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Case Report

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A Rare Case of Idiopathic Lymphedema

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ABSTRACT

Lymphedema is the swelling of a part of the body due to the accumulation of lymphoid fluid in the subcutaneous soft tissue as a result of abnormalities in lymphatic drainage. Primary lymphedema is thought to have a mixed genetic component that arises from the erroneous development of the lymphatic system, which is also responsible for the malfunction of the lymphatic system. This condition can be sporadic or genetic. In this case present a 25-year-old male patient. The patient reported a bite on his finger because of a poisonous fish at age 18 years. Afterwards, he reported marked lymphedema, which gradually and progressively spread from the left ankle to the left thigh. Then, the patient was diagnosed as primary lymphedema praecox and classified as stage 2. In this case report, it is aimed to elucidate the genetic disease associated with primary lymphedema and to expatiate on the management of this chronic disease.

Keywords: Lymphedema, genetic predisposition to the disease, early-onset Lymphedema

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INTRODUCTION

Lymphedema is a result of abnormal changes in the lymphatic drainage in the subcutaneous soft tissues, which may lead to the accumulation of lymphatic fluid in a certain part of the body.[1] Most of the cases are seen in the lower extremity; it may as well be seen in the arms, face, neck and external genital area.

Erysipelas, cellulitis anda deep vein thrombosis should be considered in the differential diagnosis.[2] Erysipelas is differentiated from these diseases as it is marked by the presence of a more localized, sharp border and accompanying systemic infection findings. Cellulite does not have a sharp border and there is usually a predisposing condition, such as a burn. It is accompanied by fever, chills, shivering, lymphadenopathy and leukocytosis. In deep vein thrombosis, the findings develop slowly; edema is absent and may be accompanied by neurogical deficit. The major finding in lymphedema is hard edema. Meanwhile, tenderness and pain are not quite obvious.

Lymphedema is usually secondary to Filariasis, some surgical interventions, trauma or infection.[3] Primary lymphedema is thought to have a complex genetic component due to the developmental lymphatic system anormalies and may arise from malfunctioning of the lympatic system. This condition may be sporadic or hereditary.

CASE REPORT

A 25-year-old male patient presented with complaints of swelling his left lower extremity extending to his left inguinal region and feeling tension and pain while walking. He was admit-

ted to our hospital for further examination and treatment. The patient is so healthy and an active working person. While he was 18 years of age, an unknown sea fish bite on one of his finger of the left leg, he reported. The patient's complaints regarding his foot started after this event and he reported the episodes of swelling increased sometimes but never regressed. Bandage and elevation as treatment protocol was applied. Physical therapy and surgery were not applied at the first admission. On the other hand, the patient's grandmother had a history of an unremarkable swelling, which started after the age of eighty. The cause of the swelling was attributed to old age with no other significant cause. There were no other significant features in the family history.

On physical examination, the skin from the left ankle to the knee was markedly swollen and tensed. However, the swelling continued indistinctly uo to the thigh. By pressing on the tibial area, there was +3 positive pitting edema (Fig. 1) and peripheral pulses were normal.

Measurements of the thigh circumferences were revealed as 45.0 cm on the right and 51.0 cm on the left, respectively.

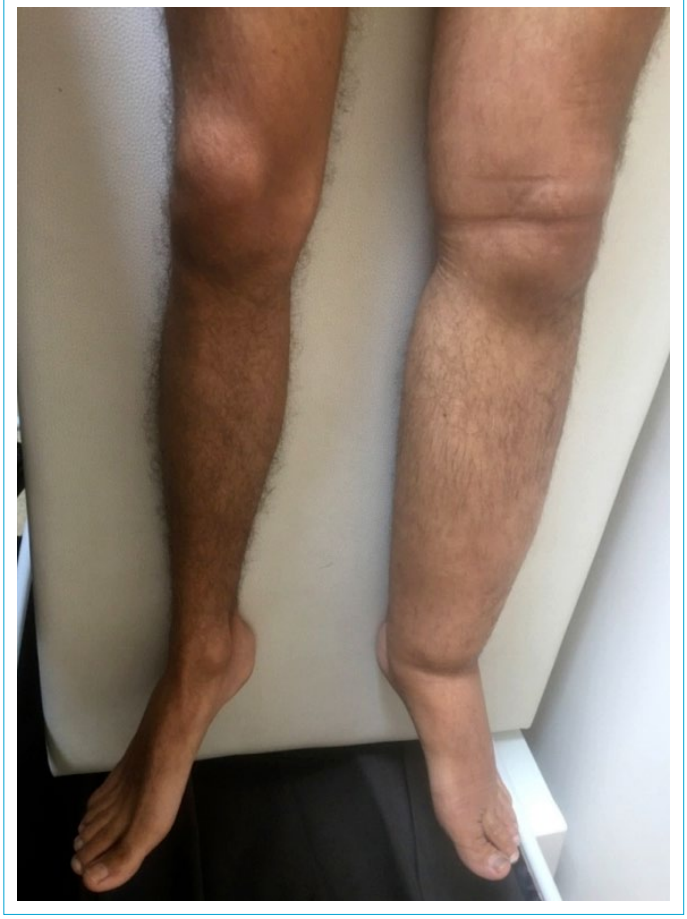

Figure 1. Comparative view of lower extremities.

Besides, measurements of the knee circumferences were revealed as 32.0 cm on the right and 38.0 cm on the left, respectively. Also, measurements of the ankle circumferences were revealed as 30.0 cm on the right and 39.5 cm on the left, respectively.

In addition to these findings, mobile, painless lymph nodes were found. They were two in the posterior cervical, three in the left inguinal and three in the right inguinal. The ultrasonography examination of these lymp nodes, the left inguinal lymph node measured as 3.6x12.8 mm and 3.0x9.0 mm, slightly fatty hilus with cortex compatible with more reactive features and lymh nodes that tend to converge with each other. On the right, there was 25.0x5.0 mm conglomerate lymphadenomegaly and the cortex-medulla differentiation could not be made. No other pathological finding was seen on physical examination.

During our follow-up, laboratory findings were sedimentation 13.0 mm/h (0.0-20.0), C-reactive protein <2.0 mg/l (0.0-5.0), hemoglobin 11.2 g/dl (12.0-16.0), hematocrit 32.3% (40.0-54.0), MCV 84.9 fl (80.0-100.0), leukocyte 7960/mm^3 (4000.0-10000.0), eosinophil 7.0% (0.5-5.0), neutrophil 43.8% (50.0-70.0), lymphocyte 43.3% (20.0-40.0), basophil 0.4% (0.0-1.0), monocyt 5.4% (3.0-12.0), platelet 279000/mm^3 (100000-450000), iron 73.0 µ/dl (31.0-144.0), iron-binding capacity 193.0 g/dl (110.0-370.0), transferring 186.0 mg/dL (215.0-365.0), transferrin saturation 37.8% (15.0-50.0), ferritin 138.0 mg/L (21.8-274.7). Aspartat transaminaz, alanine aminotransferaz, gamaglutamil transferaz, alkalen fosfataz values were normal. Hepatit markers such as Anti-HBs, HBsAg, anti-HCV, anti-HIV were negative. Peripheral smear showed normal clustering of platelets and eosinophilia. No parasites were detected in the blood taken at night for filariasis examination. The tuberculin skin test was found to be anergic. There was no abnormal finding on the lower extremity venous doppler ultrasound. The biopsy was taken from inguinal lymph nodes. In the lymph node, serial sections pathology department reported that lymphoid tissue segmented with thick fibrous tissue and CD20, CD3, Bcl-2 were naturally positive. In immune histochemical examination, CD10, cyclinD1, CD30 negative and Ki-57 marker was found in a small number of cells to be positive.

Anemia belongs to chronic disease was detected. During the time he was hospitalized there were local temperature rise and pain in the leg with lymphedema. This was interpreted as localizaed lympangitis. There was no systemic fever during our follow up. Blood culture was negative. The patient responded to antibioterapy with ampisilin/sulbactam, 1.5 g, four times daily for 12 days.

After subcutenous injection of 1 mCi Tc-99m nanocolloid

between both 1st and 2nd toes for lympatic system scintigraphy, dynamic and static imaging was performed. Department of the Nuclear Medicine reported as "*Lymphatic ducts and inguinal lymp nodes were visualized in the right lower extremity and lymph drainage was within normal limits. The lympatic channels and inguinal lymph nodes in the left lower extremity were not visualized*" (Fig. 2). In addition, in the late phase, a view consitent with the lympatic obstruction in the left lower extremity.

Since no other couse of secondary lymphedema was found, physical therapy protocols were started for treatment.

DISCUSSION

The lymphatic system plays an important role in tissue homeostasis.[4] Lymphedema is the accumulation of a protein-rich fluid in the interstitial space that arises from an anatomical or functional obstruction in lymphatics or lymph nodes.[5] Although lymphedema is seen in both genders and at any age, it is more common in women and unilateral in two-thirds of patients.[6] It can be sporadic and hereditary.

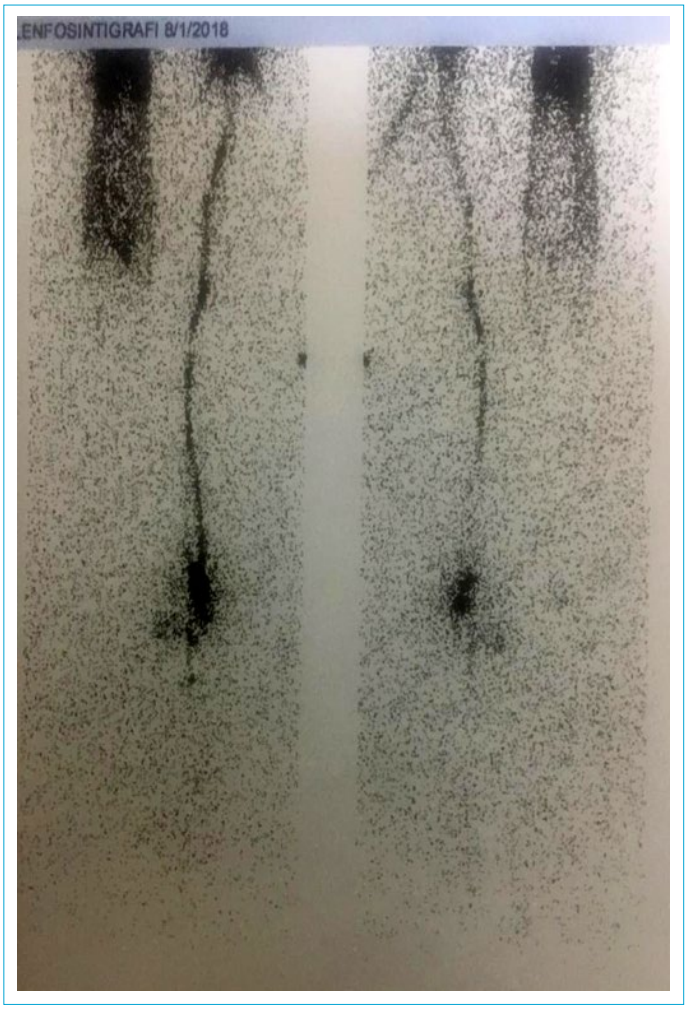

Figure 2. Lymphatic scintigrahy of the lower extremities.

Lymphatic abnormalities arise from the developmental abnormalities or dysfunction of this system.[7] Among these lymphatic malformations, lymphedema, chylothorax, chylousacids, Klippel-Trenaunay-Weber, proteus, PTEN hamartoma tumor syndrome and congenital lipomatous over growth vascular malformations with epidermal nevi and skeletal/spinal abnormalities syndrome have been reported.

Congenital lymphedema may also be associated with some syndromes, including Noonan and Turner syndromes.[8] Hereditary lymphedema is heterogeneous, with more than 10 forms of mendelian trait usually occurring with autosomal dominant features. Commonly known types of hereditary lymphedema are Milroy's disease, Meige's disease, and lymphedema-diastasis (LD). Among the hereditary forms of lymphedema, LD is most commonly associated with cardiac defects, cleft palate, photophobia and other congenital anomalies, including spinal epidural cysts. Milroy's disease may result from mutations in the vascular endothelial growth factor receptor-3 gene (VEGFR-3 or FLT4). The gene that causes Meige disease is unknown. Lymphoedema-distichiasis may occur due to mutations. Forkhead transcription factor (FOXC2) has been expressed in many tissues during the development of a gene. Familial primary lymphedema often occurs as an autosomal dominant or recessive. The age of onset is important in classification.[4]

1. Congenital (primary lymphedema congenital) (Nonne-Milroy lymphedema or type I Lymphedema).
2. Peripubertal (primary lymphedema precocious 1-35 years) (hereditary lymphedema type-II, also known as of Meige's disease or a history of lymphedema).
3. Late-onset lymphedema (primary lymphedema tarda starting after 35 years) is classified into three types.

Secondary lymphedema can be induced by external factors, such as infection, surgical intervention, or radiotherapy. These conditions may also be affected by genetic predisposition.[9] Predisposing changes have been reported in the MET gene and in the GJC2 gene.[10,11] These genetic changes have been found to increase the risk of developing secondary lymphedema following breast cancer treatment.[4]

The absence of familial forms and the unifocal nature of the lesion suggest that the cause may be a somatic mutation limited to the lesion cell, and if this germline occurs, it may be much more lethal.[12,13] Other developmental disorders have been shown to be related to similar post-zygotic mosaic mutations.[14,15]

Whether primary or secondary, lymphedema treatment is difficult.[16] Genetic findings indicate VEGF-C/VEGFR-3 sig-

naling as a target for treatment. Autologous grafts have been tested together with the adenoviral expression of VEGF-C in preclinical studies in the treatment of secondary lymphedema.

Because of its chronic nature, lower limb lymphedema (LLL) management continues for lifelong, including conservative, medical and surgical treatments.[17] Patients should be treated as soon as possible and complications, such as limb deformity and skin fibrosis, should be avoided as much as possible.

Non-operative approach consists of a two-stage program conducted by a professional team, including combined physical therapy, particularly trained lymphologists, nurses and physiotherapists.[18] The first step involves gentle hand massage to prevent damage to the lymph vessels, skin care to increase muscle mass, stimulate lymph flow and protein absorption by compression with multilayer bandages. The second step is to add compression with elastic garments and manual lymph drainage if lymphedema worsens.

Drug therapy, in combination with diuretics and benzodiazepines, is considered to be useful.[19,20] However, since diuretic agents may cause electrolyte imbalance, they can only be used for short periods in patients with malignancy.

Surgical methods include two types of approaches: physiological and ablative procedures.[19,21] Physiological techniques can only be performed in early-stage LLL without severe tissue changes in the affected limb and aim to improve the lymph flow rate. This approach has shown beneficial results in the long term and has a low complication rate. However, the success rate in the studies is quite variable.

Ablative procedures can be used for advanced LLL patients, patients with fat deposits, and patients with tissue fibrosis.[19, 21, 22] The liposuction method contains serious complications due to the use of long-term tissue-suppressing material and direct excision methods, which are useful but invasive and may lead to pain, infection, lymphatic fistulas, skin necroses and cosmetic problems.

According to the classification of chronic venous insufficiency, this case is in phlebo-lymphostatic insufficiency (stage 2) (Table 1).[23] Since no other secondary cause has been identified, this case classified as lymphedema praecox according to the age of disease onset (Type II). Further research will continue trying to determine the cause of the patient's genetic predisposition.

Disclosures

Informed Consent: Written informed consent was obtained from the patients' family for the publication of the case report and the accompanying images.

Conflict of Interest: None.

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Table 1. Clinical stages of the chronic venous failure

Stage 0	Stage 1	Stage 2	Stage 3
Sub-Clinical Stage	**Phlebo-lympho-dynamic insufficiency (Odema)**	**Phlebo-lympho-static insufficiency (lymphedema).**	**Skin changes and venous leg ulcers**
The increase in tissue flow is compensated. There is venous hypertension, no edema. It is typically associated with chronic venous insufficiency.	The dynamic insufficiency of the lymphatic system and edema are mostly in the lower part of the leg and around the medial malleolus due to gravitational forces. There is pigmentation of the skin. During night rest, edema is reduced or completely withdrawn.	There are high-pressure blood capillaries and lymph base of the red-brown wet granulation tissue at the base of the red-brown colored skin, skin pigmentation, dermatitis, lymphedema and varicose veins.	Lymphatic microangiopathy, pain, lipodermatosclerosis pigmentation, dermatitis, ulceration, the formation of small white scar, lymphedema, and varicose veins play a role in the pathophysiology. If the ulcer is prolonged and does not respond to treatment, osteomyelitis or secondary malignant lesion should be sought.

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