

# Milroy's Disease - The Rarest Cause of Lymphedema

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## Abstract

*Milroy's disease is an old term used to describe hereditary congenital lymphedema. It is the rarest of the inherited lymphedema. The cause is a mutation in the VEGFR3 gene and is inherited in an autosomal dominant manner. This gene has been mapped to the telomeric part of the chromosome 5q in the region 5q34-q35. It is characterized by lower limb lymphedema, present at birth or developing soon after. It may be associated with intestinal lymphangiectasia and cholestasis. Here we report a 57 years old male who had been suffering from bilateral leg swelling since birth and finally leveled as a case of Milroy's disease by positive family history and excluding other causes of lymphedema. We present this case due to the rarity of its occurrence.*

**Keyword:** Milroy's Disease, Lymphedema

## Introduction

Lymphedema is defined as a swelling of a part of the body caused primarily by an imbalance between the inflow and the removal of interstitial fluid and protein, and secondary by a malformation or malfunction of the lymphatic system. It was classified into primary and secondary forms. Primary lymphedema is defined as lymphedema that presents at birth or appears in childhood. The secondary lymphedema is caused by obstruction of lymphatic flow following infection, surgical excision, neoplasm, irradiation, or trauma.<sup>1</sup> On the basis of genetic susceptibility, primary lymphoedema is divided.

In famlial (hereditary), when typically only abnormality is lymphoedema with a positive family history, and syndromic, when lymphedema is only one of several congenital abnormalities and is either inherited or sporadic. Familial lymphedema, usually segregating as an autosomal dominant trait, can be classified according to the age at onset, as early onset lymphedema (primary congenital lymphedema or Milroy disease) and late onset lymphedema (lymphedema praecox or Meige lymphedema).<sup>2</sup> Milroy's disease was first described by Nonne in 1890 in Germany and it was called as Milroy's disease by Osler. In 1892, Milroy himself has presented a general discussion of the conception of the condition and his observation on the same family.<sup>3</sup>

## Case report

A 56 years old man, got himself admitted in Dhaka Medical College Hospital with the complaints of bilateral leg swelling since birth which was initially on the dorsum of the feet and gradually extended up to knee with increasing age. The right leg swelling is more predominant than left. He also had high grade intermittent fever with chills and rigor associated with pain and redness of both leg. His symptoms were episodic and ran as relapsing and remitting fashion at 5-6 months interval since childhood. He had no history of trauma or surgery in the leg. Searching his family history had revealed that several family members of his family in the last two generations had been suffering from same kind of disease.

On examination patient was febrile with a body temperature of 102°F, otherwise haemodynamically stable. There were firm pitting bilateral leg odema. The legs were erythremetous, mildly tender with raised local temperature. Thickening and depigmented lesion were present in the web of toes and on foot. Draining inguinal lymphnodes were palpable which were discrete and tender. It was free from underlying structure or overlying skin. Hair distribution on the leg was normal and all peripheral pulses in lower limbs were present. There was engorged vein over right knee having bellow upward direction. All other systemic examination revealed no abnormality.

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**Fig.-1:** Picture of patient's leg showing lymphedema and engorged veins.

His investigation profile showed, Hb-10.0gm/dl, TC-11,000/mm<sup>3</sup>, circulating eosinophil count -220, ESR-30mm in 1st hour. Urine R/M/E was normal, and bed side heat coagulation test was negative. ICT for filarial was negative and X-ray chest was normal. Doppler ultrasound of both lower limbs were normal. Lymphangiogram revealed lymphatic channels were poorly visualized, however lymphatic channel seems to be patent as activity was normal. Lymphoscintigraphy and genetic screening were not done due to nonavailability.

## Discussion

Lymphedema is caused by a dysfunction of the lymphatic system. Lymphangiography demonstrates hypoplasia or aplasia of lymphatic channels. It provokes disfigurement and disabling swelling, mostly localized at the extremities. Primary congenital lymphedema also known as Milroy disease is the rarest cause of lymphedema. The disease is hereditary and analysing the family with this disease showed that it has autosomal dominant mode of inheritance with incomplete penetrance. The genetic basis of most cases of Milroy disease has not been established.<sup>4</sup> The gene responsible for this condition is identified in the region 5q34-q35. It is located to the telomeric part of chromosome 5q. This region contains the gene for vascular endothelial growth factor receptor VEGFR3 (FLT-4). The gene encodes a receptor tyrosine kinase which is specific for lymphatic vessels. In early embryogenesis the gene is expressed in all vessels but thereafter, expression is limited to adult lymphatic vessels. Defective VEGFR3 signaling due to Mutations in the vascular endothelial growth factor receptor VEGFR3 (FLT-4) seems to be the cause of congenital hereditary lymphedema in some cases.<sup>2</sup>

In studying the pathology of the disease, McGuire and Zeek (1932), reported the results of biopsy in a typical case. Microscopy of a portion of the skin and subcutaneous tissue showed a normal epidermis but a marked condensation of the superficial portion of the dermal papillary layer composed of fine collagen fibrils which in some places were undergoing hyalinization; oedema was more pronounced in the dermis, and this, together with an increase of collagen fibres, produced a great increase in the proportion of dermis to epidermis. There was a considerable sprinkling of lymphocytes related to the capillaries and venules. The subcutaneous tissue was also thickened, consisting of masses of oedematous fatty tissue and pools of colourless fluid not contained within definite limiting boundaries.<sup>5</sup>

The age of onset of clinical features varies in the different families recorded. It may be present in the prenatal period or may develop after birth upto puberty. The oedema begins in the toes, gradually spreads up the limb, but never extends above the level of the inguinal ligament, where it is sharply demarcated; it may remain at lower levels, especially joints, for long periods. At first the oedema pits readily on pressure, though later the tissues become more indurated and thickened, and is reduced by rest with elevation of the limb. One or both limbs may be affected. There are no constitutional disturbances and the disorder is compatible with long life. Another remarkable feature of the condition is the absence of disability; in spite of grossly swollen limbs affected

persons may be quite capable of a normal existence. In addition to the above clinical features, Hope and French (1907) described acute attacks in many of their patients in which the affected limbs suddenly became red, painful, tender, and much more swollen; there was no obvious cause for the onset or remissions of these attacks.<sup>5</sup> In cases of long-lasting or congenital lymphoedema the finding of ulceration, violaceous nodules or papules, or apparent traumatic ecchymosed verruciform xanthoma may be found and should act as a diagnostic beacon warning of dangers.<sup>6</sup> Cases of angiosarcoma and lymphangiosarcoma had been reported in patients with congenital hereditary lymphoedema (Milroy's disease).<sup>7,8</sup>

Basic diagnosis can be made by the fact that swelling (generally of the legs) presents at birth and there is a family history of similar swelling. The diagnosis of lymphatic vascular disease relies heavily on the physical examination. While pitting edema may be absent, it is a common misconception that the presence of pitting precludes a lymphatic origin of limb swelling. However, in all cases, the hallmark of lymphedema is the presence of cutaneous and subcutaneous thickening, which uniquely identifies the lymphatic pathogenesis of edema formation. Currently the most precise diagnosis can be made by a thorough imaging. Direct contrast lymphography has largely been abandoned, in favor of the use of indirect radionuclide lymphoscintigraphy. The procedure requires intradermal or subcutaneous injection of an appropriate radio labeled tracer (99mTc-antimony sulfur colloid, 99mTc-sulfur colloid, 99mTc-albumin colloid, or 99mTc-labeled human serum albumin). Criteria for the diagnosis of lymphatic dysfunction include delayed, asymmetric or absent visualization of regional lymph nodes, asymmetric visualization of lymphatic channels, collateral lymphatic channels, interrupted vascular structures, and visualization of the lymph nodes of the deep lymphatic system.<sup>9</sup> Lymphoscintigraphy is performed to determine if there is lack of uptake of radioactive tracer. This can help with the diagnosis of Milroy disease (aplasia of superficial lymphatic capillaries), as other forms of lymphedema can have differing patterns on lymphoscintigraphy. In cases of unilateral swelling, lymphoscintigraphy can determine if lymphatic drainage is impaired in the 'unaffected' leg.<sup>10</sup> Other than lymphoscintigraphy, clinically relevant imaging modalities include magnetic resonance imaging and computerized axial tomography.<sup>9</sup> Molecular Genetic Testing is possible in prenatal diagnosis, using linkage analysis, in families with a VEGFR-3 mutation. However, this is available in only a few centers and the gene's variable penetrance and expressivity also creates some problem. Therefore, prenatal

sonography may be the preferable diagnostic modality in families with a history of Milroy disease.<sup>11</sup>

Because of the minimal symptoms there is usually no indication of any treatment other than bandaging to control the size of the limb.<sup>5</sup> Bandaging will reduce the swelling. The best results have been obtained with adhesive tape or pure rubber roller bandages. Jobst-type of compression with high-pressure (up to 50 to 60 mm Hg) stockings is expensive and has poor compliance because of the discomfort when applied. Ace-type elastic bandage is inexpensive, and it is more comfortable but it lacks sufficient pressure to decrease the edema significantly. Pneumatic pumping is a new method of compression. The provided actions are sequential, intermittent, pneumatic compression of the limbs which must be used together with stockings. It is effective and decreased swelling after several hours of use but they are costly and immobile. Elevation is routinely and universally recommended.<sup>1</sup> The earlier the mechanical reduction of the edema is started, the better are the results. In later stages, progressive fibrosis reduces the compression effect. In severe cases operative procedure can be applied. Among the operative procedures the Kondoleon operation or Sistrunk and other modifications have been successful. Improved results can be expected with operations performed during the early stages of lymphedema.<sup>3</sup>

### Conclusion

Milroy's disease (primary congenital lymphedema) is the rarest form of primary lymphedema. Classically it involves the legs, but the genitalia and upper limbs may also be involved. The cause of Milroy's Syndrome is a mutation in the VEGFR3 gene. The clinical features may be present at birth or develops soon after. The condition has a slow but constant progression from a mild swelling of an ankle to a swollen extremity. The swelling enlarges at a slower rate than the growth of the body. Firm, non-pitting edema, fibrokeratotic skin, verrucous growths, squaring of the toes, and a tendency toward recurrent attacks of cellulites and lymphangitis are its common manifestations. The diagnosis is made from a carefully taken clinical history including family history and findings in the physical examination. The condition could be detected prenatally via fetal ultrasonography. Radionuclide lymphoscintigraphy is a useful technique for differentiating lymphedema from other causes of swelling. Decongestive therapy is the most widely accepted form of treatment. There is no cure for Milroy's but the condition can be managed by early diagnosis and treatment. Other treatments involved will focus on the complications such as infections, pain and associated skin problems. Other therapies used may include compression pump therapy and surgical procedures.

**Conflict of Interest :** None

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