Case Reports in Oncology

Case Rep Oncol 2023;16:591–597
DOI: 10.1159/000530897
Received: November 2, 2022
Accepted: April 11, 2023
Published online: August 9, 2023

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Case Report

Generalized Lymphatic Anomaly as a Differential Diagnosis of Lytic Lesions

Greta Catani[a] Federico Waisberg[a] Diego Enrico[a] Andrés Rodriguez[a] Yanina Pflüger[a] María Laura Galluzzo[b] María del Valle Centeno[b] Isabel Colmenero[c] Mora Amat[d] Lisandro Paganini[e] Anna Frida García Herrmann[e] Matías Chacón[a]

[a]Departament of Oncology, Alexander Fleming Institute, Buenos Aires, Argentina;
[b]Department of Pediatric Pathology, Hospital Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina;
[c]Department of Pediatric Pathology, Hospital Infantil Universitario Nino Jesús, Madrid, Spain;
[d]Department of Oncology Pathology, Alexander Fleming Institute, Buenos Aires, Argentina;
[e]Department of Radiology, Alexander Fleming Institute, Buenos Aires, Argentina

Keywords
Generalized lymphatic anomaly · Lymphatic malformations · Lytic lesion

Abstract
Generalized lymphatic anomaly (GLA) is an infrequent multiorgan disease characterized by the presence of abnormal proliferation of lymphatic vessels. The diagnosis requires histological confirmation, and the treatment is controversial. We are presenting a case of a 28-year-old male patient who was diagnosed with an extragonadal mediastinal nonseminomatous germ cell tumor. He underwent chemotherapy, and during this treatment, radiologic findings evidenced lytic lesions. Multiple biopsies were performed, which revealed the presence of abnormal lymphatic vessels, characteristic of GLA. There are different etiologies of osteolytic lesions, and on some occasions, they mimic a tumoral entity. The clinical suspicion of GLA is the first step in approaching the diagnosis, particularly in young adult patients.

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Introduction

Generalized lymphatic anomaly (GLA) is an infrequent entity characterized by the proliferation of abnormal lymphatic vessels involving the viscera, skin, and bone in a micro- or macrocystic fashion. GLA can affect bones, resulting in multiple osteolytic lesions. They are usually multiple, nonprogressive, noncontiguous, and medullary-located.

Correspondence to:
Greta Catani, gcatani91@gmail.com

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There is no accurate data of epidemiology of these entities given their low incidence. Men are more frequently affected than women, with a ratio of 2:1 [1, 2]. This condition predominantly affects children and young adults.

According to the classification in the International Society for the Study of Vascular Anomalies (ISVVA) 2018, GLA is included in the lymphatic malformations (LMs) spectrum along with Gorham-Stout disease (GSD), kaposiform lymphangiomatosis (KLA), and channel-type LMs [3]. KLA was categorized as a subtype of GLA, although patients with this subentity present severe coagulation disorders [4]. The appropriate diagnosis is challenging, considering that LMs have indistinguishable radiological characteristics.

In patients with GLA, osteolytic lesions consist of diffusely dilated lymphatic vessels confined to the medullary cavity [4]. The common radiographic appearance of skeletal involvement are intramedullary multifocal cysts, with cortical preservation and no periosteal reaction.

Diagnosing GLA requires a high-grade clinical suspicion, the integration of a detailed patient history, a thorough clinical evaluation, and a variety of tests including biopsies and specialized imaging techniques. Histopathologic findings are the cornerstone for GLA diagnosis.

In this article, we describe an unusual case in a 28-year-old male patient who was diagnosed with an extragonadal nonseminomatous germ cell tumor and, during the course of the disease, presented lytic lesions which imitated a neoplastic origin. The CARE Checklist has been completed by the authors of this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530897)

Case Presentation

A 28-year-old man, without relevant medical records, came for a consultation in August 2020 about respiratory symptoms of 2 months of evolution. A thoracic computed tomography (CT) scan showed a lesion of 150 × 100 × 170 mm in relation to the left ventricle, aortic arch, pulmonary artery trunk, and hilar bronchovascular structures. It extended to the left anterolateral chest wall, occupying part of the left hemithorax. The testicular ultrasound was normal, and a cardiac Doppler ultrasound revealed mild pericardial effusion. Serum lactate dehydrogenase (LDH) was 404 ng/mL, alpha-fetoprotein (AFP) was 6,067.4 ng/mL, and beta human chorionic gonadotropin (beta hCG) was 50.97 mUI/mL.

A biopsy was performed, and the pathology report confirmed the presence of an extragonadal nonseminomatous germ cell tumor. In September 2020, the patient started chemotherapy with BEP: bleomycin 30 UI/d days 1–8–15, etoposide 100 mg/m^2 1–5, and cisplatin 20 mg/m^2 day 1–5 every 21 days. At the end of the third cycle, in October 2020, a follow-up CT scan showed minimal decrease in size of the mediastinal mass: 146 × 100 × 147 mm and the emergence of osteolytic images in the L4 vertebral body (Fig. 1a–d). A fourth cycle was completed in December 2020, with improvement of tumor markers: LDH 55 ng/mL, AFP 77 ng/mL, and beta hCG 5 mUI/mL.

In January 2021, the patient started having lumbar pain. A PET/CT scan showed multiple lytic lesions in the spine and pelvis (Fig. 1b–e), all of which were suspicious of metastatic disease. A biopsy of the lumbar region was performed, and no evidence of neoplastic disease was found. The pain increased, and it did not respond to analgesics. Due to this torpid evolution, images were repeated in March 2021, and new lytic lesions were evidenced (Fig. 2a–ef). Multiple biopsies in different osteolytic lesions were performed, without findings that suggested tumoral involvement.

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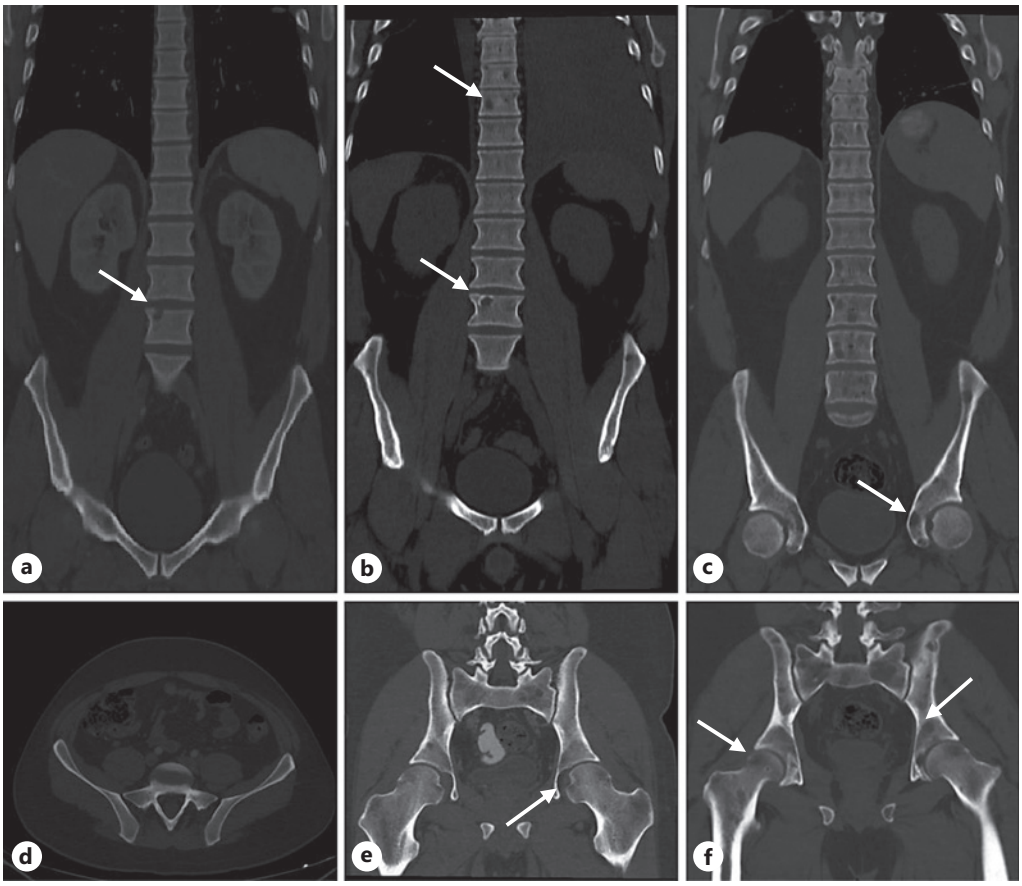

Fig. 1. Successive tomographic controls shows a progressive increase in the number and size of the osteolytic lesions throughout the entire extension of the skeleton, without cortical involvement or extension to soft tissues. **a–d** October 2020. **b–e** January 2021. **c–f** October 2021.

Even though all the biopsies were negative, the main suspicion was bone progression, given that the tumor markers never became negative (AFP: 67.2 ng/mL in February 2021). Tandem autologous bone marrow transplantation was suggested. The patient was hospitalized in May 2021 due to respiratory insufficiency secondary to tumoral lung compression and pulmonary aspergillosis. An upper left lobe partial segmentectomy was performed, which evidenced the presence of viable tumor of 140 × 70 mm. After this surgery, tumor markers finally turned negative: AFP 22 ng/mL, LDH 45 ng/mL, and hCG 6 mUI/mL.

A new bone biopsy was performed in May 2021; it showed a proliferation of vascular elements of different shapes and sizes, covered by a simple endothelium without atypia. No muscle layers were evident. The immunohistochemistry showed positivity for CD34, CD31 (Fig. 3b, c), and D2-40 (podoplanin) (Fig. 3d) and negativity for AE1-AE2, kappa, lambda, and CD138 (Fig. 3a). These findings supported the diagnosis of LM, and the final diagnosis was GLA.

The patient started with monthly injections of zoledronic acid 4 mg in July 2021, not achieving a suitable clinical response. In October 2021, the patient had progressive lesions (Fig. 1c–f), so he started a treatment with sirolimus 2 mg/day. Radiotherapy was proposed 3 months later due to increasing pain of the lumbar bone lesions.

In April 2022, the patient presented poor pain control, and an intrathecal pump implant was indicated for analgesic management. Regarding his initial diagnosis of germ cell tumor, no relapse was evidenced after 11 months of follow-up.

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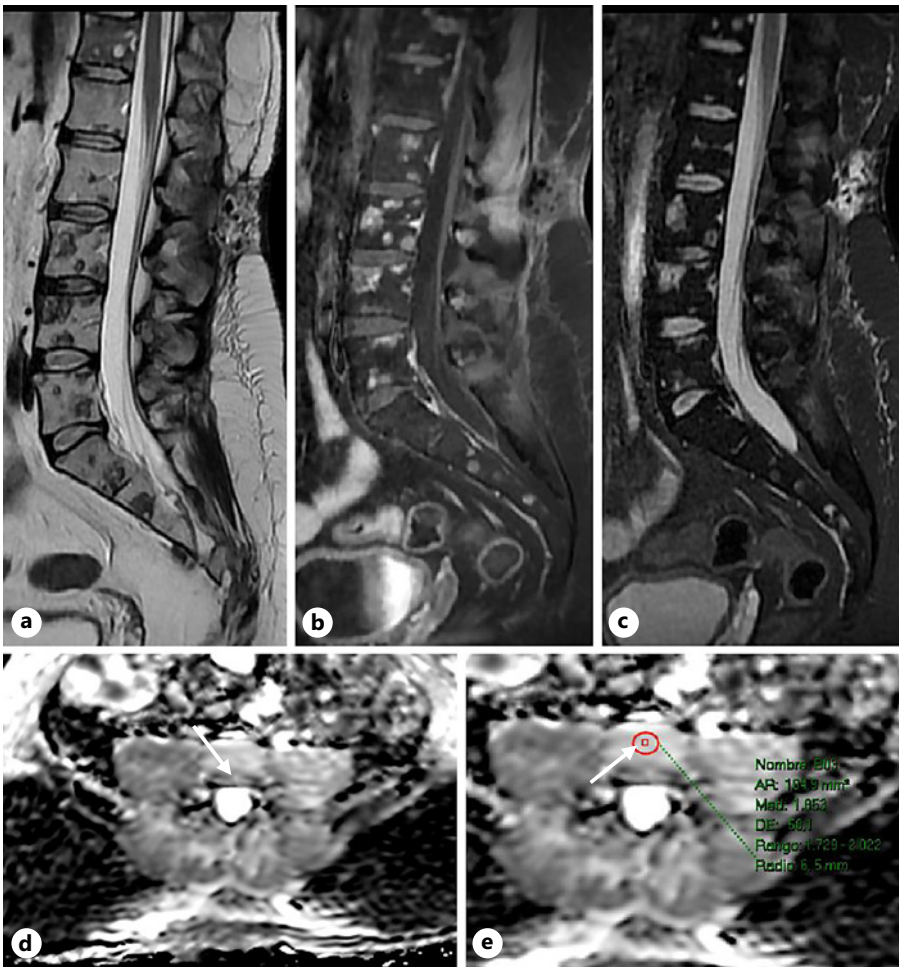

Fig. 2. In the MRI study, these lesions present high signal intensity in T2 (**a**) and STIR sequences (**b**), as well as LAVA-Flex water images (**c**), with intense enhancement after contrast administration, which represents hypervascularization. In diffusion sequences (**d**, **e**), there are no areas of restriction (ADC values 1.0 × 10.3 mm^2/seg), demonstrating the absence of high cellularity within the lesions.

Discussion

This case highlights the difficulty of achieving a diagnosis of GLA and the importance of differential diagnosis in osteolytic lesions. Our patient was being treated for a neoplastic disease which responded in the first cycles of BEP; nevertheless, new lesions in the bone were evidenced by the CT scan. Considering their characteristics, our first hypothesis was bone secondary involvement. However, the discrepancy between clinical evolution and tumor markers in a chemosensitive disease led us to perform several bone biopsies.

Facing osteolytic lesions, some of our therapeutic decisions were determined by the high suspicion of metastatic origin. Diagnosis of GLA was unexpected but perfectly explained the evolution of our case. There are certain topics that should be discussed regarding GLA: (1) differential diagnosis of lytic bone lesions, (2) the pathological findings of a bone biopsy in GLA, and (3) possible interactions between chemotherapy and GLA evolution.

GLA is a rare nonmalignant vascular anomaly and affects skeletal and nonskeletal tissue. It was first described by Rodenber in 1828 [5]. It can involve the skin, soft tissues, abdominal, and thoracic viscera. The number of lymphatic abnormalities is the cause of the pericardial,

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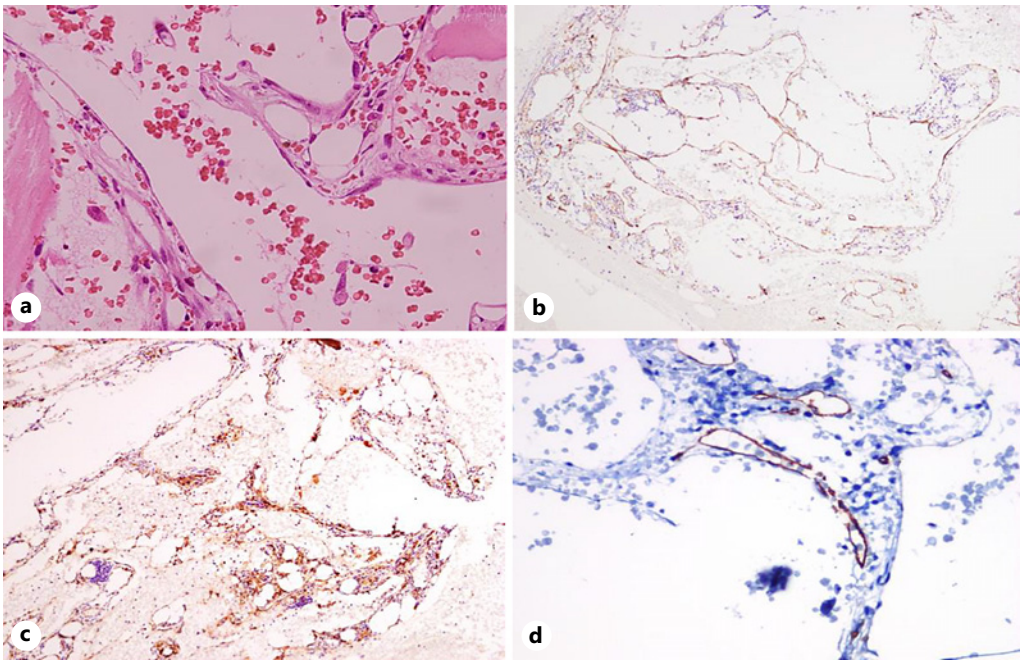

Fig. 3. Histological sections exhibit a proliferation of vascular elements with different morphologies. **a** (H-E) Thin-walled blood-filled vessels lined by a single layer of flat, cytologically banal endothelial cells. The vessels permeate the marrow and surround preexisting trabecule. Immunohistochemistry: staining evidenced CD34 positivity in lymphatic vessels (**b**). CD31 (**c**) and D2-40 (**d**) positivity are also observed in vascular structures.

pleural, or peritoneal effusions, which are commonly observed at diagnosis [6]. Multiple and destructive osteolytic lesions may originate pathological fractures, pain, and swelling. In conclusion, clinical features depend on the severity of the disease and the extent of organ involvement.

GLA and KLA are more frequently associated with vertebral involvement than GSD [7]. The lumbar spine is the most affected localization, and the number of affected bone lesions in GLA/KLA is also typically higher compared with GSD [4]. Furthermore, mortality in KLA is significantly poorer than in GLA, and patients usually evolve with progressive pulmonary disorders and serious coagulation disorders [6]. A whole-body CT scan is important to define the extent of organ involvement. Typically, CT findings are multiple lytic areas confined to the medullary cavity with well-preserved bony cortex without periosteal reaction and non-continuous pattern [2, 8].

Retrospectively, what did not allow us to suspect a benign abnormality was the dissociation between the clinical and radiological evolution of the lytic lesions. Due to this, several biopsies were performed. Typical GLA features in bone biopsies are dilated lymphatic channels lined by a single layer of endothelial cells [6].

A clear association between GLA and cancer or cancer treatment is not supported by the current literature. The etiology of this disease is unclear, and the mechanisms and factors that induce the invasion of lymphatic endothelial cells in bone remain unknown. Ozeki and colleagues argue that LMs are sporadic entities and possible biological tumoral mechanisms which include somatic changes in components of the PI3K/AKT/mTOR pathway and NRAS mutations [4, 9].

In our case, it should be remarked that LMs clearly increased during chemotherapy treatment. Potential associations between the immune and vascular regulation after

chemotherapy initiation can be hypothesized, but more evidence is necessary to clearly understand the physiopathology of these entities.

Instaurated treatment for GLA was in line with current GLA guidelines, although there is not a clear consensus regarding patient management. Depending on disease severity and burden, different treatment modalities can be offered, which include systemic treatments, radiation therapy, and surgery. Radiotherapy can be an option in those cases that have moderate to severe symptoms [10]. Systemic therapies include calcium salts, vitamin D supplements, calcitonin, pegylated interferon alpha, and bisphosphonate among others. Bisphosphonates impede bone resorption and increase mineralization by inhibiting osteoclast activity in high turnover states. Interferon, which inhibits the proliferation of blood and lymphatic vessels, is commonly offered in the case of patients with bone or generalized lymphatic lesions [11]. Modern therapies, including imatinib and bevacizumab have provided intriguing results, although further evidence is needed to incorporate these targeted therapies into current algorithms [12, 13].

Sirolimus is an mTOR inhibitor that plays a role in blocking the PI3K/AKT pathway. This mechanism is crucial for the construction of normal vessels, and any disturbances may lead to vascular malformations or tumorous growths [14]. In this setting, Adams et al. reported the results of a phase 2 clinical trial that included 61 patients with confirmed vascular anomalies, including 7 patients diagnosed with GLA. In this subgroup, all the included subjects presented a partial lesion response, defined as the reduction in size of the abnormal vascular proliferation by 20%, improvement in end organ dysfunction, or improvement in self-reported quality-of-life score [15].

To the best of our knowledge, there are no other reported cases of the increase of GLA in a patient undergoing cancer treatment for a solid tumor. Our case highlights the importance of a careful evaluation of the differential diagnosis in the setting of bone lytic lesions and to consider LMs in certain clinical scenarios.

Conclusions

In summary, clinical judgment becomes essential to understand that certain bone lesions may support further evaluation in situations of high clinical suspicion, such as the existence of a discordant response in a chemosensitive tumor. Rare bone entities should be carefully considered and incorporated into the differential diagnosis. It is essential to integrate clinical evaluation, a detailed patient history, and a variety of confirming tests including biopsies and specialized imaging techniques to reach the diagnosis of GLA. Our case illustrates how the diagnosis of GLA dramatically changed the medical therapeutic strategy in a potentially curable patient.

Statement of Ethics

The study was conducted in compliance with the terms of the Helsinki II Declaration, and the written informed consent was obtained from the patient for publication of the details of their medical case and accompanying images. Ethical approval is not required for this study in accordance with national guidelines to publish results.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have not received any funding for the study.

Author Contributions

All the authors had full access to the information of the study and read and approved the final manuscript. In particular, M.L.G., M.D.V.C., I.C., and M.A. helped us to arrive diagnosis; L.P. and A.F.G.H. found different imaging methods to describe better the lesions; and G.C., F.W., D.E., A.R., Y.P., and M.C. contributed to the critical review of the manuscript and participated in its coordination.

Data Avalilability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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