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Case Report

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Atypical Milroy's disease with predominant unilateral involvement: a case report

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ABSTRACT

Milroy's disease (MD), known as hereditary lymphedema type I, is a rare autosomal dominant primary lymphedema. It accounts for about twenty percent of all primary lymphedema. MD typically presents clinically with bilateral lower extremity lymphedema. Our case report describes a rare case of MD presenting with unilateral upper and lower extremity lymphedema in a patient admitted to our clinic. A 24-year-old woman who had been followed for lymphedema since the age of 8 was diagnosed with MD at our hospital by physical examination, venous Doppler ultrasound, whole-body lymphoscintigraphy, and molecular genetic testing. Partial improvement was observed with complete decongestive therapy, considered the gold standard treatment for lymphedema. Genetic counseling may be beneficial for the patient and family. Although MD is uncommon in the literature, many more studies are needed to identify carrier variants in the community.

Keywords: Milroy disease, hereditary lymphoedema type I, Fms-associated tyrosine kinase 4, lymphoscintigraphy, complete decongestive therapy

INTRODUCTION

Milroy's disease (MD), also known as hereditary lymphedema type I, first described by Milroy in 1892, is a primary lymphedema inherited in an autosomal dominant pattern.[1] It can manifest at birth or later in life. In the United States, primary lymphedema affects 1 in 10,000 individuals, accounting for approximately 20 percent of all primary lymphedema, with approximately 200 cases reported in the literature.[2]

The most common cause of MD is a mutation in the Fms-related tyrosine kinase 4 (FLT4) gene.[3] The FLT4 gene plays a crucial role in producing a protein called vascular endothelial growth factor receptor 3 (VEGFR3), which is essential for the development of the lymphatic system. Lymphatic vessels with mutations in VEGFR3 are also referred to as congenital aplasia of lymphatic vessels.[4] Problems in transporting lymphatic fluid cause lymphedema to accumulate in the tissues.

MD typically presents clinically with lymphedema of the bilateral lower extremities. In addition to lymphedema, it can lead to serious complications such as intestinal lymphangiectasia, cellulitis, cutaneous bacterial infections, and pleural effusion.[5] Symptoms may vary within families, and some carriers may remain asymptomatic.[6]

Previous studies have shown that FTL4 mutations reduce lymphatic vessel density by approximately 51-61% in the lower extremities and 26-33.6% in the upper extremities.[7] Therefore, although rare, lymphedema can occur in both the upper and lower limbs.[8] A multidisciplinary approach involving geneticists, physiatrists, neonatologists, dermatologists, and surgical teams is crucial to treating and following up these cases.

Our case will focus on the rare occurrence of MD presenting with unilateral lymphoedema of both the upper and lower extremities in a patient who presented to our clinic.

CASE

A 24-year-old female patient married and a housewife with a history of two miscarriages, had never had a full-term pregnancy. She had been under observation for lymphedema since the age of 8. Her aunt also had a history of lymphedema and recurrent abortion. The patient had been using oral contraceptives (OCs) for the past four years. She reported that her swelling and edema had increased further after starting the OCs and sought our advice and treatment options.

On examination, the patient had swelling, increased circumference, and fibrous bands in the right lower extremity, right upper extremity, and genital region. Hyperkeratotic papillomatous lesions were also observed in the right inguinal region and the flexor surface of the right elbow. (Figure).

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The patient had no complaints of pain on palpation. Lymphedema was assessed by limb volume measurement with a volume difference of 1954 ml and a percentage difference of 81% for the lower extremities. For the upper extremities, the volume difference was 1116 ml, with a percentage difference of 57.6%.

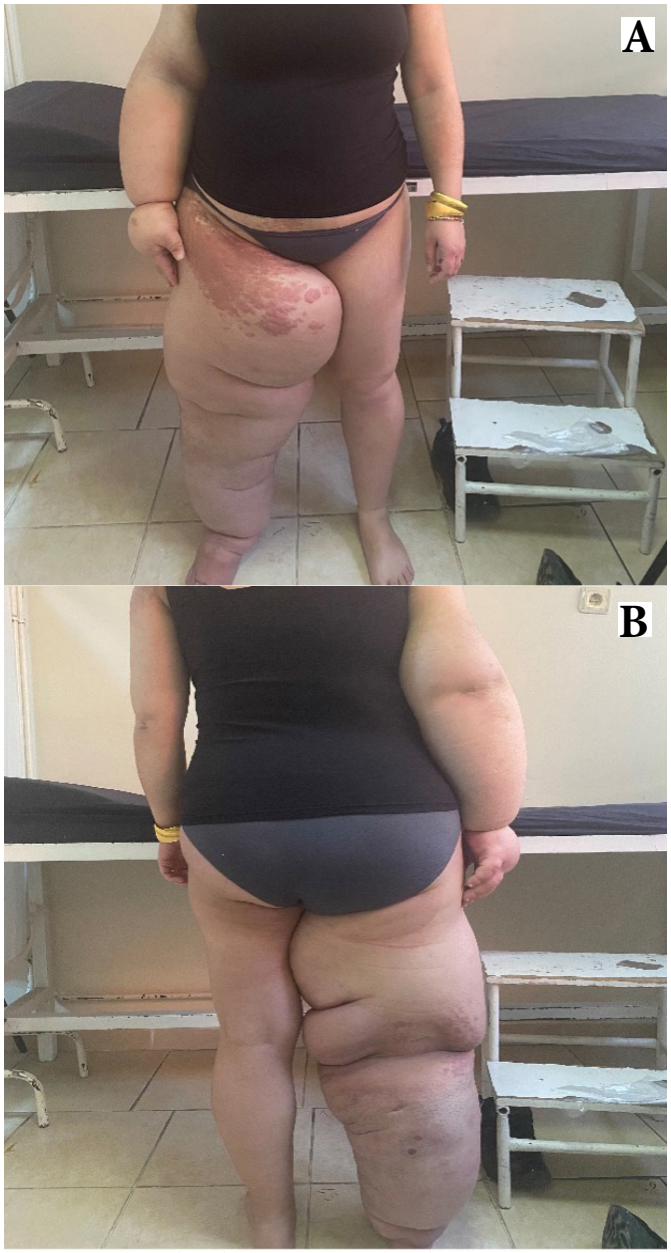

Figure. Hereditary lymphedema type 1; milroy disease
A: Anterior B: Posterior

Venous Doppler ultrasound of the lower extremities showed reflux at the saphenofemoral junction, whereas venous Doppler results of the upper extremities were normal.

Whole-body lymphoscintigraphy was performed and failed to visualise the right main, right pelvic, and right axillary lymph nodes. These findings were consistent with a grade IV lymphatic drainage disorder on lymphoscintigraphy.

Molecular genetic testing identified a mutation in the FLT4 gene located on chromosome 5q35. Based on these findings, a diagnosis of MD was established.

The patient underwent a 3-week treatment program that included skin care, manual lymphatic drainage, multilayer bandaging, diaphragmatic exercises, lymphedema exercises, walking exercises (complete decongestive therapy), and a ketogenic diet for weight loss. In addition, the patient received recommendations from dermatology for papillomatous lesions and cardiovascular surgery for venous insufficiency. At the end of treatment, after measurement and fitting, compression garments were prescribed for the right upper and lower extremities. The volume difference in the lower extremities decreased to 1092 ml, with a percentage difference of 68%, after complete decongestive therapy. In the upper extremities, the volume difference decreased to 940 ml, with a percentage difference of 48.5% after complete decongestive therapy. Written informed consent for the publication of this case report was obtained from the patient.

DISCUSSION

Milroy's disease has often been confused with other forms of congenital lymphoedema Milroy's disease should be considered if the lymphedema is congenital and localised to the lower limbs. Swelling is often "Woody" in nature and associated with secondary changes, deep wrinkles on the toes, small dysplastic ("ski jump") toenails, and papillomas. Prominent, broad, calibrated leg and foot veins are usually a good clue to the underlying diagnosis, as they are not seen in association with other causes of congenital lymphedema.[9] In our case, the right main lymphatic vessel was occluded, and lymphedema of the upper and lower extremities was observed [International Society of Lymphology (ISL) stage 3].

The current treatment of lymphedema includes conservative therapies such as manual drainage, massage, compression garments, intermittent pneumatic compression, and dietary changes, but these are ineffective and incurable for some patients.[10] For surgery, procedures such as lymphovenous shunts, lymph-lymphatic shunts, vascularised lymph node transfer, and liposuction can be invasive and expensive. Some patients may be reluctant to undergo surgery, and less invasive methods may be useful.[11,12] In our patient, a significant decrease in the stage of lymphedema and regression in volume was observed with CDT treatment.

CONCLUSION

The management of lymphoedema in MD is mainly aimed at reducing swelling and circumference discrepancies and preventing infectious factors such as lymphangitis. Genetic analysis, venous Doppler ultrasound, and lymphoscintigraphy are important diagnostic tools.[13] The gold standard treatment for lymphedema is complete decongestive therapy.[14] Comprehensive decongestive therapy includes manual lymph drainage, multi-layer bandaging, compression garments, lymphedema exercises, and appropriate skin care. Genetic counseling may be particularly useful for the patient and family. Although MD is uncommon in the literature, many more studies are needed to identify carrier variants in the community.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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