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CASE REPORT

Lymphomatoid granulomatosis in an octogenarian patient: a case report

Granulomatosis linfomatoide en un paciente octogenario: reporte de caso

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Abstract

Introduction: Lymphomatoid granulomatosis (LG) is a rare lymphoproliferative and angiodestructive disorder caused by the Epstein-Barr virus (EBV). It is usually observed between the fourth and sixth decade of life, affecting males more frequently, and is histologically classified depending on the number of EBV-positive large B cells.
Case presentation: In February 2023, an 81-year-old man presented to the dermatology department of a tertiary care hospital in Bogotá D.C. (Colombia) due to a 5x3cm ulcerative lesion with a dirty background and erythematous, violaceous, indurated borders with hematic crusts on the left hypochondrium that appeared 10 months earlier. The patient underwent multiple histopathological studies that were inconclusive, so in April 2023 he was referred to the dermatology service of a quaternary care hospital, where, based on the results of complementary studies (immunohistochemistry) and anti-neutrophil cytoplasmic antibody test in peripheral blood and EBER-ISH test, he was diagnosed with grade 3 LG in June 2023. Consequently, he started treatment with immunochemotherapy (R-mini-CHOP scheme; 6 cycles; 1 every 21 days), achieving complete remission of the disease.
Conclusion: Although LG is a rare condition that usually occurs between the fourth and sixth decade of life with a predominant initial clinical manifestation of pulmonary involvement, it should be suspected in patients with refractory skin lesions, regardless of their age since, in some cases, they may precede pulmonary lesions. Relevant histopathological studies should therefore be performed.

Resumen

Introducción. La granulomatosis linfomatoide (GL) es un trastorno linfoproliferativo y angiodestructivo raro causado por el virus de Epstein-Barr (VEB) que suele ocurrir entre la cuarta y sexta década de la vida, afecta más a los hombres y se clasifica histológicamente según el número de células B grandes positivas para VEB.
Presentación del caso. Hombre de 81 años quien en febrero de 2023 asistió al servicio de dermatología de un hospital de tercer nivel de atención de Bogotá D.C. (Colombia) por una lesión ulcerosa de 5x3cm de fondo sucio y bordes eritematosos, violáceos e indurados con costras hemáticas en el hipocondrio izquierdo que había aparecido 10 meses antes. Al paciente se le realizaron múltiples estudios histopatológicos que resultaron inconclusos, por lo que en abril de 2023 fue remitido al servicio de dermatología de un hospital de cuarto nivel de atención, donde, con base en los resultados de estudios complementarios (inmunohistoquímica) y prueba de anticuerpos anticitoplasma de neutrófilos en sangre periférica y test EBER-ISH, fue diagnosticado con GL grado 3 en junio de 2023, por lo que se inició manejo con inmunoquimioterapia (esquema R-mini-CHOP; 6 ciclos; 1 cada 21 días), logrando la remisión completa de la enfermedad.
Conclusión. A pesar de que la GL es una condición rara que suele ocurrir entre la cuarta y sexta década de la vida y cuya manifestación clínica inicial predominante es la afectación pulmonar, debe sospecharse en pacientes con lesiones cutáneas refractarias, independientemente de su edad, ya que en algunos casos estas pueden preceder las lesiones pulmonares, por lo que se deben realizar los estudios histopatológicos pertinentes.

Introduction

Lymphomatoid granulomatosis (LG) is a rare lymphoproliferative disorder caused by the Epstein-Barr virus (EBV).[1-3] Although its prevalence is unknown, it has been described that it affects more men than women, with a 2:1[1-3] ratio and that, although it can affect young patients and children, it occurs more frequently between the fourth and sixth decades of life.[3] Furthermore, although LG has been reported to have a complex relationship with the functioning of the host immune system,[1] the immunologic features associated with this condition are not yet fully understood.[3]

Histologically, LG lesions are characterized by an angiocentric and angiodestructive accumulation of infiltrates consisting of a small number of EBV-positive B-cells mixed with a prominent inflammatory background made up of T-cells, plasma cells, and histiocytes.[3] In addition, according to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms by Swerdlow *et al.*,[4] LG is a mature B-cell neoplasm.

The clinical behavior of LG varies widely, as clinical manifestations can range from a painless process to an aggressive B-cell lymphoma.[5] Also, pulmonary involvement occurs in more than 90% of cases and is usually present at the time of diagnosis; the most common radiological feature (approximately 80% of all cases) is the presence of multiple unilateral or bilateral lung nodules with peribronchovascular distribution and basal predominance.[5] Other frequent extranodal sites involve the central nervous system, skin, kidney, and liver.[3,6]

Since LG is a rare condition, there is no consensus on a standard treatment. Therapeutic options will depend on their histologic grade, so an accurate assessment of these lesions is essential. Some of the available treatment options include immune modulation (low-grade LG) and combined immunochemotherapy (high-grade LG).[6]

This article reports the case of an older adult with LG in whom the initial manifestation was a nonspecific skin lesion that required multiple histopathologic studies to confirm the diagnosis. Due to its unusual nature and the fact that many pathologists are not familiar with its histologic features, this condition is not usually considered as an initial differential diagnosis for this type of dermatologic lesions.

Case presentation

In February 2023, an 81-year-old man with no relevant medical history or occupational exposures presented to the dermatology department of a tertiary care hospital in Bogotá D.C. (Colombia) due to a 5x3cm ulcerative lesion with a dirty background and erythematous, violaceous and indurated borders with hematic crusts on the left hypochondrium since April 2022 (Figure 1). At the consultation, it was suspected that the lesion was compatible with a skin and soft tissue infection, so treatment with clindamycin (300mg every 8 hours for 7 days) and topical clotrimazole 1% (2 applications per day for 15 days) was indicated, and the patient was advised to attend a follow-up appointment in a month.

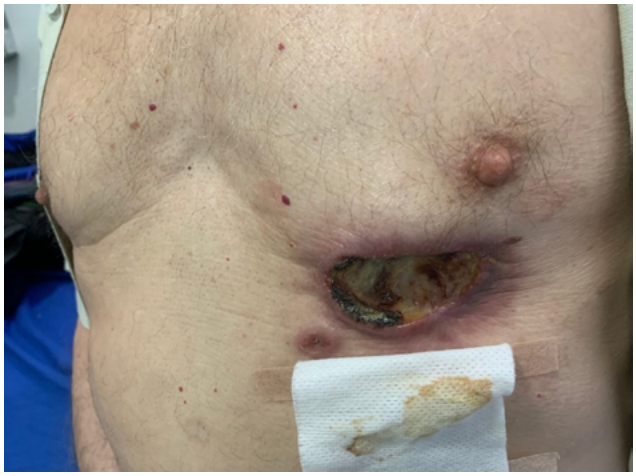

Figure 1. Ulcerative lesion of 5x3cm with a dirty background and erythematous, violaceous and indurated edges with hematic crusts on the left hypochondrium.

In a follow-up appointment with the dermatology service one month later, it was observed that the lesion had increased in size and presented purulent secretion, so it was decided to perform a biopsy, a *Leishmania* parasite culture, and a bacterial culture. At a new follow-up appointment after 25 days (while the patient remained without medical treatment, but with daily dressing changes over the lesion), the histopathological study report of the lesion was reviewed and the following findings were reported: extensive lymphohistiocytic inflammatory infiltrate with a predominance of chronic inflammatory cells in a granulomatous pattern without signs of necrosis extending into the subcutaneous adipose tissue; negative Ziehl Neelsen stain for acid-fast bacilli, and negative PAS (Periodic Acid-Schiff) stain for fungi. Parasite culture for *Leishmania* and bacterial culture were negative.

Given the complexity of the lesion and the lack of sufficient evidence to make a diagnosis, during this follow-up appointment a second sample was taken for a new histopathological study, which would be reviewed at a quaternary care hospital located in Bogotá D.C., where the patient would continue to attend his dermatology follow-up appointments. This new biopsy report, reviewed in April 2023 at a subsequent follow-up appointment, described the following findings: epidermis: presence of irregular acanthosis; dermis: presence of nodular lymphohistiocytic granulomatous infiltrate with some multinucleated giant cells around the cutaneous adnexa and in the adipose tissue; poorly formed granulomas with no signs of necrosis; and presence of perineural lymphoid infiltrate, which is angiocentric and angiodestructive, involving blood vessels.

Taking into account this last finding, complementary immunohistochemistry (IHC) studies were performed and the following was found: lymphoid infiltrate composed of CD3 T cells with homogeneous positivity for CD4, CD8, CD7, CD2 and CD5, and another group of large CD20 and PAX-5 positive B cells, which showed focal positivity for CD30 and negativity for CD15. Moreover, positivity for CD68 was identified, stressing the important component of histiocytic cells.

Based on the foregoing, LG and granulomatosis with polyangiitis were considered as differential diagnoses, so the following studies were requested during the visit to confirm the diagnosis: anti-neutrophil cytoplasmic antibody (ANCA) test in peripheral blood and EBER-ISH test with the lesion sample.

In June 2023, at a new follow-up appointment, a grade 3 LG diagnosis was confirmed as the EBER-ISH test was positive (presence of EBV in more than 50 cells per high-power field) (Figure 2). In view of the above, the patient was referred to the emergency department of the same hospital (quaternary level of care) for admission and immediate care by the hematology department.

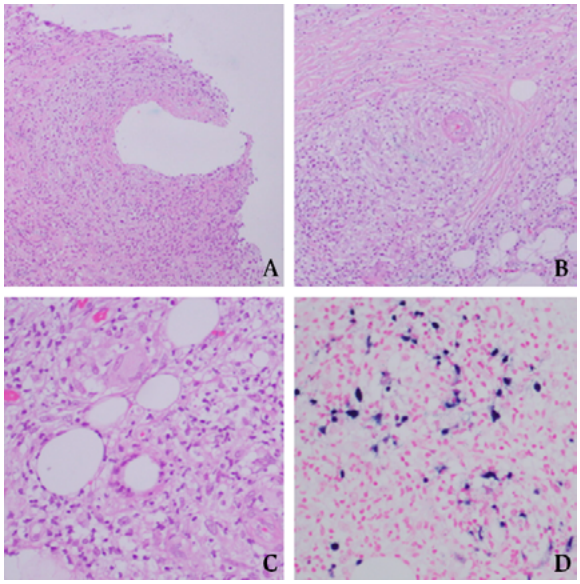

Figure 2. A-B. Hematoxylin and eosin stain (4X): angiocentric, angioinvasive and angiodestructive lymphoid infiltrate in the wall of an arterial vessel in the dermis; **C.** Hematoxylin and eosin stain (40X): granuloma consisting of epithelioid histiocytes and multinucleated giant cells; **D.** EBER-ISH test (40X): cells with strong positivity for Epstein-Bar virus marker.

During the interview in the emergency department, the patient reported unintentional weight loss (approximately 4kg) and the appearance of lymphadenopathies in the cervical region in the previous 6 months. Once he was admitted to the hospital, and after being assessed by the hematology department, the following tests were performed that same day (first day of hospitalization): brain MRI; computed axial tomography (CT) scans of the neck, chest and abdomen; myelogram; bone marrow flow cytometry; and bone marrow studies (bone marrow aspiration and biopsy). The results of these tests are described below.

In the brain MRI, no intracranial lesions suggestive of neoplasia were detected. In the neck CT, a rounded adenopathy of approximately 6.7mm in size with a hypodense center was observed at the posterior border of the left sternocleidomastoid muscle (Figure 3A). The chest CT scan showed a tumor-like mass of approximately 32x30mm with spiculated borders in the posterior segment of the right upper lobe (Figure 3B), as well as multiple random solid nodules in both lungs. The abdominal CT scan showed no evidence of lymph node involvement. Bone marrow studies (flow cytometry, myelogram, and biopsy) were normal and no signs of infiltration were evident. Finally, flow cytometry and myelogram findings were normal.

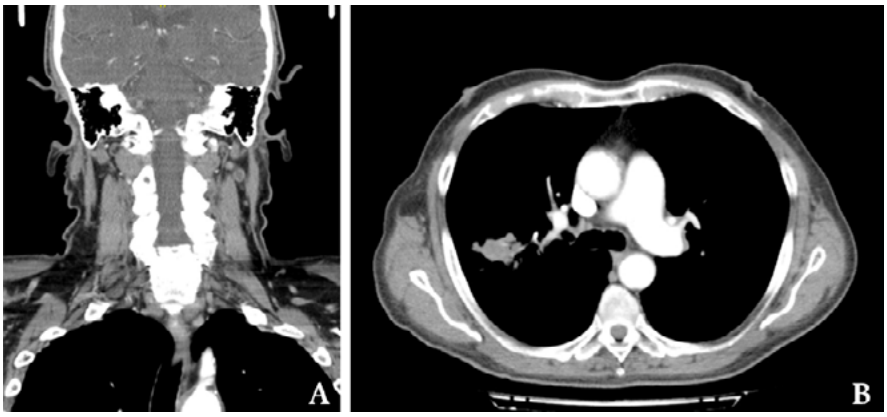

Figure 3. A. CT scan of the neck: rounded adenopathy of approximately 6.7mm with a hypodense center at the posterior border of the left sternocleidomastoid muscle; **B.** CT scan of the chest: tumor-like mass of approximately 32x30mm with spiculated borders in the posterior segment of the right upper lobe.

On the second day of hospitalization, the patient was evaluated by the surgical service to discuss the possibility of performing a cervical lymph node biopsy vs. a lung lesion biopsy to confirm whether these lesions were secondary tumors or if it was a second primary tumor. However, the patient decided not to undergo these procedures.

On the third day of hospitalization, and once the results of all the tests performed were available, taking into account the LG histologic grade and the patient's age, the hematology service decided to initiate treatment with immunochemotherapy (R-mini-CHOP scheme; 6 cycles; 1 every 21 days), administering the first cycle on the fourth day of hospitalization. Since the patient showed adequate tolerance to immunochemotherapy, he was discharged the day after receiving the first cycle and with the indication to attend the chemotherapy rooms of the hospital for the administration of the other 5 cycles on an outpatient basis. During this period, dose limiting toxicity was ruled out in routine check-ups with the hematology service. Two weeks after the end of the sixth cycle, a positron emission tomography (PET-CT) scan was requested.

In October 2023, one month after completion of the immunochemotherapy regimen, the patient attended a follow-up appointment with the hematology service, in which physical examination showed healing of the ulcerative lesion (Figure 4). Given that there were no hyperglycolytic lesions of lymphomatous infiltrative appearance in the PET-CT, complete remission of the disease was confirmed.

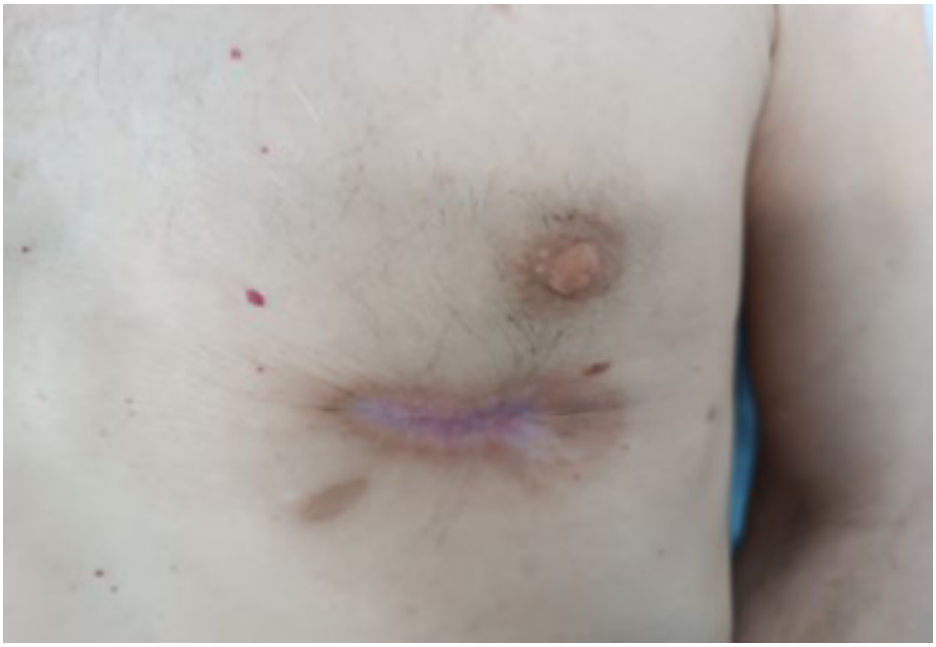

Figure 4. Healing of the lesion in the last follow-up.

Figure 5 provides an overview of the chronological order of the most significant events of the case. As of the date of writing this case report (July 2024), the patient has no signs of LG relapse.

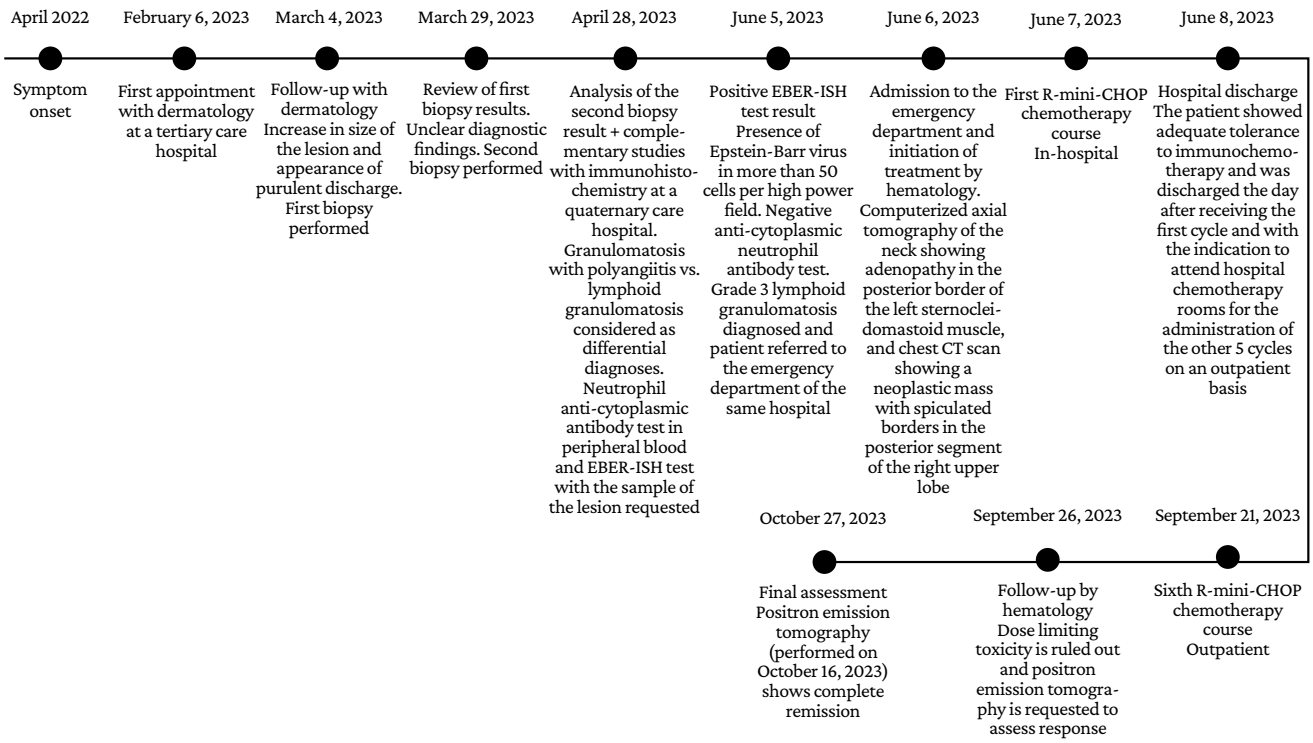

Figure 5. Relevant events in the patient's clinical course.

Discussion

LG is a rare B-cell lymphoproliferative disorder caused by the EBV, in which abnormal cells accumulate directly in the affected tissues, usually in the form of infiltrative nodular lesions, with T-cell invasion and destruction of blood vessels.[1] In most cases, the lung is involved at the time of diagnosis and imaging findings may vary from small pulmonary nodules to large necrotic lesions and even cavitations. The most common imaging feature is the presence of multiple unilateral or bilateral nodules in the lung with peribronchovascular distribution and basal predominance.[5] However, this condition can also affect the central nervous system (40%), skin (34%), kidney (19%), and liver (17%).[6]

It has been reported that skin lesions precede pulmonary lesions in up to 10% of these patients and that dermal biopsy may lead to diagnosis in these cases.[1] Skin lesions are usually heterogeneous, although they typically appear as scattered subcutaneous or dermal nodules that vary in size, predominantly on the extremities. On the other hand, while maculopapular and erythematous rashes are the most common lesions, in some cases, indurated plaques may be observed. There may also be varying degrees of ulceration and these lesions may become necrotic if the disease is not adequately treated.[1] In our patient's case, the initial manifestation was a single 5x3cm skin lesion on the left hypochondrium with erythematous, violaceous, and indurated borders, and the histopathological study eventually led to a diagnosis of LG.

Histologically, these lesions are characterized by an angiocentric and angiodestructive necrotizing infiltrative process consisting of small lymphocytes, plasma cells, histiocytes, and atypical lymphoreticular cells.[7] Moreover, malignant B cells are usually medium to large in size and positive for CD20 (in some cases positive for CD30) and negative for CD15.[8]

In our patient, the second biopsy of the lesion showed an angiocentric and angiodestructive perineural lymphoid infiltrate, and for this reason we performed complementary IHC studies, finding that the infiltrate was composed of CD3+ T cells

and groups of large B cells positive for CD20, CD30 and PAX5 and negative for CD15. We reached the diagnosis of LG and granulomatosis with polyangiitis, since both diseases exhibit lymphocytic infiltrates with giant multinucleated cells and necrotic areas, although granulomatosis with polyangiitis is a systemic vasculitis mediated by ANCAs,[9] which were not identified in our patient. Furthermore, the EBER-ISH test result was positive, finally confirming the diagnosis of grade 3 LG.

It should be noted that it has been reported that the diagnosis of LG based solely on the study of skin lesions, as in our patient, should be made with caution because it has been described that EBV is more difficult to identify in skin lesions than in lung lesions.[10] Actually, in our patient, based on the results of the second biopsy of the lesion, an EBER-ISH test was performed to confirm the presence of the virus.

On the other hand, the WHO, as pointed out by Colby,[11] recommends classifying LG into grades 1, 2 or 3 depending on the number of EBV-positive large B cells. Thus, grade 1 has less than 5 EBV-positive cells in a single high-power field, grade 3 has more than 50 EBV-positive cells in a high-power field, and grade 2 encompasses the remainder.[11] Grade 1 and 2 lesions are considered low-grade lesions, while grade 3 lesions are considered high-grade lesions.[12]

Determining the histologic grade of LG is critical because its treatment varies depending on its grade. Low grade lesions are usually treated with interferon-α,[6,12] while the use of agents that increase the host immune response such as inteferon-α and gamma globulin (in combination) have been described in immunodeficient patients due to their direct antiviral and antiproliferative effect on EBV-infected cells.[6] In turn, high-grade LG requires immediate treatment and the therapeutic approach is similar to that used in other aggressive lymphomas such as EBV-positive diffuse large cell lymphoma, mainly immunochemotherapy protocols such as DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).[6]

In the present case, although the patient was diagnosed with grade 3 LG, since he was an older patient and was not in the typical age group for the presentation of this disease (30-59 years),[3] we searched for prospective studies reporting the results of the use of attenuated immunochemotherapy protocols in older patients with diffuse large B-cell lymphoma. It was found that Peyrade *et al.*,[13] in a single-arm multicenter clinical trial, reported that the use of the R-miniCHOP (rituximab and reduced dose CHOP) regimen in patients over 80 years of age with this type of lymphoma offers an adequate balance between efficacy and safety. For this reason, it was decided to use this regimen in our patient (6 cycles; 1 every 21 days) without observing signs of dose limiting toxicity during its administration, and achieving complete remission of the disease, which was confirmed one month after completing the regimen using PET-CT.

Conclusion

LG is a rare lymphoproliferative disorder that occurs most frequently between the fourth and sixth decade of life and in which pulmonary involvement is usually the initial clinical manifestation. In some rare cases, skin lesions precede pulmonary lesions, as was the case of our patient. Therefore, this disease should be suspected in individuals with refractory skin lesions regardless of their age, in whom histopathologic studies should be performed to confirm or rule out the diagnosis.

Ethical considerations

The present case report was approved by the Research and Institutional Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Javeriana and the Hospital Universitario San Ignacio, in accordance with Minutes FM-CIE-0259-24 of March 15, 2024. Likewise, informed consent was obtained from the patient, authorizing the use of his data for the preparation of this case report.

Conflicts of interest

None stated by the authors.

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