Dermatology Practical & Conceptual

A Practical Approach to the Diagnosis of Lymphedema: A Narrative Review

Lauren Banner[1], Alexa Cohen[1], Viral Patel[1], Neda Nikbakht[1]

1 Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Key words: Lymphedema, meige syndrome, diagnosis, lymphedema praecox

Citation: Banner L, Cohen A, Patel V, Nikbakht N. A Practical Approach to the Diagnosis of Lymphedema: A Narrative Review. *Dermatol Pract Concept*. 2023;13(3):e2023132. DOI: https://doi.org/10.5826/dpc.1303a132

Accepted: January 4, 2023; **Published:** July 2023

Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding author: Neda Nikbakht, MD, PhD, FAAD, Assistant Professor of Dermatology
Director, Cutaneous Lymphoma Clinic, Department of Dermatology and Cutaneous Biology
Thomas Jefferson University, 233 S. 10th Street, Rm 409, Philadelphia, PA 19107 E-mail: Neda.nikbakht@jefferson.edu

ABSTRACT

Introduction: Lymphedema often presents as progressive, unremitting swelling and skin changes that are extremely distressing to patients. Hereditary lymphedema (HL) constitutes a type of primary lymphedema that is passed down through generations.

Objectives: The primary aims of this narrative review are to illustrate a framework to distinguish lymphedema from other causes of swelling and to differentiate the hereditary lymphedemas from each other.

Results: A literature search was undertaken using relevant search terms. The articles were evaluated to generate a diagnostic algorithm to approach the swelling of an extremity using clinical and laboratory data. First, the stemmer sign should be evaluated. If it is negative, other causes should be considered. History and additional physical exam findings suggest either a primary or secondary cause of lymphedema.

Conclusions: The hereditary lymphedemas have been classified by age of onset and then stratified by clinical criteria and genetic testing.

Introduction

Lymphedema is a manifestation of lymphatic dysfunction presenting primarily as swelling of an extremity due to the accumulation of lymphatic fluid [1]. The diseased lymphatic system slows uptake and decreases flow of interstitial fluid resulting in buildup of lymphatic fluid [2]. As the disorder progresses, the skin thickens and hardens [1]. The often progressive and unremitting swelling and skin changes can be extremely distressing to patients. Primary lymphedema refers to processes that result from intrinsic damage to lymphatic structures [1]. Hereditary lymphedema (HL) constitutes a type of primary lymphedema that is passed down through generations [1]. One of the known etiologies of its pathogenesis is primarily driven by dysfunctions in the VEGFR-3 signaling axis, which is involved in lymphangiogenesis [2]. Secondary or acquired lymphedema indicates an underlying pathology that damages the lymphatic tissue [1]. While secondary lymphedema is more common, affecting 200 million people in the world, HL has an estimated prevalence of 0.001% [1].

HL has been classified in various ways since it appeared in the medical literature. Until recently, lymphedema present at birth was designated Milroy disease, and adolescent onset lymphedema was referred to as Meige Disease [3]. Given the reported heterogeneity of these syndromes and new advances in analyzing genetic data, subsequent articles characterized lymphedema by age of onset: congenital (before age 1 year), praecox (ages 2-35 years), and tarda (after 35 years) [1] and specific diseases were assigned to each of these groups. Lymphedema congenita and praecox can be either syndromic and non-syndromic [1]. Lymphedema tarda is thought to be triggered by prior infection or trauma [1]. It is also important to consider the complications of chronic lymphedema such as skin changes, infections, malignancies and psychological effects. Elephantiasis nostra verrucosa (ENV), for example, is a severe edematous skin change resulting from longstanding lymphedema [4,5]. This can negatively impact the quality of life of patients as the limb disfiguration is uncomfortable, functionally challenging, and cosmetically unpleasant. Additionally, both congenital and acquired lymphedema have been associated with benign vascular neoplasms such as spindle cell hemangioma (SCH) and malignant angiosarcoma [6-10]. Unfortunately, there is no curative treatment for primary lymphedema, only palliative strategies [11,12]. Lymphedema and its sequelae provide diagnostic challenges, as they are rare and have several challenging differential diagnoses.

Objectives

There is a clear need for a systematic diagnostic approach that considers the current classifications of lymphedema. While lymphedema tends to be a clinical diagnosis, awareness of genetic studies can provide additional information. We present a narrative review of HL with primary aims of illustrating a framework to distinguish lymphedema from other causes of swelling and to differentiate the hereditary lymphedemas from one another.

Methods

Literature Search

Relevant articles were included regardless of the date published. Using PubMed and the OMIM genetic library. English language was a criterion for inclusion. The primary interests were the genetic basis and clinical manifestations of HL. Specific reviews and cohort studies on the diagnostic workup were included if they provided useful additional evidence. The initial search was narrowed based on titles and abstracts given their relevance to research questions. Cited articles within these identified manuscripts were also considered.

Within the PubMed database (1935-2022), there were 4,465 manuscripts in the literature that pertained to the diagnosis of hereditary lymphedema. The initial search was narrowed to 1,089 results to focus on manuscripts published in the last five years. Articles were preliminarily omitted if the focus was on treatment, cancer, or post-operative lymphedema. Thirty-nine relevant articles and their references were initially identified and reviewed to generate the backbone for the diagnostic algorithm. We also searched for lymphedema praecox which yielded 66 results of which 14 relevant articles and their references were interrogated. In addition, the OMIM database was searched for the primary hereditary lymphedemas: Milroy or Milroy-like lymphedema, hereditary lymphedema 1B, Meige lymphedema, hereditary lymphedema type 1C, lymphedema-distichiasis syndrome, yellow nail syndrome, primary lymphedema with myelodysplasia or Emberger syndrome, hypotrichosis-lymphedema-telangiectasia syndrome which yielded 72 references. In total, 120 articles were considered in this work.

Results

Diagnostic Approach to Swelling of an Extremity

Ruling out Other Causes of Edema

Lymphedema is often misdiagnosed due to its mimicry of other conditions. A decision tool was developed by the authors to assist in diagnosing swelling in an extremity (Figure 1). Lymphedema is more likely in patients with a positive Stemmer sign, which is the inability to pinch the skin on the dorsum of the second toe [13]. A study on the Stemmer sign showed the sensitivity to be high at 92% and the

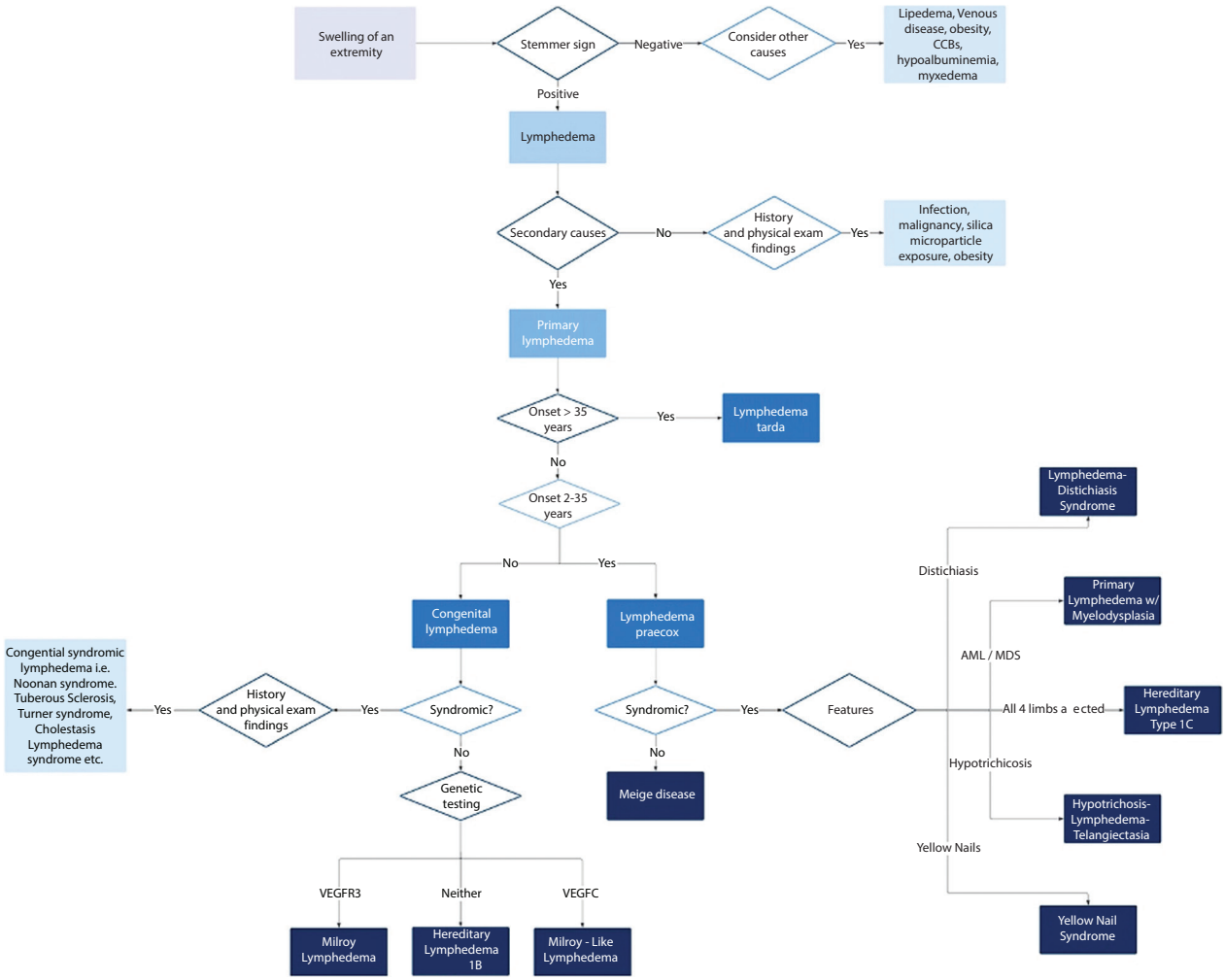

Figure 1. Approach to swelling of an extremity.

specificity to be moderate at 57% for accurately detecting lymphedema [13]. Other causes of edema such as lipedema, venous disease, hypoalbuminemia, myxedema, infection, and morbid obesity can also be ruled out with a thorough history including familial conditions and laboratory results such as CBC, albumin, and TSH [1,11]. A blood smear to detect microfilaria may have utility if the patient has traveled to an endemic area [11]. If there is no other obvious cause of extremity swelling and suspicion for lymphedema is high even with a negative Stemmer sign, lymphoscintigraphy may be considered, but it may have limited clinical utility [1,11,14]. Other diagnostic studies include magnetic resonance imaging, ultrasonography, and bioimpedance spectroscopy [11,14]. While bioimpedance spectroscopy is a non-invasive technique that has resulted in early detection of breast cancer related lymphedema, it is not widely available because it is considered investigational [11]. A recent study evaluated the diagnostic workup in diagnosing 49 adolescents with lymphedema praecox with clinical exam alone, doppler ultrasound, MRI, lymphoscintigraphy, and X-ray either alone or combined [14]. The diagnosis of lymphedema praecox did not change with additional imaging including lymphoscintigraphy [14]. However, an ultrasound of the swollen extremity may be recommended to rule out a deep vein thrombosis [14].

Categorization and Genetic Basis of Lymphedema

Once the diagnosis of lymphedema is established, the type of lymphedema should be determined. Secondary causes of lymphedema such as infection, malignancy, podoconiosis, and morbid obesity can be revealed via careful history and physical examination [1,11]. The hereditary lymphedemas can be categorized into age of onset: congenital (age < 2), praecox (ages 2-35), and tarda (age > 35) [1]. These divisions can be further subdivided. In congenital lymphedema, there are three non-syndromic types and a multitude of syndromes that are beyond the scope of this paper [1,2]. The three congenital non-syndromic lymphedema syndromes are Milroy lymphedema (HL1A), Milroy-like lymphedema (HL1D), and Hereditary lymphedema 1B (HL1B) [1]. Milroy lymphedema is caused by either a missense or inactivation mutation of vascular endothelial growth factor receptor 3 (VEGFR3) tyrosine kinase [15,16]. It may be inherited in an autosomal dominant (AD), autosomal recessive (AR), or

de novo fashion [15]. The onset of swelling is at birth, and the lymphedema is confined to the lower extremities, which contain wide caliber veins. Secondary changes include deep creases within toes, curved and brittle toenails, papillomatosis, chronic venous ulcers, hydrocele, and cellulitis [16]. HL1D has similar features to HL1A; however, the mutation is VEGF-C rather than VEGFR [17]. HL1B is clinically similar to HL1A and HL1D with a few key differences. The location of the associated gene has been narrowed to loci 6q16.2 – q22.1; however, a candidate gene FOXO3 was not implicated in the disease based on a 2008 study [18]. HL1B is distinct, progressing from the onset of lymphedema at birth to papillomas and itching in childhood and early adolescence, shrunken papillomas and scarring with keratinized hairless skin in adulthood, and finally, reduction in lymphedema in ages 40-45 [18]. These non-syndromic congenital lymphedemas are most definitively differentiated with genetic testing.

There are six currently identified conditions that constitute lymphedema praecox. Of the six, only Meige disease is non-syndromic. Hereditary lymphedema type IC (HLIC), lymphedema-distichiasis syndrome (LDS), yellow nail syndrome (YNS), primary lymphedema with myelodysplasia (Emberger syndrome), and hypotrichosis-lymphedema-telangiectasia syndrome are the five syndromes which can be differentiated by their distinct features [1]. The presence of edema in all four limbs suggests HLIC [19]; ptosis and secondary eyelash formation leading to corneal abrasions are seen in LDS [20,21]; and yellow nails and respiratory tract symptoms indicates YNS [22]. The triad of yellow nails, respiratory symptoms, and lymphedema is only present in 27-60% of patients, and the complete triad of YNS may not be present at once, increasing the diagnostic difficulty [22]. The color of the nails in YNS is yellow/green with increased curvature, onycholysis, shedding, cross-ridging, and loss of lunulae and cuticles [23]. The nails grow thicker but less rapid longitudinally [22]. This is distinct from the yellow discoloration seen in many lymphedema syndromes. As any form of lymphedema may have yellow nails as a nonspecific feature, the specific appearance of the yellow nails must be observed to definitively diagnose YNS [23]. Another lymphedema praecox syndrome is Hypotrichosis-lymphedema-telangiectasia syndrome (HLTS). It is associated with vascular malformations including aortic dilation, cutaneous telangiectasias, and defects in hair follicle development; however, lymphedema is not always present [24,25]. Finally, Emberger syndrome is the presence of myelodysplasia with or without congenital deafness in patients with lymphedema [26].

Non-syndromic Meige disease (Hereditary lymphedema type II), the most common form of primary lymphedema, was first written about in 1898 [27]. Subsequent reports of the disease defined it as pubertal onset lymphedema and remarked on the heterogeneity of the disease with features such as distichiasis, ptosis, and yellow nails [28]. In the last two decades, the lymphedema syndromes of pubertal onset have been separated by genetic and clinical features [1,12,23]. Meige disease classically presents with bilateral lower extremity lymphedema in the absence of other syndromic features [1,23]. Unilateral lymphedema may also occur [23]. Like all lymphedemas, Meige disease may be complicated by infections such as cellulitis or erysipelas [1]. The pathogenesis of the delayed onset has been proposed to be due to either a secondary infection or trauma, exposing the underlying lymphatic defect, or attributed to a hormonal effect, as symptoms predominately begin occurring in pubescent or pregnant females [29].

While genetic testing is not needed to distinguish the praecox syndromes, it may have a role in confirming the diagnosis or for research purposes. LDS is typically inherited in an AD or de novo manner with variable penetrance and is due to a loss of function (LOF) mutation in FOXC2 [20-22]. HL1C is an AD missense mutation in GJC2 [19]. HLTS is an AD or AR LOF mutation in SOX18 [24,25]. YNS is sporadically inherited; however, the mutation is unknown.[22] Emberger syndrome is either an AD or de novo LOF mutation in GATA2 [26,31].The gene FOXC2 has been ruled out as the cause of Meige disease [23].

While no gene has been explicitly determined as the cause of Meige disease, CELSR1 was proposed to be implicated in hereditary lymphedema [32-34]. A 2016 case report found that a rare early inactivating mutation in CELSR1 caused non-syndromic hereditary lymphedema in seven individuals spanning three consecutive generations [32]. Another study analyzed 95 probands for the CELSR1 gene [33].Ten patients had a loss of function mutation. Four patients had progressive or relapsing lymphedema with no other symptoms reported [33]. One patient's presentation was consistent with Noonan syndrome [33]. The remaining five had no phenotypic of lymphedema. In all but one case, the age of onset was prior to 35 years [33]. Based on the two studies, the inheritance pattern appears to be autosomal dominant with incomplete penetrance and variable expressivity [32, 33]. In the second study, five out of six females with the CELSR1 gene developed lymphedema, but only one out of four males developed lymphedema and did so later in life [33]. A third manuscript supported the female driven penetrance of the gene. All females with the variant had lymphedema, and all males with the variant served as carriers with none developing lymphedema [34]. This inheritance pattern is consistent with the higher predominance of lymphedema praecox in females [23]. Further studies are needed to provide a convincing link between this gene and Meige disease specifically.

Table 1. Pathogenesis, genetic basis, and clinical features of lymphedema [1,2, 15-30]

	Genetic basis	Key features	Category	Pathogenesis
Milroy Lymphedema (Hereditary Lymphedema Type 1A)	FLT4 (VEGFR3)	Non-syndromic	Congenital Lymphedema	Primary
Hereditary Lymphedema Type 1B	Unknown	Non-syndromic. Disease occurs in four stages		
Milroy-like Lymphedema (Hereditary Lymphedema Type 1D)	VEGFC	Non-syndromic		
Congenital lymphedema syndromes	Varies	Specific to syndrome		
Meige disease (Hereditary Lymphedema Type II)	Unknown	Non-syndromic	Lymphedema Praecox	
Lymphedema Distichiasis Syndrome	FOXC2	Ptosis, secondary eyelash formation and corneal abrasions		
Primary Lymphedema with Myelodysplasia (Emberger Syndrome)	GATA2	Myelodysplasia, congenital deafness may be present		
Hereditary Lymphedema Type 1C	GJC2	Lymphedema in 4 limbs		
Hypotrichosis-Lymphedema-Telangiectasia	SOX18	Vascular malformations including aortic dilation and cutaneous telangiectasias, hypotrichosis		
Yellow Nail Syndrome	Unknown	Triad of yellow/green nails, respiratory symptoms, and lymphedema		
Lymphedema Tarda	N/A			
Obesity	N/A		Secondary	
Infection	N/A			
Malignancy	N/A			
Microparticles	N/A			

N/A = Not applicable.

Conclusions

Overall, the ability to clearly define the clinical and molecular criteria for the hereditary lymphedemas furnishes both patients and physicians with a better understanding of the disease, which could ultimately influence therapeutic decision making.

References

1. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. *J Am Acad Dermatol*. 2017;77(6):1009-1020. DOI: 10.1016/j.jaad.2017.03.022. PMID: 29132848.
2. Brouillard P, Boon L, Vikkula M. Genetics of lymphatic anomalies. *J Clin Invest*. 2014;124(3):898-904. DOI: 10.1172/JCI71614. PMID: 24590274. PMCID: PMC3938256.
3. Figueroa AA, Pruzansky S, Rollnick BR. Meige disease (familial lymphedema praecox) and cleft palate: report of a family and review of the literature. *Cleft Palate J*. 1983;20(2):151-7. PMID: 6342849.
4. Duckworth AL, Husain J, Deheer P. Elephantiasis nostras verrucosa or "mossy foot lesions" in lymphedema praecox: report of a case. *J Am Podiatr Med Assoc*. 2008;98(1):66-69. DOI: 10.7547/0980066. PMID: 18202337.
5. Sisto K, Khachemoune A. Elephantiasis nostras verrucosa: a review. *Am J Clin Dermatol*. 2008;9(3):141-146. DOI: 10.2165/00128071-200809030-00001. PMID: 18429642.
6. Fletcher CD, Beham A, Schmid C. Spindle cell haemangioendothelioma: a clinicopathological and immunohistochemical study indicative of a non-neoplastic lesion. *Histopathology*. 1991;18(4):291-301. DOI: 10.1111/j.1365-2559.1991.tb00849.x. PMID: 2071088.
7. Farzaliyev F, Hamacher R, Steinau Professor HU, Bertram S, Podleska LE. Secondary angiosarcoma: A fatal complication of chronic lymphedema. *J Surg Oncol*. 2020;121(1):85-90. DOI: 10.1002/jso.25598. PMID: 31236970.
8. Janssens P, Dekeuleneer V, Van Damme A, et al. Angiosarcoma arising from congenital primary lymphedema. *Pediatr Dermatol*. 2018;35(6):e382-e388. DOI: 10.1111/pde.13664. PMID: 30216524.
9. Tronnier M, Vogelbruch M, Kutzner H. Spindle cell hemangioma and epithelioid hemangioendothelioma arising in an area of

lymphedema. *Am J Dermatopathol*. 2006;28(3):223-227. DOI: 10.1097/00000372-200606000-00010. PMID: 16778491.
10. Eltorky M, McC Chesney T, Sebes J, Hall JC. Spindle cell hemangioendothelioma. Report of three cases and review of the literature. *J Dermatol Surg Oncol*. 1994;20(3):196-202. DOI: 10.1111/j.1524-4725.1994.tb00466.x. PMID: 8151034.
11. Grada AA, Phillips TJ. Lymphedema: Diagnostic workup and management. *J Am Acad Dermatol*. 2017;77(6):995-1006. DOI: 10.1016/j.jaad.2017.03.021. PMID: 29132859
12. Connell FC, Gordon K, Brice G, et al. The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. *Clin Genet*. 2013;84(4): 303-314. DOI: 10.1111/cge.12173. PMID: 23621851.
13. Goss JA, Greene AK. Sensitivity and Specificity of the Stemmer Sign for Lymphedema: A Clinical Lymphoscintigraphic Study. *Plast Reconstr Surg Glob Open*. 2019;7(6):e2295. DOI: 10.1097/GOX.0000000000002295. PMID: 31624689. PMCID: PMC6635205.
14. Shah AA, Petrosyan M, Nizam W, Roberson J, Guzzetta P. Resource overutilization in the diagnosis of lymphedema praecox. *J Pediatr Surg*. 2020;55(7):1363-1365. DOI: 10.1016/j.jpedsurg.2019.09.014. PMID: 31706604.
15. Ghalamkarpour A, Morlot S, Raas-Rothschild A, et al. Hereditary lymphedema type I associated with VEGFR3 mutation: the first de novo case and atypical presentations. *Clin Genet*. 2006;70(4):330-335. DOI: 10.1111/j.1399-0004.2006.00687.x. PMID: 16965327.
16. Balboa-Beltran E, Fernández-Seara MJ, Pérez-Muñuzuri A, et al. A novel stop mutation in the vascular endothelial growth factor-C gene (VEGFC) results in Milroy-like disease. *J Med Genet*. 2014;51(7):475-478. DOI: 10.1136/jmedgenet-2013-102020. PMID: 24744435.
17. Gordon K, Schulte D, Brice G, et al. Mutation in vascular endothelial growth factor-C, a ligand for vascular endothelial growth factor receptor-3, is associated with autosomal dominant milroy-like primary lymphedema. *Circ Res*. 2013;112(6):956-960. DOI: 10.1161/CIRCRESAHA.113.300350. PMID: 23410910.
18. Malik S, Grzeschik KH. Congenital, low penetrance lymphedema of lower limbs maps to chromosome 6q16.2-q22.1 in an inbred Pakistani family. *Hum Genet*. 2008;123(2):197-205. DOI: 10.1007/s00439-007-0458-4. PMID: 18193458.
19. Ostergaard P, Simpson MA, Brice G, et al. Rapid identification of mutations in GJC2 in primary lymphoedema using whole exome sequencing combined with linkage analysis with delineation of the phenotype. *J Med Genet*. 2011;48(4):251-255. DOI: 10.1136/jmg.2010.085563. PMID: 21266381.
20. Zhu LL, Lv YN, Chen HD, Gao XH. A Chinese pedigree of lymphoedema-distichiasis syndrome with a novel mutation in the FOXC2 gene. *Clin Exp Dermatol*. 2014;39(6):731-733. DOI: 10.1111/ced.12389. PMID: 24984567.
21. Fang J, Dagenais SL, Erickson RP, et al. Mutations in FOXC2 (MFH-1), a forkhead family transcription factor, are responsible for the hereditary lymphedema-distichiasis syndrome. *Am J Hum Genet*. 2000 Dec;67(6):1382-1388. DOI: 10.1086/316915. PMID: 11078474. PMCID: PMC1287915.
22. Vignes S, Baran R. Yellow nail syndrome: a review. *Orphanet J Rare Dis*. 2017;12(1):42. DOI: 10.1186/s13023-017-0594-4. PMID: 28241848. PMCID: PMC5327582.
23. Rezaie T, Ghoroghchian R, Bell R, et al. Primary non-syndromic lymphoedema (Meige disease) is not caused by mutations in FOXC2. *Eur J Hum Genet*. 2008;16(3):300-304. DOI: 10.1038/sj.ejhg.5201982. PMID: 18197197.
24. Irrthum A, Devriendt K, Chitayat D, et al. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. *Am J Hum Genet*. 2003;72(6):1470-1478. DOI: 10.1086/375614. PMID: 12740761. PMCID: PMC1180307.
25. Wünnemann F, Kokta V, Leclerc S, et al. Aortic Dilatation Associated With a De Novo Mutation in the SOX18 Gene: Expanding the Clinical Spectrum of Hypotrichosis-Lymphedema-Telangiectasia Syndrome. *Can J Cardiol*. 2016;32(1):135.e1-135.e7. DOI: 10.1016/j.cjca.2015.04.004. PMID: 26148450.
26. Mansour S, Connell F, Steward C, et al. Emberger syndrome-primary lymphedema with myelodysplasia: report of seven new cases. *Am J Med Genet A*. 2010;152A(9):2287-2296. DOI: 10.1002/ajmg.a.33445. PMID: 20803646.
27. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 153200: 01/10/2019: available from https://www.omim.org/entry/153200?search=153200&highlight=153200
28. Wheeler ES, Chan V, Wassman R, Rimoin DL, Lesavoy MA. Familial lymphedema praecox: Meige's disease. *Plast Reconstr Surg*. 1981;67(3):362-364. DOI: 10.1097/00006534-198103000-00016. PMID: 7232571.
29. Kerchner K, Fleischer A, Yosipovitch G. Lower extremity lymphedema update: pathophysiology, diagnosis, and treatment guidelines. *J Am Acad Dermatol*. 2008;59(2):324-331. DOI: 10.1016/j.jaad.2008.04.013. PMID: 18513827.
30. Bell R, Brice G, Child AH, et al. Analysis of lymphoedema-distichiasis families for FOXC2 mutations reveals small insertions and deletions throughout the gene. *Hum Genet*. 2001;108(6): 546-551. DOI: 10.1007/s004390100528. PMID: 11499682.
31. Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). *Nat Genet*. 2011;43(10):929-931. DOI: 10.1038/ng.923. PMID: 21892158.
32. Gonzalez-Garay ML, Aldrich MB, Rasmussen JC, et al. A novel mutation in CELSR1 is associated with hereditary lymphedema. *Vasc Cell*. 2016;8:1. DOI: 10.1186/s13221-016-0035-5. PMID: 26855770. PMCID: PMC4743364.
33. Maltese PE, Michelini S, Ricci M, et al. Increasing evidence of hereditary lymphedema caused by CELSR1 loss-of-function variants. *Am J Med Genet A*. 2019;179(9):1718-1724. DOI: 10.1002/ajmg.a.61269. PMID: 31215153.
34. Erickson RP, Lai LW, Mustacich DJ, Bernas MJ, Kuo PH, Witte MH. Sex-limited penetrance of lymphedema to females with CELSR1 haploinsufficiency: A second family. *Clin Genet*. 2019;96(5):478-482. DOI: 10.1111/cge.13622. PMID: 31403174.