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Heterogeneity and Phenotypic Diversity of Multiple Sistemic Lymphangiomatosis

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Abstract

The lymphatic abnormalities should be considered as entities with local and systemic involvement, of continuous spectrum, being in the majority of cases a diagnosis of exclusion, making the differential diagnosis between entities difficult.

Gorham Stout syndrome should be suspected in a patient with rapid and progressive osteolysis findings with cortical bone loss and presence of bilateral pleural effusion of chylous features. Considering the use of radiological studies and biopsy of the lesion as diagnostic methods. Prioritizing chylothorax treatment to be present.

Generalized lymphatic abnormality or lymphangiomatosis is suspected in similar symptoms, without progressive bone involvement.

Management is complicated, as there are no clinical trials. It is suggested to start with conservative management without the cynical situation of the patient allows it, emphasizing nutrition and the priority treatment of chylothorax if present, resorting to alternatives such as radiotherapy or surgery but does not achieve adequate control.

Keywords: Lymphangiomatosis; Heterogeneity; Sporadic malformations; PI3K/AKT/mTOR pathway; RAS pathway

Introduction

Lymphatic malformations affect multiple organs and have various symptoms; there is an overlap between the different entities, so an appropriate diagnosis is difficult [1]. They are rare diseases, caused by abnormalities in the lymphatic system [2]. They are sporadic malformations, without family inheritance, and caused by somatic mutations in the PI3K/AKT/mTOR and RAS pathways involved in endothelial proliferation differentiation and growth [3] Establishing itself as possible therapeutic targets. mTOR inhibitors such as sirolimus have recently been identified as a promising treatment of lymphatic abnormalities [2].

We present three cases of lymphatic abnormalities, their clinical characteristics, overlap between entities and the therapeutic management carried out in each case.

Case 1

43 years old female patient, no family history of interest, diagnosed in 2017 with systemic lupus erythematosus. Debuting with shortness of breath, peripheral edema of lower limbs and relapsing bilateral pleural efussion at the rate of 1500cc every 7-10 days, with chylothorax characteristics, which required thoracentesis, endopleural tube placement and pleural decortication left, persisting in spite of this. Considering the diagnostic doubt of pleural effusion secondary to systemic lupus erythematosus or lymphoproliferative syndrome, given the findings of flow cytometrias, where 9% of cells with phenotype of Lymphoma Marginal Z were detected, with inguinal lymph node biopsy that reported reactive follicular hyperplasia. After multiples studies without diagnosis, the Linfogammagraphy Tc99m. Nanocoloid was performed showing a correct ascent of the radiotracer to axillary and inguinal nodes respectively without an external distribution of it. CT neck-thorax-abdomen with contrast i.v June 2019: where it was visualized with respect to previous study, increased left pleural effusion, no signs of ganglion involvement in any of the chains studied. It was visualized bone demineralization not consistent with age. Suggestive findings of sternum fracture due to insufficiency. In June 2019, she needed a new admission, by bilateral pleural effusion that required new drainage and pleural tube placement. Suspected complex lymphatic alteration, which together with findings of chylothorax, widespread lymphedema and fracture due to sternum insufficiency, could be a Syndrome Gorham Stout initiating management with propranolol and sirolimus. Despite this, the pleural effusion progressed, which conditioned acute respiratory insufficiency by entering intensive care unit, dying in later days.

Case 2

It is male patient 24 years, natural from Venezuela. No family history to highlight. At the age of 20, following a fracture of the pelvis after falling from its own height, Gorham Stout's disease was diagnosed, based on the pathological anatomy of the pelvis lesion, starting treatment with bevacizumab 10 mg/kg every 28 days, denosumab 120 mg semi-annual subcutaneous and seedal-guided pelvic radiation therapy by image at doses of 3200 cGy in 16 sessions, with excellent tolerance. He received 1 year of treatment experiencing clinical improvement as he referred. CT pelvis control: It was

confirmed the existence of an image consistent with Gorham-Stout's disease, which is evidenced by an absence of the ischiatic bone, the posterior margin of the right hemisacrum and all the subsequent tuberosity of the right iliac. Currently with sirolimus 1 mg oral every 12h.

Case 3

23 year old women with no family history of clinical relevance: Diagnosed with disseminated lymphangiomatosis, enteropathy loses protein, secondary humoral immunodeficiency and moderate malnutrition in 2008, debuting at age 12 with lower limb edema. Abdominal ultrasound: head mass of pancreas with multiple small cystic images to consider: lymphangioma or microcystic tumor mass. Subsequent imaging studies: Nuclear magnetic resonance imaging: very extensive lymphangioma affecting pancreatic head, retroperitone, mesentery, proximal yeyuno. Left paracardiallymphangioma was also observed in anterior mediastinum. Exploratory laparotomy was performed: taking biopsy: second and third duodenal portions with ingurgited mucosa, with lymphatic dilations, submucosallymphangioma and focal apical lymphangiectasia. March 2009 started with pegylated interferon (IFN), after with propranolol and enteral nutrition at a start through SNG and later through endoscopic gastrostomy with clinical response and improvement of analytic parameters. And currently in home parenteral nutrition program since 2015. The summary of the age of presentation, the clinical manifestations and the therapeutic management of the cases are shown in Table 1.

Cases	Diagnosis age	Clinical manifestations	Treatment	Evolution
1. Female	43 years old	Relapsed chylothorax Sternum fracture Widespread lymphedema	Sirolimus Propanolol Parenteral nutrition Pleural decortication	Death
2. Male	20 years old	Fracture of the pelvis (absence of isquial bone)	Bevacizumab Denosumab Radiotherapy Sirolimus	Favorable
3. Female	12 years old	Lower limb edemas Pancreatic head lymphangioma	Enteral and parenteral nutrition	Favorable

Table 1: Age, Clinical manifestations and Therapeutic management of the cases.

Discussion

Lymphatic abnormalities occur as a localized or systemic involvement of continuous spectrum, involving multiple organs, and have various symptoms [1]. There is no clear predominance of sex, no family or perinatal history, but a predominance in the incidence of the disease during the first decades of life [4,5]. There has been a clear predominance in childhood and adolescence in this series of cases, coinciding with the manifested in studies on lymphatic abnormalities. However, they have the potential to present at any age [6]. Progressive osteolysis is the most typical sign of presentation in Gorham Stout disease (GSD) [7]. Characteristically in our cases the typical signs were: relapsing chylothorax and fractured pelvis after trauma. GSD can take an asymptomatic picture with incidental finding of bone fracture to the presence of bone pain, [5,8,9] as observed in our second case and may affect spine and viscera [8]. Elevated levels of vascular endothelial growth factor 3 (VEGF-3), bone-specific alkaline phosphatase, as well as acid-based tartrate-resistant phosphatase [1] have been reported, with total acid phosphatase levels and tartrate acid phosphatase requested resilient in the first case, being normal.

In general most studies are normal, and are only useful in differential diagnosis [7]. Ozeki and Fukao describe some differences between generalized lymphatic anomaly (GLA) and kaposiform lymphangiomatosis (KLA), recently subclassified within the generalized lymphatic anomaly, versus Gorham Stout syndrome (GSD), being osteolysis in multiple GLA/KLA and non-progressive compared to GSD that is characterized by being progressive, infiltrative, with loss of cortical bone [1], which coincides with that observed by Michio Ozeki two years prior to its study [4]. In the first osteolysis is limited to the bone spinal cavity, while in Gorham Stout Syndrome it is progressive with cortical bone loss [4]. The presence of chylothorax impoverishes diagnosis [7] In the observational retrospective study of Ozeki et al. the mortality rate was 20% and the cause of the death was chest symptoms [4,10]. Finally the forecast depends on the extension site [11].

Treatment may include drugs, surgery, radiation therapy, and nutritional therapy. In patients with bone lesions, medical treatment includes interferon-alfa, propranolol, bisphosphonates, and corticosteroids, when in effective surgery is used with injury resection, fracture reduction or reconstruction [4]. Medical therapy for chest injuries includes corticosteroids, propranolol, interferon-alfa, octreotide and mammalian target of rapamycin (mTOR) inhibitors. Constituting the management of chylothorax as a priority being able to resort to thoracentesis and pleural drainage or surgery (pleurodesis, pleurectomy and thoracic duct ligation) [4,5]. Techniques performed on our patient, who after repeating chylothrax and the multiple drains resorted to pleurodesis, without reaching the ligature of the lymphatic duct due to clinical instability and the absence of conditions for surgery. A case on the successful management of the recurrent chylothorax in Gorham Stout's disease, suggest in the discussion, that if drainage through chest tube is greater than 50 ml/day for more than 1 week surgery should be considered [11].

Radiation therapy has been used when surgery is not possible or in combination with it, at a total dose of 30-45 Gy. Being used in our second case at doses 3200 cGy in 16 sessions, with good tolerance, after

the start of medical treatment with bevacizumab and denosumab, obtaining excellent response without the need to resort to surgery [4,5].

In certain studies, it is advisable to start with a conservative treatment if the patient's condition does not compromise life, for example parenteral nutrition, as has been initiated in our third case. Based on restrictive diet in fat medium-chain triglycerides, low in fat, which in most patients is not effective as demonstrated in this study and what is observed in our first case. After several months of diet she continued with lymphedema, bilateral chylothorax and protein-caloric malnutrition, ultimately resorting to parenteral nutrition use [4,11].

In patients with osteolysis bisphosphonates are an option as they inhibit bone reabsorption. Meanwhile, interferon, which inhibits the proliferation of blood and lymph vessels, is used for patients with generalized bone or lymphatic lesions. Other drugs include the anti-VEGF-A antibody bevacizumab, propranolol [1,5], in addition to steroids, vitamin D and calcitonin. Being bevacizumab a therapeutic option for our second case, with the showing improvement and resolution of osteolysis, this allowed him to wander with use of cane. A case report on the treatment of diffuse pulmonary lymphangiomatosis in a male 51 years showed improvement in lung function, especially the FEV1 parameter after 6 months of administration of bevacizumab [12].

The genetic activation of via PIK3/AKT/mTOR is involved in the development of lymphatic and blood vessels. Sirolimus is an option by decreasing the activity of lymphatic cells and stalling bone loss thus controlling the disease. The study on the use of sirolimus as a perioperative treatment in GSD saw a rapid response to the use of sirolimus in 7 weeks and the absence of chylothorax in the postoperative period [8]. It does not contrast with our first case presented, being able to refer to the complications that conditioned the prognosis as being bilateral chylothorax. Although most therapies proposed so far exert potentially beneficial effects as antiproliferative agents, lymphatic lesions such as GSD and GLA are considered malformations that slowly divide compared to highly proliferative tumor structures [13], which may be a limitation in the effectiveness of treatment.

Conclusion

Lymphatic anomalies should be thought of as entities with continuous spectrum local and systemic involvement. In most cases, it is a diagnosis of exclusion, making it difficult to diagnosis differentially between entities. Gorham Stout syndrome should be suspected in a patient with rapid and progressive osteolysis findings with cortical bone loss and presence of chemically characteristic bilateral pleural effusion, considering the use of radiological studies and biopsy of the lesion as diagnostic methods and prioritizing the treatment of chylothorax to be present. Generalized lymphatic abnormality or lymphangiomatosis is suspected of similar symptoms, without progressive bone involvement.

Management is complicated, with no clinical trials available. It is suggested to start with conservative management if the clinical situation of the patient allows it, emphasizing nutrition and priority treatment of chylothorax, using alternative such as radiation therapy or surgery but achieves adequate control.

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