

## Swelling of Extremities: Primary Lymphedema?

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### Abstract

**Background:** Primary lymphedema is a rare disorder, affecting mainly pediatric patients. It results from maldevelopment of the lymphatic vasculature. Its differential diagnosis is wide and includes secondary lymphedema (the most frequent), and several syndromes.

**Methods:** We report the case of an 8 month old girl who presents primary lymphedema, and we review the literature published on the topic.

**Conclusions:** Diagnosis of primary lymphedema might be difficult since several syndromes might present swelling. We have recently diagnosed a case of primary lymphedema. Since it is a pretty rare disorder we find it interesting for the scientific community, to learn about it. Besides, we want to emphasize the fact that performing nuclear medicine before magnetic resonance or computed tomography, avoids sedation and risk associated, hence it should be the first test to be performed. The second fact to stress is that an accurate diagnosis might be made by an adult-specialized nuclear medicine service, avoiding the inconvenience of going to a pediatric centre which might be far in distance.

**Keywords:** Lymphedema; Lymphoscintigraphy; Toddlers; Milroy disease

### Introduction

Lymph edema is a chronic and progressive swelling of tissue due to inadequate lymphatic function. It can be divided in primary (due to anomalous development) or secondary (due to injury to lymph nodes or vessels). Genitalia and lower extremities are the most frequent locations affected by this pathology. Complications include infection, functional disability, chronic cutaneous changes and psychosocial morbidity [1-5].

Primary lymphedema is thought to happen only on 10% of the patients with lymphedema, [2,6]. And it is mainly a pediatric disorder. It is rare, affecting 1.2 per 100,000 persons younger than 20 years [3,4,7]. This report is based on a case of primary lymphedema of an 8 month old girl.

### Clinical Report

A girl, 8 months old, presented with edema located on the back of her left foot associated with mild dysmorphic appearance. There is not family history of lymphedema. On her history antecedent of a surgical intervention was found, when she was 4 days old, because of an ovarian cyst on her right ovary (51 mm diameter). It was detected prenatally by ultrasound. Surgery had no incidence, and the ultrasound post surgery was normal. Neurodevelopment was accorded to her age. On the physical exam indurated edema on her feet back, more prominent on her left side, antimongoloid palpebral fissure (as her father), and mild hyperthelormism were found, no particular syndromic appearance. No extra row of eyelashes, no yellow nails, no genitalia edema. Her weight and height were within the normal percentiles.

Caryotype resulted 46XX, dismissing turner's syndrome. On the hemogram there was a mild microcytic hypochromic anemia (hemoglobin 10.4 g/dl, mcv 99.4, chm 33.8) and light hypoproteinemia (total proteins 5.7 g/dl). Urinalysis showed no proteinuria, no microalbuminuria that could explain edema. Echocardiography was performed with no abnormal result. Transfontanelar ultrasound was also normal. Because of the antecedent of surgical intervention, secondary lymphedema was the main diagnosis and an abdominal MRI

was performed: uterus of normal morphology and location for her age, left ovary of 11x15 mm with several follicles inside, biggest of 8 mm. right ovary is not recognizable; there is no free liquid no tumors on the pelvis. No lymphadenopathy of significant size.

During the weeks the tests were being performed, edema appeared on her left hand back. Primary lymphedema was then suspected and a technetium 99 m labeled lymphoscintigraphy of her low extremities was performed. It was informed as lack of radiocolloid lymphatic migration, consistent with primary lymphedema. Milroe disease genetic screening was negative (Gene FLT4, mutation in the vascular endothelial growth factor receptor 3-VEGFR3), although 3 polymorphisms (with no clinical relevance according to the literature published) were found in the patient: rs446003 in homozygosis, rs55657009 in heterozygosis, and rs2934600 in homozygosis.

With the diagnosis of primary lymphedema, treatment was started with education of the parents to moisture and massage the affected extremities. The patient was referred to vascular surgery. So far she hasn't developed any cellulitis, or functional disability. She is doing well with rehabilitation.

### Discussion

Primary lymphedema is a rare disorder in pediatrics. The progression and morbidity is not influenced by the age of onset [1]. It affects males and females equally. Clinically the edema slowly enlarges over time because of the accumulation of subcutaneous lymph, which stimulates adipose deposition and fibrosis [2]. The aetiology is

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unknown. The disease is associated with lymphatic pathway dysplasia, aplasia or hypoplasia. Most cases are sporadic, but familial forms exist. The most frequent is milroy disease, transmitted following an autosomal dominant pattern with incomplete penetrance. Mutations of the VEGFR3 gene have been detected in several affected families. This gene codes for vascular endothelial growth factor receptor 3. Milroy disease represents 2% of the cases of primitive lymphoedema. Differential diagnoses include other causes of edema and turner and noonan syndromes. Diagnosis of primary lymphedema is made by history and physical examination in 90% of patients [6,7]. It can be confirmed by lymphoscintigraphy which is 92% percent sensitive and 100% specific [2]. Some authors recommend the performance of CT or MRI as the first test [4]. However, since pediatric patients, especially toddlers may need some kind of sedation for the performance of CT or MRI with the risks associated to it, we believe lymphoscintigraphy should be the test to be done first. In our case, lymphoscintigraphy was made and interpreted by an adult-specialized nuclear medicine faculty. Accessibility to a pediatric nuclear medicine service is difficult, since there are not many pediatric hospitals with that kind of service. According to our experience, the lack of a pediatric nuclear medicine service should not mean a problem to proceed and make the most suitable test in order to achieve the right diagnosis. Since the technique

of lymphoscintigraphy is reasonable to be made on a child and generally medicine nuclear faculties are trained to read and interpret the results, diagnosis of primary lymphedema becomes easier, and there is no need to refer the patient to a third level hospital with the expenses associated to such efforts.

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