The Clinical Spectrum of Lymphatic Disease

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Lymphatic disease is quite prevalent, and often not well clinically characterized. Beyond lymphedema, there is a broad array of human disease that directly or indirectly alters lymphatic structure and function. The symptomatic and objective presentation of these patients can be quite diverse. In this review, we have attempted to provide a systematic overview of the subjective and objective spectrum of lymphatic disease, with consideration of all of the categories of disease that primarily or secondarily impair the functional integrity of the lymphatic system. Lymphedema is discussed, along with chromosomal disorders, lymphangioma, infectious diseases, lymphangioleiomyomatosis, lipedema, heritable genetic disorders, complex vascular malformations, protein-losing enteropathy, and intestinal lymphangiectasia.

Key words: **chromosomal disorders; lymphangioma; lymphangioleiomyomatosis; protein-losing enteropathy (PLE)**

Introduction

Given the central role of the lymphatic system in circulatory, metabolic, and immune-related homeostasis, it is not surprising that genetic, developmental, and acquired disorders of this system manifest through a broad array of predictable sequelae. The lymphatic-specific manifestations range from blunted immune responses[1] and impaired metabolic status[2] to the appearance of the debilitating and disfiguring form of regional swelling generally termed *lymphedema*.[3]

Lymphatic disease is quite prevalent, and often not well clinically characterized.[3,4] Acquired disease of the lymphatics most often takes the form of lymphatic circulatory disruption, typically resulting from trauma, infection, neoplasia, or from iatrogenic causes.[3,5] When regional lymphatic flow is insufficient to maintain tissue homeostasis, interstitial fluid accumulates and swelling ensues.

Beyond lymphedema, there is a broad array of human disease that directly or indirectly alters lymphatic structure and function. Not surprisingly, the symptomatic (TABLE 1) and objective (TABLE 2) presentation of these patients can be quite diverse. Diagnosis and differential diagnosis poses distinct challenges. In this review, we have attempted to provide a systematic overview of the categories of disease that primarily or secondarily impair the functional integrity of the lymphatic system.

Lymphedema

Heritable congenital lymphedema of the lower extremities was first described by Nonne in 1891.[6] In 1892, Milroy[7] described the familial distribution of congenital lymphedema, noting the involvement of 26 persons in a single family, spanning six generations.[8] **Nonne–Milroy's lymphedema** is characterized by unilateral or bilateral swelling of the legs, arms, and/or face with gradual and irreversible fibrotic changes. Additional, distinct variants of heritable lymphedema have subsequently been described. In 1898, Meige reported cases of lymphedema in which the age of onset was after puberty, and which often appeared alongside acute cellulitis.[8] In 1964 another variety of pubertal-onset lymphedema[9] was reported, in which the affected individuals had distichiasis (i.e., an auxiliary set of eyelashes).[10] Patients with the Nonne–Milroy's syndrome, **Meige's syndrome**, and the **lymphedema–distichiasis syndrome** typically present with pitting edema that is commonly limited to the legs. Although autosomal dominant transmission characterizes heritable lymphedema, the molecular mechanism and the pathogenesis differ among the various entities identified.

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TABLE 1. Symptomatic correlates of lymphatic disease

Symptom	Lymphatic disease
Edema	Gorham's disease
	Hennekam's syndrome
	Intestinal lymphangiectasia
	Klinefelter's syndrome
	Klippel–Trenaunay syndrome
	Lymphedema–distichiasis
	Lymphedema–hypoparathyroidism
	Meige's disease (lymphedema tarda)
	Milroy's disease
	Neurofibromatosis
	Protein-losing enteropathy
	Stewart–Treves syndrome
	Triploidy syndrome
	Turner's syndrome
	Yellow nail syndrome
Decreased appetite	Noonan syndrome
Recurrent vomiting	Noonan syndrome
	Intestinal lymphangiectasia
Difficulty swallowing	Noonan syndrome
Joint pain	Blue rubber bleb nevus syndrome
	Noonan syndrome
Muscle pain	Noonan syndrome
Skin lesions	Blue rubber bleb nevus syndrome
	Maffucci syndrome
	Neurofibromatosis
Back pain	Neurofibromatosis
Diarrhea	Intestinal lymphangiectasia
	Protein-losing enteropathy
Weight loss	Protein-losing enteropathy
Abdominal pain	Protein-losing enteropathy
Infertility	Turner's syndrome
Jaundice	Aagenaes' syndrome
Severe itching	Aagenaes' syndrome
Dry eyes	Turner's syndrome
Absent menstruation	Turner's syndrome
Discoloration of urine	Filariasis
Wheezing	Lymphangioleiomyomatosis
	Lymphangiomatosis
	Pulmonary lymphangiectasia
Dyspnea	Intestinal lymphangiectasia
	Lymphangioleiomyomatosis
Nausea	Lymphangioleiomyomatosis
	Pulmonary lymphangiectasia
Hemoptysis	Lymphangioleiomyomatosis
Increased appetite	Prader–Willi syndrome
Fever	Filariasis
Bloating	Lymphangioleiomyomatosis
Abdominal distension	Lymphangioleiomyomatosis
Sputum production	Lymphangioleiomyomatosis
Chest pain	Lymphangioleiomyomatosis
Noisy respiration	Lymphangioleiomyomatosis
One or more bone fractures	Cystic angiomatosis

TABLE 2. Objective correlates of lymphatic disease

Objective correlate	Lymphatic disease
Facial abnormalities	Hennekam's syndrome
	Noonan syndrome
	Triploidy syndrome
Webbing of the neck	Noonan syndrome
Heart murmur	Noonan syndrome
Mental retardation	Hennekam's syndrome
	Noonan syndrome
Distichiasis	Lymphedema distichiasis
Ascites	Protein-losing enteropathy
"Shield chest"	Turner's syndrome
Short stature	Edwards' syndrome
	Intestinal lymphangiectasia
	Maffucci's syndrome
	Turner's syndrome
Absent/incomplete puberty	Klinefelter's syndrome
	Turner's syndrome
Delayed puberty	Hennekam's syndrome
Gynecomastia	Klinefelter's syndrome
Holoprosencephaly	Edwards' syndrome
	Patau syndrome
Hypotelorism	Patau syndrome
	Triploidy syndrome
Microphthalmia	Patau syndrome
	Triploidy syndrome
Anophthalmia	Patau syndrome
Rocker-bottom feet	Patau syndrome
Cutis aplasia	Patau syndrome
Omphalocele	Patau syndrome
Apneic episodes	Edwards' syndrome
Microcephaly	Edwards' syndrome
Muscular hypotonia	Triploidy syndrome
Low-set ears	Triploidy syndrome
Yellow nails	Yellow nail syndrome
Enlarged liver	Aagenaes' syndrome
Hypotonia	Prader–Willi syndrome
Hypomentia	Prader–Willi syndrome
Hypogonadism	Prader–Willi syndrome
Obesity	Prader–Willi syndrome
Râles	Lymphangioleiomyomatosis
	Pulmonary lymphangiectasia
Enlarged lymph nodes	Lymphangioleiomyomatosis
Unequal arm/leg	Maffucci's syndrome
Bone deformities	Maffucci's syndrome
Hematemesis	Blue rubber bleb nevus syndrome
Melena	Blue rubber bleb nevus syndrome
Rectal bleeding	Blue rubber bleb nevus syndrome
Vesicles	Lymphangioma circumscriptum
Hydrops fetalis	Cystic hygroma
Hernias	Patau syndrome

In numerous families afflicted with Nonne–Milroy's lymphedema, the disorder has been linked to a mutation in flt4, the gene that encodes the vascular endothelial growth factor receptor 3 (VEGFR-3).[11] Insufficient tyrosine kinase signaling by VEGFR-3 leads to the faulty development of aplastic or hypoplastic peripheral lymphatic channels.[11]

Mutations leading to haploinsufficiency of the nuclear transcription factor, FOXC2, have been implicated in the pathogenesis of lymphedema–distichiasis.[12] More recently, the molecular defect has been linked to abnormal morphogenesis of the lymphatic valve apparatus,[13] which helps to explain the clinical pattern of lymph reflux that is observed in these patients. Valve defects and abnormal pericyte/lymphatic endothelial cell interactions characterize the FOXC2 defect of lymphedema–distichiasis.

Chromosomal Disorders

Chromosomal disorders can lead to the birth of viable individuals with multiple organic defects (TABLE 3). These disorders are uncommon; hence the chromosomal basis can be readily overlooked or misdiagnosed. Confirmatory identification can be achieved only through detailed cytogenetic studies. Many of these disorders severely distort lymphatic function. **Turner's syndrome** and **Klinefelter's syndrome** are linked to the sex chromosomes, while **Edwards' syndrome** and **Patau syndrome** are linked to autosomal chromosomes. **Triploidy syndrome** denotes the presence of an extra copy of all the chromosomes.

Turner's syndrome, first described in 1938,[14] is the most common sex-linked chromosomal aberration in females.[15] The patients described by Turner were later identified as having either a partial or complete absence of one X-chromosome. More recently, the classification for Turner's syndrome has been broadened to include patients who display mosaicism, or possess chromosomal complements, such as 45.X/46,XX.[16] Patients with Turner's syndrome are short in stature and typically present with amenorrhea.[17] This syndrome is typically associated with gonadal dysgenesis, leading to drastically reduced levels of the female sex hormones.[16] Neonates with Turner's syndrome often display congenital lymphedema of the hands and feet.[18] As a consequence of the sex chromosome loss, these patients are at high risk for a variety of disorders, including diabetes, hypothyroidism, osteoporosis, and congenital heart disease.[16] Exogenous administration of estrogens and related derivatives has been proposed as potential therapy. Administration of growth hormone increases final height in females with Turner's syndrome but, paradoxically, growth hormone in conjunction with low-dose estrogen therapy decreases the final height in these patients.[19]

Klinefelter's syndrome, first described in 1942,[20] is a disease of males, with an observed frequency of approximately 1:600.[21] It is caused by the presence of more than one X and/or Y chromosome.[22] The syndrome is characterized by hypogonadism that presents with extremely variable phenotypes. The only common symptom is infertility.[22] The genotypes are variable, including 47,XXY, 48,XXYY, 48,XXXY, 49,XXXYY, and 49,XXXXY. Clinical characteristics include small testes, azoospermia, tall stature, and gynecomastia. These findings can be reconciled by the hormonal findings, namely, low testosterone levels, and absent feedback inhibition from testosterone, leading to an abundance of circulating FSH, LH, and estradiol levels.[22] In situations where cognitive facilities are affected, androgen therapy has shown promising results in promoting language development and learning abilities, and a more normal adolescent development.[22]

Triploidy syndrome is estimated to occur in 15–20% of spontaneous abortions due to chromosomal abnormalities. Triploidy can result from an extra set of maternal or paternal chromosomes, as well as from double fertilization.[23] The few live births with this syndrome have a short life span, averaging 20 hours,[24] although survival up to 10.5 months has been reported.[25] In most cases an enlarged placenta results, along with an edematous fetus, dysplastic cranial bones, ocular defects, and abnormalities in limbs, male genitalia, and various internal organs.[26]

Edwards' syndrome, also known as trisomy 18, was first described in 1960.[27] After trisomy 21, it is the second most common autosomal trisomy, with a prevalence of 1 in 6000–8000 live births. Patients' anomalies include cranial abnormalities, webbing of the neck, malformed ears, and mental retardation.[27] Only 5–10% of children survive for more than a year because feeding difficulties, cardiac and renal malformations, and other defects. The clinical presentations of **Edwards'** and **Patau syndrome** may appear similar to physicians who do not frequently encounter these syndromes. Patau syndrome, or **trisomy 13**, is rare and the most lethal of the viable trisomies.[28] The median survival for newborns is less than 3 days. Though clinical features of patients vary, mental deficiency is a consistent marker of the disease.[28] Holoprosencephaly is also associated with Patau syndrome, which disrupts mid face development.[28] Cardiac abnormalities can be present[29] and cardiopulmonary arrest is a major cause of death.

TABLE 3. Chromosomal disorders

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Turner's syndrome	Short stature; swollen hands/feet at birth	Ovarian failure; hypoplastic or hyperconvex nails; underdeveloped breasts and genitalia; webbed neck; short stature, low hairline in back; simian crease (a single crease in the palm); and abnormal bone development of the chest	Elevated liver enzymes	X-linked dominant inheritance	Absence of one set of genes from the short arm of one X chromosome	Hydronephrosis; pyelonephritis; idiopathic hypertension; diabetes; osteoporosis; congenital lymphedema; webbed neck; nail dysplasia; high palate; short fourth metacarpal; hearing loss; hypothyroidism; liver function abnormalities	Karyotype (only one X)	Noonan
	Webbed neck; drooping eyelids; "shield-shaped" broad, flat chest; absent or incomplete development at puberty, including sparse pubic hair and small breasts; infertility						Ultrasound (kidney)	
	Dry eyes						Echo/MRI; audiology	
	Absent menstruation; absent normal moisture in vagina; painful intercourse							

TABLE 3. *Continued*

TABLE 3. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Klinefelter's syndrome (addition of more than 1 extra X and/or Y chromosome)	Infertility; gynecomastia (development of breasts in males)	Lack of secondary sexual characteristics; lack of facial/body/sexual hair; high-pitched voice; female type of fat distribution; testicular dysgenesis	Cytogenetic studies		Small, firm testes with seminiferous tubular hyalinization; sclerosis; degenerated Leydig cells; histology of gynecomastic breasts; hyperplasia of interductal tissue	Mitral valve prolapse	ECG to detect mitral valve prolapse	
			Hormone testing: high plasma FSH, LH, estradiol levels, low plasma testosterone			Varicose veins	Radiographs to detect lower bone mineral density, radioulnar synotosis, taurodontism	
			Increase in testosterone in response to hCG					
			Increased urinary gonadotropins (abnormal Leydig cell function)					
			Serum osteocalcin levels decreased; hydroxyl-proline/creatinine ratio increased (increased resorption, decreased deposition)					

Continued

TABLE 3. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Patau syndrome	Scalp defects	Holoprosencephaly (brain does not divide completely into halves)	Cytogenetics			Cardiac defects		
Trisomy chromosome 13	Cleft lip/palate	Hypotelorism	Prenatally FISH on interphase cells			Patent ductus arteriosus		
	Facial defects (absent or malformed nose)	Microphthalmia				Ventricular septal defect		
	Hernias	Anophthalmia				Atrial septal defect		
		Rocker-bottom feet				Dextrocardia		
		Microphthalmia cutis aplasia				Capillary hemangiomata		
		Omphalocele				Polycystic kidneys/other renal malformations		
Edwards' syndrome (trisomy 18)	Stop breathing; poor feeding	Apneic episodes, marked failure to thrive; severe growth retardation, mental retardation; malformations (e.g., microcephaly, cerebellar hypoplasia, hypoplasia/aplasia of corpus callosum, holoprosencephaly)	Conventional cytogenetic studies			Cardiac ventricular septal defects with poly-valvular heart disease	ECG for cardiac defects	Arthrogryposis

TABLE 3. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
						Atrial septal defects; patent ductus arteriosus; overriding aorta; hypoplastic left heart syndrome; tetralogy of Fallot; transposition of great arteries Pulmonary hypoplasia; abnormal lobation of lung Thyroid hypoplasia		
Triploidy syndrome		General dysmaturity; muscular hypotonia; large posterior fontanel; hypertelorism; microphthalmia; colobomata; cutaneous syndactaly Abnormalities of the skull, face, limbs, genitalia (male karyotype), various internal organs Fetal hypoplasia, microstomia, low-set ears			Triploid cell lines may have disappeared from peripheral blood so evidence of triploidy can only be found in the cultured skin fibroblasts			

Lymphangioma

Lymphangioma (TABLE 4) is a congenital lymphatic malformation that arises during embryologic development. Lymphangiomata may arise from segments of lymphatic vascular tissue that either fail appropriately anastomose, or may represent portions of lymph sacs that become grouped together during development.[30] Lymphangiomas are normally detected within the first 2 years of life.[30] The presence of multiple or widespread lymphatic vascular malformations of this type can be termed **lymphangiomatosis**. MRI is the most useful diagnostic approach, since it permits analysis of the lymphatic system within various tissue layers.[30] Surgical excision is the commonly employed therapeutic approach. The lesions are classified by size and depth of formation, with the smaller, superficial form designated as **lymphangioma circumscriptum,** while the deeper lesions are divided into **cavernous lymphangiomas** and **cystic hygromas.**

Lymphangioma circumscriptum is characterized by the presence of numerous superficial vesicles that are approximately 1–2 mm in diameter and often filled with clear fluid.[31] Subcutaneous lymphatic sacs are connected via dilated lymphatic channels to these thin-walled vesicles, without connections to the normal lymphatic system.[32] The defining presentation of lymphangioma circumscriptum is the oozing of colorless fluid.[31]

Cavernous lymphangiomas are large, loosely defined masses of soft tissue with lymphatic dilation in the dermis, subcutaneous tissue, and intermuscular septa.[30] The overlying skin generally remains uninvolved, although skin changes, such as hyperplasia and hyperpigmentation, may occur.

Cystic hygromas, which are fluid-filled lesions, are caused by the failure of jugular lymphatic sacs to connect to and to drain into the jugular veins, thereby leading to the stagnation of lymphatic fluid. These sacs then enlarge, and the fluid they contain fills lymphatic vessels and connective tissues, forming the definitive lesion. They are similar to cavernous lymphangiomas, although the hygromas are often encased within a fibrous capsule.[30] They commonly occur near lymphatico–venous junctions, and force fluid to accumulate in dilated lymphatics, leading to progressive lymphedema.[33] Cystic hygromas are commonly associated with other conditions, including Turner's syndrome, Klinefelter's syndrome, and various trisomies.[30] Surgical excision is only employed for superficial lesions. Cystic hygromas that are more deeply rooted require nonsurgical treatments, including intralesional injection of sclerosing agents, such as bleomycin[34] and OK-432,[35] both of which can induce regression of the hygromas.

Infectious Diseases

Lymphatic dysfunction can arise as a consequence of invading pathogens. Lymphatic filariasis and lymphangitis (TABLE 5) are two such conditions, initiated by organisms that infiltrate and infect the lymphatic system, inhibiting lymph flow and impairing normal immune function.

Globally, more than 129 million patients are afflicted by filariasis. This condition, frequently disfiguring and disabling, is characterized by markedly impaired lymphatic function and lymphangiectasia. The prevalence of lymphatic filariasis lags behind only malaria and tuberculosis in the magnitude of its impact on the global burden of disease.[36] Patients are infected by filariae, or parasitic worms, which take up residence in the lymphatic structures. The offspring of filariae circulate in blood.[36] The resulting compromised lymphatics mediate adenolymphangitis, which results in fibrosis and stenosis of the lymph nodes and limits the formation of new lymph channels. While the common clinical presentations often include hydrocele, lymphedema, and tropical pulmonary eosinophilia, infected patients can remain asymptomatic.[37] Diagnosis hinges upon detection of microfilariae in the blood and localization of obstructing lesions in the lymphatics using a combination of ultrasound and Doppler.[36] Traditionally, treatment has centered around antiparasitic medications, including diethylcarbamazine, albendazole, and ivermectin.[38,39] Newer approaches include antifilarial chemotherapy, along with antibiotics such as tetracyclines.[40]

Lymphangitis is caused by the inflammation of lymphatic channels through tissue infection. Pathogenic organisms include bacteria, fungi, viruses, and protozoa.[41] Patients present with fever, chills, muscular pain, and headache.[42] The distinguishing characteristic of this condition is the presence of erythematous, irregular cutaneous streaks in the affected part of the body. The lymph nodes can be enlarged and tender.[41] Patients generally have a history of trauma, often minor, or skin infection.[43] The treatment approach mandates the utilization of appropriate antimicrobials.[41]

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is characterized by the spread of abnormal smooth muscle cells (LAM

TABLE 4. Lymphangioma

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Diagnostic methods	Differential diagnosis
Lymphangioma (uncommon, hamartomatous, congenital malformations of lymphatic system that involve skin and subcutaneous tissues); superficial vesicles			Factor VIII-related antigen is present in hemangiomas but negative or weakly positive in lymphangiomas		Vesicles represent dilated lymph channels that cause the dermis to expand. The lumen is filled with lymphatic fluid and often contains red blood cells, lymphocytes, macrophages, neutrophils; lined by flat endothelial cells	MRI biopsy	Dabska's low-grade angiosarcoma; dermatitis herpetiformis; herpes simplex; herpes zoster; lipomas; lymphangiectasia; malignant melanoma; metastatic carcinoma of the skin; neurofibromatosis; Stewart Treves syndrome
Lymphangioma circumscriptum (more deep-seated)	Verrucous changes; clear	Persistent, multiple clusters of translucent vesicles that contain clear lymph fluid					
Cavernous lymphangioma	Solitary rubbery nodule with no skin changes	Superficial saccular dilations from underlying lymphatic vessels that occupy papilla and push upward against the overlying epidermis			Large, irregular channels in reticular dermis, lined by single layer of endothelial cells		

TABLE 5. Infectious diseases

Disease condition	Symptoms	Signs	Laboratory findings	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Lymphatic filariasis	Fever; inguinal or axillary lymphadenopathy; testicular and/or inguinal pain; skin exfoliation; and limb or genital edema; cloudy, milk-like urine	Episodic attacks of fever associated with inflammation of the inguinal lymph nodes, testis, spermatic cord, lymphedema, or a combination of these; abscess formation at nodes; cellular invasion with plasma cells/eosinophils/macrophages with hyperplasia of lymphatic endothelium; lymphatic damage and chronic leakage of protein-rich lymph in the tissues; thickening of skin and chronic infections contribute to the appearance of elephantiasis	Detection of microfilariae in blood	Fibrosis of affected lymph nodes; stenosis of lymphatics with limited collateral channel formation; cutaneous changes: hyperkeratosis, acanthosis, lymph and fatty tissue, loss of elastin fibers, and fibrosis	Bacterial/fungal lymphadenitis; relapsing cellulitis	Chest radiograph Ultrasound (lymphatic obstruction of inguinal and scrotal lymphatics) Lymph node or skin nodule biopsy	Angioedema; asthma; Hodgkin's disease; hydrocele; leprosy; lymphedema; lymphoma (non-Hodgkin's); Milroy's disease, scrotal/testicular trauma
Lymphangitis	Erythematous cutaneous streaks; fever, chills, malaise; headache; anorexia; myalgia; recent skin trauma	Erythematous and irregular linear streaks extend from primary infection site toward draining regional nodes; tenderness and heat; blistering of skin; lymph nodes swollen and tender; children may be febrile/tachycardic	CBC (marked leukocytosis) and blood culture (leading-edge culture or aspiration of pus)				Contact dermatitis

cells) through both the pulmonary interstitium and the axial lymphatics, leading to the cystic destruction of the lung along with lymphatic wall thickening[44] (TABLE 6). LAM is also characterized by the presence of pulmonary cysts and angiomyolipomas, tumors comprised of LAM cells, adipose tissue, and underdeveloped blood vessels.[45] LAM is an extremely rare disease, found in fewer than 1 in a million individuals. It affects mainly women of childbearing age.[46] The chief symptoms and clinical presentations associated with LAM are pulmonary, including pneumothorax, progressive dyspnea, chylous pleural effusions, cough, hemoptysis, and chyloptysis.[44] Non-pulmonary findings include lymphangioleiomyomas, the large cystic masses commonly found in the abdominal and retroperitoneal regions, and chylous ascites. The pulmonary cysts can be detected through high-resolution chest tomography. The key diagnostic tool is tissue biopsy of either the lungs or lymphatics with immunohistochemical staining for the antigen HMB45.[47] The target of this antigen is the melanoma-related glycoprotein 100, which is specific for LAM cells. Treatment is often focused on preventing or minimizing pneumothorax through pleurodesis and pleurectomy.[48] Additionally, embolization of angiomyolipomas is performed if necessary. Because LAM presents in young females and is found to be heightened in the presence of increased estrogen, it was believed that progesterone would have therapeutic effects. However, it has been shown that progesterone can only slow the progression of the disease, while also producing numerous negative side effects.[49,50] Current research is focused on determining whether rapamycin may be helpful in treating angiomyolipomas.[44]

Lipedema

Lipedema (TABLE 7) was first described by Allen and Hines[51] in 1940 as a bilateral, gradual accumulation of fatty deposition in the lower extremities and buttocks.[52] The body habitus superficially resembles that of bilateral lower extremity lymphedema, although the involvement of the two limbs is substantially more symmetrical than in lymphedema, and there is almost always sparing of the feet. The condition is found almost exclusively in females. Affected individuals often describe a family history of large legs.[53] Lipedema is further characterized by the presence of normal cutaneous architecture, lacking the fibrotic changes often seen in lymphedema.[54] Malleolar fat pads in lipedema patients are prominent, while they are normal in lymphedema patients. Furthermore, the edema is characteristically non-pitting.[53] Patients often complain of severe pain in, or aching of, the lower extremities, often below the knees.[53] Histologic sampling reveals edematous adipose cells that are sometimes hyperplastic.[55] The chief diagnostic finding that distinguishes lipedema from lymphedema is the presence of normal dynamic lymphatic function by lymphoscintigraphy.[53] However, the microlymphatic function can become distorted in lipedema, and a component of secondary lymphedema often supervenes. The usual elements of complex decongestive physiotherapy, which have an ameliorating effect upon lymphedema, add little value for patients with lipedema.[56] Suction lipectomy is a promising treatment that has been demonstrated to significantly reduce the size of extremities.[56]

Heritable Disorders

There is an array of syndromic heritable disorders that are associated with dysfunction of the lymphatic system (TABLE 8). Often, these syndromes are also associated with abnormal facial and mental development. Because these disorders are rare, insights into the expression of disease are often limited or incomplete. A useful organizational schema is to classify the disorders by their autosomal recessive (**Hennekam's syndrome**, the **Prader–Willi syndrome**, and **Aagenaes' syndrome**) or autosomal dominant (**Noonan syndrome**, **Adams–Oliver syndrome**, and **neurofibromatosis**) modes of genetic transmission.

Autosomal Recessive

Hennekam's syndrome was first described in 1989 following the study of an inbred family from a small fishing town in the Netherlands. The condition is characterized by lymphangiectasia, severe lymphedema, facial abnormalities, and mental retardation.[57] Since the original description of the syndrome, only 24 patients have been diagnosed with this condition; nevertheless, since these descriptions span 11 widely separated countries, the genetic anomaly is believed to be diffuse.[58] The facial disfiguration representative of this syndrome includes a flat face and nasal bridge, small mouth, ear defects, and widely spaced eyes.[57] Gabrielli *et al.* have proposed that these facial anomalies may be the consequence of jugular lymphatic obstruction.[59] Such lymphatic obstruction would result in facial lymphedema with resultant cutaneous overdistention, and facial distortion. Others have theorized that the associated intestinal lymphangiectasia might promote protein loss, thereby causing peripheral edema, ascites, and the loss of lymphocytes and vitamins,[58] all of which are seen in patients with

TABLE 6. Lymphangioleiomyomatosis and lymphangiomatosis

Disease condition	Symptoms	Signs	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Lymphangioleiomyomatosis	Dyspnea; hemoptysis; chyloptysis; nausea, bloating, abdominal distension: cough; sputum production; wheezing; chest pain gurgling in the chest	Râles; pneumothorax; chylothorax; chylous pleural effusions; lymphadenopathy	Sporadic		Renal hamartomas; lymphedema; chylopericardium; cystic soft tissue masses; uterine fibroids; pulmonary hemorrhage; hemosiderosis	Biopsy: Open Lung Transbronchial + HMB45 staining (LAM cells) Tissue biopsy of involved lymphatics Other: High-resolution computerized tomography (HRCT) of thorax/abdomen Pulmonary function test (airflow obstructions, impaired gas transfer) Chest radiograph	Asthma; spontaneous pneumothorax; emphysema; tuberous sclerosis; interstitial pulmonary fibrosis; pulmonary lymphangiectasia; bronchiolitis; leiomyosarcoma
Lymphangiomatosis	Presents in late childhood; can occur in any tissue in which lymphatics are normally found; predilection for thoracic and neck involvement; wheezes (misdiagnosed as asthma)			Multiple lymphangiomas (well-differentiated lymphatic tissue that present as multicystic or sponge-like accumulations; benign proliferations of the lymphatic channels with abnormal connections to the lymphatic system); anastomosing endothelial lined spaces along pulmonary lymphatic routes accompanied by asymmetrically spaced bundles of spindle cells	Pericardial or pleural effusions; chylous effusions; chyloptysis; hemoptysis; chylopericardium; chylous ascites; protein-wasting enteropathy; peripheral lymphedema hemihypertrophy; lymphopenia; disseminated intravascular coagulopathy; coexistence of lytic bone lesions and chylothorax	Bone biopsy lymphangiography chest radiograph CT imaging MRI	Asthma

asymmetrically spaced bundles of spindle cells

coagulopathy; coexistence of lytic bone lesions and chylothorax

TABLE 7. Lipedema

Disease condition	Symptoms	Signs	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Lipedema	Insidious onset in adolescence with progression; lower extremity edema with foot sparing; peau d'orange; easy bruising; pain; varicose veins; weight gain	Non-pitting edema; absent Stemmer's sign	Sporadic	Fibro-sclerosis; damage to the deep venous system	Cellulitis; degenerative arthrosis	Lymphoscintigraphy normal	Lymphedema; obesity; elephantiasis; myxedema

this syndrome. Interestingly, differences in presentation and symptoms are vast, suggesting differential expressivity of a single gene.[58]

The **Prader–Willi syndrome** shares with Hennekam's syndrome the attributes of facial anomaly and mental retardation. Patients generally also manifest neonatal hypotonia, hypogonadism, hyperphagia, and small hands and feet.[60] A short, young woman with many of these characteristics was first described in 1864, but Andrea Prader officially described the syndrome in 1956.[61] This syndrome is an example of genomic imprinting, where the clinical expression of the disease is dependent on the parent from whom the abnormality was inherited. The syndrome has been linked to chromosome 15, and is paternally inherited.[62] If the abnormal chromosome comes from the mother, then the phenotypic expression differs, a condition described as **Angelman's syndrome**.

Aagenaes' syndrome is another autosomal recessive lymphatic condition. It consists of cholestatic liver disease in conjunction with generalized lymphedema.[63] The edema is most commonly found in the lower extremities, as well as in the hands and scrotum.[63] This syndrome was first studied by Aagenaes in 1968, and most patients who bear the diagnosis are from a single region in southwestern Norway.[64] Most patients follow the general pattern of lymphedema progression and simultaneous cholestatic regression with age.[64] The pathology of the two components of the disease is distinct, with the liver disease attributed to giant-cell transformation, and the lymphedema to lymphatic vessel hypoplasia.[64] Symptoms include itching and jaundice, and there is often a growth delay during childhood.[64] Nutritional and vitamin supplements have been shown to have therapeutic value for patients.[64]

Autosomal Dominant

In 1883 a medical student, Kobylinski, described a young patient with a webbed neck. This is the first documentation of the **Noonan syndrome**, a congenital syndrome consisting of a webbed neck, mental retardation, short stature,[65] and cardiac defects, particularly pulmonary valve stenosis.[66] Additionally, many patients have lymphatic vessel dysplasia, neonatal lymphedema, intestinal or pulmonary lymphangiectasia, and cystic hygromas.[65] Analysis of patients with this condition reveals that the genetic abnormality can either occur sporadically or as an autosomally dominant form of genetic transmission. Collins and Turner found that while the sporadic mutation was distributed evenly among socioeconomic groups, the familial mutation was predominantly found among

TABLE 8. Heritable disorders

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Adams–Oliver syndrome	Defects of the scalp and cranium associated with distal limb anomalies and occasional mental retardation			Most autosomal dominant; some sporadic autosomal recessive		**Cardiovascular system**: Tetralogy of Fallot and pulmonary atresia **Head and neck:** Acrania of the flat bones with normal bones of the cranial base; hypoplastic facies and microcephaly **Hand and foot:** Hypoplastic nails; simple syndactyly; bony syndactyly; transverse reduction defects; ectrodactyly; polydactyly; brachydactyly **Spine:** Occasional spina bifida **Skin:** Aplasia cutis congenita of the scalp **Nervous system:** Hydrocephalus, epilepsy	Radiographs; echocardiography	

TABLE 8. Continued

			Laboratory	Genetic defect		Associated	Diagnostic	Differential

TABLE 8. Continued

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Noonan syndrome	Decreased appetite; frequent or forceful vomiting; dysphagia; severe joint or muscle pain	Facial abnormalities, webbing of the neck; chest deformities; heart murmur; mental retardation	Thrombocytopenia; prolonged activated partial thromboplastin time	Autosomal dominant or sporadic		Pulmonary valvular stenosis; cryptorchidism lymphedema; osteoporosis; vasculitis progressive high-frequency sensorineural hearing loss; pleural effusions; hydrops fetalis	Bleeding diatheses (factor XI deficiency); karyotype to distinguish from Turner's syndrome (XO); electro- and echocardiography; audiologic evaluation	Turner syndrome; Trisomy 21; Escobar syndrome
Neuro-fibromatosis	Coffee-colored macular lesions; freckling in non-sun-exposed areas; back pain	Neurofibromas; optic glioma; hamartomas on iris; distinctive bony lesions		Autosomal dominant (no family history in 50%); high mutation rate	Vasculopathy (arterial stenoses due to intimal cellular proliferation); fibromuscular hyperplasia of arteries leads to renal artery stenosis; cerebral infarction; aneurysm (rare)	Impaired respiration or deglutition; interstitial pulmonary fibrosis; renal artery stenosis; cerebral infarction; short stature; scoliosis; hypertension developmental delay	MRI CT imaging	
Aagenaes' syndrome (cholestasis with malab-sorption)	Predominantly in Norwegian patients; jaundice; severe pruritis	Hepatomegaly		Possibly autosomal recessive	Generalized lymphatic anomaly (lymph-edema due to lymph vessel hypoplasia); giant-cell hepatitis with fibrosis of portal tract	Hepatic cirrhosis; growth retardation; rickets; peripheral neuropathy; recurrent cellulitis; hyperlipidemia; bleeding (vitamin K deficiency)	Liver biopsy (giant-cell transformations)	

Continued

TABLE 8. ***Continued***

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Hennekam's syndrome	Edema; facial anomalies moderate developmental problems	Lymphedema; lymphangiectasia; facial anomalies; delayed onset of puberty; moderate mental retardation	Hypoproteinemia	In one report of 10 familial cases, equal sex ratio, increased parental consanguinity, no vertical transmission; consistent with autosomal recessive		Papillae nervi optici	Audiometry	
			Hypogammaglobulinemia Hypoalbuminemia Hypocalcemia Leukopenia with lymphopenia			Slight tortuosity of the veins Yellow macula Conduction deafness Narrow upper thorax Congenital heart defect Umbilical hernias Contractures Syndactyly Brain cyst Pyloric stenosis Hearing loss Blood vessel anomalies Atonic seizures		

TABLE 8. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Prader-Willi syndrome	Neonatal hypotonia; fetus small for gestational age; undescended testes; delayed motor development slow mental development very small hands and feet in comparison to body rapid weight gain; insatiable appetite, food craving; almond-shaped eyes; narrow bifrontal skull; morbid obesity; skeletal (limb) abnormalities, striae	Hyptonia; hypomentia; hypogonadism; obesity	Genetic testing, including chromosomal analysis for methylation patterns in PWS region; Southern blot hybridization/PCR; analysis for underlying uniparental disomy; fluorescent *in situ* hybridization (FISH) can confirm prenatal diagnosis; evaluation for hypogonadism: measurements of insulin-like growth factor-1 (IGF-1) and IGFBP-3; assessment of thyroid/adrenal and pituitary status	Genomic imprinting; differential gene expression based upon parent of origin (loss of paternal gene or maternal disomy)		Cardiopulmonary compromise; diabetes; orthopedic problems	Cranial MRI (to evaluate for hypopituitarism); serial dual-energy X-ray absorptiometry (DEXA) scanning for detection/monitoring of osteoporosis; scoliosis studies; chest X-ray; abdominal ultrasonography; CT and gastrointestinal imaging	Infantile hypotonia; neonatal sepsis; developmental delay/ mental retardation, obesity, and hypogonadism; Albright hereditary osteodystrophy; Bardet-Biedl syndrome; Cohen syndrome; Borjeson-Forssman-Lehmann syndrome; Some patients with Fragile X syndrome; Possible 6q or 1p deletions

lower groups.[67] In order to ascertain the pathophysiology of the condition, patients were lymphangiographically investigated. The documented abnormalities included lymphatic vessel aplasia and hypoplasia and diminished lymphatic flow.[65] It has been hypothesized that the webbed neck phenotype results from the regression of cystic hygromas when lymphatic obstruction is alleviated.[65] Additionally, embryonic lymphedema may prevent proper migration of tissues during development, leading to the anomalies, such as the cryptorchidism, hypertelorism, and low-set ears that are common in these patients.[65] Prenatal diagnosis is often accomplished ultrasonographically, with detection of cystic hygromas and edema.[65]

Adams–Oliver syndrome comprises congenital cutis aplasia, or absence of all skin layers, which generally manifests as scalp and skull defects, along with distal limb abnormalities.[68] Although patients often have severe defects of the skull, central nervous system defects have not been reported. Intelligence and intellectual development is normal.[69] While the most common mode of inheritance is autosomal dominant,[70] sporadic cases and autosomal recessive inheritance have also been documented.[70] Some affected individuals also have associated cardiac defects. Pousti *et al.* have postulated that the genetic defect decreases the stability of embryonic blood vessels, thereby disrupting vascular development, particularly in the cranial vertex and limbs.[69]

Neurofibromatosis is a single-gene disorder of the nervous system. The responsible gene has been mapped to chromosome 17.[71,72] The protein involved is neurofibromin, a tumor suppressor, and an inhibitor of cellular growth and differentiation in neurons, glial cells, and Schwann cells.[73] This loss of inhibition results in uncontrolled cell growth of central and peripheral nervous system cells, and can lead to the formation of the tumors (neurofibromas) when both alleles of the gene are lost, as well as non-tumor manifestations if a single allele is mutated.[74] Clinical characteristics include hyperpigmented macules, neurofibromata, and benign intracranial calcifications.[74] Neurofibromatosis is inherited in an autosomal dominant manner, but clinical expression varies greatly.[74] Useful diagnostic modalities include MRI and CT imaging. Currently, clinical trials are under way to ascertain the effect of pirfenidone, an antifibrotic compound, on the neurofibromas, while other investigators are attempting to develop new methods of measuring the growth of neurofibromas through volumetric MRI.[75]

Complex Vascular Malformations

Various disorders represent the result of abnormal development of, or insult to, the blood vascular and lymphatic vascular systems (TABLE 9). These diseases often have a superficial component, and present as irregularities of the skin, in the form of nodules or lesions. Since the pathology of these conditions is complicated, therapies are focused upon alleviating the dermal afflictions.

Cystic angiomatosis is a congenital condition[76] of unknown etiology, defined by the presence of numerous cystic skeletal lesions.[77] The lesions are generally round or oval, and they vary widely in size.[77] Although the clinical course is varied, the lesions most frequently present during the first few decades of life.[78] The cystic lesions may be due to dilated blood vessels or lymphatic channels, or both.[76,77] The cysts are encircled by a single, flat layer of endothelial cells.[76] Patients present with soft tissue masses, and sometimes have pain and swelling due to pathologic fracture.[77,79,80] Cystic angiomas are easily detectable on radiographs since they represent areas of destroyed bone that are sharply defined by a sclerotic rim.[77] Biopsies, often in affected areas of the rib, are performed to confirm the diagnosis.[76] Chemotherapy and radiotherapy have been attempted, but generally have been ineffectual.[76]

Maffucci's syndrome was first described in 1881; since then, fewer than 200 cases have been reported.[81] The syndrome is characterized by the presence of hard subcutaneous enchondromas and hemangiomas[82] due to mesodermal dysplasia.[83] Most of these tumors are benign, with a 15–20% incidence of malignant trasnsformation.[82] Dyschondroplasia, improper formation of bone in cartilage, is seen.[84] Maffucci's syndrome often impairs lymphatic system function, leading to edema and secondary infection.[85] Most individuals afflicted with this syndrome are phenotypically normal at birth; lesions appear during childhood and may progressively worsen.[83]

Diffuse **hemangiomatosis** is defined by the presence of non-malignant, visceral hemangiomas that affect at least three organ systems.[86] The lesions are attributed to a congenital defect. The vascular hamartomas are postulated to arise as a consequence of deficiencies in pericytes in the vascular wall.[86] This condition is extremely rare, with fewer than 70 reported cases.[87] All described patients have lesions of the skin, liver, brain, lungs, and gastrointestinal tract.[87] Therapy with corticosteroids and interferon-α has been attempted.[87] The mechanism of the favorable response to these medications is not known.[87]

TABLE 9. Complex vascular malformations

TABLE 9. Complex vascular malformations

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Proteus syndrome	Partial gigantism; long face; wide nasal bridge; mouth open at rest; upper body wasting; learning disabilities; occasional seizures	Cutaneous and subcutaneous lesions, including vascular malformations, lipomas; hyperpigmentation; and several types of nevi		Somatic mosaicism for a dominant, unidentified lethal mosaicism	Connective tissue nevi resemble tightly compacted, collagen-rich connective tissue; epidermal nevi generally exhibit a combination of hyperkeratosis, parakeratosis, acanthosis, and papillomatosis		Radiographs; CT/MRI	Neurofibromatosis Klippel Trenaunay Weber syndrome
Maffucci's syndrome	Soft, blue-colored growths in distal aspects of extremities; short stature; unequal arm/leg length	Enchondromas with multiple angiomas; bony deformities; dark, irregularly shaped hemangiomas		Sporadic, manifests early in life (~ 1–5 years); 25% of cases are congenital	Thrombi often form within vessels and develop into phleboliths: these appear as calcified micro-vessels; chondrosarcomas diagnosed by poorly differenttiated pleiomorphic chondrocytes	Enchondromas develop from mesodermal dysplasia; unequal leg length; pathologic fractures, malunion of fractures; chondrosarcoma, hemangiosarcoma, lymphangiosarcoma	CT/MRI bone biopsy if enchondromas evolve	Kaposi's sarcoma; Klippel Trenaunay Weber syndrome; Proteus sydnrome

Continued

TABLE 9. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Blue rubber bleb nevus syndrome	Multiple skin lesions: protuberant, dark blue, compressible blebs	Lesions are asymptomatic, but may be painful or tender; hyperhidrosis of skin overlying the lesion; fatigue (from blood loss); hematemesis, melena, or frank rectal bleeding; joint pain; blindness (cerebral or cerebellar cavernomas that hemorrhage into occipital lobes)	Fecal occult blood; CBC; screen for iron deficiency anemia; urinalysis (hematuria may be caused by bladder lesions)	Sporadic, autosomal dominant inheritance also reported	Vascular tissue with tortuous, blood-filled ectatic vessels, lined by single layer of endothelium, with surrounding thin connective tissue; dystrophic calcification may be present		Imaging: radiographs are useful in suspected bone or joint involvement MRI; endoscopy for gastrointestinal lesions	Kaposi's sarcoma; Klippel–Trenaunay Weber syndrome; Maffucci's syndrome; venous lakes

TABLE 9. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential Diagnosis
Diffuse hemangiomatosis	Neonatal premonitory findings: small red macule; telangiectasia, or blue macule at the hemangioma site	Neonatal visceral, non-malignant hemangiomas; vascular hamartomas		Congenital defect	Lesions have dilated thin-walled channels lined by a single layer of flattened endothelial cells, with few focal areas of endothelial proliferation; no other cellular hyperplasia or pleomorphism; well-formed vascular channels; abnormal capillaries coursing in their normal situation through muscle suggests that hemangiomas are hamartomas	Thrombocytopenia and hemangioma; pneumothorax; sclerosis; gastrointestinal hemorrhage; anemia; central nervous system involvement; hydrocephalus; hemorrhage; heart failure; scarring; ulceration	Biopsy	
Cystic angiomatosis	Soft tissue masses, localized pain and swelling related to pathologic fracture	Dyspnea with or without cyanosis, ascites, splenomegaly, hepatomegaly; anemia; soft tissue masses		Vascular malformation of congenital origin	Dilated, cavernous thin walled vascular channels lined by flat endothelial cells (similar to LAM)	Osler–Weber–Rendu syndrome	Radiologic: round or ovoid geographic osteolytic lesions with sclerotic borders, little residual central trabeculation, no periosteal reaction or significant matrix formation	Multifocal Langerhans cell histiocytosis; hyperparathyroidism; metastatic carcinoma; lymphoma; mastocytosis; sarcoidosis; phakomatoses; Maffucci's syndrome

Continued

TABLE 9. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Klippel Trenaunay syndrome		Capillary hemangioma/port-wine stain: distinct, linear border; nevus flammeus; large, lateral, superficial vein beginning at foot/lower leg to entry point in the thigh/gluteal area; bony/soft tissue hypertrophy: limb hypertrophy/ length discrepancies				Lymphedema; spina bifida: hypospadias; polydactyly; syndactyly; oligodactyly; hyperhidrosis; hypertrichosis; paresthesia; decalcification of involved bones; chronic venous insufficiency; dermatitis; poor wound healing; ulceration; thrombosis; emboli	Doppler ultrasound: differentiation of vascular tumors from vascular malformations	Maffuci syndrome; Proteus syndrome
							CT/MRI effective for visualizing extent of lesions and infiltration of deeper tissues	
							Plain film radiography: measurement of long bones	
							Color Doppler ultra-sound/duplex scanning: visualize patency of deep venous system	
							Angiography	

TABLE 9. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Cystic hygromas	Single or multiple fluid-filled lesions that occur at sites of lymphatic–venous connection; primarily in neck and axilla	Lymphedema	Hypoproteinemia	Congenital; autosomal recessive	Dilated, disorganized lymph channels due to failure of lymph sacs to establish venous drainage	Turner's syndrome; autosomal trisomies (trisomy 21); Klinefelter's syndrome; Noonan syndrome; Proteus syndrome; hereditary lymphedema; effusions: pleura, pericardium, abdomen	Chest X-ray: evaluate mediastinum/chest	Hemangiomas; lymphangiomas; vascular malformations; neck tumors; encephalocele; meningocele; branchial cyst; lipoma; laryngocele; thyroglossal duct cyst; dermoid cyst; teratoma (rare)
		Hydrops fetalis					MRI: evaluation of the cystic component of hygroma CT to detect hilar involvement	

Continued

TABLE 9. *Continued*

Disease condition	Symptoms	Signs	Laboratory findings	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Gorham's disease	Dull aching pain or insidious onset (limitation of motion, progressive weakness); swelling	Massive bone loss		No familial predisposition	Non-malignant proliferation of thin-walled vessels; proliferative vessels may be capillary/ sinusoidal or cavernous; wide capillary-like vessels	Fracture; hemangiomas; angiomatosis of blood vessels/sometimes lymphatic vessels; chylous pericardial and pleural effusions; vertebral disease	Radiographs: regional osseous destruction	Massive osteolysis; acro-osteolysis of Hajdu and Cheney syndrome; idiopathic multicentric osteolysis; multicentric osteolysis with nephropathy; hereditary multicentric osteolysis; neurogenic osteolysis; acro-osteolysis of Joseph; acro-osteolysis of Shinz; Farber's disease; Winchester's syndrome; osteolysis with detritic synovitis
							Radioisotope bone scans: increased vascularity initially, with eventual areas of decreased uptake where osseous tissue is diminished CT/MRI blood tests and radiographs to exclude infection, cancer, *inflammatory, and endocrine disorders*	

Gorham's disease is the uncontrolled growth of non-malignant vascular channels that lead to lysis of the affected bone.[88,89] The condition is associated with angiomatosis of blood and lymphatic vessels.[89] The shoulder[90] and pelvis[91] are most frequently affected in this disease. Chylous pericardial and pleural effusions are associated with this condition, and chylothorax can sometimes result from dilation of lymphatic vessels with reflux into pleural cavity.[89] Treatment involves surgery, with resection or bone reconstruction, and radiation.[89]

Proteus syndrome is a congenital overgrowth of numerous body tissues and cell lines.[92] Named for the character in Greek mythology who had the ability to change his shape at will, this condition is polymorphic in nature.[93] It is characterized by subcutaneous tumors, hyperostosis, hyperplastic connective tissue in the soles and palms, pigmented nevi, and partial gigantism of hands or feet.[92,93] Cell components appear normal, although there are signs of hyperplasia or disorganization of cells.[92] The condition is rare, with only a few hundred estimated afflicted persons. It is sporadic and mosaic, in that individuals have certain cells with mutations and others that are normal.[92] There is currently no molecular marker for this condition, which is often mistaken for **Klippel–Trenaunay syndrome** (KTS), **Maffuci's syndrome**, or **neurofibromatosis**, among others. Since orthopedic complications often arise, particularly scoliosis, treatment is generally surgical or takes the form of physical therapy.[92] Future directions will involve characterizing the molecular defect responsible for the condition, thereby paving the way for accurate diagnosis and pharmacologic therapy.[92]

Klippel–Trenaunay syndrome represents a combination of vascular malformations, including capillary anomalies (port wine stain), varicose veins, and the hypertrophy of bone and soft tissue.[94] While Klippel–Trenaunay syndrome generally manifests in a single extremity, it can also affect multiple limbs or the entire body.[94] Histologically, the condition manifests as dilated telangiectatic vessels in the upper dermis which do not spontaneously regress.[95]

Recent studies to pinpoint the genetic abnormality leading to this condition have been insightful. Some Klippel–Trenaunay syndrome patients have a mutation in the VGFQ gene, which, analogously to vascular endothelial growth factor is an angiogenic factor. These mutations are either chromosomal translocations or point mutations, and both tend to enhance the effect of the protein.[96] The condition is phenotypically diverse, and therefore it is hypothesized that it is genetically heterogeneous as well, and that other genes may also be implicated.[96] Complications arising from Klippel–Trenaunay syndrome include pain and lymphedema. Doppler ultrasounds are employed to distinguish Klippel–Trenaunay syndrome from hemangiomas, while CT and MRI is used to determine the depth of tissue involvement.[97–99] Lymphoscintigraphy is employed when the lymphatics are thought to be involved,[100] particularly when patients present with lymphedema. Treatment is aimed at providing symptomatic relief in the form of elevation and compression stockings for edema.[101,102]

Blue rubber bleb nevus consists of vascular nevi of the skin and hemangiomas of the gastrointestinal tract that lead to hemorrhage and anemia.[103] The name arises from the fact that the nevi are blue and rubbery, and also soft and easy to compress.[104] The venous malformations are either congenital or present in the first years of life, and progress in both size and number over time.[103,105] The condition is sporadic, though certain instances of autosomal dominant inheritance have been reported.[103] Deformities of surrounding bone may occur as the result of increased pressure from hemangiomas.[106] Treatment includes transfusions and iron replacements[103] for gastrointestinal blood loss, and endoscopy is employed for less-invasive treatments, such as sclerotherapy, for the lesions.[105] Pharmacologic treatments including corticosteroids and interferon-α have been found ineffective: lesions regress, but then return once treatment is stopped.[105]

Protein-Losing Enteropathy and Intestinal Lymphangiectasia

Loss of lymphatic fluid and plasma protein within the lumen of the gastrointestinal tract can lead to edema and hypoproteinemia (TABLE 10). These phenomena are encountered in a variety of afflictions, including protein-losing enteropathy (PLE) and intestinal lymphangiectasia. The mechanisms that predispose to this form of protein loss are not yet fully understood; however, patients with PLE typically have local lymphatic obstruction and stasis,[107] while those with lymphangiectas have dilated lymphatic vessels in the intestinal villi.[108]

Protein-Losing Enteropathy

Patients with PLE have excessive protein loss into the gastrointestinal lumen leading to hypoproteinemia.[107] PLE is associated with numerous disorders, including inflammatory bowel disease, infection, celiac disease, intestinal lymphangiectasia, thoracic duct obstruction, and cardiac disease.[109] Generally, obstruction of lymphatic vasculature yields increased hydrostatic pressure throughout the lymphatic system of the gastrointestinal

TABLE 10. Protein-losing enteropathy and intestinal lymphangiectasia

Disease condition	Symptoms	Signs	Genetic defect inheritance	Pathology	Associated conditions	Diagnostic methods	Differential diagnosis
Protein-losing enteropathy		Edema, diarrhea	Sporadic		Inflammatory bowel disease; infection; celiac disease; intestinal lymphangiectasia; thoracic duct obstruction; and cardiac disease	Documentation of hypoalbuminemia without proteinuria; reduced plasma gamma globulins, cholesterol, alpha-1 antitrypsin; lymphopenia; nuclear studies	Intestinal lymphangiectasia
Intestinal lymphangiectasia	Severe edema, ascites; pleural effusion; hypoproteinemia			Thickening of small bowel wall; dilatation of intestinal micro-lymphatics	Inflammatory and neoplastic disease	CT imaging	

tract, resulting in lymph stasis. Protein-rich lymphatic fluid is consequently lost within the lumen of the gastrointestinal tract through the lacteals in the intestinal microvilli. Protein loss in patients with PLE is nonselective, in contradistinction to glomerular diseases, where loss is size-dependent,[110] and includes plasma proteins, albumin, globulins, and transferrin.[109] If loss of albumin exceeds its rate of synthesis, edema develops. Other clinical manifestations include ascites and pleural and pericardial effusions.

Diagnosis often relies upon identification of the characteristic laboratory abnormalities, which include: hypoalbuminemia without proteinuria; reduced plasma concentrations of gamma globulins, cholesterol, and alpha-1 antitrypsin; lymphopenia; and malabsorption of fat and fat-soluble vitamins.[109] While intravenously administered radioactive macromolecules, such as Cr-51, In-111, and I-125, are used to tag and quantify protein loss,[109] abdominal scintigraphy can additionally demonstrate sites of protein loss.[107] The most commonly employed diagnostic tool is the measurement of endogenous proteins. As an example, both fecal concentrations and clearance of alpha-1 antitrypsin are much higher in PLE patients than in unaffected individuals.

Recommended medical care depends on the underlying cause. For patients with lymphatic obstruction, severely reducing dietary fat intact, along with supplementation of medium chain triglycerides, can reduce the hydrostatic pressure within the lymphatic system and thereby decrease protein loss. Intravenous albumin replacement,[111] small bowel resection,[112] or high-dose steroid therapy may also prove beneficial.[113,114] For patients with congenital heart disease, recent studies suggest that heparin may reduce leakage of protein into the intestinal lumen.[111]

Intestinal Lymphangiectasia

Intestinal lymphangiectasia is a rare condition characterized by severe edema, thickening of small-bowel wall, PLE, ascites, and pleural effusion.[115] If lymphatic fluid and proteins are lost into the gastrointestinal tract, patients may present with generalized edema due to hypoproteinemia.[108] The condition may be primary, resulting from a congenital lymphatic vascular disorder, or secondary, as a consequence of inflammatory or neoplastic involvement of the lymphatic system.[116] The pathogenesis remains unclear. Yang and Jung propose that intestinal lymphangiectasia may develop when lymphatic obstruction involves a segment of the bowel.[117] Holt proposes that dilated intestinal lymphatics may rupture, producing a leak of lymph into the

intestinal lumen.[118] Typically dilatation of lymphatic channels in the intestinal villi leads to a malabsorption of fat because long-chain fatty acids can no longer be adequately processed by these abnormal lymphatic vessels.[108]

CT imaging is often employed in the diagnosis of intestinal lymphangiectasia. The images reveal diffuse, nodular thickening of the bowel wall with ascites[119] and hypo-dense streaks in the small bowel, reflecting the markedly dilated lymphatics.[120] Replacement of dietary long chain fatty acids with a medium chain triglyceride formula reduces intestinal protein losses.[118]

Conflicts of Interest

The authors declare no conflicts of interest.

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