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Case Report

Nonne-Milroy Syndrome – A Case Report and Review Study with Clinical Aspects

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Abstract

Milroy disease is a condition causing lymphedema in the legs and feet due to damage to the lymphatic system. This condition can cause fluid accumulation in the legs and feet before delivery and sometimes throughout the body. It can also cause lower limb edoema, hydrocele, and skin abnormalities. Milroy disease is an autosomal dominant disorder that interferes with the lymphatic system's normal operation. It is diagnosed through symptoms, clinical examination, and genetic tests. Treatment aims to control symptoms and prevent skin infections and certain cancers. Genetic tests may confirm the diagnosis.

Key words: FLT4; VEGFR-3; Nonne-Milroy; ICT; ECM; HLTS; VLNT

Introduction

Milroy disease is a condition causing lymphedema in the legs and feet due to damage to the lymphatic system. This condition can cause fluid accumulation in the legs and feet before delivery and sometimes throughout the body. It can also cause lower limb edoema, hydrocele, and skin abnormalities. Milroy disease is an autosomal dominant disorder that interferes with the lymphatic system's normal operation. It is diagnosed through symptoms, clinical examination, and genetic tests. Treatment aims to control symptoms and prevent skin infections and certain cancers. Genetic tests may confirm the diagnosis.

Description

Nonne-Milroy syndrome, a rare primary lymphedema, is associated with firm, non-pitting edoema in the lower extremities of the leg or feet or toes. Duplex ultrasonography and lymphoscintigraphy revealed intact blood vessels and lymphatic aplasia in both lower limbs. After ruling out alternative hereditary causes, the patient was diagnosed with either primary lymphedema or Nonne-Milroy syndrome. He was treated with bilateral pleurodesis and tetracycline, and after a year of follow-up, no recurrence was observed.

Lymphedema is classified as primary (idiopathic) and secondary (acquired), with secondary having a pathogenic change. Primary lymphedema is a congenital abnormality resulting in abnormal interstitial protein-rich fluid buildup, while secondary lymphedema is a result of lymphatic blockage or disruption of lymphatic arteries. Lymphatic vessels can be hypoplastic or hyperplastic, but are nonfunctional in primary lymphedema. The diagnosis of primary lymphedema was made due to the patient's congenital lymphedema.

Case Study

I discuss the case of a 7-year-old kid in India who had swollen lower limbs and his scrotum, with flare-ups and remissions of the symptoms. A congenital defect in lymphatic drainage may have been the cause of the vaginal edoema that appeared at 6 months of age. Milroy's illness and other potential causes of paediatric lymphedema are examined.

Since birth in India, a child male patient with age 7, In the mammary, axillary, infra-axillary, lower inter-scapular, and infra-scapular regions on the left side of his chest, as well as the infra-axillary and infra-scapular regions on the right, there was stony dullness with reduced vesicular breath sound. His ESR was not elevated, and his Mantoux and immunochromatographic card tests (ICT Immunochromatography (or lateral flow tests) Combining migration-based capillary flow separation of the sample molecules and reagents on a solid substrate. The identification and detection procedures are based on the antigen–antibody immune reaction) for filaria were also negative. The equilibrium of interstitial fluid is maintained in large part by lymphatics. In the sixth to seventh weeks of an embryo's life, the human lymphatic system begins to develop.

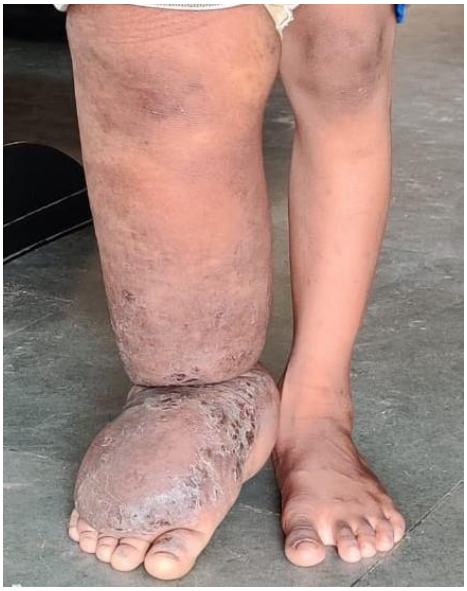

Image 1: Male Child with Lymphedema

Lymphedema is a condition characterized by the buildup of protein-rich fluid due to inadequate lymphatic transit and drainage. It is typically diagnosed through history gathering, physical examination, and ultrasound. Isotopic lymphoscintigraphy is a potent diagnostic imaging technique that can be performed with minimal invasiveness and safety for the lymphatic endothelium, the inner cellular lining of blood vessels and the lymphatic system. This technique is particularly useful for detecting lymphedema due to its minimally invasive nature and low risk of side effects. This exercise discusses the use of lymphoscintigraphy in modern medicine and its role in treating cancer patients with lymphatic system flow pathology. It highlights the multidisciplinary team's role in diagnosing lymphedema, with primary and secondary forms being the main types. Primary lymphedema can occur alone or in conjunction with other disorders. The patient had congenital lymphedema, which can have various hereditary origins, including Turner's syndrome, Noonan syndrome, Yellow nail syndrome, Lymphedema-distichiasis syndrome, Hypotrichosis-lymphedema-telangiectasia syndrome (HLTS), and Milroy disease, an uncommon type caused by a FLT4/VEGRF3 gene mutation. These conditions can cause symptoms such as scant hair, lymphedema, and telangiectasia. Milroy disease patients have aplastic or hypoplastic superficial lymphatics, leading to a deadly condition called chylothorax. This rare but deadly illness occurs between the second and fourth decade of life, causing lymph buildup in the chest cavity. Hereditary lymphedema can cause pleural effusions, but the cause remains unclear. The condition is known as atypical Nonne-Milroy syndrome. Over time, thoracic involvement and leg edoema worsen, and treatment involves non-operative methods like compression therapy and manual lymphedema drainage.

Diagnosis

Only conservative measures can be taken. Certain treatments for lymphedema disorders may possibly alleviate specific symptoms; no cure and it is usually congenital. Genetic counseling can be done. May have similar health conditions, delays, disorders, and physical traits associated with other lymphatic genetic diseases and chromosome #5 abnormalities.

Prognosis

A rare complication is the appearance of lymphangiosarcoma (Within a median of 10 years after mastectomy, lymphphangiosarcoma is characterised by skin alterations in the form of purple-colored elevated cutaneous lesions that proceed to ulceration in a lymphedematous arm.) or angiosarcoma (Angiosarcoma is a kind of cancer that develops in the lining of lymphatic and blood vessels. It frequently affects the skin and can take the form of an ever-expanding lesion that resembles a bruise. An uncommon kind of cancer called angiosarcoma develops in the lining of the blood vessels and lymph vessels) in patients with persistent lymphedema. Some patients may develop protein-losing enteropathy (The small intestine is continually being harmed, irritated, or swollen in enteropathy) and visceral involvement. Chylous ascites and chylothorax rarely occur. Milory disease does not normally affect life expectancy.

Clinical characteristic in observation

Milroy disease is a rare autosomal dominant disorder characterized by lower-limb lymphedema, often seen before or after delivery. Symptoms include hydrocele, large veins below the knees, upslanting toenails, papillomatosis, and anomalies of the urethra in males. The disease is primarily caused by a gene deficiency, with a significant gene deficiency identified as the predominant cause. About 20% of infected individuals develop cellulitis, which can harm lymphatic vessels, with males being more likely to contract the illness.

Diagnosis/Testing

A proband with congenital or infantile-onset lower-limb lymphedema and a lack of radioactive colloid uptake in the ilioinguinal (The sentinel lymph node (the first node to receive lymph from a tumour), which may be removed and examined for tumour cells, is found using lymphoscintigraphy. The ilioinguinal nerve is a mixed nerve that originates from the anterior rami of the T12 and L1 nerve roots), as well as by the discovery of a heterozygous pathogenic variant in FLT4 by molecular genetic testing, are considered to have Milroy disease.

Management

A lymphedema therapist can treat manifestations like edoema, urethral anomalies, hydroceles, and cellulitis by applying tailored stockings, massage, compression hosiery, bandaging, supportive shoes, toe gloves, and proper skin care, enhancing limb aesthetics and reducing risk.

Prevention of secondary complications- Good skin care, timely antibiotic treatment of infections, and preventive antibiotic use for recurring bouts can all minimise the frequency of cellulitis.

Surveillance- It is appropriate to follow up regularly at a clinic that specialises in treating lymphedema.

Agents/circumstances to avoid- Drugs that may induce leg edoema; prolonged periods of inactivity with the legs in a dependent posture.

Wounds to limbs Evaluation of relatives at risk- In order to determine whether relatives of an afflicted person may benefit from receiving appropriately fitting compression hosiery and counselling on how to lower

their risk of developing cellulitis of the legs and feet, evaluation of the apparent asymptomatic at-risk relatives is necessary.

Establishing the Diagnosis: Milroy disease is diagnosed when a proband has lower-limb lymphedema, lack of radioactive colloid uptake, and/or a heterozygous pathogenic variant in FLT4 (VEGFR3) through molecular genetic testing. This can be identified using gene-targeted testing or complete genomic testing. Gene-targeted testing is more effective due to the disorder's wide phenotypic range, unlike those with similar physical properties to other hereditary disorders.

Genetic Counselling: Milroy disease is an autosomal dominant hereditary condition, with most individuals having a afflicted parent. If a proband carries the FLT4 pathogenic variation, there is a 50% chance that siblings will inherit it. Heterozygous sibling variants may be more severe due to intrafamilial variability and lower penetrance. Prenatal testing and preimplantation genetic testing are available if the FLT4 mutation is found in an afflicted family member. Pregnancy may cause foot enlargement, pleural effusions, and edoema.

Diagnosis-Suggestive Findings

Milroy disease should be suspected in individuals with the following clinical features, radiographic findings, and family history.

Clinical features

Lower-limb swelling that is:

Usually (not always) bilateral

Present at birth or develops soon after

Note: In neonates the swelling predominantly affects the dorsum of the feet; with age, the swelling may improve or progress to affect the below-knee region (rarely extending above the knees).

Large-caliber veins below the knees

Upslanting and small, dysplastic toenails

Deep interphalangeal creases of the feet

Hydroceles in males

No internal clinically significant lymphatic issues (e.g., intestinal lymphangiectasia, pleural or pericardial effusions)

Radiographic findings: Typically, lymphoscintigraphy shows that there is little tracer absorption into the peripheral lymphatics. As a result, neither drainage channels nor absorption in the ilio-inguinal nodes are seen. This is a sign of Milroy disease and is referred to as "functional aplasia". Although the lymphoscintigraphic findings are distinctive and helpful for diagnosis, the test is not always necessary.

Lymphedema Medication: Retinoid-like Agents (Tretinoin, retinyl palmitate, retinaldehyde, isotretinoin, and tazarotene).

Anthelmintics (Anthelmintic is the term used to describe a drug used to treat infections of animals with parasitic worms)

Topical Skin Products 9+Antibiotics

Lymphoscintigraphy: About 20% of those who are affected develop cellulitis, with males significantly more likely to contract the infection than females [Brice et al 2005]. Milroy disease is frequently distinguished from other lymphatic conditions by the presence of cellulitis, which can harm the body's natural lymphatic vessels and increase the degree of swelling. In the toe web spaces, a radioactive colloid is injected, and the ilioinguinal nodes' uptake is periodically evaluated. To ascertain if there is a deficiency in radioactive tracer uptake, lymphoscintigraphy is done. Different patterns on lymphoscintigraphy can be seen in Milroy illness and other types of lymphedema [Connell et al 2013, Sarica et al 2019]. Lymphoscintigraphy can identify whether there is a problem with lymphatic drainage in the limb that is "unaffected" in situations of unilateral edoema.

Surgical Intervention: VLNT together with therapeutic lipectomy proved to be a reliable technique in moderate cases of Milroy disease, providing an alternative path for lymph drainage, and reducing the lymph load and the excess of subcutaneous adipose tissues, thus improving patients' quality of life

Conclusion:

Generally, pilocytic tumors are thought to be a benign process with good overall prognosis. IVPAs, however, are rare, and little is known about their natural course. These should therefore be dealt as a separate entity with close clinical and radiological follow up, particularly in cases with sub-total resections, since they may present with aggressive recurrences.

Consent:

Untreated lymphedema can lead to lymphangiosarcoma, a cancer that can shorten a patient's life expectancy. Mismanaged lymphedema can also cause sepsis, a potentially fatal infection that spreads rapidly. Lymphedema is swelling caused by protein-rich lymph buildup, often affecting the arm or leg. Primary lymphedema is common in the legs, while secondary lymphedema can occur in other body parts due to damage or trauma.

Patient Consent Statement: The author attests that they have all necessary patient permission form preparing manuscript. The patient has granted permission to use his photo. The patient is aware that his initials and name will not be published.

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