Generalized Lymphatic Anomaly: a case report

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Summary

Complex Lymphatic Anomalies are a group of rare diseases characterized by a non-neoplastic proliferation of lymphatic vessels. They include Generalized Lymphatic Anomalies and Kaposiform Lymphangiomatosis (both with involvement of visceral organs and bone with multifocal and non-progressive osteolysis) and Gorham-Stout Disease (characterized by a predominant involvement of bone with destruction of the bone matrix causing absorption of bone – the so-called “vanishing bone” disease – and a far less frequent visceral involvement). Because of the rarity of these diseases, the diagnosis may be confused by their similar clinical presentation. We describe a case of a young man with Generalized Lymphatic Anomalies with a diffuse involvement of the skeleton and of the spleen. The aim of this report is to point out the characteristics of different types of lymphatic anomalies to allow a correct diagnosis and a more adequate therapy.

KEY WORDS: Complex lymphatic anomalies; Generalized Lymphatic Anomalies; Gorham-Stout disease; lymphatic anomalies; lymphangiomatosis.

Introduction

Complex Lymphatic Anomalies are a group of similar diseases characterized by a non-neoplastic proliferation of dilated lymphatic vessels of unknown etiology (1). They include Generalized Lymphatic Anomaly (GLA) (2), Gorham-Stout Disease (GSD) (3) and Kaposiform Lymphangiomatosis (KLA) (4). Although the diagnosis may be confused by their similar clinical presentation, patients with GLA show involvement of both visceral organs (spleen, liver, mediastinum, lungs and soft tissues) and bone with multifocal and non-progressive osteolysis; GSD is characterized by a predominant involvement of bone with destruction of the bone matrix causing absorption of bone (the so-called “vanishing bone” disease); and KLA, that presents similar localization to GLA, but is characterized by proliferation of vessels with clusters or sheets of spindle endothelial cells. In GSD visceral involvement is far less frequent than that of GLA and KLA.

Lymphatic anomalies are rare diseases and no solid epidemiological data are available. Retrospective studies showed that the age at presentation ranges from 10 to 22 years (with an earlier onset in KLA), while the sex distribution is equal in every three diseases (5, 6). While natural history studies are lacking in these conditions, some patterns of outcomes and prognosis are emerging from clinical experience. Patients with lytic bone disease may present with pathologic fractures and, in particular, osteolysis can lead to skeletal instability in GSD. Obstruction or anomalies of the lymphatic system can result in leakage, manifesting as pleural effusions and ascites (1). Patients with KLA can present severe manifestations as coagulation disorders (thrombocytopenia, hypofibrinogenemia and prolonged PT and/or aPTT) (4). Definitive diagnosis is made by biopsy but imaging, in particular MRI, can be useful (7).

The aetiology of these diseases remains unknown. Recent studies showed a pivotal role of vascular growth factors, such as VEGF, and inflammatory cytokines, including IL 6 and TNFα, while there seems to be an imbalance between osteoclast and osteoblast activity, especially in GSD-related osteolytic lesions (8-10). Treatment includes medical therapies (interferon, sirolimus, bisphosphonates and anti-angiogenetic factors), radiation and surgery.

We describe a case of a young man with GLA referred to the Rheumatology Unit of the University of Pisa.

Case report

A 21-year-old man with a history of back, abdominal and head pain was admitted to our Hospital in November 2017. In 2002, when he was 6 years old, he was found to have a spleen enlargement (longitudinal diameter 14 cm), with many nodules and many osteolytic lesions at the skull, the left femur and the left fibula. Laboratory tests, included screening for infectious diseases, were all normal. In 2002 two bone biopsies were performed, one at the left femur and one at the skull, with histological findings of normal bone tissue. Then, he underwent splenectomy and histo-pathological examination revealed several anomalies of lymphatic vessels with formation of cystic lesions with variable size up to 1 cm of diameter. After that, he remained untreated. In 2004, a MRI that showed an increase of the osteolytic T2-hyperintense lesion of the skull and in other
bone sites, which prompted the diagnosis of bone-lymphangiomatosis. Then, he was treated with Interferon (600000 UI tri-weekly). After six months, no progression of the bone lesions was found, so the treatment was withdrawn and he entered a follow-up program with conventional radiography. Thirteen years later he was admitted to the emergency room because the acute onset of abdominal pain. A CT scan showed a marked evolution of the bone disease with multiple osteolytic lesions in almost every skeletal segment (skull, dorsal and lumbar vertebrae, ribs, scapulae and femurs) (Figure 1 A, B), but did not show any anomaly of abdominal organs. Two months later, he started complaining back pain. When the patient was admitted to our Unit, physical examination showed pain induced by palpation in every spinal segment and a widespread tenderness of the abdomen. Laboratory tests are substantially unremarkable. In particular, plasmatic levels of the principal cytokines and growth-factor involved in osteolytic diseases and proliferation of lymphatic vessels (IL1, IL1-ra, IL17, VEGF, VCAM, ICAM, OPG, RANK) were all normal. A thoracic radiography and an abdominal echography excluded signs of lymphatic effusions or other cystic lesions of visceral organs. A MRI of the thoracic and lumbar spine showed T2-hyperintense hemangioma-like lesions completely replacing the normal marrow signal in multiple vertebral bodies without evidence of cortical destruction (Figure 2). A Total Body Scintigraphy with HydroxyDiphosphonate-Tecnetium 99m showed inhomogeneous distribution of the tracer at the spine, the skull and the sternum, but absence of specific hypermetabolic area. Then the patient was referred to the Orthopedic Unit to undergo a CT-guided biopsy of the right iliac crest (Figure 1 C). At the histopathologic examination the medullary spaces of the bone fragment were partially occupied by a proliferation of dilated vessels filled with erythrocytes and lined by flattened endothelial cells devoid of cellular atypia. Some vessels were extremely dilated and assumed a cyst-like appearance. Endothelial cells were positive for the immunohistochemical markers CD31 and podoplanin, whereas CD34 was negative, suggesting at least partial lymphatic differentiation. These findings were consistent with the diagnosis of cystic angiomatosis of bone (Figure 3). The history of spleen involvement and the skeletal involvement with sparing of the cortical bone allowed us to make a diagnosis of GLA. After the biopsy the patient was treated with e.v. zoledronic acid (4 mg), and analgesics for controlling bone pain. The patient was discharged with moderate pain with the prescription of paracetamol as needed and sirolimus in accordance with the available evidence of the literature.

Discussion

We report a case of GLA, a rare condition characterized by proliferation of normal mature lymphatic vessels with formation of cysts in numerous body organs. Recently this condition has been included, as well as GSD and KLA in a disease category named Complex Lymphatic Anomaly (1). GLA may present at birth but the onset was described also in children and young adults. Presentation is variable and it can involve several different sites including bone, liver, spleen, mediastinum, lungs and soft tissues. The clinical history is directly related to the affected sites and widthness of the disease (11). GSD is characterized by progressive

Figure 1 A-C - Bone-CT scan shows multiple osteolytic lesions at the skull and lumbar vertebra (A, B). CT-guided localization of a lesion of the left iliac crest that was removed for histological examination (C).
IL-6 that is known to enhance osteoclasts activity (10). Recent studies have provided clearer biologic and molecular explanation of the pathogenesis of GSD: the proliferating vascular tissues are actually derived from lymphatic endothelium, identifying GSD as a disorder of lympho-angiogenesis (9); in the other hand, controversy has been expressed regarding the role of osteoclasts in the pathogenesis of GSD.

As shown by Lala et al. (5) the distribution of osseous changes in GLA and in GSD appears to be different: contiguous involvement across joints is seen in GSD, whereas GLA is usually characterized by involvement of a greater number of bones, which are often non-contiguous. Areas commonly affected by GSD include ribs, cranium, clavicles, and cervical spine, while in GLA thoracic spine, scapulae, and humerus are more frequently affected. Patients can have pain and swelling in the affected area. While GSD mainly involves bones, sometimes it can involve the viscera, with a presentation GLA-like. Furthermore, while appendicular and axial bones are equally involved in GLA, in GSD there is a relative sparing of the appendicular skeleton. An important complication is chylothorax, which is commonly seen in both conditions, caused by disruption of the thoracic duct or pleural lymphatics by adjacent osteolysis (12).

Bone changes can be visualized with conventional radiography. In GLA we observe well-defined, round lytic lesions with sclerotic margins and with no associated periosteal reaction or soft tissue mass, while in GSD we see more often cortical osteolysis with progressive resorption of bone segments. This findings can be found also on CT scan, but bone marrow changes and soft tissue involvement are best assessed with MRI. MRI can clearly illustrate and characterize the extent of osseous involvement. The lytic lesions of lymphangiomatosis typically appear T1-hypointense and T2-hyperintense on MRI (7). On histologic examination of bone biopsy of patients with GLA variably sized lymphatic channels are seen both in the cortical and the cancellous bone. These channels have a small wall made by flattened endothelium without a small muscle coat. Immunochemistry assay are positive for endothelial-lymphatic marker such as CD31, D2/40 and CD34. Abnormal lymphatic vessel with an anastomotic and infiltrative pattern can be observed in osteolysis with loss of cortical bone; the aetiology and the pathophysiology of this rare condition is still not completely understood. There seems to be an imbalance between osteoclast and osteoblast activity where the osteoclastogenic role prevails, resulting in loss of bone tissue; for this reason, this condition was also called “vanishing bone” disease.

Several theories have been suggested in order to explain the pathogenesis of the disease (8, 9). Initially, the disease was thought to reflect an abnormal proliferation of blood vessels (3). In 1996 Devlin et al. found the crucial role of

Figure 2 A, B - Sagittal T2-weighted dorsal and lumbar MRI. Multiple T2-hyperintense lesions in every vertebral segment without cortical involvement with preserved morphology (A, B). Note the involvement of posterior arch at multiple levels.

Figure 3 - Hematoxylin and eosin stained section showing a proliferation of dilated vessels filled with erythrocytes within the medullary spaces of cancellous bone.
periosteum. Histological findings are similar in GSD, but abnormal lymphatic channels are numerous and the cortical bone is partially destroyed (5).

Treatment of Complex Lymphatic Anomalies depends on the presence of symptoms and on the extension of the anomalies. “Wait and see” strategy can be used in asymptomatic, small and limited lesions. Surgical treatments, as thoracentesis, paracentesis, pleurodesis, or percutaneous sclerotherapy are used in case of confined and symptomatic lesions, while medical approach is needed in case of widespread involvement (both visceral and osseous) (1). Because of the rarity of these conditions, the medical therapy is based on evidences by case reports and case series. Principal treatments have anti-angiogenic/lymphogenic effects, as pegylated-interferon (13), or bevacizumab (14), a humanized monoclonal anti-VEGF antibody, but also therapies with bisphosphonates, corticosteroids, propranolol, and sildenafil are reported (1). In our case, the patient was treated with sirolimus. Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR), a serine/threonine-kinase implied in the vascular and lymphatic proliferation. In a phase II study, sixty-one young patients with complicated vascular anomalies, included complex lymphatic anomalies, were treated with a twice-daily dose of sirolimus. After 6 and 12 months, every patients with GLA presented a partial response (>20% reduction of lesions extension, improvement of organs dysfunction, or improvement of the quality of life) (15). Furthermore, a report of a patient with GSD and pleural effusion suggested that the combination of sirolimus with zoledronic acid has a synergistic effect in down-regulation of the mTOR-pathway, because it has been demonstrated that the zoledronic acid interferes in the intracellular signalling by inhibiting the prenylation of proteins involved in the mTOR cascade (16).

Conflict of interest

The Authors declare that they have no conflict of interest.

References