

Unilateral Primary Congenital Lymphedema of the Upper Limb in an 11-Month-Old Infant: A Clinical and Pharmacological Perspective

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Abstract

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BACKGROUND: Lymphedema is the accumulation of a protein-rich fluid in the interstitial space due to reduced lymph transport capacity. Congenital primary lymphedema affecting only one of the upper limbs is a rarity.

CASE REPORT: We present a case of an 11-month-old infant presenting with swelling of the right upper limb, which had gradually progressed over the past five months. Lymphoscintigraphy was suggestive of lymphatic blockade in the right upper limb. All other investigations were within normal limits. A diagnosis of primary congenital lymphedema affecting the right upper limb was made. The patient was managed conservatively with complex decongestive therapy and was requested regular follow-up. The lymphedema did not increase within four months of follow-up.

CONCLUSIONS: Complex decongestive therapy is the cornerstone of the management of primary congenital lymphedema. New investigational therapies such as leukotriene B4 antagonists hold a promise for patients with lymphedema.

Introduction

Lymphedema is a chronic localised swelling caused due to excessive accumulation of lymphatic fluid in the interstitium and resulting from defective lymphatic drainage [1]. Lymphedema can be primary or secondary. Primary lymphedema results from developmental abnormalities leading to pathological lymphatics. Secondary lymphedema is an acquired dysfunction of normally developed lymphatics [1] [2]. Congenital subtype of primary lymphedema is defined as swelling that has an onset at birth up to two years [3]. Primary congenital lymphedema affects the lower limbs in the majority of the cases, and unilateral

involvement of one of the upper limbs is a rarity [4]. We present a case of an 11-month-old infant with primary congenital lymphedema affecting the right upper limb in isolation.

Case report

An 11-month-old infant presented to the department of paediatrics with a swelling of the right upper limb. The swelling was first noticed by the parents at around seven months after birth and had been gradually growing since then (Figures 1 and 2).

No history of fever, trauma, pain, surgery, rash, drug intake or weight loss was present. The parents of the patient did not have a consanguineous marriage. The family history of the presence of similar swellings in other close family members was absent. The height and weight of the infant were appropriate for his age. The general examination did not reveal any abnormality. Local examination of the right upper limb showed nonpitting, nontender oedema without any signs of inflammation. Radial, ulnar, and brachial pulses were palpable. No abnormal growth was found in the axillae or breasts. Generalized lymphadenopathy was absent. Examination of the left upper limb, both lower limbs, and genitalia did not reveal any abnormality. Routine blood and urine tests were within normal limits. Liver, kidney, and thyroid function tests were within normal ranges.



Figure 1: An 11-month-old infant with unilateral lymphedema of the right upper limb

Peripheral blood smear and antigenic testing for microfilariae were negative. Duplex ultrasound of the right upper limb, chest X-ray, HRCT of the chest did not reveal any abnormalities. Lymphoscintigraphy was suggestive of lymphatic blockade in the right upper limb. Based on the clinical features, and investigations a diagnosis of primary congenital lymphedema affecting the right upper limb was made.

The patient was treated conservatively and was advised regular follow-up. Conservative management included elevation of the affected limb, compression bandages, and skin care. The

lymphedema did not show any progression in the next four months of follow-up.



Figure 2: Unilateral swelling of the right upper limb

Discussion

Primary lymphedema has an estimated prevalence of 1.15 per 100000 [5]. It is categorised according to the age of onset as congenital (before two years), praecox (before 35 years), and tarda (after 35 years) [1] [2]. Isolated involvement of one of the upper limbs is one of the rarest forms of congenital lymphedema as 92 % of cases of congenital lymphedema involve the lower extremities [4] [6].

Around 20 genes have been identified to be associated with primary lymphedema. Some of these genes include FLT4, VEGFR3, FOXC2, CCBE1, GCJ2, SOX18, GATA, and PNP14 [7]. Genetic mutations explain only around one-third of the cases of primary lymphedema, mostly of inherited forms. These genes encode/regulate proteins of the vascular endothelial growth factor receptor-3, and other tyrosine kinase receptors and exert their effects via the RAS/MAPK and the PI3/AKT pathways [7] [8]. Genetic analyses for truncating the affected gene were not carried out in our patient due to his financial constraints. Some diseases such as filariasis, soft-tissue tumours, Kippel-Trenaunay syndrome, and chronic venous insufficiency mimic isolated primary lymphedema of the upper limb. In each of these conditions, the swelling progresses gradually and painlessly over a period of weeks or months [9]. Each of these conditions were systematically ruled out in our patient through the clinical history, examination, and appropriate investigations.

Management of primary lymphedema is done via decongestive lymphatic therapy, which includes an intensive and maintenance phase. Both these phases include the use of compression bandages, therapeutic exercises, skin care, manual lymphatic drainage, and patient education [10]. Our patient did not show any

increase in lymphedema after undergoing a month of intensive and three months of maintenance decongestive therapy. However, the parents of the child were advised monthly follow-ups and look out for an increase in the size of the swelling, signs of inflammation, hyperkeratotic skin lesions, and verrucous growths.

Currently, there is no effective pharmacotherapy for primary lymphedema. Short-term administration of diuretics is found to be effective in some patients in the initial stages of lymphedema. Long-term administration of benzopyrones increases hydrolysis and absorption of tissue proteins at the site of lymphedema. Intra-arterial autologous lymphocyte injection is suggested to enhance the proteolysis of extracellular proteins and reduce lymphedema in some reports. Zinc supplementation and low-fat diet were found to be effective in reducing lymphedema in a few reports. Use of propranolol has been suggested to improve some symptoms of lymphedema in a report. Surgical interventions such as debulking procedures, resection approach, buried-dermal flaps, microsurgical techniques, and liposuction are rarely indicated due to their low success rates. Surgical therapy is usually tried only when conservative management has failed [1] [11].

Preclinical evidence suggests that exogenous injection of human recombinant vascular endothelial growth factor C restores lymphatic flow. Also, adipose-derived stem cells have shown potential in lymphedema therapy [12]. Drugs targeting the PI3/AKT/mTOR signalling pathway such as mechanistic target of rapamycin inhibitors are also being evaluated for reducing lymphedema in some somatic overgrowth disorders [2]. Leukotriene B4 affects lymphangiogenesis in animal models and is elevated in patients with lymphedema. Hence, drugs antagonising the effect of leukotriene B4 such as ketoprofen, and bestatin are presently being evaluated in Phase-2 of clinical trials [13].

In conclusion, primary congenital lymphedema affecting only one of the upper limbs is an extremely rare disorder. Conservative management via decongestive therapy prevented further progression of the lymphedema in our patient. Investigational therapeutic agents such as leukotriene B4 antagonists provide an exciting prospect for patients with lymphedema.

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