Newfound features associated with Hennekam Syndrome (*Intestinal Lymphangiectasia-Lymphedema-Intellectual-Disability Syndrome)* complicated with comorbid Waldmann's disease resulting in celiac disease

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Abstract

As far as we know, this is the 51st case of Hennekam Syndrome (HS) worldwide and the first one in an African American.[1] Our patient met all diagnostic criteria for HS, type 2 (FAT4 mutation), as the disease onset was in adolescence.[2,3]

Primary intestinal lymphangiectasia (Waldmann's disease, WD) is a consequence of HS, which ultimately results in protein-losing enteropathy (PLE) and worsening interstitial lymph buildup.[4,5] Based on our findings, celiac disease (CD), a complication not yet reported in HS, may arise from WD. Other autoimmune diseases may be seen in HS: a previous report demonstrated positive anti-TSH antibodies in HS patients.[5] We propose that in HS, increased interstitial lymph (WD, if intestinal) with protein loss induces TNF-α- and IL-6-mediated immune reactions in the affected visceral organs, causing autoimmune pathologies.[4,5,6,7]

The interstitial lymph fluid-induced TNF-α and IL-6-mediated immunopathogenic reactions lead to the destruction of the intestinal mucosa.[4,6] The chronic inflammatory increase in TGF-β causes gastric mucosa hypertrophy, which results in gastric fold thickening. Eventually, wider tight junctions develop, increasing gastric mucosa permeability, which leads to gastropathy. [4,6]

Considering our patient's history of gastroenteritis and the literature stating that CD is a non-mucosal cause of gastropathy and PLE, we suggest that sequelae of GI complications in HS occur in a cause-and-effect chain. HS results in WD, which causes CD, which in turn results in hypertrophic gastropathy and loss of parietal and chief cells, which eventually leads to malabsorption and PLE (Fig. 1).[7,8,9,10,11,12,13]

Other findings for HS included keratoconjunctivitis sicca (dry eye disease), fibrous lymphedema exhibiting lymphorrhea, chylous ascites, anemia, and PTH abnormalities. Autoimmunity (CD) and WD are concomitant comorbidities of HS.[4,5,7]

HS mutations can be compound heterozygous, and there is a need to identify more nearby genes that can cause concomitant co-morbidity.[2] FAT1 mutation has been associated with hypertrophy of cardiomyocytes. This is consistent with the present patient's echocardiogram showing mild concentric left ventricular hypertrophy.[14,15] The concomitant presence of pathologies that all involve FAT genes suggests gene mutations in proximity.

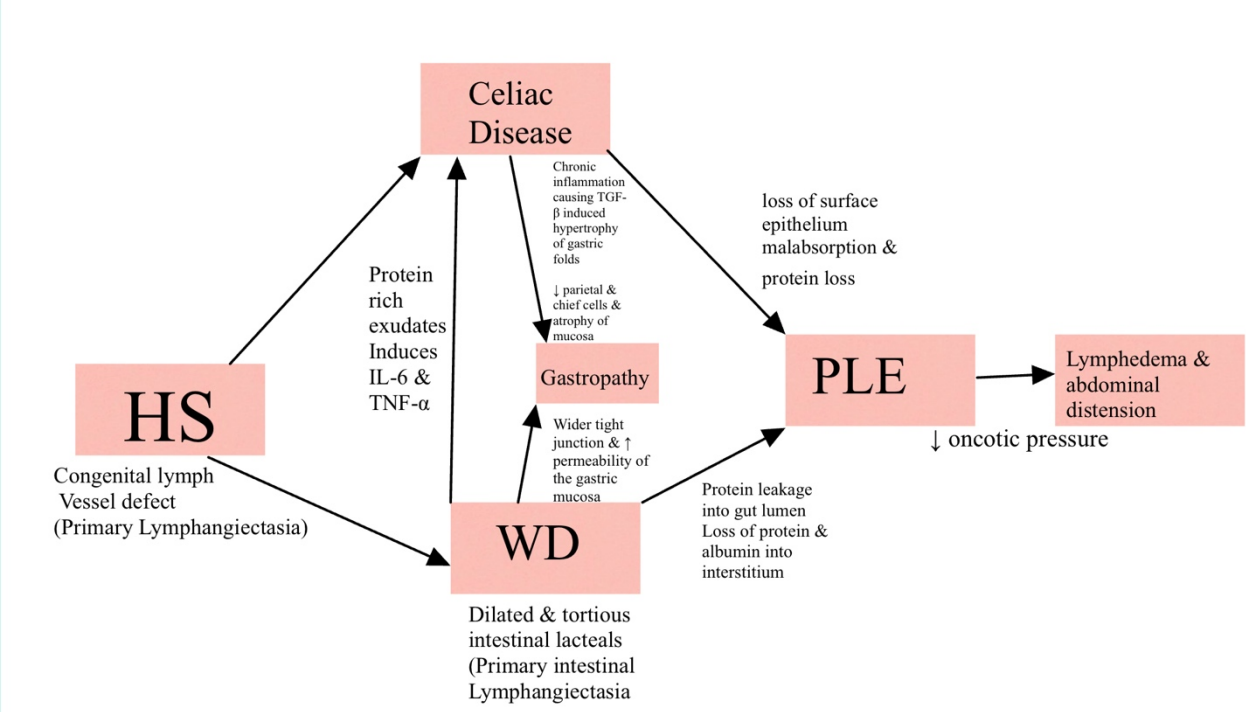


Figure 1: Proposed Order of Events for lymphangiectasia causing Celiacs and PLE (HS = Hennekam Syndrome, WD = Waldmann's disease, PLE = protein-losing enteropathy)[7,8,9,10,11,12,13]

Introduction

Hennekam syndrome lymphangiectasia, AKA intestinal lymphangiectasia–lymphedema–intellectual disability syndrome, is an autosomal recessive disorder characterized by generalized

lymphatic dysplasia that affects various organs. Lymphangiectasias are present in the intestines, pleura, pericardium, thyroid gland, and kidneys. Several patients have demonstrated congenital cardiac and blood vessel anomalies, pointing to a disturbance of angiogenesis in at least some of the patients.[16] Additional features of the disorder include facial dysmorphism and cognitive impairment since there is widespread lymphatic blood vessel expansion[17,18]
First discovered in 1980 by Dr. Hennekam et al., this syndrome is caused by mutated lymphatic vessel formation, which results in poor lymph drainage in various parts of the body, forming increased fluid in the interstitium of the body cavities.[4,19,20] The increased interstitial fluid results in dilation of the lymphatic vessels, termed lymphangiectasias, in the abdomen (and other visceral organs) and in increased interstitial space with lymphatic build-up (lymphedema), which most often occurs in the extremities.[5,19] Visceral lymphangiectasias lead to effusions in the affected location.[17] This causes various organ dysfunctions, including the intestines, limbs, genitals, thyroid, kidney, pericardium, and pleural tissue, producing sequelae of pathologies such as peripheral lymphedema, chylous ascites, protein-losing enteropathy (PLE), malabsorption, chylothorax, pleural and pericardial effusion, hypothyroidism, and kidney dysfunction. Intestinal lymphangiectasias causing PLE also result in malabsorption (notably of fat-soluble vitamins), iron deficiency anemia, hypoalbuminemia, hypogammaglobulinemia, electrolyte abnormalities (hypocalcemia and hypomagnesemia), and lymphopenia.[5,7,17,21,24] These abnormalities can cause brain defects and contribute to seizures most often seen in Hennekam Syndrome (HS) patients.[4,8,9,10,11] The lymphedema seen in HS can be distinguished from other lymphedema syndromes by most commonly manifesting in the lower limbs first, then presenting in the intestine, lungs, and other organs later in life. [6,7,2,22,24]

Because it is a congenital syndrome caused by genetic mutations, it also affects other areas besides the interstitial. Other HS features include growth delays, mild to severe mental disability, blood vessel anomalies, dental and facial abnormalities, such as super mammary or missing teeth, gingival hypertrophy, hypertrophic alveolar ridges, and high palate. HS also involves matrotrophic ridging (abnormally shaped head) and facial abnormalities, including broad nasal bridge, hypertelorism, broad forehead, low-set dysplastic ears and narrow meatus, epicanthal folds, small mouth, smooth philtrum, periauricular tag and pits, narrow external ear canals, hirsutism, alopecia or hypertrichosis, pterygium colli (webbed neck), limb and digit abnormalities such as camptodactyly, and syndactyly of mainly digits 2, 3, and 4. Other limb

findings include abnormal hand creases, and foot deformities such as club foot. In addition, central nervous system anomalies, vertebral defects such as scoliosis, pectus excavum, hypersplenism, umbilical hernia, renal or urinary abnormalities, microcephaly, hypoplastic corpus callosum, pachygyria, seizures, hearing defects, and glaucoma have been reported.[1,23,24,21,19] Some patients also presented with food allergies and atopic dermatitis.[17] It should be noted that the presence of both low albumin and iron-deficiency anemia could indicate that lymphangiectasias may cause silent GI bleeding.[24,25] Iron deficiency anemia could also be attributed to malabsorption secondary to PLE.[5,7]

Esophagogastroduodenoscopy and colonoscopy of the RUQ in a patient with HS have revealed lymphangiectasias in the GI tract, which showed pinpoint white lesions in the distal duodenum and proximal jejunum, dilated lacteals, edematous ileocecal valve, and large white subepithelial elevations in the terminal ileum as well.[26] Intestinal lymphangiectasia in and of itself is also known as Waldmann's disease (WD), which can be primarily due to congenital issues or secondarily caused by another pathology. Hennekam syndrome can cause Waldman's disease when the interstitial fluid buildup progresses to involve the abdomen, causing chylous ascites.[4,9,12,13] Long-standing lymphangiectasias in the bowel have shown extensive changes along the length of the small intestine, and fibrosis causes obstruction and infection. These changes can affect the permeability of intestinal cells, compromise the ability to maintain proteins, and lead to PLE.[7,8,9,10,11,27,28]

HS can cause Waldmann's disease (WD), which involves dilated lymphatic vessels and intestinal lymphangiectasias. While WD only refers to the intestinal area, HS shares the same pathophysiology (dilated or ineffective lymph vessels due to the MT gene), albeit being a systematic lymphangiectasia with swelling. Many factors can cause WD, but it inevitably leads to PLE; protein loss leads to further fluid leakage into the interstitium, worsening the pre-existing dilation of vessels.[5,7,12]

In addition to protein loss, increased permeability has been proposed to result in lymphocyte accumulation in the interstitial space. This is troublesome because it allows antigens to react with lymphocytes in the interstitial space, causing havoc and giving rise to an array of autoimmune diseases.[29] The chronic inflammation occurring with long-standing lymphatic fluid in the interstitial space will also induce factors activating VEGF-C and D, stimulating angiogenesis, which leads to thickened lymphatic endothelial vessels and fibrosis.[29]

PLE is accompanied by hypoproteinemia, hypoalbuminemia, and fat malabsorption (notably fat-soluble vitamin deficiency), despite normal kidney and liver function. Other deficiencies include zinc, copper, and selenium.[4] This manifest as ascites and lymphedema of the lower legs, and a positive stool test for A1T1.[8,11] Hepatic protein synthesis will be ramped up to maintain an osmotic gradient. The rapid rate of synthesis of prealbumin, transthyretin, IgE, and insulin will be normal or high (other proteins that would exhibit the same character for being normal or increased in PLE). In contrast, low levels of lipids, iron and other trace elements, and lymphopenia are secondary to lymphatic obstruction.[10,11]

PLE is categorized into two types of mucosal diseases, erosive and non-erosive, and a third type involving increased interstitial lymph nodes. Non-erosive type conditions, not entailing erosion of the intestinal mucosa, include celiac disease, H. pylori, Menetrier's disease (AKA giant cell gastric hypertrophy), eosinophilic gastroenteritis, microscopic colitis, and small intestinal bacterial overgrowth.[4,29,30,31,32,33] The mechanism for PLE is triggered when one of these conditions ultimately causes loss of surface epithelial cells in the intestine and consequent malabsorption and hence PLE.[4,8,9,10,11,28]

Lymphedema refers to the process of dilated lymphatic vessels that can occur in any visceral organ. These dilations can eventually be at risk for rupture, at which point the term lymphangiectasia predominates.[2,20,22,34]

Since its initial discovery, and although rare, HS has been recorded in approximately 50 patients worldwide.[24] Many HS patients may currently be undiagnosed due to the complexity of HS nature and the many organs interested. Currently, three main gene mutations are associated with HS, all of which disrupt the pathway involved in the budding, migration, and proliferation of lymph endothelial progenitor cells during development. Depending on the patient's mutation, three subtypes have been identified: type 1, type 2, and type 3.[2,24,27]

HS type 1 involves the autosomal recessive CCBE1 mutation, coding for a calcium-binding EGF collagen protein. When mutated, it presents at birth, so it is easily discovered compared to other HS types.[6,35,36] Type 2 involves a FAT4 mutation either autosomal recessively acquired or through a compound heterozygous mutation: the lack of knowledge on the various genetic mutations causing defective lymph vessel formation or drainage represents an additional barrier to HS screening and diagnosis.[2,24] Type 3 was recently discovered; it includes an ADAMTS13

mutation which normally functions to activate VEGFC by inducing its cleavage.[2,27,37,38] A few other contributory mutations causing lymphedema have been reported (FLT4, GCJ2, PTPN14), and others causing syndromic primary lymphedema (FOXC2, SOX18, GATA2, IKBKG, LYVE-1.[6,27] Since these mutations comprise only a small amount of HS patients, genetic heterogeneity is suggested. This raises the need to identify more mutations involving embryonic development of the lymphatic vessels that cause or contribute to HS, as well as to possibly overlapping co-morbid conditions.[2,3]

The cause of intestinal lymphangiectasias, whether primary or familial, its association with various forms of autoimmune or inflammatory changes, and the manifestation of PLE and inevitable physical presentation of lymphedema in patients are still incompletely elucidated.[5,9,28,34] These terms must be further distinguished and explicated, and the order of events between them needs to be established to determine the most effective intervention.

Case Report

A 26-year-old African American male patient presents to the clinic in a wheelchair for gross bilateral leg and ankle swelling and ulcers for the past 3 months (Fig. II, III, IV). He is on furosemide, whose dosage was doubled three times since the its initial institution, albeit with minimum relief. The patient has no erythema, bruising, scars, rash, or jaundice.

He has not always been using a wheelchair. As a child, he ambulated normally without any issues until his preteen years, when the sudden onset of massive lymphedema occurred. Initially, it was most notable at the hips and ankles and subsided rapidly. Later, the swelling became episodic, reoccurring approximately once a year. With the onset of swelling, the patient also began to gain weight very rapidly, causing him to use a wheelchair. He currently requires it for most of his daily life activities. The reported swelling is aggravated by the mildest activity or any attempts to walk more. In between swelling episodes, he presents a clear, odorless discharge from his feet, irrespective of the swelling status. In addition, he has not been able to wear shoes for many years.

The previous month's laboratory examinations showed low vitamin D, a significant increase in IgA and transglutaminase antibodies, and abnormally low TSH. BMP and CMP were normal.

The patient has not sought his podiatrist's care for his recent complaints. He has no known allergies, and his vaccinations are up to date. His medications only include furosemide and ergocalciferol (Vit D.)

In the week before the visit, he experienced worsened orthopnea (the patient has slept upright since birth), and decreased appetite. His mother reports he is "unable to tolerate eating sugar the way he used to." She also reports recent-onset odd eating behavior (she caught him eating raw syrup, and heavy cream at another time, over the previous month, which she defines as very unusual). Additionally, she reports he may have been feeling mildly nauseous recently, although no vomiting was observed. The previous week he had a bout of diarrhea, loose in nature, which progressed to sticky, hard constipation before eventually normalizing. These episodes have happened before as well. One month earlier, he started saying "ouch" when touched in some body areas (notably, the legs and the abdomen) and now appears to have abdominal tenderness. His mother reports he has been guarding his abdomen, and she noticed him "holding the sides of his stomach the most." No erythema, tenderness, or skin changes on the affected area are reported. Additionally, no complaints of chest pain, palpitation, or shortness of breath are made. Furthermore, the patient reports dry eyes (Keratoconjunctivitis Sicca) and has complained about this for many years, although no vision changes, irritation, pain, erythema, or discharge of eyes are reported.

His past medical history includes bilateral leg swelling and ulcers (03/2022); celiac disease (weakly positive anti-transglutaminase IgG autoantibodies and significantly high IgA) with onset 05/22; Keratoconjunctivitis Sicca (dry eyes) for many years; hyperglycemia since 03/22; low TSH levels since 04/22 (also previously abnormal in 2020 and 2019); vitamin D deficiency; hyper-PTH and abnormal serum Ca2+ levels; atherosclerosis of native arteries in the extremities with intermittent claudication bilaterally (03/22); right ankle and foot arthritis in 2019, not attributed to swelling but due to an injury at school; gastroenteritis and upper respiratory infections (both of which occurred in 2018); obesity (BMI >49.5) in 2018, with a diagnosis of pre-diabetes type 2 in 12/2006; tarsal coalition deformity ("flat foot") since 2016, reported as secondary to the onset of swelling.

Psychiatric disorders include autism spectrum disorder, severe mental disability (both congenital), and anxiety disorder since 2019. He has no surgical history.

Family history involves the father's hypertension and the mother's hyperlipidemia and hypertension. His mom is the patient's caretaker and lives in a single-level home with parents and siblings. His diet involves a strong preference for fried food, and he is reported to consume fast food regularly. Other social history information was non-contributory.

Physical Findings:

Vitals: BP 126/82, RR 16 BPM, pulse **59** BPM, Temp 97.2, O2 Sat 100%, BMI 53.5

General: African American male patient with central obesity, wheel-chair use, head turned down and to the left, looking at mom throughout the encounter with occasional eye contact even when talked to; responds only to mom and every response is mainly in alveolar clicks or one-word answers (monosyllabic speech); patient in no acute distress without any nervousness/restlessness

HEENT: atraumatic, normocephalic

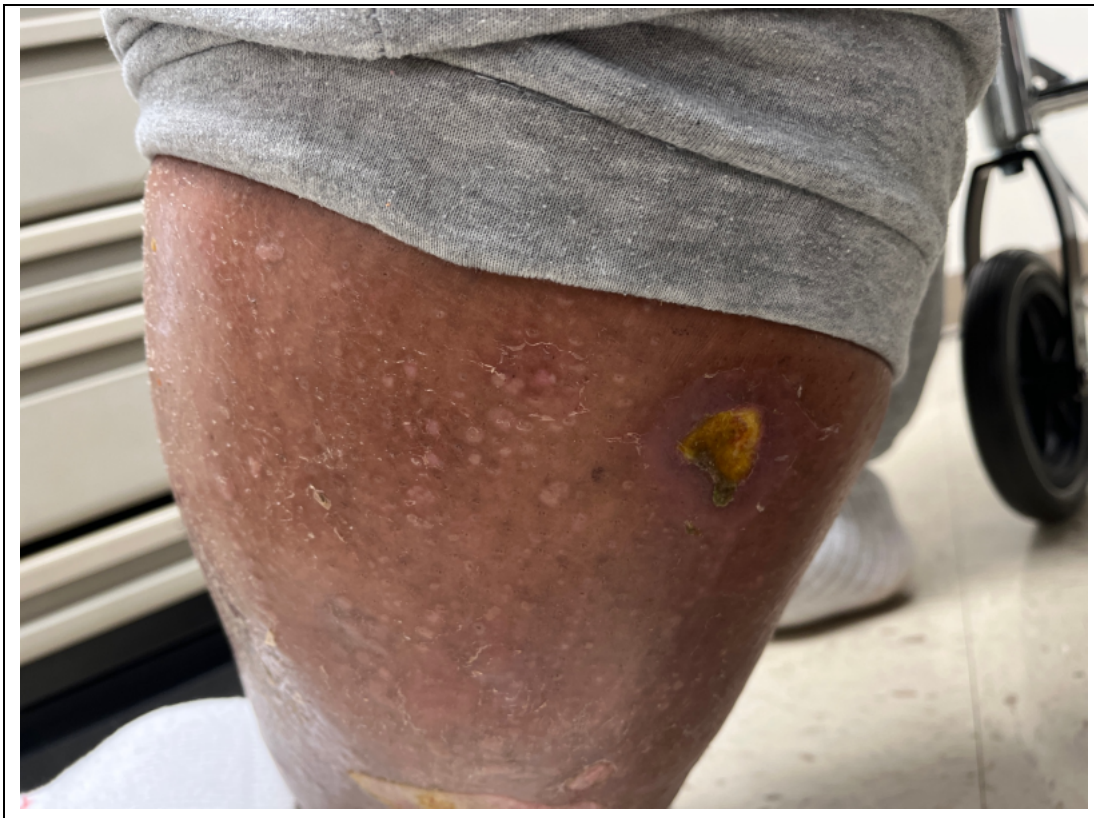
CVS: s1/s2 normal, +gallops appreciated (S3), -m/r

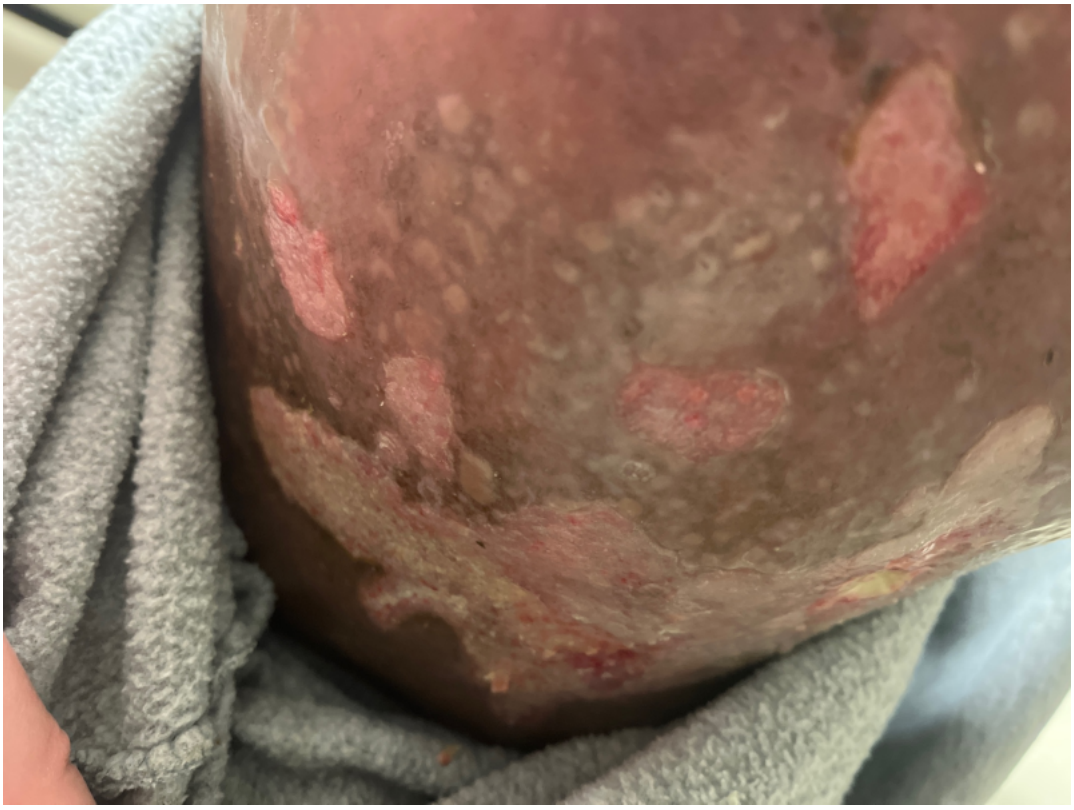
Resp: CTAB, -w/r/r, radial pulse normal bilaterally and regular

Abd: +protuberant abdomen, +guarding to approach to abdomen (remaining exam limited by the patient's autism)

Ext: +gross edematous legs bilaterally and dorsally characterized as hard, pitting edema +3, with clear, odorless discharge (lymphorrhea) from both lower leg and foot. The anterior aspect of the bilateral shin has a fibrotic and vesicular appearance with multiple punched-out ulcers. Bilateral legs with centrally yellow scabs with raised edges, +stemmer's sign, socks do not fit and are soaked, +guarding to approach to the left leg, no pain at palpation, atraumatic, physical inspection of ulcer showed no improvement when compared to the previous visit, -pain to palpation, -fever

Neuro: EOM intact bilaterally; the patient appears grossly neurologically intact





Figures 2, 3, 4: Our 26-YO patient on a wheelchair and presenting with bilateral lymphedema and lymphorrhea[4,5]

Remarkable Lab values (Table I):

RDW 17.8 % (high)

Low:

- Hgb (13.2 GM/DL)
- MCV (79 Fl)
- MCHC (25.5 pg)
- MPV (8.9 FL)

High:

- globulin (5.4 mg/dl)
- total protein (8.7 mg/dl)

albumin 3.3 mg/dl (low)

+ T-Trans glutaminase IgG 7 U/ml (weakly positive for celiac)
serum IgA 738 mg/dl (extremely high)
TSH < 0.005 (Extremely low)
Ca2+ 10.1 mg/dl (high)

PTH 82 ng/ml (high)
Vit D 11.3 mcg (low)
BMP/CMP wnl (normal)
Cl- 98 mmol/L (low)

Na+ 135 mmol/L (low)

Low HDL (31 mg/dl)
Normal: LDL (48 mg/dl), TG (99 mg/dl), cholesterol (98 mg/dl) - all 3 within desirable levels

Bradycardia - significant drop in pulse at the most recent visit (pulse of 59 bpm) compared to his usual baseline pulse of 97 bpm at all previous visits

Echocardiogram revealed mild concentric left ventricle cardiomyopathy. Ejection fraction was 70% (normal). All other echo findings were unremarkable, including those of the right ventricle, both atria, and all valves.

Radiologist notes: the patient has cognitive impairment, could not lie supine, would not allow the sonography technologist to touch him, and kept reaching for the ultrasound probe.

CBC Report	Result	Ref. Range	Unites	Level Status
WBC count	7.4	3.5-10.5	x10E3/UL	Normal
RBC count	5.18	4.32-5.72	x10E3/UL	Normal
Hemoglobin	**13.2**	**13.5-17.5**	**DM/DL**	**Low**
Hematocrit	40.9	38.8-50.0	FL	Normal
MCV	**79.0**	**81.2-95.1**	**PG**	**Low**
MCH	**25.5**	**26.0-34.0**	**GM/DL**	**Low**
MCHC	32.3	31.0-37.0	FL	Normal
RDW standard deviation	50.4	34.7-51.0	%	Normal
RDW coefficient of variation	**17.8**	**11.6-14.4**	**%**	**High**
Platelet count	313	150-450	x10E3/UL	Normal
Mean platelet volume	**8.9**	**9.4-12.4**	**FL**	**Low**
Immature granulocytes % auto	**0.3**		**%**	
Neutrophils % auto	62.2	34 - 71	%	Normal
Lymphocytes % auto	29.1	15 - 44	%	Normal
Monocytes % auto	7.1	0 -10.0	%	Normal
Eosinophils % auto	1.0	0-7.0	%	Normal
Basophils % auto	0.3	0-0.2	%	Normal
Immature granulocytes # auto	0.02	0-0.03	x10E3/UL	Normal
Neutrophils # auto	4.58	2.0-7.0	x10E3/UL	Normal
Lymphocyte # auto	2.14	0.8-3.70	x10E3/UL	Normal
Monocytes # auto	0.52	0.2-0.9	x10E3/UL	Normal
Eosinophils # auto	0.07	0-0.54	x10E3/UL	Normal
Basophils # auto	**0.02**	**0-0.2**	**x10E3/UL**	Normal
NRBC ABS	0		x10E3/UL	
NRBC PCT	0		%	

Table 1: Patient's CBC at the time of presentation.[4,5,7]

Discussion

The hard, bilateral, gross lower extremity swelling with fibrosis, chylous reflux, and lymphorrhea in this patient favor the diagnosis of lymphedema (over that of edema).[2] Our patient also had positive (Stemmer's sign) "hard" lower extremity swelling; this further distinguishes lymphedema from edema.[2,6,7,22,24] The edema was most prominent on the dorsum of the foot, which also is a distinguishing characteristic of lymphedema.[2,7] The patient experienced gross bilateral edematous swelling episodes, which were reported as pitting +3 and hard in nature,

exhibiting a fibrotic appearance on the anterior shin. Hard, fibrotic, and clear discharge (chyle reflux) has been associated almost exclusively with primary lymphedema and is usually a sign of late-onset grade 3-4 lymphedema.[2,22,24] Our patient's socks did not fit and were soaked on palpation: these were attributed to the clear, odorless discharge secreted through the skin of the lower extremities. This is noted as lymphorrhea (chyles secretion) and is a characteristic feature of primary lymphangiectasia.[3,14]

The patient's mother reported that the swelling episodes began during the patient's preteen years; they were most notable in the ankles and hips and occurred approximately once a year, although the lymphorrhea was present even when the swelling had receded. Indeed, she reported that the patient was normally ambulatory until his teens, when he began gaining weight rapidly: the onset of the swelling episodes significantly impacted his daily living and caused him to always use a wheelchair. Since the onset of these symptoms was not at birth but later in life, we suggest that our patient has type 2 HS involving the FAT4 gene mutation.[2,3] The patient's mother claimed he had episodes where he was "full of fluid," a term also used in HS-induced experimental zebrafish.[2] The patient had not worn shoes for years due to worsening lower extremity swelling. On his initial chief complaint appointment, he also had multiple punched-out ulcers in the lower legs with centrally yellow scabs with raised edges. There was no ulcer improvement at subsequent visits despite increasing the dosage of furosemide: ulcers were reported to be either spreading and enlarging or the same size as in the earlier visits, which further indicated that edema in the legs was lymphedema as it did not resolve or regress with high doses of diuretics. Treatment for lymphedema should instead include diet change, i.v. albumin, or surgery if dire.[5] Diuretics may slightly help initially but will eventually exacerbate lymphedema since the edema in PLE is caused by protein loss and should not be mistaken for edema caused by excess water.[4] The patient exhibited guarding to any approach to his legs and abdomen, although fever was absent and inspection did not reveal any remarkable findings.

The patient's laboratory examinations for BMP/CMP were consistently normal, signifying no kidney or liver dysfunction. PLE is suggested by low albumin (3.3 mg/dl) and, especially, by the high serum protein (8.7 mg/dl) since in PLE hepatic protein synthesis is increased.[4] These findings, including hypoalbuminemia, are consistent with those found in HS patients.[4,5,25]

The patient struggled with dry eyes (keratoconjunctivitis sicca) for years. Defective lymph vessels have been reported to cause lymphangiosis in the eyes, resulting in dry eye disease. His furosemide therapy can be ruled out as a possible culprit as this complaint pre-existed with the commencement of diuretic treatment.[25] HS has been associated with constrictive pericarditis due to the lymph fluid buildup around the pericardium.[2,4,17,24,39] Our patient reported sleeping in the seated position since birth. However, recently, this symptom has become more noticeable.

On physical examination, S3 gallop sounds were found at heart auscultation. On his last visit, he was bradycardic with reported pulse from 96 of the previous visit – and even earlier ones - to 59 at the current visit. His most recent bradycardia may have been due to various potential causes, such as drugs, heart block, and sinus bradycardia (autonomic dysfunction).

Echocardiography revealed mild concentric left ventricular hypertrophy. His left ventricular hypertrophy could be indicative of familial restrictive cardiomyopathy [3,40,41] FAT4 mutation has also been termed NFATC3, which has also been associated with cardiomyocyte hypertrophy. This is consistent with our patient's echo showing mild left ventricular hypertrophy.[14,15] This is also suggestive of restrictive cardiomyopathy of the familial type, which is related to a FAT1 mutation.[3,4,40,41,42] The presence of two pathologies involving the FAT genes suggests a possible interplay of different gene mutations that are related by location (close proximity).

The cardiologist noted had been exceedingly difficult to perform the patient's echocardiogram because of his autism, mental disability, and resistance to being touched. This point is relevant, and we should ensure that physicians are fully aware of such potential barriers in managing these patients. Patients with HS with significant mental disabilities should be sedated during imaging, and extensive interaction with the patient is required.

Our patient also had a history of upper respiratory tract infection and gastroenteritis, both occurring in 2018: these are both features associated with HS.[4,17,24]

The patient's abdomen was protuberant on physical inspection. Since the previous week, he had recently started saying "ouch" when touched in various places, most notably his abdomen & legs. HS consists of an increase in interstitial fluid everywhere in the body. In our patient, this was speculated to be most notable in the abdomen and legs, as attested by the patient's

sensitivity and swelling in both leg and abdominal tissues. The increase in abdominal interstitial fluid indicates WD as a co-complication of HS. HS causes poor feeding due to alveolar/oral structural abnormalities or abdominal lymphangiectasias (WD), which would both cause swelling in the abdomen.[3,4,5,43]

He recently had a bout of diarrhea that was loose in nature and then progressed onto sticky, hard stools and then normalized. The patient's mother reported such episodes to have often occurred throughout the years. The patient's diarrhea could explain the low chloride levels observed in the laboratory results. He continued to exhibit abdominal tenderness without improvement through his visits: he guarded specifically the sides of his abdomen but was not able to localize or elaborate his complaint any further due to his intellectual conditions. He reported nausea but no vomiting. In addition, there had been a recent decrease in appetite, even for favorite foods. Additionally, he had a recent change in feeding behavior in the form of intolerance to sugary or fatty foods, and mild elevations in his legs were noted after heavy or fatty food consumption. It has been reported in the literature that in HS, it is critical that foods in the diet strictly conform to a high protein, low fat, and high medium-chain fatty acids (MCFA) composition. This is because medium-chain triglycerides directly enter the portal circulation and are transported to the liver, as opposed to long-chain fatty acids (LCFAs), whose uptake occurs in the intestines and which should be avoided in patients with intestinal lymphangiectasias.[4,5,7]

Waldmann's disease (Primary intestinal lymphangiectasias) has been associated with celiac disease.[4,7,12,22] In the present case, T-Transglutaminase IgG (7 U/ml) value was weakly positive for celiac disease, and the presence of these antibodies has been found to be indicative of WD, suggestive of primary intestinal lymphangiectasia secondary to HS.[4,7] The patient had an extremely high serum IgA level (738 mg/dl; normal interval, 90-386 mg/dl), suggesting celiac disease and intestinal lymphangiectasias (WD) secondary to HS.[4,7,22] Our interpretation was that his significantly high IgA and TTG-IgG levels are weakly associated with celiac disease, and villous atrophy results from the intestinal lymphangiectasias and the damage to the intestinal-interstitial barrier caused by TNF- α- and IL-6- induced immune reactions[4,6,7]

Our patient presented with a severe autism spectrum disorder and intellectual disability. The monosyllabic speech and alveolar clicks comprised most of our patient's responses; both have

been associated with previously reported HS patients.[43,44,45] The clicks are part of an array of reflexes babies initially do before complete tongue muscle functionality develops.[43] They have been reported with developmental delay. Therefore, if the alveolar clicks in our patient were due to developmental delay, it would also explain why HS patients present with feeding problems since muscle functionality and coordination are incomplete or absent.[43] However, one of the features of HS includes hypertrophic alveolar ridges, which could also be part of the reason he produced alveolar clicks.[44]

HS has been reported to present with scoliosis, other musculoskeletal issues, and habitus abnormalities.[1,2,24] Our patient did not report any spinal issues; however, he used a wheelchair. He initially ambulated at birth and throughout childhood, but the onset of leg swellings and the rapid weight gain in his preteen years marked his need for a wheelchair. Doubling the weight within a short time is also a reported feature in HS.[6]

HS has been associated with absent neck holding and webbed neck.[1,23,24,44,45] Our patient sat sideways in a wheelchair, his face turned downwards and to the left, looking at his mother throughout his clinical encounter. Our patient's asymmetrical cervical muscle tone could be due to the absence of neck holding reported in HS.[1,5] HS has also been associated with limb deformities.[1,2,22, 23,24] Our patient had long-standing established care with a podiatrist prior to his chief complaint clinic visit. He reported that he had been unable to wear shoes for many years because of swelling episodes. He reported a tarsal coalition (flat feet) secondary to swelling episodes and unilateral arthritis of the right ankle in 2019. However, his arthritis of the right ankle was not congenital or idiopathic but was claimed to be due to an injury at high school.

In terms of his laboratory findings, the combination of a high RDW of 17.8% and a low MCV of 79 Fl indicated iron deficiency anemia. Iron deficiency anemia and hypoalbuminemia could indicate that lymphangiectasias caused silent GI bleeding[5,7,25]. Both HS and WD have been noted to cause anemia.[24,25,47] The Low chloride of 98 mmol/L can be attributed to either his recurring bouts of diarrhea or the possible gastropathy-induced destruction of parietal and chief cells in the stomach.[4] Our patient also had low HDL and below average cholesterol/HDL ratio (indicating lipid abnormality): these were also related to lymph circulation abnormality. Although his HDL/cholesterol ratio was < 3 and his laboratory report stated his risk of heart attack was low,

despite his other indications for arterial atherosclerosis, he had a history of atherosclerosis. Based on previous literature, HS causes neoangiogenesis, which could be a potential explanation for this finding.[16] His HgbA1 was 6.0, signifying hyperglycemia. Lymph flow dysfunction has been associated with obesity, type 2 diabetes mellitus, and insulin resistance, thus possibly explaining this finding.[47]

HS also affects endocrine function due to the increased interstitial fluid around visceral glands such as the thyroid gland. The thyroid gland is particularly affected, with consequent thyroid hormone irregularities.[5,17,24] Our patient's previous laboratory values showed significantly low TSH levels (< 0.005) and a high T3 in 2019 and again in 2020. He also had a high PTH and abnormal calcium levels (10.1 mg/dl, i.e., on the upper end of the normal range). High PTH, low vitamin D, and abnormalities in calcium serum levels have also been highlighted in patients in HS.[16,17,48] Low vitamin D and osteomalacia have been reported in PLE caused by primary lymphangiectasia (WD) and HS.[7,10,26,31,33,48,49,50,51] Our patient also had chronically low vitamin D on laboratory tests, which prompted further assessment for osteomalacia and celiac disease in the first place.

To our knowledge, our patient was rescheduled at least three times due to his ambulatory status and mobility difficulties. The lack of motivation to establish a therapeutic alliance with the newly assigned physician may have been due to the fact that his previous care provider had relocated. HS patients previously reported in the literature were noted to be at an elevated risk of being lost to follow-up, causing them to present with a fatal complication later in life.[16,22,35,52] This suggests an increased need for HS patients to stay with the same doctor for as long as possible, one who is knowledgeable about their disease and keen to establish a connection with them. Doctors should also be capable of adequate communication methods when patients present with congenital language delays or mental disabilities. Some studies have shown that symbols and toys, as well as having one provider only in the room, help establish a better connection with children with autism. During the missed appointments, our plan was to draw a human body and draw the patient where he has been tender. If a primary care physician change occurs in an HS patient, physicians must be cautious about delivering a detailed and comprehensive background of the patient's medical record. In addition, this should be followed by specific preferences and

personality traits that could facilitate connection with new physicians and more efficient communication between the patient and the provider.

The presence or absence of autism spectrum disorder can also be included in patients with HS. This further suggests exploring gene mutations involved in HS and evaluating their spectrum based on location.

Hard, fibrotic, and clear discharge through the skin (chyle reflux of lymphoedema) is seen only in grade 4 late-onset primary lymphedema, suggesting a congenital etiology of our patient's chief complaint (Table II).[2,3,14]

Harrison's Principles of Internal Medicine 21e >Chronic Venous Disease and Lymphedema

Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson+

TABLE 282-3Stages of Lymphedema

Stage 0 (or Ia)
A latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist for months or years before overt edema occurs.
Stage I
Early accumulation of fluid relatively high in protein content that subsides with limb elevation. Pitting may occur. An increase in proliferating cells may also be seen.
Stage II
Limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as excess fat and fibrosis supervene.
Stage III
Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

Source: Adapted from The 2013 Consensus Document of the International Society of Lymphology: Lymphology 46:1, 2013.

Table 2: Stages of Chronic lymphedema, Harrison's principle of Medicine [53]

Because HS is diagnosed only based on the presence of its features, its identification can be challenging for providers since it is an exceedingly rare disease. The diagnosis relies less on laboratory data and imaging than on utilizing the data from a physical examination (through a detailed examination of its findings) and the patient's history. Both were especially important in the management of this case's patient. When we only rely on instrumental data (laboratory and imaging), it is much more challenging to suspect HS, and its diagnosis may be missed. This leads to further complications that might have been prevented, leading to higher mortality and high loss of follow-up.[16,26,35,52] As this case exemplifies, an accurate diagnosis of HS requires listening and seeing the patient not only limited to their current chief complaint but also

wholistically in the context of their past medical history. In this case, our patient was 26 years old and presented with an array of events that had occurred from birth, suggesting congenital etiology. All these led to his chief complaint of gross lymphedema with lymphorrhagia of the lower extremities, which is when the diagnosis was made.[22] The importance of diagnosing this helps us be proactive about what to ask for and look for during routine checkups.

The challenges of providing care for patients with HS are inherent in the many organs it affects but also entail ensuring patient compliance with the treatment recommendations. Treatment non-adherence results in poor patient outcomes. Our patient, who had an intellectual disability and autism, was not compliant with the treatment recommendation of compression socks and resisted wound care changes, which made it much harder to allow for ulcer improvement, which was nonexistent in our patient. Our patient continually picked up his ulcers when bothered or unsupervised. Due to his intellectual disability and autism spectrum disorder, he also had difficulty understanding the severity of his bilateral lymphedema and the risk for cellulitis or eventual leg amputation.[22] Thus, the HS-associated intellectual disability also makes HS diagnosis and management challenging.

Although congenital and not curable, diagnosing HS is essential as it drastically allows for the improvement of medical care provided as well as enhancing patients' quality of life.

Many of the cardiac structures on our patient's echo were not well visualized. The technician reported the patient's resistance to being touched by the probe and, conversely, attempted to grab the probe from the operator.

Treatment options possibly helpful for patients with HS are still under investigation. One study used octreotide to treat two patients with HS. Octreotide can be used to decrease protein and albumin loss caused by PLE in Hennekam syndrome.[5,49] HS patients must adhere to a strict diet with no low-chain triglycerides. Use of emollients and good care of the skin to prevent cellulitis and lymphangitis are essential.[53] Another novel drug that has been used with PLE secondary to GI disorders is cetuximab, especially in patients with PLE secondary to non-erosive mucosal disorder; the drug works as an antibody against epidermal growth factor.[4]

Although our patient had autism, which initially raised suspicion for Menkes-Hennekam syndrome (MHS), upon analysis of his signs and symptoms, there was higher suspicion of an HS diagnosis.[54] Future research will possibly elucidate whether HS has distinctive mutations or

whether it is on a spectrum of common mutations (including gene mutations causing autism spectrum disorder)[29] overlapping with MHS.

One more issue that must be further clarified and standardized across the literature regards the use of the terms primary lymphedema and lymphangiectasias, and the cause and effect relationship of the disorders, that is, whether one is caused by another or whether it results in another. HS can cause primary congenital lymphedema and as well as primary abdominal lymphangiectasias (otherwise termed as WD); it can ultimately cause PLE, and these cause-effect relationships need to be elaborated and distinguished from each other, so that literature reviews on this topic can become more effective.[4] The terms that we found in our literature search associated with HS or interchangeably used to identify HS are the following: generalized lymphatic dysplasia, Hennekam lymphangiectasia-lymphedema syndrome, intestinal lymphagiectasia-lymphedema-mental retardation syndrome, lymphedema-lymphangiectasia-intellectual disability syndrome.[5,24,27,28]

Conclusions

Diagnosing HS is critical for many reasons, and genetic testing may not be available or accurate, since the gene mutations causing HS only account for 20-25% of HS cases and are still being uncovered.[2,45] Relying solely on imaging or labs for diagnosing patients with HS is not adequate. Before ordering genetic testing for HS, physicians need to have a high index of suspicion by adequately considering the whole picture of the patient's current medical condition within the context of the previous history, carefully examining the physical examination's findings, in combination with laboratory test and imaging. A higher number of efficiently diagnosed HS patients would result in furthering our knowledge of the various genetic mutations that cause it.

Additional Information

Abbreviations

HS = Hennekam Syndrome

WD = Waldmann's Disease

PLE = protein-losing enteropathy

MHS = Menkes-Hennekam Syndrome

PTH = parathyroid

TSH = thyroid stimulating hormone

CMP = comprehensive metabolic panel

BMP = basic metabolic panel

MCFAs= medium triglyceride chain acid

LCFA = long chain fatty acids

WNL = within normal limits

RDW = red cell distribution width

MCV = mean corpuscular volume

MCHC = mean corpuscular hemoglobin concentration

MPV = mean platelet volume

TTG-IgG = Tissue Transglutaminase Antibody, IgG

RUQ = right upper quadrant

Declaration

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors declare that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors declare that there are no other relationships or activities that could have influenced the submitted work. **Patient consent to publication:** Written consent for the publication of photographs and other case details that could identify our patient was obtained from our patient and can be obtained upon journal request prior to manuscript submission.

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