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CASE REPORT

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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Key Clinical Message

Adequate evaluation of patients with Hennekam Syndrome (HS) is challenging for physicians, because of multi-organ involvement and complex pathophysiology. We report the first case in an African American with lymphedema, who developed protein-losing enteropathy (PLE) and was successfully diagnosed with HS from cause-and-effect complications by Waldmann's Disease (WD) and comorbid Celiac Disease (CD).

Abstract

As far as we know, this is the 51st case of HS worldwide and the first one in an African American. The examined patient met all diagnostic criteria for HS, suggesting a dysfunction in the development of the lymphatic system, with associated comorbidities including developmental delay, gastrointestinal pathologies, facial and hearing abnormalities, and cardiac defects. Primary intestinal lymphangiectasia (WD) is a consequence of HS, which ultimately results in PLE and worsening interstitial lymph buildup. Based on our findings, 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-thyroid stimulating hormone antibodies in HS patients. 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. The interstitial lymph fluid-induced TNF-α and IL-6-mediated immunopathogenic reactions lead to inflammation and subsequent destruction of the intestinal mucosa. 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, and leading to gastropathy. Considering the examined patient's history of gastroenteritis and the literature stating that CD is a non-mucosal cause of gastropathy and PLE, it is suggested that sequelae of GI complications occur in a cause-and-effect chain in HS. HS

results in WD, which causes CD, resulting in hypertrophic gastropathy and loss of parietal and chief cells, eventually leading to malabsorption and PLE (Figure 1). HS primarily affects various organs due to inflammatory-mediated damage and accumulation of lymph fluid. Other findings for HS include keratoconjunctivitis sicca (dry eye disease), fibrous lymphedema exhibiting lymphorrhea, chylous ascites, anemia, and parathyroid abnormalities. Immune impairment in HS predisposes patients to autoimmune disorders, therefore autoimmunity (CD) and WD are concomitant comorbidities of HS. HS-associated comorbidities are primarily due to inflammation and damage to immune cell transport or underlying health conditions affecting proper lymphatic function. However, it is suggested that HS mutations may disrupt the development of the lymphatic system leading to further complication. complications can be compound heterozygous, and there is a need for further research to identify nearby genes that can cause concomitant co-morbidity.

KEYWORDS

Celiac, Hennekam, lymphangiectasia, lymphedema, Waldmann's

1 | INTRODUCTION

Hennekam syndrome (HS) 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.[1] Additional features of the disorder include facial dysmorphism and cognitive impairment since there is widespread lymphatic blood vessel expansion.[2,3]

First discovered in 1980 by Dr. Hennekam et al., this syndrome is caused by mutated lymphatic vessel formation, which results in poor lymph drainage and increased fluid in the interstitium of the body cavities.[4–6] The increased interstitial fluid results in dilation of the lymphatic vessels, termed lymphangiectasias, in the abdomen and lymphatic build-up (lymphedema), which most often occurs in the extremities.[5,7] Visceral lymphangiectasias lead to effusions eventually produce 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, iron deficiency anemia, hypoalbuminemia, hypogammaglobulinemia, electrolyte abnormalities, and lymphopenia.[2,7–10] These abnormalities can cause brain defects and contribute to seizures.[4,11–14] The lymphedema seen in HS can be distinguished from other lymphedema syndromes by its ascending manifesting at the lower limbs first, then presenting in the intestine, lungs, and other organs later in life.[5,6,10,15,16]

Other HS features include growth delays, mild to severe mental disability, dental and facial abnormalities, and limb deformities. Some patients also presented with food allergies and atopic dermatitis.[6] The presence of both low albumin and iron-deficiency anemia could indicate that lymphangiectasias may cause silent GI bleeding.[10,17] Iron deficiency anemia could also be attributed to malabsorption secondary to PLE.[7,8]

Intestinal lymphangiectasias in the GI tract, also known as Waldmann's Disease (WD), have shown pinpoint white lesions in the small intestine, also resulting in dilated lacteals and edematous ileocecal valve.[18] WD can be primarily due to congenital issues or secondarily caused by another pathology. HS can cause WD when the interstitial fluid buildup progresses to involve the abdomen, causing chylous ascites.[4,12,19,20] Long-standing lymphangiectasias in the bowel eventually leads to fibrosis at the small intestine, causing obstruction and infection. These changes can affect the permeability of intestinal cells, compromising the maintenance of proteins, and lead to PLE.[8,11–14,21,22]

While WD only refers to the intestinal area, HS shares a similar pathophysiology of dysfunction in the lymphatic system, 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.[7,8,19]

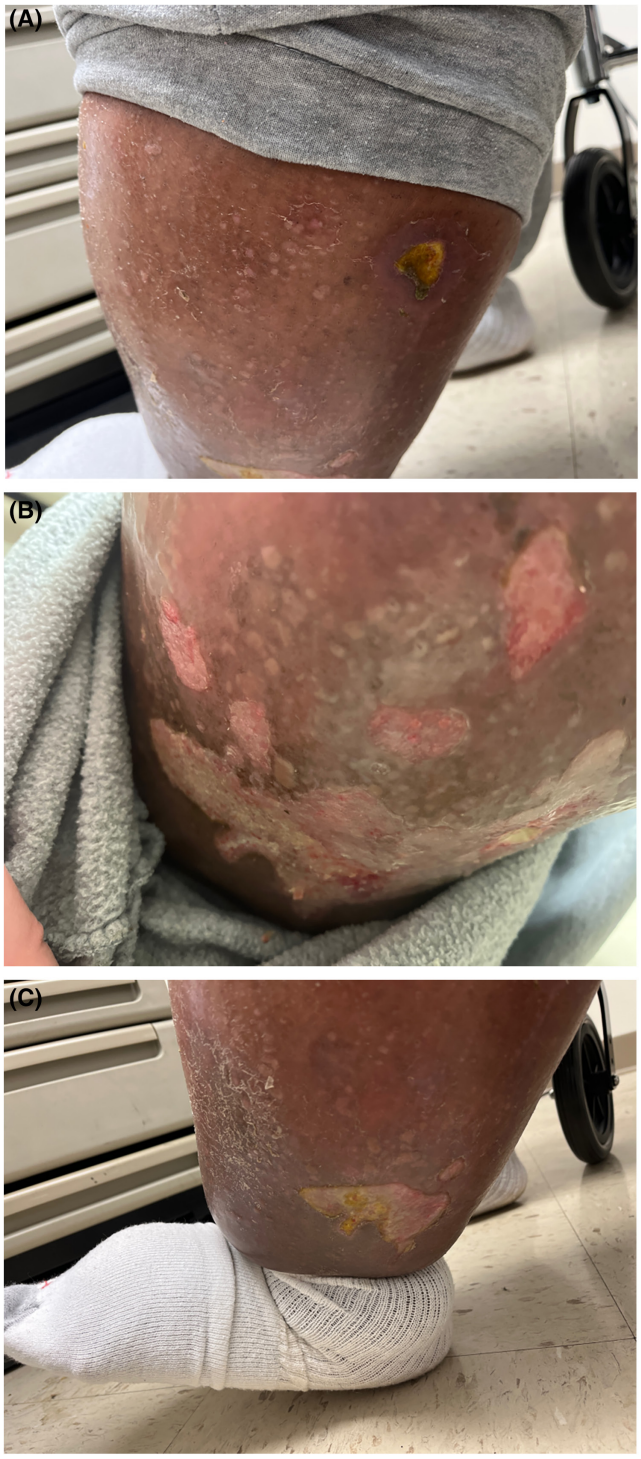

FIGURE 1 Our 26-YO patient on a wheelchair and presenting with bilateral lymphedema and lymphorrhea.

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.[23] 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.[23]

PLE is accompanied by hypoproteinemia, hypoalbuminemia, and fat malabsorption. Protein loss may manifest as ascites, lymphedema of the lower legs, and a positive stool test for A1T1.[11,14] Hepatic protein synthesis will be ramped up to maintain an osmotic gradient after protein loss. The liver will rapidly process proteins like prealbumin, transthyretin, IgE, and insulin. However, low lipids, low iron, and other trace elements, and lymphopenia are secondary to lymphatic obstruction.[13,14]

There are different types of PLE including, non-erosive type, not entailing erosion of the intestinal mucosa, which includes Celiac Disease, *Helicobacter pylori* gastritis, and Menetrier's disease (AKA giant cell gastric hypertrophy).[4,23–27] The mechanism for PLE is triggered when one of these non-erosive conditions ultimately causes loss of surface intestinal epithelial cells and consequent malabsorption.[4,11–14,22] Lymphedema will proceed as dilated lymphatic vessels rupture, at which point lymphangiectasias form.[6,15,16,28]

Since its initial discovery, and although rare, HS has been recorded in approximately 50 patients worldwide.[10] Many HS patients may currently be undiagnosed due to the complexity of HS nature and the many organs interested. The cause of intestinal lymphangiectasias, whether primary or familial, its association with various forms of autoimmune or inflammatory changes, the manifestation of PLE, and the inevitable physical presentation of lymphedema in patients are still incompletely elucidated.[7,12,22,28] 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. Since these mutations comprise only a small amount of HS patients, genetic heterogeneity is suggested (Figure 1). This raises the further need to identify and analyze mutations involving embryonic development of the lymphatic vessels that cause or contribute to HS, as well as to possibly overlapping co-morbid conditions.[15,29]

2 | CASE REPORT

A 26-year-old African American male patient with autism spectrum disorder and mental disability presents to the clinic in a wheelchair for a 3-month history of gross bilateral leg and ankle swelling and ulcers (Figures 1A,B,C). He is on the incremental dosage of furosemide, albeit with minimum relief. There is no erythema or jaundice.

Days before the visit, he experienced worsened orthopnea, decreased appetite, and a diarrhea episode which progressed to constipation. A month earlier, abdominal and extremity tenderness was noted.

The patient ambulated normally until his preteen years when suddenly massive lymphedema episodes with intermittent lymphorrhea from his feet occurred. He gained weight from the swelling, causing him to use a wheelchair.

Medical history includes keratoconjunctivitis sicca (dry eyes), pre-diabetes, obesity (BMI >49.5), gastroenteritis, and upper respiratory infections. Celiac Disease was reported from a weakly positive T-Trans glutaminase IgG and high serum IgA. Abnormal serum calcium levels, hyper-parathyroid (PTH), low thyroid stimulating hormone (TSH) levels, and vitamin D deficiency were reported from lab examinations in the past 7 months. Tarsal coalition deformity ("flat foot") was reported as secondary to the onset of swelling. In the past 7 months, bilateral atherosclerosis in the extremities and intermittent claudication have been reported.

Medications only include furosemide and Vitamin D.

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 his 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.

2.1 | Physical exam findings

The patient is noted to have central obesity (BMI = 53.5) and responding in alveolar clicks, or one-word answers (monosyllabic speech) noted upon physical examination.

On his last visit, he was bradycardic with a reported pulse from 96 on previous visits 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).

S3 gallops were found upon heart auscultation. An echocardiogram revealed mild concentric left ventricle cardiomyopathy.

Physical examination confirms a protuberant abdomen and abdominal guarding.

There are 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, positive stemmer's sign, and socks do not fit and are soaked. There is also guarding to approach the left leg and a physical inspection of the ulcer showed no improvement when compared to the previous visit.

Red blood cell laboratory testing (Table 1) revealed low hemoglobin (13.2 g/dL), high red cell distribution width (RDW) (17.8%), and a low mean corpuscular volume (MCV) (79 FL) indicating iron deficiency anemia. Low albumin (3.3 mg/dL) confirmed hypoalbuminemia. A low chloride (98 mmol/L) can be attributed to his recurring diarrhea or gastropathy-induced destruction of parietal and chief cells. basic metabolic panel (BMP) and comprehensive metabolic panel (CMP) were normal, ruling out kidney or liver dysfunction.

In addition to laboratory findings, with a thorough physical examination and past medical history, this patient was diagnosed with HS with comorbid WD and CD.

3 | DISCUSSION

Considering the patient's history of gastroenteritis and Celiac Disease, and non-mucosal gastropathy in Protein

TABLE 1 Patient's CBC at the time of presentation.

CBC report	Result	Ref. range	Units	Level status
Hemoglobin	13.2	13.5–17.5	GM/DL	Low
Mean Corpuscular Volume (MCV)	79.0	81.2–95.1	FL	Low
Mean Corpuscular Hemoglobin (MCHC)	25.5	26.0–34.0	PG	Low
RDW coefficient of variation	17.8	11.6–14.4	%	High
Mean platelet volume	8.9	9.4–12.4	FL	Low

Note: Normal Results: White Blood Cell (WBC) count $7.4\times10E^3/\mu L$; Red Blood Cell (RBC) count: $5.18\times10E^6/\mu L$; Hematocrit (HCT): 40.9%; Mean Corpuscular Hemoglobin Concentration (MCHC): 32.3 GM/DL; Red Cell Distribution Width (RDW) standard deviation: 50.4 FL; Platelet count: $313\times10E^3/\mu L$. Immature granulocytes % auto: 0.3%; Neutrophils % auto: 62.2%; Lymphocytes % auto: 29.1%; Monocytes % auto: 7.1%; Eosinophils % auto: 1.0%; Basophils % auto: 0.3%; Immature granulocytes # auto: $0.02\times10E^3/\mu L$; Neutrophils # auto: $4.58\times10E^3/\mu L$; Lymphocyte # auto: $2.14\times10E^3/\mu L$; Monocytes # auto: $0.52\times10E^3/\mu L$; Eosinophils # auto: $0.07\times10E^3/\mu L$; Basophils # auto: $0.02\times10E^3/\mu L$; Nucleated Red Blood Cell (NRBC) Antibodies = $0\times10E^3/\mu L$, NRBC Percentage: 0%. Units: GM/DL, grams/decaliter; FL, femtoliters; PG, picograms; $\times10E^3/\mu L$, multiplied by 10 to the power of 3/microliters.

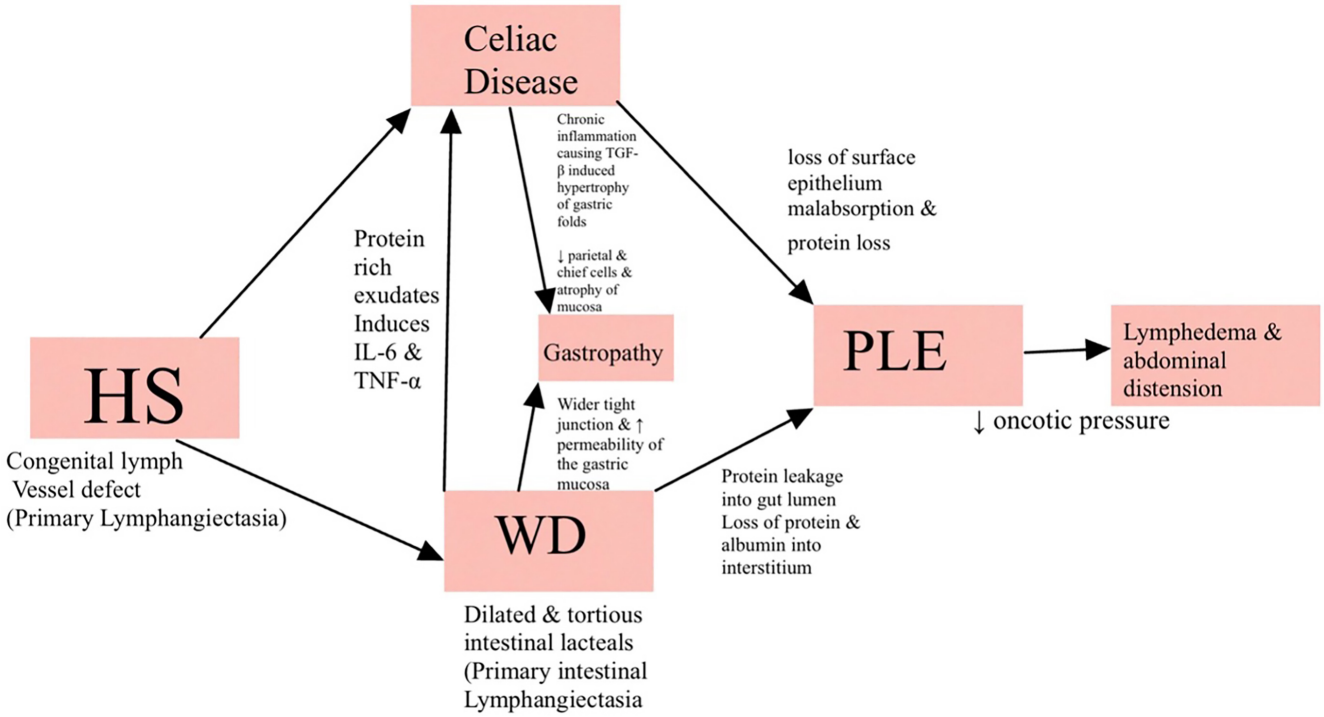

FIGURE 2 Proposed order of events for lymphangiectasia causing Celiac Disease and PLE (HS, Hennekam Syndrome; PLE, protein-losing enteropathy; WD, Waldmann's Disease).

Loss Enteropathy, it is suggested that GI complications in HS may occur in a cause-and-effect chain. Autoimmunity, such as CD and Waldmann's Disease are coexisting comorbidities of HS (Figure 2).[4,7,8]

HS mutations leading to an abnormal build-up of fluid leads to the swelling and subsequent lymphedema. As swelling progresses from the legs to the intestine, dilation of vessels at the small intestine may eventually lead to the leaking of the proteins to the GI, a decrease in protein levels in the blood, and malabsorption as seen in WD. Primary intestinal lymphangiectasias from WD have been associated with Celiac Disease.[4,8,16,19] This patient is suggested to have HS, favoring congenital etiology, comorbid with Waldmann's Disease lymphedema and Celiac Disease. Other complications to be noted include insulin resistance, cardiovascular involvement, developmental delay, and treatment management (Figure 2).

In this case, the examined 26-year-old patient 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.[16]

At the center of HS and WD comorbid with CD, lies the first sign of inflammation—swelling. The hard, bilateral, gross lower extremity swelling with fibrosis, chylous reflux, and lymphorrhea in this patient suggests lymphedema (over that of edema).[15] The patient examined also had positive Stemmer's sign, "hard" lower extremity swelling, distinguishing lymphedema from edema.[5,8,10,15,16] The edema was most prominent on the dorsum of the foot, further characterizing lymphedema.[8,15] The patient experienced gross bilateral edematous swelling episodes, with a fibrotic appearance on the anterior shin. Hard, fibrotic, and clear discharge is notable for chyle reflux, a sign of late-onset grade 3–4 lymphedema in primary lymphedema.[10,15,16] The patient's unfitting, soaked socks are attributed to the clear, odorless discharge secreted through the skin of the lower extremities. This is noted as lymphorrhea (chylous secretion) and is a characteristic feature of primary lymphangiectasia.[29,30]

Primary lymphangiectasia (WD) and HS eventually lead to PLE. PLE is accompanied by hypoproteinemia, hypoalbuminemia, and fat malabsorption, despite normal hepatorenal function. PLE is suggested in this patient 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.[4,7,17]

Low vitamin D and osteomalacia have also been reported in PLE caused by primary lymphangiectasia (WD) and HS.[8,13,18,28,30–33] This patient also had chronically low vitamin D on laboratory tests, which prompted further assessment for osteomalacia and Celiac Disease in the first place given the malabsorption of vitamins caused from PLE and subsequent hypertrophic gastropathy.

Waldmann's Disease has been linked with Celiac Disease.[4,8,16,19] In the present case, T-Transglutaminase IgG (7 U/mL) value was weakly positive for Celiac Disease, and the presence of these antibodies is indicative of WD, suggestive of primary intestinal lymphangiectasia secondary to HS.[4,8] 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.[4,8,16] It is interpreted that a significantly high IgA and tissue transglutaminase antibody-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.[4,5,8]

The immune-mediated response through inflammatory cytokines can promote stress signals, which may interfere with endocrine functions. In obesity, as seen in this patient, adipose tissue inflammation can attract immune cells and cytokines will be triggered interfering with insulin signaling, creating insulin resistance, and predisposing to diabetes. His HgbA1 was 6.0, signifying hyperglycemia. Lymph flow dysfunction has been connected to obesity, type 2 diabetes mellitus, and insulin resistance, thus possibly explaining this patient's hyperglycemia.[34]

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.[2,10,23] The examined 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.[2,4,28]

The examined patient also had a history of associated features with HS including upper respiratory tract infection and gastroenteritis in 2018.[2,4,16] Additionally, defective lymph vessels have been reported to cause lymphangiosis in the eyes, resulting in dry eye disease which can suggest why the patient struggled with dry eyes (keratoconjunctivitis sicca) for years.

A weakened autoimmune system leads to vascular impairment from long-standing lymphatic fluid in the interstitial space causing chronic inflammation. HS causes neoangiogenesis, which could be a potential explanation for this patient's inflammatory-induced fibrosis and atherosclerosis.[35]

Vascular impairment may also lead to anemia. 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 lymphangiectasia caused silent GI bleeding.[7,8,17] Both HS and WD have been noted to cause anemia.[10,17,34] 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] The patient also had low HDL and below average cholesterol/HDL ratio (indicating lipid abnormality): these were also related to lymph circulation abnormality.

HS has been associated with constrictive pericarditis due to the lymph fluid buildup around the pericardium.[2,4,10,36] On physical examination, S3 gallop sounds were found at heart auscultation which could indicate constrictive pericarditis. Further cardiovascular involvement is confirmed in this patient from echocardiography findings of mild concentric left ventricular hypertrophy possibly indicative of familial restrictive cardiomyopathy.[29,37,38]

Although further genetic investigation is suggested, FAT gene mutations may be involved in this patient. There is evidence that FAT4 mutation, also termed NFATC3, in HS has also been related to cardiomyocyte hypertrophy. This is consistent with the patient's echo showing mild left ventricular hypertrophy.[25,39] This is also suggestive of restrictive cardiomyopathy of the familial type, which is related to a FAT1 mutation.[4,29,37,38,40] The presence of two pathologies involving the FAT genes suggests a possible interplay of different gene mutations that are in close proximity. In addition, the patient's mother reported that the swelling episodes began during the patient's preteen years. 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 later in life rather than at birth, it is suggested that this patient has type 2 HS involving the FAT4 gene mutation.[15,29]

Although this patient had autism, which initially raised suspicion for Menkes-Hennekam Syndrome (MHS), upon analysis of his signs and symptoms, there was a higher suspicion of an HS diagnosis.[41] 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)[23] overlapping with MHS.

The genetical component is one of many complexities in diagnosing HS. However, its diagnosis relies less on laboratory data and imaging and more on utilizing the data from a physical examination (through a detailed examination of its findings) and the patient's history. 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. When reliance is placed solely on instrumental data (laboratory and imaging), it is much more difficult 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.[1,18,42,43] 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.

However, it is important to note that performing a thorough patient history and physical exam may be limited in patients with HS, given patients, like this patient, have presented with a severe autism spectrum disorder and intellectual disability. The monosyllabic speech and alveolar clicks comprised most of this patient's responses; both have been associated with previously reported HS patients.[44–46] The clicks are part of an array of reflexes babies initially do before complete tongue muscle functionality develops.[44] They have been reported with developmental delay. Therefore, if the alveolar clicks in the 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.[33] However, one of the features of HS includes hypertrophic alveolar ridges, which could also be part of the reason he produced alveolar clicks.[46]

Doctors should 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 in the room, help establish a better connection with children with autism. It is suggested that HS patients 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. During the missed appointments, the plan was to draw a human body and draw the patient where he had 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.

In these patients, there are also barriers in performing physical examinations to adequately screen and diagnose HS. In this patient's case, many of the cardiac structures on the 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.

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. The patient examined, 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 this patient. The 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 of cellulitis or eventual leg amputation.[16]

Proper management and treatment may be challenging for physicians given the limited communication. Therefore, HS may be misdiagnosed or not treated properly. For example, in this patient's initial chief complaint appointment, he also had lower extremity ulcers with no improvement despite diuretic (furosemide) therapy. Of note, the patient's laboratory examinations for BMP/CMP were consistently normal, signifying no kidney or liver dysfunction. 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]

Although congenital and not curable, diagnosing HS is essential as its diagnosis improves proper medical care and treatment, as well as enhancing patients' quality of life. 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 HS.[7,30] HS patients must adhere to a strict diet with no low-chain triglycerides. The use of emollients and good care of the skin to prevent cellulitis and lymphangitis are essential.[47] 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]

Accurately diagnosing HS helps us be proactive in patient history and identifying signs and symptoms during routine checkups. Therefore, deeper exploration of the association of genetics in HS and treatment options is needed. Further clarification and standardization across literature is also necessary regarding the use of the terms “primary lymphedema” and “lymphangiectasias,” and the cause-and-effect relationship of the disorders (Figure 2), that is, whether one is caused by another or whether it results in another. HS can cause primary congenital lymphedema 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.[48] The terms in the literature search connected with HS or interchangeably used to

identify HS are the following: generalized lymphatic dysplasia, Hennekam lymphangiectasia-lymphedema syndrome, intestinal lymphangiectasia-lymphedema-mental retardation syndrome, lymphedema-lymphangiectasia-intellectual disability syndrome.[7,17,21,22]

4 | CONCLUSIONS

Diagnosing HS is critical for many reasons, and genetic testing may not be available or accurate. 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, and carefully examining the physical examination's findings, in combination with laboratory tests and imaging. A higher number of efficiently diagnosed HS patients would result in furthering our knowledge of the various genetic mutations that cause it.

AUTHOR CONTRIBUTIONS

Tannaz Safari Vejin: Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing – original draft; writing – review editing. **Maria E. Zepeda:** Supervision; writing – review editing. **Benjamin S. Yglesias:** Data curation; methodology; supervision. **Peter Devito:** Data curation; supervision.

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CONFLICT OF INTEREST STATEMENT

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 3 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.

DATA AVAILABILITY STATEMENT

The original image in Figure 1 and other postulations from this report are available within the article, licensed under CC BY-NC. For additional access or inquiries, contact the corresponding author.

CONSENT

Written consent for the publication of photographs and other case details that could identify our patient was obtained from our patient and can be provided upon journal request prior to manuscript submission.

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