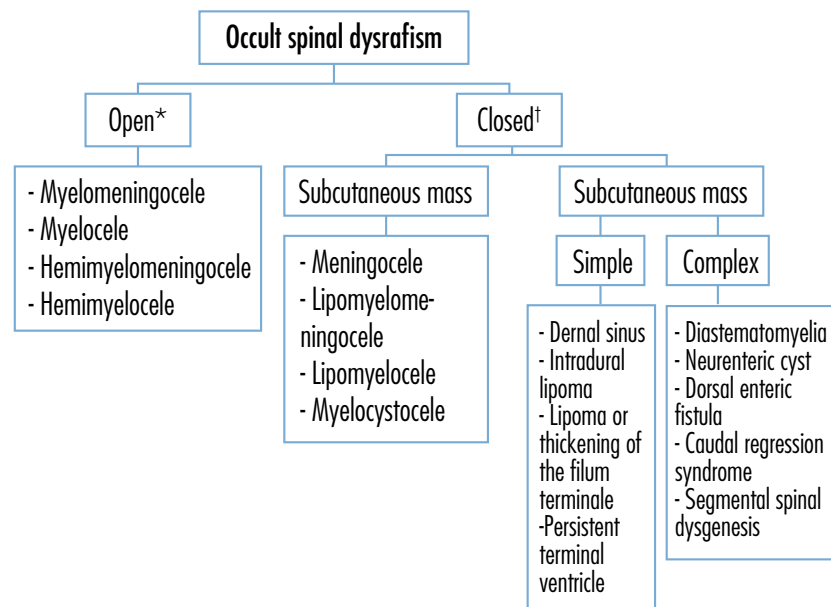


Figure 2. Classification of occult spinal dysraphism

* It accounts for 98% of all cases of spinal dysraphism.

† It accounts for 2% of all cases of spinal dysraphism.

Source: Own elaboration based on Copp *et al.* (23) and Wallingford *et al.* (24).

Although myelocystocele is the most common spinal dysrafism in patients with OEIS (25), the reported patient had a lipomeningocele, which is a herniation of cerebrospinal fluid, meninges, and neural tissue through the posterior spinal bone defect. It is also associated with the presence of lipomas that extend from the subcutaneous cell tissue to the spinal canal and with diastematomyelia, which is characterized by a “splitting” of the spinal cord in one or more segments. According to Tortori-Donati *et al.* (26), it is classified into two types:

Type I: The arachnoid mater and the dura mater do not divide. There is only one dural sac for both hemicords. It represents 60% of diastematomyelias and 50% occur without bony spur.

Type II: The arachnoid mater and the dura mater divide into two and contain both hemicords, so each has its own subarachnoid space that joins up and down forming a single subarachnoid space. 95-100% occur with bony spur (27,28).

Alterations associated with the OEIS complex include cardiac anomalies; kidney anomalies, as in the patient reported here, who presented with grade 4 right ureterohydronephrosis that required percutaneous nephrostomy, increased nuchal translucency, and elevated serum alpha-fetoprotein (29,30).

For prenatal diagnosis, several ultrasound criteria have been classified as major and minor (11) (Table 2). Nevertheless, despite the existence of such criteria, not all anomalies can be identified prenatally and are often mistaken for some differential diagnoses such as omphalocele or gastroschisis. Therefore, the diagnosis is usually confirmed with other imaging aids such as magnetic resonance or color Doppler, used to ratify bladder exstrophy and differentiate it from the omphalocele (10,31).

Table 2 Major and minor criteria for prenatal ultrasound diagnosis of OEIS complex.

Major criteria *	Minor criteria *
Difficulty in bladder visualization Infraumbilical defect of the anterior abdominal wall Omphalocele Lumbosacral myelomeningocele	Lower limb defects Kidney abnormalities Ascites Widened pubic arches Hydrocephalus Narrow thorax Single umbilical artery Prolapse of intestinal ileum into the amniotic cavity

*Observed in more than 50% of patients.

Source: Own elaboration based on Copp *et al.* (33)

Patients with OEIS complex require immediate multidisciplinary care, followed by individualized surgical treatment to close the abdominal wall safely, prevent short bowel syndrome and urinary and fecal incontinence, preserve kidney function, and achieve functional and aesthetic genital reconstruction. While most cases are sporadic, family cases have been reported, which could suggest one or more specific genes that may play a key role. This makes genetic counseling and study of the utmost importance (8,34).

The prognosis of patients with OEIS complex varies depending on the severity of structural defects, the extent of cloacal exstrophy (due to its renal and pulmonary complications), and the severity of the neural tube defect. Thus, an adequate interdisciplinary management of the less severe forms may improve prognosis and lethality of this entity.

The patient in the case described here had the advantage that her OEIS complex was not lethal and that she was treated in a hospital with various medical specialties where she could undergo diagnostic imaging and receive the required medications, which allowed for a more comprehensive diagnosis-treatment with greater benefits. However, it should be noted

that at the time of the writing this article the patient had not undergone all the procedures indicated since this is an entity that requires life-long interventions, management, and surveillance.

CONCLUSIONS

The OEIS complex is a rare and complicated congenital condition that can only be detected in less than 25% of cases by ultrasound in the second trimester of gestation due to the wide spectrum of anatomical variants. This occurs because malformations depend on the degree of cloacal septation and, therefore, other imaging resources such as MRI or color Doppler are often required to confirm the diagnosis.

The prognosis of the OEIS complex is unfavorable, so an interdisciplinary team of neonatologists, geneticists, pediatricians, urologists, pediatric surgeons, neurosurgeons, orthopedists, pediatric neurologists, radiologists and maternal-fetal specialists is needed to provide parents with comprehensive counseling to define pre-birth management, plan appropriate perinatal management, and achieve a better quality of life for patients. For this reason, it is important to raise awareness of this entity since an adequate clinical approach will help to better guide treatment and prognosis.

ETHICAL CONSIDERATIONS

The informed consent of the patient's parents was obtained for the present case, while privacy and anonymity were preserved.

CONFLICTS OF INTEREST

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A PATIENT WITH DEXTROCARDIA AND CHAGAS DISEASE: CASE REPORT AND LITERATURE REVIEW

Keywords: Dextrocardia; Chagas Disease; American trypanosomiasis; Situs inversus.

Palabras clave: Dextrocardia; Enfermedad de Chagas; Tripanosomiasis americana; *Situs inversus*.

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ABSTRACT

Introduction: About half a million patients in Colombia are currently infected with *Trypanosoma cruzi*. However, little is known about patients with Chagas disease and anatomical defects such as dextrocardia.

Case presentation: A 52-year-old male patient with a 4-year history of dyspnea, chest pain, lower limb edema and syncope (requiring hospitalization), arrhythmias and dextrocardia, underwent serological tests for *T. cruzi* that were positive. A literature review was conducted to find case reports of patients with dextrocardia or situs inversus and Chagas disease in order to determine the proper treatment.

Conclusion: Cases of patients with dextrocardia and Chagas disease are rare. Besides the reported case, only three other cases were found in the literature, which were relatively similar, although they could be considered more severe. According to the findings, the use of etiological treatment is acceptable in patients with coronary anatomic abnormalities and *T. cruzi* infection. The present case draws attention to the importance of adequately approaching and monitoring this type of patient.

RESUMEN

Introducción. En la actualidad, en Colombia hay aproximadamente medio millón de personas infectadas con *Trypanosoma cruzi*; sin embargo, no hay mucha información sobre pacientes que viven con enfermedad de Chagas y anomalías anatómicas como la dextrocardia.

Presentación del caso. Paciente masculino de 52 años con cuadro clínico de aproximadamente cuatro años de evolución consistente en

disnea, dolor torácico, edema de extremidades inferiores, síncope (que requirió hospitalización), arritmias y dextrocardia, a quien se le practicaron pruebas serológicas para *T. cruzi* que resultaron positivas. Con el fin de establecer el tratamiento adecuado, se realizó una revisión de la literatura buscando reportes de casos de pacientes con dextrocardia o situs inversus y enfermedad de Chagas.

Conclusión. Los casos de pacientes con dextrocardia y enfermedad de Chagas son poco frecuentes: además del caso reportado, en la literatura solo se encontraron tres reportes adicionales, los cuales fueron relativamente similares, aunque podrían considerarse más severos. Según los hallazgos, el uso de tratamiento etiológico es adecuado en pacientes con anomalías anatómicas cardiovasculares e infección por *T. cruzi*. El presente caso llama la atención sobre la importancia de tener un enfoque y seguimiento adecuados en este tipo de pacientes.

INTRODUCTION

At least 4.8 million people in Colombia are at risk of contracting Chagas disease, and almost half a million are currently infected (1). Several meta-analyses recently estimated the prevalence of the disease with a range between 2-4% (2,3). Unfortunately, according to the consolidated information from the data published in the 2016 epidemiological weeks and data from the public health surveillance system, screening tests have not been widely performed and between 2008 and 2015, only 65 000 tests were performed among the population at risk, representing only 1.35% of that population. Of the taken tests, approximately 10% were positive (4).

Furthermore, according to data consolidated and provided by the Red Nacional de

Bancos de Sangre (Colombian National Blood Network in internal conferences) in 2016 and based on information from the public health system, the network tested over 5 million blood units in 2014 and 2015 and less than 10% were positive. However, in 2018, this national network confirmed that 10% of total donors in 2016 tested positive for molecular markers of Chagas disease (5). Regardless, this is not a representative sample because most blood units were collected from major city health centers, which may not reflect the actual distribution of the disease.

A flaw of this screening process is that there are no records regarding the follow-up of these patients (2). Another worrying aspect is that the National Clinical Guideline, which has not been revised since its creation, has a poor to moderate overall quality; this is also true for several other epidemiological reports of the disease (6,7). Another significant problem is that not all public health laboratories have the installed capacity to perform the diagnostic tests and not all laboratories can carry out the three recommended tests (8). Therefore, the country had to modify the diagnostic algorithm to eliminate this diagnostic access barrier (9).

Depending on the stage of the disease, two separate methods for diagnosing Chagas disease must be used. The first one is utilized in the acute phase, where confirming the presence of the parasite in peripheral blood is critical (10). The second strategy must be used during the chronic phase, when indirect assays have more sensitivity; two or more types of tests (Immunofluorescence Assay, Hemagglutination Assay, or ELISA) must be used at the same time when they are used (11).

Once diagnosed, treatment, which presents barriers to access as well (8,12), can be started. Currently, two medications are being used. The first one is nifurtimox (13), which is

given in doses of 8-10mg/kg/day for 60-90 days (14). Despite its side effects, this drug is relatively effective in children in the chronic phase of the disease; therefore, its use is advisable in this population (15). Anorexia, nausea, weight loss, anxiety, excitability, psychological alterations, nausea, vomiting, diarrhea, among others, are some of the side effects associated with this medication (16). The second drug is benznidazole (13). Its efficacy is comparable to nifurtimox, but with a lesser number of adverse effects (17) and more effective in the acute phase. However, its cure rate is low in the chronic phase (18,19). The recommended dose ranges between 5-10 mg/kg/day for 60 days. Side effects include skin alterations, bone marrow depression, thrombocytopenic purpura, agranulocytosis, kidney failure, liver failure, gastrointestinal effects, among others (14).

In Colombia, the indications to start treatment are: 1) all cases in the acute phase, 2) congenital infection, 3) all diagnosed patients under 18 years of age, 4) patients in the chronic phase with disease reactivation, and 5) accidental exposure (20).

Although knowledge of Chagas disease is always increasing, little is known about patients living with it and congenital anatomic abnormalities such as dextrocardia, situs inversus totalis, or others. This could be explained because it is a relatively rare condition; for example, its prevalence in the United States is estimated at about 2 patients per 10 000-20 000 inhabitants (21).

The most common type of dextrocardia is mirror image, in which the morphology and anatomy of the various parts of the heart are normal, but they are not in their usual position (right to left reversal). Changes in electrocardiography and imaging scans are helpful diagnostic aids, but clinical approach, clinical judgment and suspicion are also needed

(22,23). Inverted P, QRS, and T waves in D1, as well as a progressive increase in R waves in precordial leads, are common electrocardiographic findings (21).

Patients with Chagas disease and dextrocardia may present with syncope, palpitations, chest pain, anxiety, dyspnea, and reduction of functional class (22,24,25). Clinical findings include bradycardia, tachypnea, ventricular tachycardia, mitral systolic murmur, right bundle branch block, antero-superior left bundle branch block, cardiomegaly, atrioventricular block, among others. Negative waves (P, QRS, and T) can be detected in D1 on the electrocardiogram (22,24,25). These signs and symptoms are somewhat similar to those that Chagas disease patients typically experience.

The present article reports the case of a patient with dextrocardia and *Trypanosoma cruzi* infection.

CASE DESCRIPTION

Medical history until 2017

This is a 52-year-old mestizo male patient from the department of Santander, Colombia, who works as a dealer of various products and comes from a middle-income family (level 3 on a stratification scale from 1 to 6). He denies any relevant family history. His medical history includes hypertension, currently treated with enalapril 20mg P.O. per day since being diagnosed four to five years ago. Moreover, he was diagnosed with dextrocardia when he was 20 years old. His physical examination was normal, with a heart rate of 66 heartbeats per minute, respiratory rate of 18 breaths per minute, blood pressure 124/82, and temperature 36.5°C.

He reported a 4-year history of dyspnea (functional class II/IV), fatigue, dizziness, chest pain, lower limb edema, and syncope that re-

quired hospitalization. Complementary tests were conducted during his hospital stay, including a 12-lead electrocardiogram, two-dimensional echocardiography, 24-hour Holter monitoring, and a chest X-ray. The electrocardiogram showed ventricular extrasystoles and supraventricular tachycardia. Chest X-ray (25/07/2018) showed dextrocardia (Figures 1 and 2). Serologic testing for *T. cruzi* was positive, leading to the diagnosis of chronic Chagas disease (anti-*T. cruzi* IgG ELISA with whole extract and synthetic peptide-based ELISA) (13,26).

Table 1. Findings in echocardiogram and Holter monitoring.

Echocardiogram	24-hour Holter monitoring
27/07/2017 Dextrocardia, situs inversus totalis. Right atrium to the left. Left cavities to the right. Apex pointing to right. LVEF: 60%. Left ventricle end-diastolic diameter: 5.0cm (3.7-5.6); Left ventricle systolic diameter: 2.9 (2.0-3.8)	27/07/2017 First-degree atrioventricular block, occasional monomorphic ventricular extrasystoles, occasional conductive atrial extrasystoles. QTc Interval 413mseg. Normal ST segment
07/07/2018 LVEF: 65%. First-degree diastolic dysfunction, minimum tricuspid insufficiency. Left ventricle systole: 2.7cm. Left ventricle diastole: 4.2cm.	09/07/2018 Mild ventricular and supraventricular arrhythmia.
08/08/2019 Dextrocardia, apex pointing to right. Adequate biventricular function. First-degree aortic valve insufficiency. Upper limit of the ascending aorta. LVEF: 60%. Left ventricular systole: 2.5cm. Left ventricular diastole: 4.3cm.	15/08/2019 High-grade ventricular arrhythmia. Mild ventricular and supraventricular arrhythmia

LVEF: left ventricular ejection fraction; QTc: corrected QT interval.

Source: Own elaboration.



Figure 1. Anteroposterior projection of chest X-ray. Dextrocardia is clearly visible.

Source: Chest X-ray taken by health services. Obtained during the course of the study.

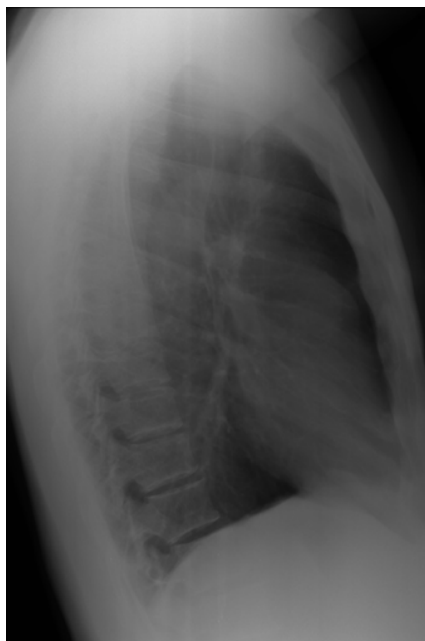


Figure 2. Lateral projection of chest X-ray.

Source: Chest X-ray taken by health services. Obtained during the course of the study.

10/09/2018: The patient reported dyspnea (functional class II/IV) and thoracic pain. Dextrocardia was discovered during clinical examinations. Etiological treatment for Chagas disease (benznidazole 5 mg/kg/day for 60 days) was started and completed successfully. Treatment was temporally suspended for 5 days from day 12 due to gastrointestinal manifestations (severe nausea, vomit, and diarrhea) that limited his activities of daily living. He also experienced fatigue and weakness. The patient presented a pruriginous rash that was treated with antihistamines. Afterwards, treatment was continued without further complications. The patient lost 4kg due to the side effects of the treatment.

16/09/2019: The patient claimed that his condition had not worsened at the follow-up appointment. He had no pain and no further alterations in his functional class. No other member of his family has been diagnosed with Chagas disease. He has not acquired a new illness, nor has he undergone any extra therapies or procedures. His condition was defined as stable, with a favorable prognosis and a long-life expectancy. Furthermore, it was made clear that a lifelong follow-up was needed to avoid complications and further deterioration of his condition. The timeline of the case is presented in Figure 3.

Search strategies

PubMed, Scopus, SciELO, Redalyc, Lilacs, and Google Scholar were used to conduct the literature review. Five terms related to the patient's condition were combined in the search strategy: 1) Chagas disease, 2) Dextrocardia, 3) Humans, 4) Situs inversus, and 5) Situs solitus. The search included all studies conducted up until November 19, 2019, with no date restrictions.

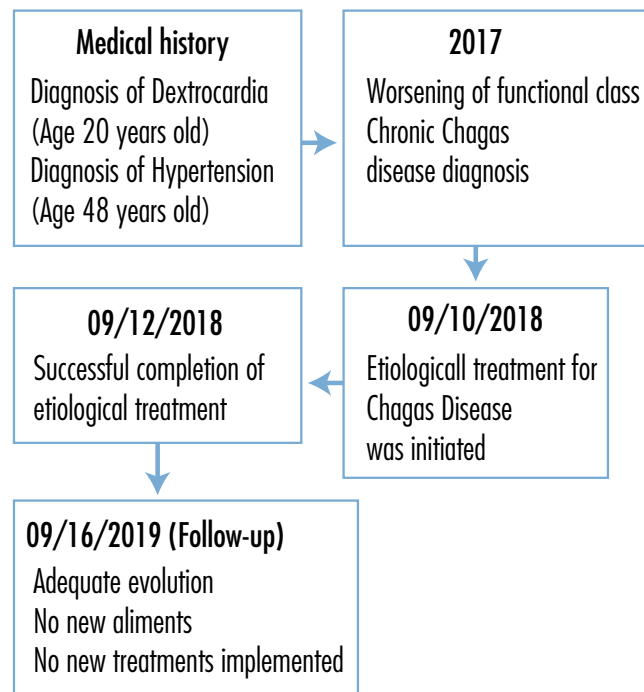


Figure 3. Timeline of the clinical evolution of the patient.

Source: Own elaboration.

Study selection and data extraction

Cases or series of cases of dextrocardia or situs inversus and Chagas disease with at least one patient were eligible for inclusion. If a study described a single case, it was classified as a case report, and if it described more than one patient, it was classified as a series. Publications not written in English, French, Spanish, or Portuguese were excluded. Two reviewers independently screened the search results for inclusion and extracted data using a standardized data extraction form. Disagreements were resolved through discussion until consensus was reached. Information about first author, country, year of publication, number of patients, sex, clinical manifestations, treatment, characteristics of the report and outcome was extracted.

Quality analysis

Each study was subjected to a quality assessment. To that end, both reviewers used a standardized data extraction form to extract the data. Coherence, findings, discussion, conclusion, the manner in which the case was reported, and diagnostic reasoning was evaluated.

The literature review yielded 230 studies (Figure 4) and 27 duplicates were removed. After screening titles and abstracts, 196 studies were excluded, for a total of 7 full texts evaluated. 3 of these studies met the inclusion criteria (Table 2). The 3 reported cases were female, with a mean age of 37.3 ± 1.2 . Dyspnea and syncope were the two most common symptoms. Table 3 shows other characteristics.

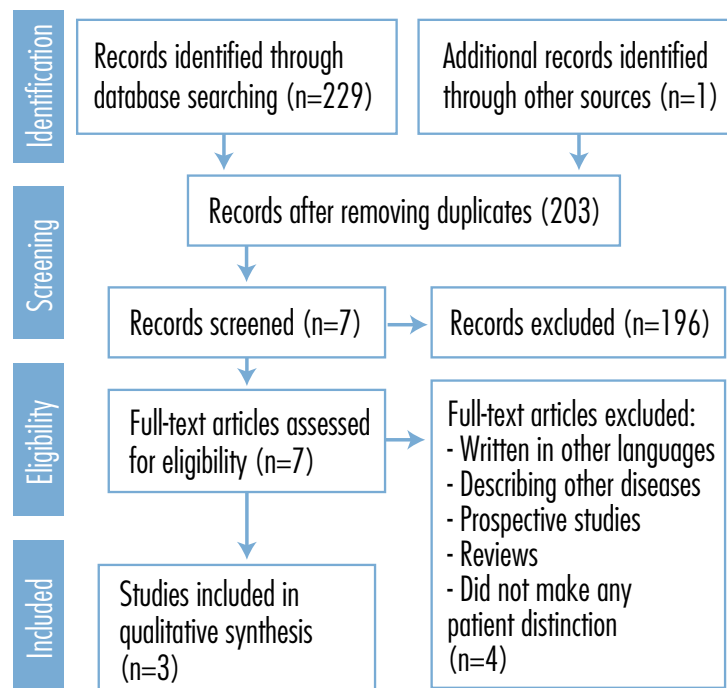


Figure 4. PRISM strategy.

Source: Own elaboration.

Table 2. Case reports included after the systematic search of literature.

Ref.	Title	Year
(24)	Bloqueio atrioventricular total em dextrocardia e doença de Chagas: implante de marca-passo dupla-câmara com upgrade para estimulação biventricular	2015
(22)	Ablation of epicardial ventricular tachycardia in a Chagasic patient with situs inversus totalis: A case report	2017
(25)	Associação entre cardiomiopatia chagásica crônica e dupla lesão mitral reumática em uma paciente com situs inversus totalis	2012

Source: Own elaboration.

Quality analysis results

Regarding the overall quality analysis, the results were fairly consistent. All the articles presented deficiencies in the reporting. However, follow-up and the use of different diagnostic aids were adequate in general. In general, however, follow-up and the use of various diagnostic aids were satisfactory. The studies omitted details

about the patients' demographics, medical and family history, and most of them did not explain the timeline according to the CARE guidelines, although they are not a quality assessment tool. Discussions were relatively solid, but they could be improved and extended. Patients' perspective was not described in any of the cases, and there was no explicit information on the patient's informed consent in some of the reports.

Table 3. Characteristics, symptoms and findings of the cases found in the literature search.

Ref.	Sex/ Age	Signs and Symptoms	MRI	EKG	RX	Echocar- diogram	Cineangi- ography	Other	Diag- nosis	Treatment	Out- come
(24)	F/38	Initial: Syncope, bradycardia	NA	Atrioven- tricular block, bra- dycardia. Negative P, QRS and T waves in D1	Car- diac apex point- ing to the right	LVEF: 60%, left ventricle 46mm x 30 mm and left atrium 35mm	Normal ventricular function and coronography. Dextrocardia.	NA	Chronic Chagas and dextro- cardia	Du- al-chamber peace- maker	Alive
		Subse- quent: Dyspnea, functional class III	NA	NA	NA	LVEF 28%, left ventricle 65.1 mm x 56.4 mm and left atrium 51.7 mm. Diffuse hypokinesis. Cardiac dysfunction	NA	NA	NA	Cardiac resynchro- nization therapy	
		Posttreat- ment: Functional class II	NA	NA	NA	LVEF 26%	NA	NA	NA	Adjust- ments in therapy. LVEF remained constant.	
(22)	F/36	Ventricular tachycar- dia and syncope	Dextro- cardia, left ventricle apex pointing to the right Position of the liver in- verted in relation to the heart.	Ventricu- lar tachy- cardia	NA	NA	NA	NA	Chronic Chagas and dextro- cardia	Epicardial ablation	Alive
(25)	F/38	Palpitations and dys- pnea. Mitral systolic murmur	NA	Function- al right bundle branch block Functional left ante- ro-superi- or bundle branch block	Car- diac apex point- ing to the right Cardio- megaly	LVEF 49%, left ventricu- lomegaly and atriomegaly, double mitral lesion with moderate stenosis and insufficiency	NA	NA	Con- genital Chagas and dextro- cardia	NA	Alive

Ref.: Reference number; LVEF: left ventricle ejection fraction; NA: not applicable.

Source: Own elaboration based on Craveiro *et al.* (24), Oliveira *et al.* (22) and Passos *et al.* (25).

DISCUSSION

Chagas disease is one of the most prevalent parasitic diseases in the Americas (27). The present article reported the case of a patient with dextrocardia associated with Chagas disease. To date, there is not much information available on this type of patient. Not only situs inversus totalis is a rare condition (2 cases per 10 000 are estimated in the United States) (21), but co-infection with Chagas disease seems to be even rarer. The literature search yielded only three cases, which are relatively similar to the one presented in this article, although they could be considered more severe due to the characteristics of the clinical manifestations and the treatment required.

On the other hand, the present case was the only one that clearly stated that the patient received etiological therapy for Chagas disease and reported a male patient. It stands out because it emphasizes the difficulties and challenges that this condition poses for establishing a treatment. There is no clear care standard for this specific kind of patient, side effects could be severe, and adherence is challenging due to such side effects and therapy length.

Still, it is important to use and complete the etiological treatment in patients with abnormal cardiac anatomy. The treatment reported here was not only necessary but also appropriate, as it minimized the likelihood of potential complications, which could be fatal in patients with anatomical abnormalities. In the event of side effects, therapy may be temporarily suspended, or other solutions considered.

As stated above, unlike the other cases found in the literature, the patient reported here is a male. When comparing this patient's clinical evolution and symptoms to those described by Craveiro *et al.* (24), it was possible to establish that the clinical presentation of

our case was not as severe, whereas his young female patient required the implantation of a peacemaker. Nonetheless, her evolution was equally satisfactory. Regarding the case published by Oliveira *et al.* (22), which involved invasive procedures as treatment, she also had an adequate evolution. The last case (25) also had anatomical abnormalities that required other treatments and procedures to prevent complications and fatal outcomes.

As stated above, the findings of the overall quality analysis were relatively homogeneous. While these findings are similar to those reported in a study evaluating the consistency of evidence of acute outbreaks of Chagas disease, no other quality review of similar cases has been identified (7). The checklist used to evaluate the reviewed articles is not a quality assessment tool, which is a flaw in our approach to this case study (28). However, there was little knowledge on demographics, medical, and family history, and most of the cases lacked a timeline.

One difficulty of the quality analysis process was that there were several approaches. In a systematic review, Sanderson *et al.* (29) found 86 different tools, of which 48% were checklists, 38% scales, and 14% were summary judgement checklists. Moreover, some were created for general use, others for critical reading processes, and others were tools designed with a sole purpose in mind and can only be used in the original article. Since there are multiple tools, there is no consensus on their use (29). For example, the use of domains instead of checklists has been proposed by some organizations (30), especially as some checklist items are not justifiable and others are not related to quality or internal or external validity (30).

Finally, the strengths of this case report involve an extensive literature search, a thorough medical examination, the comprehensive assessment of the case, and the use of etiological

treatment. In contrast, the weaknesses include the lack of additional blood and laboratory tests, and other imaging studies to assess more exhaustively the clinical condition of the patient, for example, to assess the possibility of situs inversus totalis.

CONCLUSION

This case highlights the importance of adequately approaching and treating patients with two conditions that can affect the cardiovascular system in particular and the whole anatomy in general. While this patient received sufficient follow-up, complications and challenges in this area are still a possibility and could hinder the comprehensive assessment of patients.

ETHICAL CONSIDERATIONS

Written informed consent was obtained for the publication of this case, the photographs, and the pictures obtained during the course of the research.

PATIENT'S PERSPECTIVE

The patient claims to be in good health. He understands both conditions and is aware that they are chronic. He says that will follow the recommendations and advice given to him.

TRANSPARENCY

The authors declare that all the information contained in these pages is accurate, truthful, and transparent, that no important aspects of the case were omitted, and that all relevant characteristics or discrepancies were reported.

CONFLICTS OF INTERESTS

None declared by the authors.

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PELVIC ABSCESS MISTAKEN FOR MALIGNANT OVARIAN TUMOR IN A POSTMENOPAUSAL WOMAN. CASE REPORT

Keywords: Abscess; Fibroma; Ovarian Neoplasms; Postmenopausal; Case Reports.

Palabras clave: Absceso; Neoplasias ováricas; Fibroma; Posmenopausia; informes de caso.

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RESUMEN

Introducción. Los abscesos tubo-ováricos son poco frecuentes en la posmenopausia y se asocian con patologías ginecológicas benignas como endometriosis, pólipo endometrial o leiomioma uterino, y con patologías malignas como adenocarcinoma de endometrio, tumores malignos epiteliales y no epiteliales de ovario, carcinoma escamocelular de cérvix y adenocarcinoma de colon. Su presentación representa un reto diagnóstico y terapéutico para el médico.

Presentación del caso. Paciente femenina de 72 años, quien consultó por cuadro clínico de tres días de evolución consistente en dolor y distensión abdominal asociados a fiebre y síntomas urinarios irritativos y retención urinaria. Los exámenes de ingreso mostraron leucocitosis con neutrofilia y CA-125 en 222 U/mL. El ultrasonido y la resonancia magnética evidenciaron una masa retrouterina solido-quística de 15 cm. Ante sospecha de tumor versus absceso tubo-ovárico, se realizó biopsia dirigida por tomografía mediante la cual se encontró material purulento fétido. Se practicó laparotomía que confirmó masa pélvica retrouterina sólido-quística con contenido purulento, adherencias y compromiso inflamatorio de las trompas uterinas. El resultado de patología informó fibroma ovárico y absceso tubo-ovárico. La paciente evolucionó de satisfactoriamente en el posoperatorio y en los controles posteriores.

Conclusiones. El caso reportado ilustra cómo, en ocasiones, un posible diagnóstico de carcinomatosis por cáncer de ovario puede ser realmente una patología benigna (absceso tubo-ovárico) que responde bien a un tratamiento médico-quirúrgico. Las imágenes diagnósticas y los marcadores tumorales son de gran ayuda para diferenciar una patología ovárica maligna de un proceso benigno.

ABSTRACT

Introduction: Tubo-ovarian abscesses are rare in postmenopausal women. They have been associated with benign gynecological conditions such as endometriosis, uterine polyp or leiomyoma, and malignant diseases such as endometrial adenocarcinoma, epithelial and non-epithelial malignant ovarian tumors, squamous cell carcinoma of the cervix, and adenocarcinoma of the colon. Their presentation represents a diagnostic and therapeutic challenge for clinicians.

Case report: A 72-year-old female patient was admitted with a 3-day history of abdominal pain and distension, fever, irritative urinary symptoms and urinary retention. Lab tests on admission showed elevated white blood cells and neutrophils count, and CA-125 at 222 U/mL. Ultrasound and magnetic resonance imaging revealed a solid retrouterine cystic mass of 15 cm. Suspecting tumor versus tubo-ovarian abscess, a tomography-directed biopsy was performed, finding foul-smelling purulent material. An exploratory laparotomy was performed with intraoperative findings of solid-cystic retrouterine pelvic mass with purulent content, adhesions, and inflammatory involvement of the uterine tubes. Pathology reported ovarian fibroma and tubo-ovarian abscess. The patient evolved satisfactorily in the postoperative period and in the subsequent follow-up appointments.

Conclusions: The reported case illustrates how a possibility of ovarian cancer with peritoneal carcinomatosis can actually be a benign condition (tubo-ovarian abscess) that responds well to medical-surgical treatment. Diagnostic imaging and tumor markers are helpful in differentiating a malignant ovarian disease from a benign process.

INTRODUCTION

Tubo-ovarian abscess (TOA) is a complication of pelvic inflammatory disease (PID), which consists of the formation of a purulent collection and distortion of the normal structure of the fallopian tubes and ovary (1). TOA may be accompanied by disabling complications such as pelvic pain, ectopic pregnancy, and rupture of the abscess or intestinal obstruction (2). This type of abscess accounts for 1-2% of admissions to gynecology services and usually occurs in women of reproductive age after exposure to sexually transmitted infections (3), although it has also been observed without preceding sexual activity.

Risk factors for developing a TOA include demographic variables such as low socioeconomic status, risky sexual behavior (multiple sexual partners, previous episodes of PID and early onset of unprotected sex), and recent application of intrauterine devices (3). Age is also a relevant risk factor since it has been found that the younger the age, the higher the risk of PID.

Other factors that may contribute to the development of this phenomenon are cervicovaginal microbiota, cervical ectropion with a larger transformation zone that favors the exposure of columnar epithelium to sexually transmitted infections, and the higher frequency of risky sexual behavior in young patients (4).

Only 1.7% of TOA occurs in postmenopausal women (5). It should be noted that this complication is associated both with benign gynecological conditions (stage III and IV endometriosis, endometrioma, endometrial polyp, uterine leiomyoma) (6,7) and with malignant gynecological and non-gynecological diseases (endometrial adenocarcinoma, malignant epithelial and non-epithelial ovarian tumors, squamous cell carcinoma of the cervix and adenocarcinoma of the colon) (1,8-10).

CASE PRESENTATION

A 72-year-old female patient from Bogotá, Colombia, Hispanic, housewife and affiliated to the public health scheme, attended the gynecology service of a quaternary care university hospital due to abdominal distention associated with intermittent urinary retention, urinary irritative symptoms, and 3 days unquantified fever.

The patient had consulted another health care institution two weeks earlier for similar symptoms and was diagnosed with upper urinary tract infection by *Escherichia coli* resistant to quinolones and ampicillin. She received hospital treatment with a third-generation cephalosporin for 10 days.

Relevant medical history included high blood pressure and stage 3A chronic kidney disease. She had also undergone cystopexy with mesh reinforcement 10 years ago and had 5 pregnancies, 4 deliveries and 1 abortion. At the time of consultation, she had no active sex life and had no postmenopausal bleeding. No data were obtained from the last cytology.

On admission examination, the patient was found with normal vital signs, distended abdomen with diffuse pain, no signs of peritoneal irritation, and positive bilateral fist percussion. No mass was palpated in the abdomen. The gynecological examination established that the external genitalia were atrophic. Bimanual palpation revealed elastic vagina with normal temperature and short, atrophic, and closed cervix displaced anteriorly by a painful, firm, fixed mass of about 12cm in diameter that occupied the bottom of the recto-uterine pouch and distended the posterior fornix. This mass prevented the individualization of the uterus and its adnexa and gave the clinical impression of a pelvic abscess, without being able to rule out an adnexal tumor. The results of the admission lab tests are shown in Table 1.

Table 1. Lab test results

Date	Laboratory	Results
5/12/2019 (admission)	Hemoglobin	14 g/dL
	Leukocytes	21.880/mm ³
	Neutrophils	19.290/mm ³
	Platelets	425.000/mm ³
	Creatinine	0.6 mg/dL
	BUN	12.8 mg/dL
	Electrolytes	Normal
	Arterial gases	Normal
7/12/2019	Lactate dehydrogenase	223 U/L
7/12/2019	BhCG: 0.14 mIU/mL	0.14 mIU/mL
10/12/2019	CA-125	222 U/L
10/12/2019	Carcino-embryonic antigen	1.40 ng/mL
10/12/2017	Alpha-fetoprotein	1 UI/mL

Source: Own elaboration.

The initial patient's diagnosis was a recurrent complicated urinary tract infection and, given the risk of a multidrug-resistant bacteria, antibiotic treatment was initiated with meropenem (1g every 8 hours intravenously (IV)). A transabdominal and transvaginal ul-

trasound was subsequently performed, showing a solid-cystic lesion of 115x62x139mm located in the recto-uterine pouch and with low-resistance Doppler flow at the center of the lesion. The mass pushed the uterus forward (Figure 1).

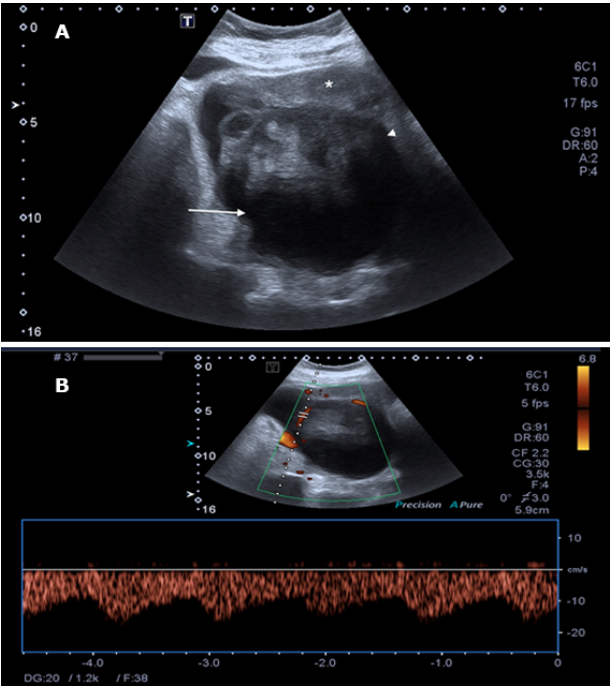


Figure 1. Transabdominal ultrasound obtained using Toshiba Xario 100 with 6mHz convex transducer. A) Uterus (*) displaced by a solid (arrowhead) and cystic (arrow) lesion; B) Doppler of the lesion with low-resistance flow in the solid component.

Source: Document obtained during the course of the study.

A contrast-enhanced computed tomography (CT) of the abdomen and pelvis showed that the mass had the appearance of a pelvic abscess with liquid density lesions with multiple septa in both adnexa. These lesions were accompanied by edema of the surrounding fat, reactive-looking lymph nodes in retroperitoneum, and scarce free fluid in the cavity. It should be noted that the solid component of the mass was not evident with this diagnostic method (Figure 2).

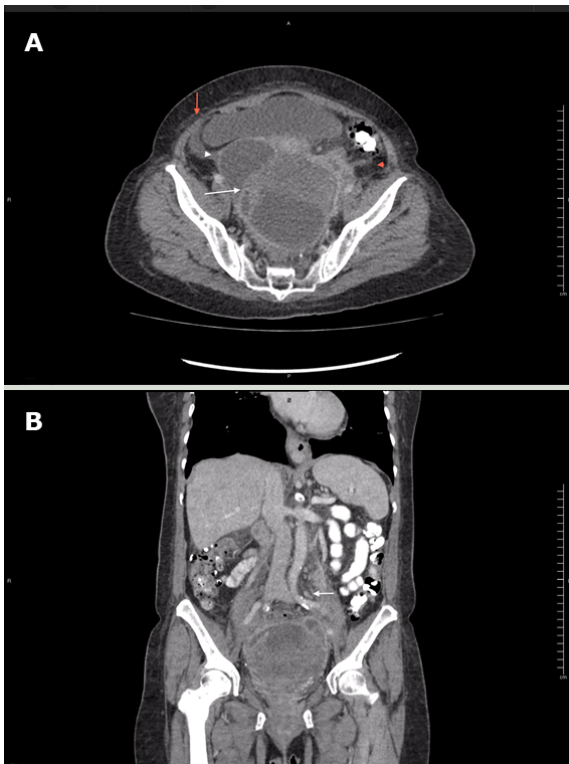


Figure 2. Contrast-enhanced CT scan obtained during arterial phase using an 80-slice multidetector system by Toshiba. A) axial plane: left ovarian lesion with multiple septa, hypodense center, marginal enhancement (white arrow), adjacent fat stranding (red arrowhead) and scarce free fluid (red arrow), and cystic-looking lesion in right adnexa (white arrowhead); B) coronal plane: multiple, retroperitoneal lymph nodes (white arrow).

Source: Document obtained during the course of the study.

The patient was evaluated by the gynecologic oncology service, which considered the possibility

of ovarian carcinoma with a low probability of abscess. Contrast-enhanced magnetic resonance imaging (MRI) was requested, finding right adnexal mass compatible with simple cyst and left adnexal mass with solid and cystic component of 152x120x103mm; the solid zone had low signal on T2, without enhancement or restriction, and the cystic component showed significant restricted diffusion and low apparent diffusion coefficient (ADC). This technique also showed that the mass pushed the uterus, bladder, and rectum, and confirmed the presence of scarce fluid in the cavity (Figure 3).

Given the findings, a complex adnexal mass M3 was considered. The risk of malignancy index was IRM-1: 1998 and IOTA - ADNEX model: 8 (84% malignancy) (Table 1).

Upper digestive tract endoscopy was performed, finding grade B erosive esophagitis and chronic gastritis, and a colonoscopy showed grade II internal hemorrhoids and diverticulosis; a colon biopsy was taken. The patient was again assessed by gynecologic oncology, which considered the possibility of ovarian carcinoma with a low probability of abscess.

A CT-guided biopsy was performed for histological study, staging and evaluation of surgical benefit, finding abundant purulent foul-smelling material. In view of the diagnostic doubt of malignant tumor versus TOA, an exploratory laparotomy was performed using a midline laparotomy infraumbilical incision.

Laparotomy showed a double-lobed retrouterine pelvic mass of 10x7x5cm and solid-cystic appearance. It was attached to the pelvic walls, the posterior side of the uterus, the pouch of Douglas, and the anterior surface of the sigmoid rectum. One of the locules of the mass had a smooth, purplish, renitent surface with liquid content. The mass had a 6cm light brown solid component in one of its poles, thick walls, and it was firmly adhered to neighboring structures. It was also full of foul-smelling purulent material (Figure 4).

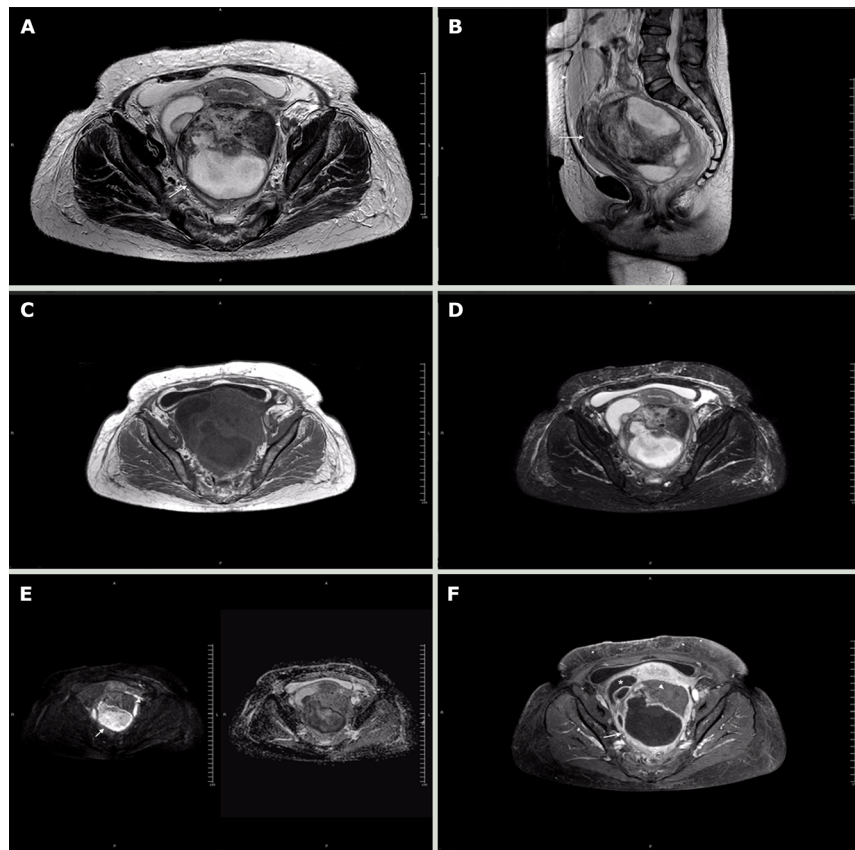


Figure 3. Magnetic resonance imaging obtained using a 1.5T Philips MRI machine. Axial T2-weighted slices. A) axial plane; B) sagittal plane; C) axial T1; D) axial STIR sequence; E) B500 and axial ADC map; F) axial T1 with fat suppression and contrast.

Note: The cystic component is marked in B) with the arrow and shows restricted diffusion in G); the solid component does not show restricted diffusion (G-arrowhead) or enhancement (H-arrowhead). The displacement of the uterus (arrow) and bladder (arrowhead) is evident in C). The asterisk in F) marks the location of the right ovarian cyst.

Source: Document obtained during the course of the study.

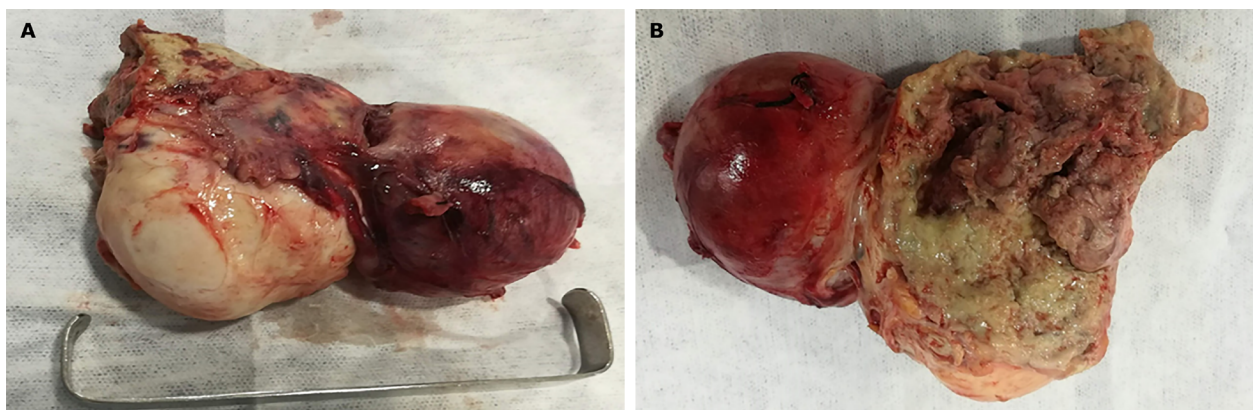


Figure 4. Surgical specimen of pelvic mass. A) ovarian fibroma (solid) on the left and abscess (cystic component) on the right; B) thickened and fibrinopurulent walls of the abscess on the right side of the solid component.

Source: Own elaboration.

Laparotomy also established that the Cook 8 Fr multipurpose drainage catheter that had been placed by interventional radiology was well located in the abscess and that the fallopian tubes were edematous and involved in the inflammatory process. In addition, serous fluid was found on the subdiaphragmatic surface.

Due to the patient's condition, purulent material culture, bilateral salpingo-oophorectomy, multipurpose catheter removal, drainage, and abdominopelvic cavity washing were performed. Jackson-Pratt drains were left in the pouch of Douglas and the abdominal wall was sutured in planes. On the fourth postoperative day, along with the infectious diseases service, the antibiotic treatment was switched to piperacillin-tazobactam (4.5g every 8 hours IV) after obtaining negative urine and blood cultures at 72 hours.

Pathology report revealed benign stromal ovarian fibroid tumor with areas of necrosis, neutrophil infiltrate, congestion, and edema, corresponding to a TOA. Subdiaphragmatic fluid samples with reactive mesothelial hyperplasia were negative for malignancy, as were colon biopsies obtained during colonoscopy. *Enterococcus raffinosus* of the usual pattern was isolated in the purulent fluid of the pelvic collection.

Following the surgical procedure, acute kidney injury KDIGO 3 was observed, which was associated with drug-induced nephrotoxicity (dipyrrone and metoclopramide) and resolved upon discontinuation. The patient progressed satisfactorily, was discharged 5 days after surgery and completed 14 days of parenteral antibiotic treatment without adverse reactions. The patient was asymptomatic during follow-ups at one week and one month after surgery.

DISCUSSION

TOA is a condition rarely observed after menopause. Gockley *et al.* (11), in a retrospective

study with 61 postmenopausal women, found a wide range in the age of presentation of this disease—from 50 to 87 years—, which coincides with other retrospective studies and case reports (5,6,9,10).

TOA is usually polymicrobial with aerobic and anaerobic bacteria. *Enterococcus fecalis*, *Escherichia coli*, *Bacteroides fragilis*, *Pep-tostreptococcus magnus*, *Streptococcus sp*, *Pseudomonas aeruginosa* and *Clostridium perfringens* can be isolated (6).

Most patients with TOA present with abdominal pain as the first symptom (84%), followed by fever (34%), nausea or vomiting (28%), or vaginal bleeding (45%). This condition is also accompanied by comorbidities such as diverticulitis (34%), high blood pressure (25%), and diabetes (10%) (6,9).

37% of women with TOA have history of a recent pelvic surgery. On physical examination, a palpable mass can be found in only 55% of cases; signs of peritoneal irritation are not common (6). In laboratory studies, the levels of leukocytes (mean 13.700/mm³) and CA-125 are usually high, the latter in 77% of patients (mean 101 U/mL), as was the case of our patient. The size of the abscess varies with a mean of 6.0cm (range 1-15cm), and there seems to be no preference for laterality, and at least 10% of cases are bilateral (11).

The patient in the present case was admitted with symptoms similar to those reported in the literature and irritative urinary symptoms that, together with the recent history of urinary tract infection, initially led to suspect the recurrence or persistence of a urinary tract infection. However, based on her clinical evolution and the findings of the abdominal examination, imaging studies were requested; those results, together with elevated levels of CA-125, led to suspect ovarian carcinoma, pelvic abscess-TOA, and abscessed tumor.

The main purpose of the evaluation of an adnexal mass is to rule out malignancy, but since there are no non-invasive techniques to diagnose ovarian cancer, surgical exploration is required, which in many women results in the extraction of benign masses (12).

The treatment of TOA in post-menopause consists of the rapid initiation of broad-spectrum antibiotics, parenteral clindamycin 600mg IV every 6 hours plus gentamicin 3-5 mg/kg IV every 24 hours, cefotetan 2g IV every 12 hours plus doxycycline 100mg IV every 12 hours, or ampicillin/sulbactam 3g IV every 6 hours plus doxycycline 100mg IV every 12 hours (13). IV antibiotic therapy may be switched to oral therapy after 24 hours of clinical improvement, and the recommendation is to complete 14 days with doxycycline. If TOA is preceded or associated with a recent gynecological procedure, extended coverage with metronidazole or clindamycin should be added for anaerobes (14,15).

It should be noted that the decision to combine antibiotic therapy with surgical drainage depends on the patient's clinical condition and the size of the abscess (14). When the patient has clinical deterioration, signs of sepsis, or suspected abscess rupture, surgical management should be performed. If the patient is stable, the decision to perform surgery will be made taking into account the size of the abscess (even though there is no consensus, some authors have proposed that surgery should be performed when the abscess is between 5 and 8cm in diameter) (14-16).

Some authors have found that women in post-menopause are more likely to develop malignant tumors, both gynecological and non-gynecological, compared to pre-menopause women (12,17). For example, Gockley *et al.* (11) found in their study that 13.1% of patients with TOA had cancer; four of them had endometrial adenocarcinoma, one had mucinous borderline

tumor, two had uterine malignancies, and one had colon adenocarcinoma. Lipscomb & Ling (6) also showed a higher incidence (30%) of malignancy, including endometrial adenocarcinoma and serous malignant ovarian tumor.

Given the high frequency of co-existing cancer with TOA, it has been proposed that surgical management in post-menopause should be individualized and dependent on risk factors for malignancy and differential diagnoses, because in this age group, intraoperative and post-surgical complications are more frequent and include sepsis, infection of the operative site, intestinal injury, and rectovaginal fistulas (11,14).

On the other hand, some case reports and retrospective cohorts have found coexistence between TOA and benign lesions in postmenopausal women, including endometrial polyps (10%), uterine fibroids (3%), and benign serous cystadenomas (2%), usually diagnosed incidentally (6,7,10,11,17). In the present case, the diagnosis was made based on a pelvic mass approach, in which, due to the age group, imaging findings and tumor markers led to suspect a malignant ovarian tumor. However, the CT guided biopsy allowed finding purulent material, so surgical management was decided, revealing the co-existence of TAO with ovarian fibroma.

Ovarian fibroma is a benign ovarian sex cord-stromal tumor, which is made up of collagen-producing fibroblasts, accounting for 4% of ovarian neoplasms. It is the most common pure ovarian stromal tumor (18) and is most common in adolescents and young women. At least 1% of these tumors may be associated with ascites and hydrothorax (Meigs syndrome), and 11.3%, with increased CA-125 levels (range of 36-1848 U/mL), which are higher in large tumors (>10cm in diameter).

Due to its clinical, imaging, and serological characteristics, ovarian fibroma is often mistaken for malignant epithelial tumors in postmenopausal

women, so these patients are usually taken to surgical procedures (oophorectomy or unilateral salpingo-oophorectomy). In general, the prognosis of this type of fibroma is good and the recurrence rate is very low (19,20).

The literature review conducted for this report yielded no record of concomitant TAO and ovarian fibroma in postmenopausal patients; however, as mentioned above, some other benign ovarian tumors may co-exist with TOA.

In the present case, TOA explains the leukocytosis with neutrophilia presented by the patient, as well as the unquantified fever, since no persistent or recurrent urinary tract infection was demonstrated. CA-125 can be elevated in malignant epithelial ovarian tumors, but also in physiological conditions such as menstruation and pregnancy and in benign processes such as endometriosis and inflammatory diseases of the peritoneum (21-23), such as the patient in the present case.

Several malignancy indexes have been developed using biomarkers to identify which patients with adnexal masses should be referred to gynecologic oncology, including OVA1 and ROMA (12,24) and MIA2G (overa®); the latter uses the following biomarker results: apolipoprotein A-1, CA-125, human epididymis protein 4, follicle-stimulating hormone, and transferrin. Fredericks *et al.* (25) found that the combination of a positive MIA2G test result with an ultrasound had greater sensitivity (93.5%) and specificity (85%) than either of the two individual tests.

From the point of view of diagnostic imaging, in general, complex ovarian or pelvic masses in postmenopausal patients should make the clinician consider malignancies, especially when accompanied by one or more positive tumor markers; however, some characteristics may help discriminate between benign and malignant lesions. In this sense, radiologists take clinical and laboratory characteristics as pretest odds to calculate the final risk of malignancy.

According to the literature, there are more than 80 predictors of ovarian malignancy, among which ADNEX stands out. It is based on the imaging criteria described by the IOTA group (International Ovarian Tumor Analysis) and has an area under the ROC curve of 0.943 (95%CI: 0.934-0.952) to differentiate between benign and malignant lesions (26-29). Additionally, O-RADS is an ovarian-adnexal imaging-reporting-data system that provides a risk stratification designed to make consistent interpretations, assign a risk of malignancy, and give a treatment recommendation (30).

According to the IOTA group consensus and the studies that support it, malignancy predictors in ultrasounds include the presence of solid and cystic components, papillary projections, multiple septa, thick septa, and Doppler flow in the solid component; the total size of the lesion and the size of the solid component are also considered (22,23).

Characterization of indeterminate masses is not easy, but complementary imaging studies perform as follows:

- Doppler: sensitivity 84% (95%CI: 81-97) and specificity 82% (95%CI: 79-85)
- CT scan: sensitivity 81% (95%CI: 73-85%) and specificity 87% (95%CI: 81-94)
- Simple MRI: sensitivity 76% (95%CI: 70-82) and specificity 97% (95%CI: 95-98)
- Contrast-enhanced MRI: sensitivity 81% (95%CI: 77-84) and specificity 98% (95%CI: 97-99)

Finally, it should be noted that currently one of the best predictors of ovarian malignancy, along with contrast, is the ADC value. A low value in a solid component suggests a malignant lesion, while a low value in a liquid component suggests an abscess. In the present case, a low ADC was found in the liquid component, which is in favor of abscess, and a high ADC

in the solid component, suggesting a benign tumor lesion (32).

CONCLUSIONS

The reported case illustrates how, sometimes, a possible diagnosis of ovarian cancer carcinomatosis may actually be a benign condition, such as TOA, which responds well to medical-surgical treatment. Diagnostic imaging and tumor markers are of great help in differentiating a malignant ovarian condition from a benign process.

ETHICAL CONSIDERATIONS

The patient provided her informed consent for this case report.

CONFLICTS OF INTEREST

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TOXICODERMA AS AN ADVERSE EVENT IN A COVID-19 PATIENT: CASE REPORT

Keywords: COVID-19; Coronavirus Infections; Drug-Related Side Effects and Adverse Reactions; Medication Therapy; Lopinavir.

Palabras clave: COVID-19; Infecciones por coronavirus; Efectos colaterales y reacciones adversas relacionados con medicamentos; Hidroxicloroquina; Lopinavir.

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RESUMEN

Introducción. La infección por SARS-COV2, que en principio se pensó solo causaba manifestaciones respiratorias, también puede ocasionar síntomas gastrointestinales, renales, neurológicos, cardiovasculares e incluso cutáneos según algunos reportes.

Presentación del caso. Paciente femenina de 36 años quien asistió al servicio de urgencias por cuadro clínico consistente en disnea, astenia, adinamia, odinofagia leve y cefalea. Como antecedentes de relevancia se registró obesidad, tabaquismo y ocupación como trabajadora de la salud. Dados los síntomas, se indicó tratamiento antimalárico y antirretroviral para tratar COVID-19, diagnóstico que fue confirmado a los tres días de ingreso, pero al cuarto día de instaurado este manejo la mujer presentó polidipsia y *rash* macular, pruriginoso y generalizado. Por sospecha de toxicodermia, el tratamiento fue suspendido y con esto el cuadro cutáneo mejoró. Luego de 8 días de hospitalización, la paciente recibió el alta, junto con recomendaciones de bioseguridad y confinamiento durante 28 días.

Conclusiones. El caso descrito corresponde a un evento de toxicodermia en una paciente con COVID-19 en manejo con antirretroviral y antimalárico. A partir de los hallazgos, se establece que la exploración minuciosa de piel y mucosas en los pacientes con sospecha o diagnóstico confirmado de COVID-19 puede ser de gran ayuda para la correcta caracterización de esta nueva enfermedad.

Palabras clave: COVID-19; Infecciones por coronavirus; Efectos colaterales y reacciones adversas relacionados con medicamentos; Hidroxicloroquina; Lopinavir.

ABSTRACT:

Introduction: SARS-COV2 infection, which was initially associated with respiratory manifestations only, can also cause gastrointestinal, kidney, neurological and cardiovascular symptoms according to some reports.

Case presentation: A 36-year-old female patient attended the emergency department due to dyspnea, asthenia, adynamia, mild odynophagia and headache. The patient's medical history included obesity, smoking, and working as a health care worker. Considering the symptoms, antimalarial and antiretroviral treatment was indicated to treat COVID-19, a diagnosis that was confirmed three days after admission. However, on the fourth day of treatment, the patient presented with polydipsia and macular, pruritic, and generalized rash. Due to suspicion of toxicoderma, the treatment was suspended, and the skin condition improved. After 8 days of hospitalization, the patient was discharged with biosecurity recommendations and mandatory isolation for 28 days.

Conclusion: The described case is a report of toxicoderma in a patient with COVID-19 under treatment with antiretroviral and antimalarial drugs. Based on the findings, a thorough examination of skin and mucosa of patients with suspected or confirmed COVID-19 will undoubtedly contribute to the correct characterization of this new disease.

Keywords: COVID-19; Coronavirus Infections; Drug-Related Side Effects and Adverse Reactions; Medication Therapy; Lopinavir.

INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. The first cases were reported in December 2019 and it was declared a pandemic by the World Health Organization in March 2020 given the high rate of contagion and rapid global spread. Such is the impact of this condition that about 36.3 million cases and one million deaths had been reported by mid-October 2020 worldwide (1).

The SARS-CoV-2 infection has been characterized mainly by respiratory symptoms; however, since the onset of the pandemic, different manifestations of the disease have been reported, including gastrointestinal, kidney, neurological, and cardiovascular symptoms (2-4). Although less common, skin manifestations associated with COVID-19 have also been reported (5).

The following is the first case of an adult patient diagnosed with COVID-19 in Bogotá, Colombia, who presented with skin manifestations due to an adverse dermatological reaction associated with the therapy established to treat this disease. It is worth mentioning that, at the time of writing this case report, there is no proven treatment for patients with COVID-19.

CASE PRESENTATION

A 36-year-old female patient from Bogotá, with low socioeconomic status and a health care worker, was admitted to the emergency department of a quaternary care center located in Bogotá due to dyspnea, asthenia, adynamia, mild odynophagia, and headache. The woman reported a history of obesity, smoking and epidemiological nexus with COVID-19.

Although the patient was alert and oriented on admission, tachycardia and tachypnea were observed; during the physical examination,

she had wet mucous membranes, anicteric sclerae, normochromic conjunctiva, no adventitious sounds, and skin in normal condition. Lab test results yielded the following values: lactate dehydrogenase: 191.8 U/L, hemoglobin: 14.2 g/dL, leukocytes: 6 130 (cells/mL), neutrophils: 64.5%, lymphocytes: 22.3% and platelets: 152 000 (cells/mL). Furthermore, computerized axial tomography of the chest was performed, which showed ground-glass opacity in the middle lobe medial segment. She was admitted to the hospital, and a nasopharyngeal swab was collected to perform an RT-PCR test and confirm the diagnosis of COVID-19; the result of this test was available 3 days later and was positive.

From the first day of hospital stay, compassionate drug treatment (6) was initiated with dual therapy (antimalarial and antiretroviral). Hydroxychloroquine 200mg every 12 hours prior to a 400mg intravenous loading bolus and lopinavir plus ritonavir 400mg every 12 hours were administered. On the fifth day of symptom onset and fourth day of treatment, the patient presented polydipsia and macular, pruritic, and generalized rash that started in the face and advanced to the trunk and limbs with macules and papules that disappeared when pressed, without mucosal involvement.

Given the new symptoms, a sample was taken for arterial blood gases. pH was 7.33, pCO₂ 68.3, pCO₃ 16.9, and lactate 4.03 mmol. A single dose of hydrocortisone 200mg IV was administered; however, pruritic rash and facial warmth persisted, so loratadine 10mg every 12 hours was prescribed for one day, followed by a switch to diphenhydramine hydrochloride 50mg every 12 hours orally for 2 days. On day six of hospitalization, and due to suspected toxicoderma, antimalarial and antiretroviral treatment was discontinued, resulting in improved skin symptoms.

The patient was discharged after eight days of hospitalization; during that period, no supplemental oxygen or ventilatory support was required, but she did present an episode of fever treated with ampicillin/sulbactam (3g every 6 hours) and piperacillin/tazobactam (4.5g every 6 hours). On discharge, recommendations were given for 28-day isolation and antibiotic treatment with oral moxifloxacin.

DISCUSSION

At the time of writing this case report, a dilemma arose as to whether to consider the patient's skin symptoms as a cutaneous manifestation associated with COVID-19 or as an adverse reaction to the use of hydroxychloroquine and lopinavir/ritonavir for the treatment of that disease. Given this scenario, the available literature was reviewed, and some case reports and case series were found documenting skin manifestations associated with COVID-19 and a single report of an adverse event due to chloroquine use.

The first series of cases published was prepared by Recalcati (7), who, from a cohort of 88 cases with COVID-19 treated at the Lecco Hospital in Lombardy, Italy, established that 18 patients developed skin manifestations, of which 8 had skin involvement on admission and 10 after hospitalization. The lesions identified in this study were erythematous rash (14 patients), generalized urticaria (3 patients), and varicelliform eruptions (1 patient). The most compromised body region was the chest with mild or absent pruritus and spontaneous resolution of the lesions within a few days.

Another case series in 8 dermatological units reported skin lesions in 22 patients with COVID-19, who presented with slightly pruritic papulovesicular varicelliform exanthem, predominantly thoracic, with a range of 4 to 15 days of duration and without facial or mucosal

involvement. Other associated symptoms were fever (95.5%), cough (73%), headache (50%), asthenia (50%), rhinorrhea (45%), dyspnea (41%), hyposmia (18%), hypogeusia (18%), odynophagia (4.5%), diarrhea (4.5%), and myalgia (4.5%) (8).

Magro *et al.* (9) attempted to define the role of complement system activation and microvascular thrombosis in 5 patients with severe and persistent manifestations of COVID-19. To this end, they studied lung and skin tissue with lesions (retiform purpura) and without lesions, finding deposits of terminal complement components C5b-9 and C4d in the microvasculature. This suggested that some serious cases of this disease may have a microvascular lesion syndrome mediated by the pathways of complement activation and an associated procoagulant state.

Also, some case reports describe skin manifestations in adults and children such as petechiae, erythema, rash, urticaria, and livedo reticularis in the presence of COVID-19, although most of these patients are asymptomatic and have no histologic support (10-13). Finally, Hunt & Koziatek (14) published the case of a patient with SARS-CoV-2 infection who had generalized fever and rash, maculopapular and non-pruritic morbilliform eruptions, and required ICU management.

Toxicoderma is an adverse skin reaction associated with the use of medicines. Its clinical presentation may vary in terms of injury types and severity, so the diagnosis must be rapid and accurate to establish appropriate treatment (15). Maculopapular rash is a common manifestation of toxicoderma located mainly in the limbs and trunk and does not affect the mucous membranes. Toxicoderma lesions resolve with discontinuation of the causal drug (16). It should be noted that Huang *et al.* (17) reported the presentation of rash as

an adverse event in a patient with COVID-19 who received chloroquine.

With this in mind, and in the face of the clinical case presented, it was established that the dermatological manifestation of the patient was an adverse event to treatment with hydroxychloroquine and lopinavir/ritonavir since there was initial facial involvement, accompanied by flushing and heat, which improved after discontinuation of this treatment.

It is worth remembering that the use of hydroxychloroquine and lopinavir/ritonavir for the compassionate management of COVID-19 was initially based on the compatibility of SARS-CoV-2 with other viruses (studied *in vitro* and modeled). However, its use is not recommended currently due to the adverse cardiovascular events that they may cause (18).

Currently, physicians and scientists are investigating the skin manifestations of COVID-19, their physiopathological mechanism, and characteristics in different population groups. They emphasize the importance of promoting among clinicians the identification of skin lesions without apparent cause, as they may be diagnostic tools that guide the clinical suspicion of COVID-19 and the implementation of preventive isolation measures that contribute to reducing virus transmission (19-21). In this way, a thorough examination of the skin and mucous membranes of patients with confirmed or suspected COVID-19 helps to correctly characterize this new disease and establish its possible relationship with adverse drug reactions, as happened in the present case.

In summary, the authors consider it necessary for health professionals to report adverse events associated with compassionate drugs since this information will guide clinical practice, at least while drug efficacy and safety results for COVID-19 are available.

This report recognizes as a limitation that no confirmatory biopsy of the skin manifestation was performed.

CONCLUSIONS

According to the findings and the literature, the case described is an event of toxicoderma in a patient with COVID-19 under antiretroviral and antimalarial treatment. However, it is clear that there is still much to be said about this disease, and further research on its manifestations is needed.

In this sense, a thorough examination of the skin and mucous membranes of patients with suspected or confirmed diagnosis of COVID-19 will be useful to characterize the disease correctly.

ETHICAL CONSIDERATIONS

The present report did not pose any risk to the patient because it synthesized retrospective information. The patient consented to the review of her medical records and authorized the publication of her case for academic and scientific purposes.

CONFLICTS OF INTEREST

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PHYSICAL THERAPY TREATMENT IN A PARA-POWERLIFTING AND PARA-SWIMMING ATHLETE WITH ACHONDROPLASIA. CASE REPORT

Keywords: Achondroplasia; Disabled Person; Rare Diseases; Adapted Sport; Physical Therapy.

Palabras clave: Acondroplasia; Persona con discapacidad; Enfermedades raras;
Deporte adaptado; fisioterapia.

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RESUMEN

Introducción. La acondroplasia es una condición congénita causada por una mutación del gen codificador de crecimiento del fibroblasto que afecta la osificación endocondral y genera discapacidad estructural; además, es la causa más común de talla baja desproporcionada. Por su parte, el deporte adaptado es una disciplina deportiva que se ajusta al colectivo de personas con discapacidad y una estrategia diseñada para generar inclusión y mejorar la calidad de vida de sus participantes. Se presenta el caso de una paciente con acondroplasia a quien se le diseñó un plan fisioterapéutico de intervención enfocado a minimizar el riesgo de lesiones y prevenir la pérdida de funcionalidad como consecuencia de la práctica deportiva.

Presentación del caso. Paciente femenina de 27 años diagnosticada con acondroplasia y practicante de levantamiento de potencia adaptado y natación paralímpica, a quien mediante valoración fisioterapéutica y de la aptitud física se le encontraron alteraciones posturales y en el patrón de marcha. Dado que por su condición de base no es recomendable que practique los deportes en los cuales compite, se le diseñó un programa de entrenamiento y recomendaciones dirigido a preservar su funcionalidad y mejorar su desempeño en la práctica deportiva. El plan fue puesto en práctica y tolerado de forma adecuada por la deportista.

Conclusiones. Los planes de entrenamiento que favorezcan el mantenimiento de la condición física óptima de los participantes de deportes adaptados les permiten a estos deportistas realizar su práctica sin afectar su expectativa de vida ni su funcionalidad. El análisis del presente caso muestra cómo el fisioterapeuta desempeña un rol importante en esta población, pues los puede ayudar a disminuir las posibles complicaciones que se deriven de entrenamientos y competencias.

ABSTRACT

Introduction: Achondroplasia is an autosomal dominant congenital condition caused by a mutation of the fibroblast growth encoding gene, which affects endochondral ossification. It is the most common cause of disproportionate short stature, generating physical disability. In the presence of disability, adapted sport emerges as a strategy designed to generate inclusion and, thereby, improve the quality of life of disabled people. The aim was to develop a physical therapy plan that included recommendations to minimize the risk of injury and prevent loss of functionality as a consequence of sports practice.

Case presentation: This is the case of a 27-year-old Colombian athlete diagnosed with achondroplasia who competes in the para-powerlifting and swimming modalities. Physiotherapeutic and physical fitness evaluations were carried out, finding obesity and postural and gait pattern alterations. The available literature does not recommend practicing these sports in this type of patient; however, a training program and recommendations were designed to preserve her functionality and improve her sports performance. The plan was put into practice and tolerated adequately by the athlete.

Conclusions: Training plans that promote the maintenance of optimal physical condition in adapted sports participants allow them to continue practicing their sport without compromising their life expectancy or functionality. The analysis of the present case illustrates how physical therapists play a key role in this population to minimize the possible complications derived from training and competitions.

INTRODUCTION

Achondroplasia is an autosomal dominant congenital disorder caused by the mutation of the fibroblast growth encoder gene (1), which is found in the short arm of chromosome 4 and is a type of chondrodystrophy. It is the most common bone dysplasia and is associated with disproportionate short stature. Its annual incidence worldwide varies between 1/10 000 and 1/30 000 live births (1,2).

Physical examination allows suspecting achondroplasia, which is confirmed by radiological tests. Its phenotype is characterized by proximal shortening of the long bones, trident-shaped hands, normal-length trunk, short vertebral pedicles, squared pelvis, contracted skull base, macrocephaly, hypotonia, and ligamentous hyperlaxity (1,3,4). Intelligence and life expectancy are not affected by this condition, although comorbidities such as obstructive sleep apnea, middle ear dysfunction, and spinal stenosis increase the risk of death (5). In turn, hypotonia, hyperlaxity, overweight tendency, and postural alterations increase the risk of craniocervical junction injury and degenerate articular cartilage, causing gonarthrosis in early adulthood and leading to inability to walk (6).

Although physical activity is recommended in patients with achondroplasia, it is advisable to avoid strength sports such as gymnastics, competitive swimming, acrobatics, and contact or jumping sports, as they may be risk factors taking into account the aspects mentioned above (7). However, despite the recommendations, a large number of people with this condition practice such sports competitively in Colombia (8).

Adapted sport is a sports modality in which a series of modifications are made to enable individuals with various types of disability to participate (7). Its purpose is to allow this

population to integrate into society and increase their participation. Participants in adapted sports must go through an adaptation process in which training focuses on mobility and acquisition of proper technical sport gestures based on each individual's abilities in order to obtain autonomy and, later, compete (9).

Although preparation and participation in adapted sports competitions can lead to injuries and increased musculoskeletal impairment, these types of sports become relevant in the lives of athletes. They bring benefits, mainly in the emotional and social areas, because they are inclusive and contribute to the overall development of the person with a disability (10). High-performing athletes also receive economic benefits; for example, in Colombia, 125 athletes with physical disabilities compete in para-swimming and 52 in para-powerlifting, and they are paid during the preparation phase for the competitions to which they qualify (8).

There are multiple paralympic sports, but the present case report only analyzes the two sports that the patient practices. Para-powerlifting is an adaptation of powerlifting, and the only discipline in this modality is the barbell bench press, which consists of the development of maximum strength (11). In turn, paralympic swimming includes four styles (freestyle, breaststroke, backstroke, and butterfly), and swimmers may compete individually or in teams combining the four styles in the individual medley or relay races. Swimmers are classified according to the type and severity of their disability and compete in an olympic-size swimming pool (12).

The American Physical Therapy Association (APTA) approach (13), which defines physical therapists as health professionals who study human body movement to preserve the individual's functionality, was used to manage the reported patient. Functionality is understood as the ability of a person to carry out

the activities of daily living according to their context. Consequently, physical therapists have different roles such as rehabilitation and habilitation care; risk prevention and reduction; improvement of physical performance; and primary, secondary, and tertiary care, among others, through the examination, evaluation, diagnosis, prognosis, and intervention phases. The International Classification of Functioning, Disability and Health (ICF) (14) was considered to determine what aspects could be involved in the patient.

With this in mind, the following is the case of a patient with achondroplasia who practices competitive adapted sports in the modalities of para-powerlifting and para-swimming. A physiotherapy plan of secondary intervention was designed for this patient to minimize the risk of injuries, prevent functional capacity loss, and improve fitness to optimize her performance.

CASE PRESENTATION

This is the case of a 27-year-old Hispanic female patient diagnosed with achondroplasia who lives in a low-middle-income household in Bucaramanga and was diagnosed with achondroplasia in the prenatal stage. Physiotherapeutic and physical fitness evaluations were carried out, finding postural and gait pattern alterations.

At the time of the assessment, the patient stated that she was in good health and reported a family history of grandparents with diabetes, high blood pressure, osteoporosis, lupus erythematosus, and two paternal half-siblings with unspecified neurological disorders. Her personal medical history included depression with suicidal ideation arising from society's reactions to her physical appearance, which improved through sports practice and did not require pharmacological treatment.

On physical examination, her blood pressure was 100/60 mm/Hg; heart rate, 80bpm; respiratory rate, 15Brpm; height, 124cm; and weight, 50.3kg, for a body mass index (BMI) of 32.7 (grade I obesity); the percentage of body fat calculated through skin folds was 28%. In addition, the patient reported pain of 4/10 according to the verbal rating scale in the knees when performing activities such as jogging, jumping a rope, and climbing and descending stairs.

The patient stated that she practiced S6 paralympic swimming in free, backstroke and butterfly styles in 2-hour sessions, four times a week, for 2 years; it should be noted that this adapted swimming category includes short-stature athletes (15). She also reported that she had joined the para-powerlifting team 3 months before the assessment and that she trained for 2 hours, 6 times a week, lifting a load of 60kg in the bench press.

Since both modalities practiced by the patient are part of the sports that should be restricted in people with achondroplasia (16), because they may accelerate their degenerative joint process and increase the risk of injury and death due to the movement style that they require, preventive physiotherapy intervention was considered necessary.

Physiotherapy assessment

The patient underwent two physiotherapy assessments, one at the first visit and the other three months later to follow up. The aspects found during the initial assessment are described below.

Given the lack of adapted tests to measure aerobic capacity, the modified Bruce protocol was used, obtaining a VO₂ max of 44.18 mL/kg/min (17). The test was suspended before

it could be completed because the patient experienced knee pain after increasing the treadmill incline. Although oxygen consumption was classified as good for age (reference value 39-48.9), the perceived exertion was 4 (moderate exertion) according to the modified Borg scale.

The range of motion was normal, but the patient had hypermobility according to the Beighton scale (18): fifth metacarpophalangeal joint passively flexed until 100°, hyperextension of the elbow and knees, and trunk flexion that allowed the palms of the hands to rest on the floor. Muscle strength was normal on the Robert Lovett scale (19).

Posture was assessed by planimetry with a grid. Asymmetry of the shoulders and genu varum were seen in the anterior view, and genu recurvatum, lumbar hyperlordosis, forward head position, and forward right shoulder were seen in the lateral view; the latter aspect affected the bench press practice because the bar was tilted toward the left side. When evaluating the sole, it was established that the woman had cavus feet (20).

The observational analysis of the gait found that the patient performed the stance and swing phases appropriately, but gait determinants were altered due to increased pelvic rotation and knees in permanent flexion, impacting stance phase knee flexion and causing widening of the base of support (20).

Moreover, it was found that the most affected system in the patient was the musculoskeletal system. She also reported that the most troublesome aspects that affected her personally, according to the CIF (14), were: E325 acquaintances, peers, colleagues, neighbors, and community members; E330 people in positions of authority; E345 strangers; E445 individual attitudes of strangers; and

E460 societal attitudes. All these factors made her a victim of discrimination and mockery throughout her life. On the other hand, she said that the following were facilitating aspects: e310 immediate family; e315 extended family; E320 friends; E355 health professionals; E410 individual attitudes of immediate family members; and E420 individual attitudes of friends. This means that the patient feels that her personal (negative attitude toward her condition and emotional instability), family (absence from family events), work (rejection by co-workers and job rejection), and sports (not being able to perform high-impact sports) roles are affected.

According to the APTA, the patient's physiotherapeutic diagnosis was musculoskeletal domain and D pattern: limited joint mobility, motor function, muscle performance, and range of motion associated with bone tissue dysfunction (13).

It should be noted that the medical diagnosis of achondroplasia syndrome caused the patient to have activity limitations such as D4502 walking on different surfaces, D4552 running, and D4553 jumping, and restrictions on mobility such as D470 using transportation, D475 driving, etc. (14).

Physiotherapy treatment plan

The intervention and training plan proposed by the physical therapists consisted of a physical training program that emphasized joint protection based on the patient's conditions and the sports she practiced. Its design included three exercise blocks to strengthen the muscles in a general way (Table 1), allowing the patient to perform other training additional to the regular training. Each activity had a basic description and prescription, which were established according to the physical fitness assessment.

Table 1. Training plan.

Block	Exercises	Series	Repetitions	Intensity *	Frequency	Tool
Block 1	Warm-up 20 minutes					
	Shoulder external rotation	3-4	10-12	70-75% Rmax	2 times/week	Dumbbells or elastic bands
	Shoulder lateral raise	3-4	10-12	70-75% Rmax	2 times/week	Dumbbells
	Front fly	3-4	10-12	70-75% Rmax	2 times/week	Dumbbells
	Shoulder extension	3-4	10-12	70-75% Rmax	2 times/week	Dumbbells or elastic bands
	Knee extension	3-4	10-12	70-75% Rmax	2 times/week	Machine or elastic bands
	One-leg press	3-4	10-12	70-75% Rmax	2 times/week	Horizontal press
	Abductors	3-4	10-12	70-75% Rmax	3 times/week	Pulley or elastic bands
	Buttocks	3-4	10-12	70-75% Rmax	3 times/week	Pulley
	Core (planks)	4	60 s	Body weight	3 times/week	Mattress
	Trunk extension	4	10	Body weight	2 times/week	Exercise ball
	Dynamic stretching 10 minutes					
Block 2	Warm-up 20 minutes					
	Pulley row	3-4	10-12	70-75% Rmax	1 times/week	Pulley
	Upright row	3-4	10-12	70-75% Rmax	1 times/week	Pulley
	Shoulder internal rotation	3-4	10-12	70-75% Rmax	1 times/week	Dumbbells
	Squats	3-4	10-12	Body weight	2 times/week	Exercise ball
	Knee flexion	3-4	10-12	70-75% Rmax	2 times/week	Machine
	Adductors	3-4	10-12	70-75% Rmax	2 times/week	Pulley or elastic bands
	Quadruped hip extension	3-4	10-12	70-75% Rmax	2 times/week	Ankle weights
	Scissor squats	3-4	10-12	20 kg	2 times/week	Bar
	Dynamic stretching 10 minutes					
Block 3	Warm-up 20 minutes					
	Shoulder flexion	3-4	10-12	70-75% Rmax	1 times/week	Pulley
	Shoulder abduction	3-4	10-12	70-75% Rmax	1 times/week	Body weight
	Shoulder extension	3-4	10-12	70-75% Rmax	1 times/week	Dumbbell or band
	Reaches	3-4	10-12	Body weight	2 times/week	Bosu ball
	Half squat band hip abduction	3-4	10-12	Body weight	2 times/week	Elastic bands
	Gastrocnemius muscle (heel lift)	3-4	10-12	Body weight	2 times/week	Decline bench press
	Triceps	3-4	10-12	70-75% Rmax	2 times/week	Bar
	Biceps	3-4	10-12	70-75% Rmax	2 times/week	Bar
	Supine and prone forearm	3-4	10-12	70-75% Rmax	2 times/week	Bar
	Dynamic stretching 10 minutes					

Rmax: repetition maximum.

* Repetition maximum should be reevaluated every 3 months to carry out the progression of the exercise.

Source: Own elaboration.

Within this training plan, and to reduce the risk of joint injuries due to hyperlaxity, it was suggested to avoid postures involving axial loads on the joints and performing submaximal ranges of motion. The plan also established that before each training, a warm-up should be carried out, including joint mobility and multilateral dynamic exercises, as well as low-impact functional training. It was also recommended to include breathing exercises and adequate hydration throughout the training and make a generalized dynamic stretching to cool down.

Furthermore, the patient was advised to avoid jumping, running, deep squats requiring knee flexion $>90^\circ$, jogging, using elliptical machines, and ascending and descending stairs, which are all activities that are not recommended due to her underlying condition (21). Also, to reduce future complications, she was advised to avoid high-impact and repetitive activities, as well as continuous traumas that pose a risk of injury to the tibiofemoral joint due to instability. Psychosocial support was also recommended to prevent the relapse of depressive symptoms and emotional distress due to rejection and negative attitudes of the environment.

The training plan and the recommendations were socialized with the patient, who put them into practice and showed great acceptance and satisfaction. The relevance of including this plan in weekly training sessions and following the recommendations mentioned above to optimize the performance of their daily living activities was emphasized.

The intervention plan was designed to ensure an average life expectancy for the patient and maintain functionality. The importance of following the recommendations, especially in sports practice, was also emphasized, as the analysis of the deficiencies and limitations detected in the physical therapy assessment was taken into account. No incidents or adverse

events occurred during the implementation of the proposed activities.

A three-month follow-up revealed that the patient was adherent to the training plan, which was confirmed by her para-powerlifting coach, who also reported adequate tolerance to all the exercises recommended. It was established that the athlete complied with the suggested recommendations for joint protection, except for avoiding jumping, an activity that can accelerate the degeneration of the articular cartilage of the knees. She explained this behavior by stating that she perceived that jumping the rope favors her aerobic capacity and helps her lose weight.

Some of the changes reported in comparison with the initial assessment include weight loss, reaching 48kg; remission of knee pain during jogging, jumping, and climbing and descending stairs; and improvement in sports performance by increasing bench press load to 65kg.

DISCUSSION

Achondroplasia is considered a rare disease (22), so there is not enough literature to guide intervention plans or sports practice recommendations. However, as with athletes who do not have any disability, people with achondroplasia must follow a structured fitness program before participating in high-level competitions (23). It is also recommended to consider the specific characteristics of the athlete when designing a training plan for patients with this condition, for example, the shortening of their limbs, since this aspect can lead to earlier fatigue and the need for longer and more frequent rest periods. Furthermore, to practice adapted powerlifting, it may be useful to use a thinner training bar because these athletes fail to make an effective grip by not being able to fully close the hand due to their short fingers, which favors wrist injuries (15).

The proposed recommendations in the present case were based on the proper positioning of

the body and the importance of avoiding maximal ranges of motion that could cause injury due to the patient's hyperlaxity. However, during press bench press exercises, the athlete is exposed to spine overextension, which could be harmful due to her history of spinal stenosis. In this regard, previous studies report that an exercise plan that emphasizes the strengthening of the trunk's anterior muscles allows minimizing the extent of extension and favor a more aligned posture of the spine (24). This aspect should be considered at the time of exercise prescription.

The limitations of the case include that there are no validated tests to measure aerobic capacity, bearing in mind that the test used did not measure the actual aerobic capacity of the patient because its score of perceived exertion on the modified Borg scale was 4. It is not useful either to establish BMI in people of short stature, so the results obtained in these aspects of the assessment may not be reliable. In this regard, Sims *et al.* (25) proved that people with achondroplasia have a higher energy expenditure when walking and running because cadence increases, so VO_2Max should be calculated through indirect calorimetry, which could provide a more reliable measurement.

Also, despite the existence of scales adapted to measure BMI, Wagner & Sandt (26) proposed that the predisposition of people with achondroplasia to gain weight is associated with the fact that they have less body area to distribute the extra mass because their bones are small, but the other structures have a normal size. This aspect favors the increased risk of injury and should therefore be considered when devising weight-loss strategies.

The main strength of this clinical case is that the training and recommendations plan was developed in an interdisciplinary manner, with the participation of a physician, a physiotherapist, three eighth-semester physical therapy students and

a specialist in physical culture and sports. This allowed considering different relevant points of view. In addition, the patient's adherence to the plan allowed evaluating its effectiveness (27).

Since there are no well-defined or standardized physical training protocols for people with achondroplasia (28), coaches of athletes with this condition should consider collaborating with physical therapists to make an appropriate assessment of all deficiencies and risk factors that may occur. This will also allow designing a training plan to enable athletes to perform optimally and minimize the risk of injury.

CONCLUSIONS

A physical therapy management plan was designed for a patient with achondroplasia after analyzing her impairments and limitations. This plan was intended to provide the necessary care so that, despite the impact that her sports practice could have on her joints, the patient could continue to perform her practices without affecting her life expectancy or functionality.

Adapted sport is a tool that helps people with disabilities explore their maximum potential, favoring their inclusion and participation in society. However, due to health implications, the practice of high-performance sports must be monitored according to the athlete's physical condition.

The analysis of the present case shows how physical therapists play an important role in physiotherapy assessment and diagnosis and in the design of secondary intervention plans to prevent and minimize the possible complications resulting from sports practice, which can have a detrimental effect on athletes' quality of life.

PATIENT'S PERSPECTIVE

When asking the patient for her opinion on the proposed training plan and recommendations,

she said she felt comfortable with it because it included various activities that provided her with tools to strengthen her training. She also stated that she tolerated well the exercises and complied with most of the recommendations, resulting in significant improvements in her overall health. She added that she could even perform activities that are not recommended for her condition, such as jumping rope, which she does not wish to withdraw from her training plan because it is her preferred type of cardiovascular exercise.

ETHICAL CONSIDERATIONS

Resolution 8430 of 1993 of the Ministry of Health of Colombia (29) was taken into account to prepare this case report, and the informed consent of the patient was obtained.

CONFLICTS OF INTEREST:

None stated by the authors.

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