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REVIEW

Primary Lymphoedema and Lymphatic Malformation: Are they the Two Sides of the Same Coin?

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Abstract *Objectives:* To clear the confusion regarding the relationship between the 'primary lymphoedema' and (truncular) lymphatic malformation (LM); the latter is one of congenital vascular malformations.
Materials & Methods: A literature review was carried out on the primary lymphoedema either existing as an independent LM lesion or as a component of the Klippel–Trenaunay syndrome.
Results: The review was able to provide a contemporary guide/conclusion on the definition and classification, clinical evaluation and clinical management regarding conservative (physical) therapy, reconstructive surgical therapy and ablative/excisional surgical therapy, for the primary lymphoedema as an LM.
Conclusions: Primary lymphoedema can be considered as 'congenital' since its majority represents a clinical manifestation of the truncular type of LM arising during the later stages of lymphangiogenesis. Such embryological staging information of the LM is critical for proper management of the primary lymphoedema when it exists with other congenital vascular malformations (Klippel–Trenaunay syndrome).

2. Basic non-invasive to minimally invasive tests will provide an adequate diagnosis and lead to the correct multidisciplinary, specifically targeted and sequenced treatment strategy.

3. The mainstay of current management of the primary lymphoedema/truncular LM is complex decongestive therapy; and the reconstructive as well as ablative surgical therapy remain adjunctive therapies at best.

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There has been significant confusion regarding the relationship between the 'primary' lymphoedema and lymphatic malformation (LM); further, the definition of 'primary' lymphoedema remains controversial.

Many still believe that 'primary lymphoedema' and (truncular) LM are two different disease entities. However, in our experience, the majority of 'primary' lymphoedemas constitute the clinical manifestation of LM.[1,2] Nevertheless, primary lymphoedema has been managed as a chronic lymphoedema without consideration of its background as a congenital vascular malformation (CVM).[3,4]

For this reason, we decided to review the neglected aspect of the 'primary' lymphoedema as an LM lesion for a better understanding of what we consider to be the two sides of the same coin.

Literature review was able to provide a contemporary guideline on the definition and classification, clinical evaluation and clinical management for the primary lymphoedema as an LM.

Primary lymphoedema can be considered as a clinical manifestation of the truncular type of LM arising during the later stages of lymphangiogenesis.[5,6] Its evaluation should begin as an LM following a differential diagnosis with secondary lymphoedema.[7,8]

Basic non-invasive to minimally invasive tests will provide the necessary information for an adequate diagnosis as an LM[9,10] and subsequent management with complex decongestive therapy as well as reconstructive/ablative surgery.[11,12]

Definition and classification—primary lymphoedema as LM

The current concept regarding 'primary' lymphoedema accepts its definition as a clinical manifestation of an LM developed during the later stage of the lymphangiogenesis.[13,14]

However, primary lymphoedema also includes other types of lymphoedema of an 'idiopathic' nature without an identifiable aetiology (e.g., radiation, surgery and infection).[15,16]

Nonetheless, primary lymphoedema has been considered to be 'congenital' since the great majority is caused by a congenital defect in the lymph transporting system including the lymphatic channels and the nodes (e.g., aplasia, hypoplasia and hyperplasia).[17,18]

There are some lymphoedemas that are without clear relationship to their congenital origin and they do not fit the conventional concept of a 'congenital' condition. Such an idiopathic condition needs further clarification to reduce the confusion in terminology.

Similarly, not all primary lymphoedemas have anatomically evident 'truncular' defects in the lymphatic system. A unique primary lymphoedema, 'lymphoedema—distichiasis syndrome'[19] has only one anomaly, that is, lack of intraluminal valves of the lymphatic collectors, resulting in lymph reflux. Another condition with a well-documented genetic defect, 'hereditary/familial lymphoedema' also known as Milroy's disease,[20] does not have a gross macro-structural defect of the lymphatic vessels. Initial and collecting lymphatics are present but there is impairment of absorption at the level of the initial lymphatics, reflecting a functional defect.

Such primary lymphoedema that developed as a hereditary/familial lymphoedema remains in controversy due to lack of insufficient anatomical defect to support conventional concept for the vascular malformation. That all lymphoedemas currently grouped as 'primary' are genuinely primary still remains to be established.

There is also some controversy regarding the current classification of primary lymphoedemas based on the time of onset of clinical manifestations: congenital, 'praecox' and 'tarda' to constitute one spectrum of the disease where an arbitrary end point of age 35 years is used to separate 'tarda' from 'praecox'. However, there are some conditions classified as 'tarda' that can hardly fit as a 'primary' disorder.[21,22]

By the same token, some congenital lymphoedemas, by classification, are not true congenital defects but postnatal obliterations of lymph collectors/lymph nodes, which simply mimic the congenital/prenatal condition. In a true sense, these are not a malformation of the lymphatic system; nonetheless, they are classified as congenital lymphoedema since they are found at birth.[23,24]

Hence, it is difficult to claim that 'primary' always reflects 'congenital' in the case of lymphoedema.

It has become controversial to define primary lymphoedema on the basis of LM alone. Nevertheless, not only for its clinical management but also for its prognosis, primary lymphoedema should be considered as an LM till proven otherwise.

An LM is one of the two most common forms of CVMs,[1,2] the other being venous malformation (VM). An LM exists either as an independent (predominant) lesion or as a combined lesion with other CVMs—VMs,[25,26] arterio-venous malformations (AVMs[27,28] and/or capillary malformations (CMs)).[29] Such combined conditions have been classified separately in the Hamburg Classification[30] as haemolymphatic malformations (HLM)[31,32] (Table 1).

The majority of clinical conditions considered as 'primary' lymphoedema are due to 'truncular' LM arising during the later stages of lymphangiogenesis.[33,34] They result in hypoplasia, hyperplasia or aplasia of lymph vessels and/or lymph nodes. Such embryological staging of the LM is critical for a proper understanding of the LM as one of the CVMs. A basic knowledge of LM is required whenever primary lymphoedema is believed to underlie limb swelling.

The LM is further classified into two subgroups based on the embryological stage when developmental arrest occurred. 'Extratruncular' lesions develop at an earlier stage of embryogenesis and 'truncular' lesions originate at a later stage.

The truncular LM is better known as primary lymphoedema while extratruncular lesions are known as cystic/cavernous lymphangiomas.[18]

These two different types of LMs resulting from different embryologic stages are often mistakenly identified as two different and unrelated disease entities. However, these lesions are inseparable and often co-exist, affecting each other profoundly.

A clear understanding of primary lymphoedema as a truncular type of LM is necessary to establish its contemporary classification as a vascular malformation.

Extratruncular LM lesions

Extratruncular lesions are the result of premature embryonic tissue that fails to involute and remains in the condition of

Table 1 Hamburg Classification of Congenital Vascular Malformation (CVM), modified.[a,b]

Main classfication based on its predominent vascular component:
Predominantly arterial defects
Predominantly venous defects
Predominantly AV (arterio-venous) shunting defects
Predominantly lymphatic defects
Predominantly capillary malformation
Combined vascular defects
Subclassification based on its embryological stage of the defect:
Extratruncular forms - developmental arrest at the earlier stages of embryonal life:
Diffuse, infiltrating
Limited, localized
Truncular forms - developmental arrest at the later stages of embryonal life:
Aplasia or obstruction
Hypoplasia; Aplasia; Hyperplasia
Stenosis; Membrane; Congenital spur
Dilatation
Localized (aneurysm)
Diffuse (ectasia)

[a] Both extratruncular and truncular forms may exist together in same vascular malformation; may be combined with other various malformations (e.g. capillary, arterial, AV shunting, venous, hemolymphatic and/or lymphatic); and/or may exist with hemangioma.
[b] Based on the consensus on the CVM classification through the international workshop in Hamburg, Germany, 1988, which was upheld by subsequently founded ISSVA (International Society for Vascular Anomaly).

'earlier' stages of embryonic life as for example, the reticular stage.[35,36] The cystic/cavernous lymphangioma is a remnant of embryonic tissue that developed before the lymphatic/vascular trunks were formed. This gives it the designation of a pretruncal embryonic lesion.

Extratruncular lesions maintain the unique embryonic characteristics of the mesenchymal cells that grow when provoked or stimulated by various conditions such as trauma, menarche, pregnancy, surgery or hormonal changes. They will never disappear and will remain throughout adult life and because of their origin, will continue to grow.

Extratruncular lesions present as diffuse infiltrating conditions that exert mechanical pressure on surrounding tissues and organs, including nerves and muscles (e.g., cystic hygroma). Such lesions usually form a closed system independent of normal lymph-conducting pathways without direct communication although they could co-exist with lymphoedema-causing truncular lesions.

Truncular LM lesions

By contrast, truncular lesions are the result of developmental arrest occurring at later stages of foetal development during the formation of the lymphatic trunks, vessels and nodes long after the reticular stages of vascular development have ceased.[35,36] These are termed post-truncal foetal lesions.

Truncular lesions, therefore, no longer have the evolutional power to grow or recur. They have lost the embryonic characteristics of mesenchymal cells and have no risk of recurrence, but have a significant lymphodynamic impact on the involved lymph-transport system.

Truncular lesions occur in various clinical conditions as the result of an incomplete development of the axial or truncal lymphatic vessels. Depending on the severity or extent of the abnormality occurring during the last maturation period of the lymphatic system, various conditions, such as aplasia, hypoplasia or hyperplasia of lymphatic vessels and/or lymph nodes, may result. These may be clinically manifest as obstruction or dilatation. When the endoluminal valves are absent or defective, reflux becomes the most important clinical manifestation.

Clinical evaluation—primary lymphoedema as LM

The evaluation of primary lymphoedema as one of the chronic lymphoedemas[4,5] should start with a differential diagnosis with secondary lymphoedema and its various causes — infection, surgery and radiation — and then proceed to its full evaluation as a truncular LM followed by its proper staging as chronic lymphoedema.[37,38]

Appropriate periodical clinical staging of the lymphoedema status is essential for the proper selection of the therapy regimen;[7,38] depending upon its stage, timely addition of supplemental therapy (e.g., surgical therapy) can be instituted to improve its management.[39,40] Detailed information on how to assess the clinical staging is well-documented elsewhere by many, including the International Society of Lymphology (ISL).[37]

The evaluation of primary lymphoedema as an LM should start with basic evaluation of the CVM as a whole and include consideration of the potential risk of other combined CVM lesions (e.g., Klippel—Trenaunay syndrome).[31,32] In such a circumstance, the evaluation of extratruncular LM should be included when the clinical findings alone cannot rule out its co-existence.

Clinical evaluation should proceed with complete clinical history, including family history and physical examination.

Based on this initial assessment, an appropriate combination of non-to-minimally invasive tests can be selected to confirm the clinical impression as explained in detail elsewhere.[1,2,5,12,18,41–44]

Usually, a combination of the lymphoscintigraphy (LSG) and Duplex ultrasonography will provide the basic information necessary to insure an adequate diagnosis and lead to the correct multidisciplinary treatment strategy for the primary lymphoedema by independent truncular LM alone. However, a few specific tests[41–44] can be added as options when more detailed information is mandated to rule in/out other CVMs involved together.

Radionuclide LSG[45,46] is the most essential test and remains the 'gold standard' for the evaluation of lymphatic function. Periodic appraisal of the LSG is preferred for adequate laboratory staging to supplement clinical staging necessary for better clinical management, in our experience. However, its cost/benefit value remains debatable.

Together with LSG, Duplex ultrasonography[43,47] for evaluation of venous function is indicated in every case of lymphoedema. This is because accurate assessment of venous function is essential to rule out accompanying abnormal venous conditions that often act as predisposing factors for the deterioration of the LM condition. One of the best examples of this is aplasia/hypoplasia of the iliofemoral venous system found in 4% of CVMs.[48]

Duplex ultrasonography is also able to provide more information in lymphoedematous limbs, such as location and evidence of fluid collections, node dilation/atresia and tissue alterations/echogenicity.

Magnetic resonance imaging[44] is not mandated for the primary lymphoedema as a routine but it is essential for the basic assessment of extratruncular LM involved; however, its intrinsic proprieties as a lymphatic vessel/node imaging include its ability to differentiate congenital abnormalities of lymphatic/organ/tissue in lymphoedematous patients, hence orientating towards LM.

Many other tests suggested for the evaluation of the CVMs remain as optional and may be added when indicated.[1,2,5,10,14] For example, segmental bio-impedance analysis has gained popularity and scientific validation in lymphoedema assessment in general and it could be added among diagnostic methods as an option.

Invasive tests are necessary on some occasions to provide more information for an accurate differential diagnosis. However, these tests should be considered as road-mapping for subsequent therapy.

Percutaneous lymphangiography using regular contrast material to the extratruncular LM lesion by a direct puncture technique is seldom needed to refine the extratruncular LM-related diagnosis and can be deferred until needed to verify the extent/severity of the lymphangioma lesion for subsequent therapy.

Conventional oil-contrast lymphangiography has been abandoned due to its potential risk of damage to the lymph vessels by the oil contrast agent. However, it is still useful when the benefit outweighs the risk in selected patients with chylous dysplasia and gravitational reflux disorders to better define the extension of the pathologic alterations and sites of lymphatic and chylous leakage. However, conventional lymphography using the patent blue dye is still popularly used by lymphatic surgeons as a road map to handle either truncular or extratruncular LM lesion safely.

Fine-needle aspiration biopsy with cytological examination should substitute excisional biopsy of regional lymph nodes that often aggravates the condition while providing limited information on the cause of lymphoedema.

Diagnosis should aim at proper clinical and laboratory staging[38] of the disease and should include periodical assessment of clinical and sub-clinical infections in the early and latent stages for effective prevention of various conditions such as tinea pedis. Diagnostic evaluation should include appropriate assessment of patient compliance since the outcome of successful management is largely dependent on this crucial factor.

Lymphoedema in children can be a part of the syndrome if there are other concomitant phenotypic abnormalities. However, diagnosis has to be made mainly on the basis of careful personal and family history and physical examination during the initial phase.

Further investigations may include appropriate genetic testing for the detection of specific hereditary syndromes with discrete gene mutation (e.g., FOXC2 for lymphoedema—distichiasis and vascular endothelial growth factor receptor (VEGFR)-3 for Milroy's disease).[49,50] Genetic testing combined with phenotypic descriptions may provide a better understanding of familial lymphangiodysplastic syndromes and other congenital/genetic—dysmorphogenic disorders, which can manifest as lymphoedema.

Clinical evaluation with periodical interval should include proper documentation of the staging of lymphoedema (e.g., ISL Stage 1 through III),[13,37] severity of oedema (volume) (mild — moderate — severe), proper description of the skin and subcutaneous tissue changes and functional assessment of the affected limb. A thorough assessment of the gathered information will be able to guide precise management decisions and selection of therapeutic options.

Clinical management—primary lymphoedema as LM

When truncular LM (primary lymphoedema) and extratruncular LM lesions co-exist, extratruncular LM lesions (i.e., lymphangiomas) should have a treatment priority. The extratruncular lesion often accelerates the deterioration of the truncular lesion by increasing the lymphatic burden to an already jeopardised lymphatic system. When the LM lesions co-exist with other CVMs, the treatment priority should generally be given to others such as VM or AVM if they are clinically significant 'major' lesions.[51,52]

The detailed information on the management of extratruncular LM will be referenced in other publications.[1,2,18]

A. Conservative (physical) therapy

Contemporary management of truncular LM aims to control its clinical manifestation as primary lymphoedema.

Complex decongestive therapy (CDT) is now the treatment of choice regardless of the condition/clinical stage. It consists of exercise/movement, manual lymphatic drainage (MLD) and compression (bandaging, garments) therapy, in

addition to basic skin care, education for risk reduction of infections and trauma.[53,54]

However, CDT is a strategy to control the oedema and does not result in 'cure'. CDT generally is effective only during the treatment programme period. To maintain long-term control often means continuous patient commitment and requires a lifetime pledge.

MLD is likely to decompress lymphatic congestion effectively by physiologic stimulation of a poorly functioning lymph transporting system through the opening of collateral lymph pathways. MLD-based CDT, with or without combination with sequential intermittent pneumatic compression (SIPC) therapy, is still most effective for the truncular LM lesions, whether alone or combined with extratruncular LM lesions.

SIPC using pumping devices is particularly useful in those cases that are treated by passive physical therapy (elderly, patients in bed, with serious disabilities, etc.) in whom spontaneous/isotonic physical exercise is not possible or is highly compromised.[55,56]

However, there is a significant concern regarding the possible negative side effects by pressotherapy, resulting in tissue fibrosis at the root of the limb by the stagnating proteins.

B. Surgical therapy—reconstructive surgery

The goal of reconstructive surgery for the primary lymphoedema is identical to that for the secondary lymphoedema, aiming at the repair of damaged lymph-transport system to restore the lymphatic function. There are several methods: lympho-venous or lympho-lymphatic bypass anastomosis, lympho-lymphatic segmental interposition and free lymph node transplantation.[57—60] They are more theoretically sound than CDT with a possible chance of 'cure' in early stage lymphoedema.

Nevertheless, the truncular LMs have an extremely variable number and condition of lymph vessels and lymph nodes as exemplified by the various forms of dysplasias, such as lymphangiodysplasia, lymphadenodysplasia and lymphangioadenodysplasia (Papendieck's classification).[61]

Candidates for reconstruction are, therefore, rare among the primary lymphoedemas due to the variable anatomy, although some have reported different findings.[62] Surgery outcomes are also variable, but generally not as successful as those of secondary lymphoedema patients that have surgically correctable lesions along the major lymphatics/collectors, in our experience.[4—6]

Furthermore, the surgical lymphatic reconstruction is generally time-consuming and requires dedication and expertise in the use of microsurgical techniques. This is especially true in primary lymphoedema caused by truncular LM due to its anatomical complexity.[61]

In the majority of the cases, CDT provides satisfactory results in the management of lymphoedema in its early stage. Lymphatic reconstruction is, therefore, selected only when CDT-based therapy fails to prevent the progress of lymphoedema and where there is clear risk of further damage to the lymphatic system. The recruitment of the ideal candidate for reconstructive surgery in the early stages of lymphoedema, while dysfunction is reversible, is of outmost importance due to the risk of losing critical numbers of lymph vessels available for surgical reconstruction.

Therefore, we consider reconstructive surgery as an adjunctive therapy to a CDT-oriented treatment regimen with specific indication (Table 2). Together with CDT, both methods are mutually complementary and remain useful.

However, there have been considerable doubts regarding CDT's real benefit due to limited scientific evidence and the lack of sound data, especially for long-term follow-up scientific studies; similarly, a lack of reproducibility of the outcomes presented by the very few teams mandates a well-balanced double-blind multicentre prospective study.

C. Surgical therapy—ablative/excisional surgery

Various methods introduced throughout the decades (e.g., Charles procedure) have been known for severe morbidity and poor long-term results. Recently, the original techniques were reintroduced aiming to reduce its morbidity (e.g., modified Auchincloss/Homans procedure).[63—66] Once the lymphoedema advances to an irreversible stage, it has a tendency to progress steadily despite aggressive CDT with or without complementary compression therapy.[39,67]

When chronic lymphoedema reaches the later/end stage (stage III and IV), most of the normal tissues become fibrosclerotic and present technical difficulties for efficient CDT application. Such a condition increases a tendency for recurrent local and/or systemic episodes of sepsis.[39]

An excisional surgery becomes a measure of last resort in such a case once the multidisciplinary team admits its failure to arrest progress towards the end stages with CDT and with evidence of steady deterioration despite maximum treatment (Table 2).

However, without adequate postoperative CDT, excisional surgery alone cannot maintain the initial success of surgery and will most probably fail in the long-term.[67]

Table 2 Contemporary Indications for the Surgical Treatment of Primary Lymphedema.

Indications for Reconstructive Surgery:
1) Failure to respond to proper care at earlier clinical stage (stage I or II[a]).
2) Progress of the disease to advanced stages such as from stage I to stage II or stage II to III despite proper treatment.
3) Chylous-reflux combined with extremity lymphedema.
Indications for ablative/excisional Surgery:
1) Failure to implement proper care at clinical stage III or IV[a] (end stage) with increasing technical difficulty to wrap the limb adequately.
2) Progress of the disease to the end stages in spite of maximum available treatment.
3) Increased frequency and/or severity of local and/or systemic episodes of sepsis.

[a] New staging method proposed by Lee & Bergan (Lymphology 38 (3):122-129, 2005).

Liposuction—circumferential suction-assisted Lipectomy

Liposuction is a newly proposed method to reduce the morbidity involved in the traditional excisional techniques; rather, liposuction was designed to obliterate the epifascial compartment by a selective removal of excessive adipose tissue alone, which developed by secondary lymphoedema of the upper limb, following the mastectomy.[68] However, its efficacy has not been proven for the primary lymphoedema, which has entirely different background as a truncular LM. But when the primary lymphoedema reaches the end stage with no risk of collateral damage to the viable lymph vessels by the suction, entire tissues become fibrosclerotic with a very limited amount of fat tissue available for the liposuction procedure to improve local swelling. Other than publications on the 'secondary' lymphoedema following radical mastectomy, this method lacks scientific merit with regard to the primary lymphoedema.

Prospect—primary lymphoedema as LM

During the past few decades, advanced technology has brought new information to the CVMs, especially in the genetic aspect of primary lymphoedema of LM origin.

Recently, basic investigations of the lymphatic circulation have led to identification of key molecular processes that promote normal vascular development and differentiation in this vital circulatory system. These developments have conducted further to the identification of critical endothelial markers that have advanced the study of human lymphatic disease.

Delineation of the genetic and molecular abnormalities of several primary, heritable lymphatic disorders, including VEGFR-3 for Milroy disease, FOXC2 for lymphoedema—distichiasis syndrome and SOX18 for lymphoedema-hypotrichosis, has provided a better understanding of familial lymphangiodysplastic syndromes and other congenital/genetic—dysmorphogenic disorders, which can manifest as primary lymphoedema.[49,50,69]

The appropriate identification of the gene defects to be corrected heralds a new era of gene therapy in lymphatic vascular diseases.[70,71]

Therapeutic implementation of gene modification during embryonic development and also to the abnormal function in adults will become the 'ultimate' dream/goal of gene therapy to correct the mechanisms of LM.

Summary

1. Primary lymphoedema can be considered to be 'congenital' since the majority is caused by congenital defects in the lymph transporting system including both the lymphatic channels and the nodes (e.g., aplasia, hypoplasia and hyperplasia). However, it remains to be proven that all lymphoedemas currently grouped as 'primary' are appropriately classified.
2. The majority of primary lymphoedemas represents a clinical manifestation of the truncular type of LM arising during the later stages of lymphangiogenesis. Contemporary classification, including embryological staging as one of the vascular malformations, is mandated for proper diagnosis and management of the primary lymphoedema as truncular LM in conjunction with other CVMs.
3. Subsequent to differential diagnosis with secondary lymphoedema, evaluation of primary lymphoedema should start as an LM. Basic non-invasive to minimally invasive tests will provide basic information necessary to insure an adequate diagnosis and lead to the correct multidisciplinary, specifically targeted and sequenced treatment strategy.
4. The mainstay of current management of the primary lymphoedema/truncular LM is CDT, and reconstructive/ablative surgical therapy remains an adjunctive therapy at best.

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