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Case Report

Rapid lymphatic malformation expansion: Imaging, association with asymptomatic *Streptococcus* infection, multidisciplinary management, and therapeutic approach ☆,☆☆

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ABSTRACT

Lymphatic malformations are congenital anomalies of the lymphatic system that can occur anywhere in the body and typically present in early childhood. They are often painless, slow-growing, and asymptomatic, but may lead to a wide range of symptoms depending on their size and location. Rarely, congenital malformations may not be diagnosed until later in childhood or adolescence, despite being present from birth. In some individuals, lymphatic malformations can expand quickly, especially in the setting of an inflammatory process. We present the case of an 8-year-old boy who had a rapidly enlarging, nonpainful mass on his right neck and a positive *streptococcus* throat swab. After evaluation by multiple specialists and imaging studies, he was diagnosed with a multilocular, multicystic lymphatic malformation. He was treated with fluoroscopy-guided doxycycline sclerotherapy, and has had near total resolution of neck swelling. This case report is significant because it highlights the potential benefits of a multidisciplinary approach to the diagnosis and management of lymphatic malformations. Additionally, it emphasizes the importance of considering congenital malformations in the differential diagnosis of neck masses, even in older children. Finally, it also adds to the growing body of evidence that hypothesizes that strep throat infections may trigger the sudden expansion of previously asymptomatic congenital lymphatic malformations.

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Introduction

The lymphatic system is composed of a network of lymphatic vessels that extend throughout the body. These vessels carry fluid that is composed of immune cells, proteins and lymph [1]. Lymphatic vessels return interstitial fluid that has extravasated from blood capillaries back to blood circulation in a unidirectional network of vessels and thus maintains tissue fluid homeostasis. The one-way transport system is essential to the role of the immune system, maintenance of interstitial fluid volume, protein concentration, and fat metabolism [1,2]. A single layer of lymphatic endothelial cells constitute lymphatic capillaries and allow immune cell entry and transport of macromolecules with the interstitial fluid [3].

Lymphatic malformations are rare, congenital, low-flow dysplasias that are described by the International Society for the Study of Vascular Anomalies (ISSVA) as distinct vascular tumors. These vascular anomalies commonly occur in the head and neck and lead to the accumulation of fluid in tissues, resulting in lymphedema [2,4]. The lymphedema occurs as a result of the inability of the lymphatic vessels and nodes to clear lymph. The lymphatic masses are composed of varying cysts that can be classified as macrocystic or microcystic. In the macrocystic type, 1-3 large cystic lesions are present, while the microcystic type contains aggregates of small cystic lesions. Additionally, these malformations can lead to a dysfunctional circulation of chyle, leading to a chylous effusion [5,6]. The precise genetic mechanisms underlying lymphatic malformations is not fully understood and currently under investigation, but recent literature suggests that the majority of congenital lymphatic malformations are associated with mutations to the PIK3CA gene, which plays an important role in the mTOR (mammalian target of rapamycin) pathway [7]. It is now recognized that the pathogenesis of lymphatic malformations is distinct from the etiology of primary lymphedema, a condition in which several other genes have been implicated, such as lymphangiogenic growth factor vascular endothelial growth factor receptor (VEGF)-C and its receptor, vascular endothelial growth factor receptor (VEGFR), along with its cascading signals, and downstream genes such as FOX2, GATA2, CCBE1, and ADAMTS13 [2].

Case presentation

An 8-year-old boy was brought to his pediatrician because of neck swelling that started 4 days prior. He had no pain, fever, itching, sore throat, fatigue, cough, otalgia, sick contacts, or other symptoms. Medical history included obesity. His prenatal course, birth, and early childhood were unremarkable. He was developmentally normal and received all immunizations according to a routine schedule. There was no family history of cancer, anatomic defects, or lymphatic conditions. On physical exam, he had a soft, nontender, nonerythematous, right-sided neck mass measuring 4 × 5 cm. He had full range of motion of the neck and the remainder of his exam was normal. Although he had no signs or symptoms of infection, a swab of the oropharynx was performed due concern

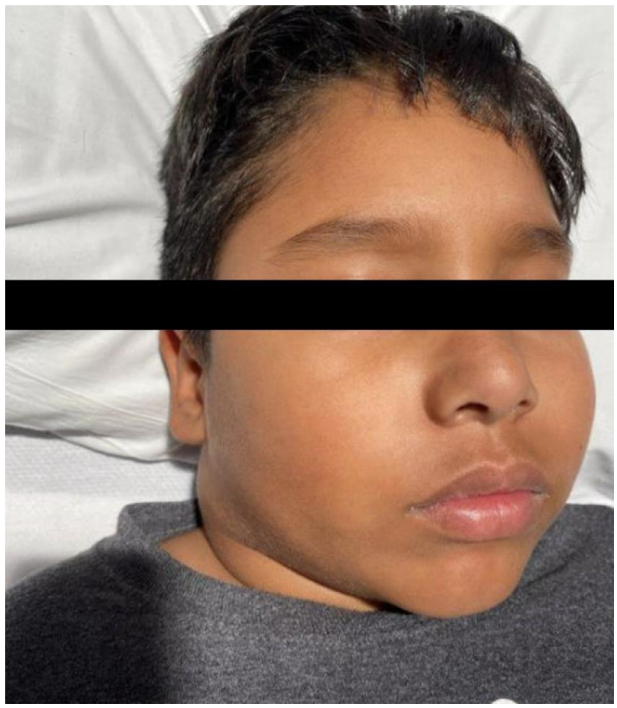

Fig. 1 – Right sided neck swelling 8 days after onset of symptoms.

from *streptococcal*-induced lymphadenitis and high regional incidence of respiratory infections at the time. He tested positive for *streptococcal* infection and was prescribed oral amoxicillin. Testing for coronavirus disease 2019, influenza, and respiratory syncytial virus were negative.

Three days following the initial examination, the pediatrician called the patient's mother to assess the patient's progress. She reported that despite adequate adherence to the prescribed antibiotic treatment, his neck mass had become firmer, prompting the patient to seek assistance from his school nurse, who had been applying warm compresses. The patient was re-evaluated the next day, where his physical exam findings were similar to his earlier office visit, except the mass was firmer and had grown to 5 × 6 cm (Fig. 1). The early differential diagnosis included reactive lymphadenopathy and lymphadenitis. However, due to the lack of response to antibiotics, atypical character, and the increased firmness of the mass beyond what is typically seen in these conditions, a decision was made to send the patient to the emergency department. In the ED, he had a normal white blood cell count, mild anemia (hemoglobin 10.5 g/dL) and slightly elevated serum proteins (7.9 g/dL), alanine transaminase (77 U/L), and C-reactive protein (1.62 mg/dL). He was evaluated by the pediatric hospitalist, interventional radiology, hematology/oncology, and otolaryngology. The team admitted the patient for further evaluation and started intravenous clindamycin (13 mg/kg).

On ultrasound, a large, multilocular, multicystic lesion in the right neck soft tissues containing numerous cystic components was seen (Fig. 2). Most of the cystic lesions contained simple anechoic fluid, although some contained internal de-

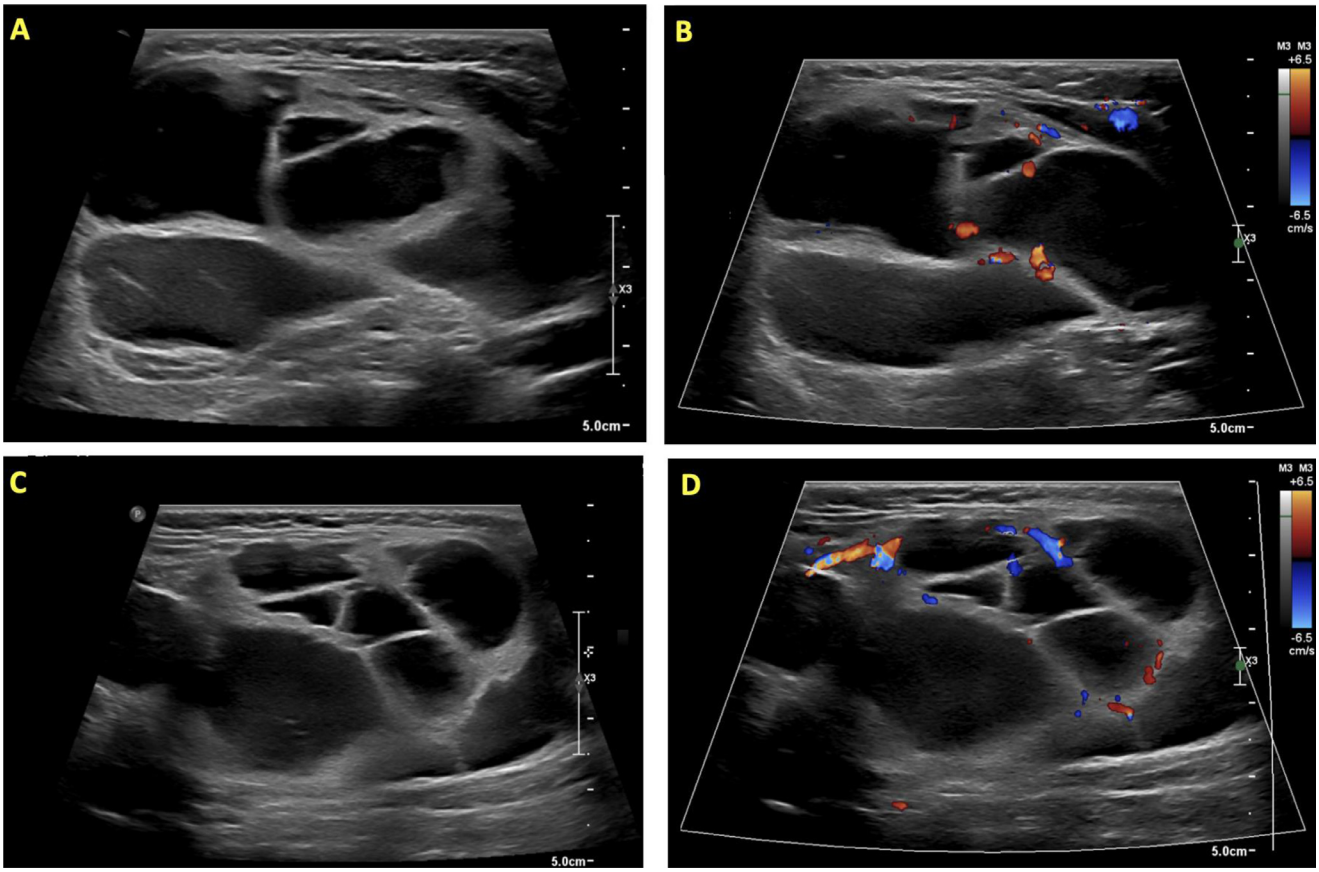

Fig. 2 – Ultrasonography of the right neck in (A) transverse view, (B) transverse view with Doppler, (C) sagittal view, and (D) sagittal view with Doppler, demonstrating multiple loculations and cystic components within the tissue. There is moderate blood in septations between the cystic lesions.

bris. There was moderate blood flow in septations between the cystic lesions, but no solid, nodular, or mass-like areas with internal blood flow were observed. Adjacent soft tissues showed no definite inflammatory changes.

Computed tomography (CT) revealed a lobulated, multilocular cystic structure in the posterior lateral right neck (Fig. 3). It also showed anterolateral mass effect upon the right sternocleidomastoid muscle and anterior-posterior narrowing of the right internal jugular vein due to mass effect. There was mild enlargement of the adenoids, palatine tonsils, and lingual tonsillar tissue.

On magnetic resonance imaging (MRI), the lesion measured 5.3 × 5.1 × 7.2 cm and had numerous septations (Fig. 4). It was T2 hyperintense, with T1 hyperintense contents compatible with proteinaceous or hemorrhagic debris. Following contrast, there was enhancement of the septations but no focal nodular enhancement.

He was diagnosed with a macrocystic lymphatic malformation and was discharged on oral clindamycin. Thirty-nine days after initial onset of symptoms, he underwent outpatient doxycycline sclerotherapy by interventional radiology with fluoroscopic and ultrasonographic guidance (Fig. 5). The Siemens System was used for fluoroscopic radiation exposure, with a fluoroscopic time of 0.8 minutes and a dose area product of 97.04 microGy-m2. The skin dose was 10.2 mGy. Four dominant macro cysts were identified and injected with 100 mg of doxycycline each, for a total of 400 mg. The cysts were accessed using a 19 gauge sheathed Yueh needle, with minimal intercommunication observed between them. He tolerated the procedure well without complications.

The patient was re-evaluated in the multispecialty vascular anomalies clinic several weeks later, where he and his mother reported significant reduction in neck swelling and no residual symptoms. Ultrasound revealed mildly prominent lymph nodes within the right neck soft tissues, a single, 12 × 3 mm residual, and other smaller cysts (Fig. 6). The multidisciplinary treatment team concluded that he exhibited a near complete clinical response and required no long-term follow-up.

Discussion

Lymphatic malformations are typically diagnosed and treated in children and adolescents with assistance from clinical-radiologic confirmation. Lesions in the head and neck have the potential to negatively affect physiologic and psychosocial development [8]. Current state of the art imaging of lymphatic vessels include x-ray lymphography, lymphoscintigra-

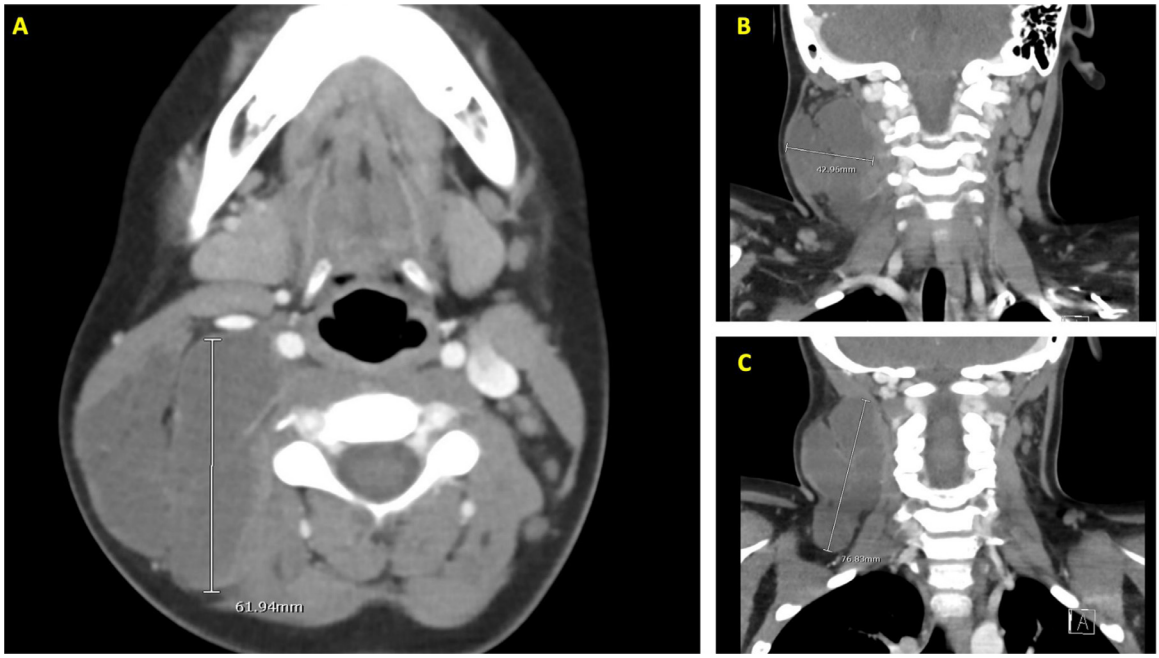

Fig. 3 – Computed tomography showing a lobulated multilocular cystic structure in the posterior lateral right neck measuring 6.2 x 4.3 x 7.7 cm. (A) Axial view demonstrating multiple cystic components measuring 6.2 cm. (B) Coronal view of the lymphatic malformations measuring 4.3 cm and (C) Coronal view measuring 7.7 cm.

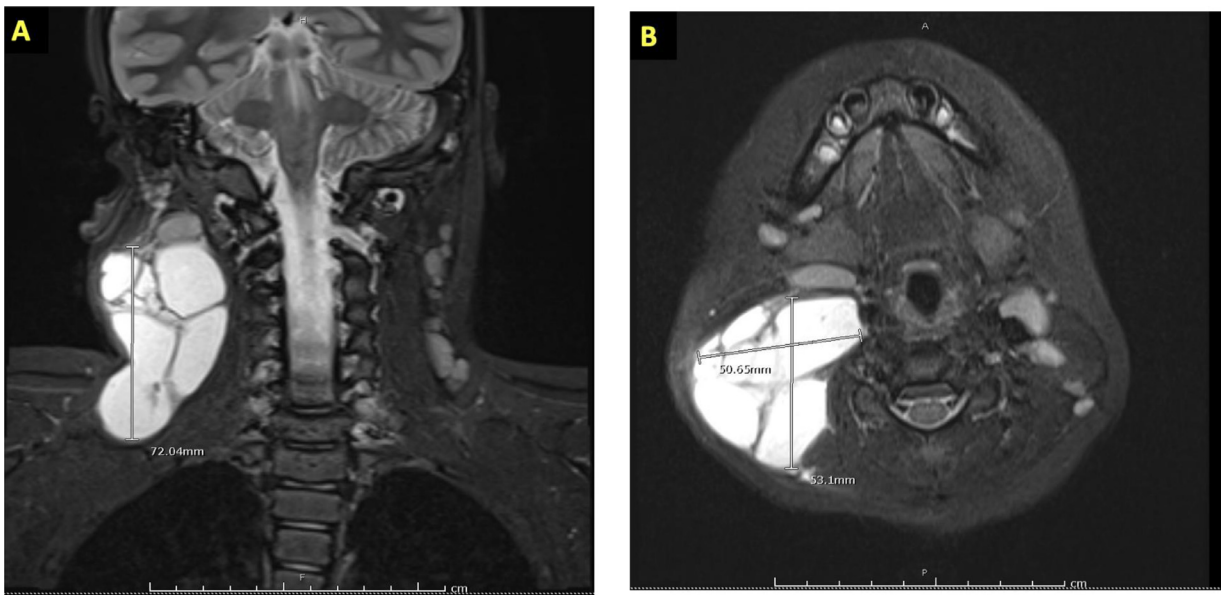

Fig 4 – Magnetic resonance imaging revealing a multilocular, lobular cystic structure in the posterolateral right neck with numerous septations. The lesion measured (A) 7.2 cm in a coronal view and (B) 5.3 x 5.1 cm in an axial view.

phy, SPECT/CT, NIR lymphography, and MR lymphography. Interstitial injection of tracers prior to imaging of the lymphatic system allows for better visualization [9]. Treatment of lymphatic malformations is managed via surgery or sclerotherapy, with no distinction in which method is more effective [8]. Commonly used sclerotherapy agents, such as picibanil (OK-432), bleomycin, Ethibloc, sirolimus, and doxycycline, generally yield positive clinical outcomes [7,10].

Lymphatic malformations are predicted to occur every 1 in 2,000 live births [11]. Although they are a fairly rare congenital defect, they are typically benign and nonthreatening. As appeared in this case, most macrocystic lymphatic malformations are located in the neck, and a majority of them (54%) are located in the posterior triangle [12]. Half of lymphatic malformations are discovered at birth and 90% are identified by 2 years of age [12,13]. Much less commonly, they can be found

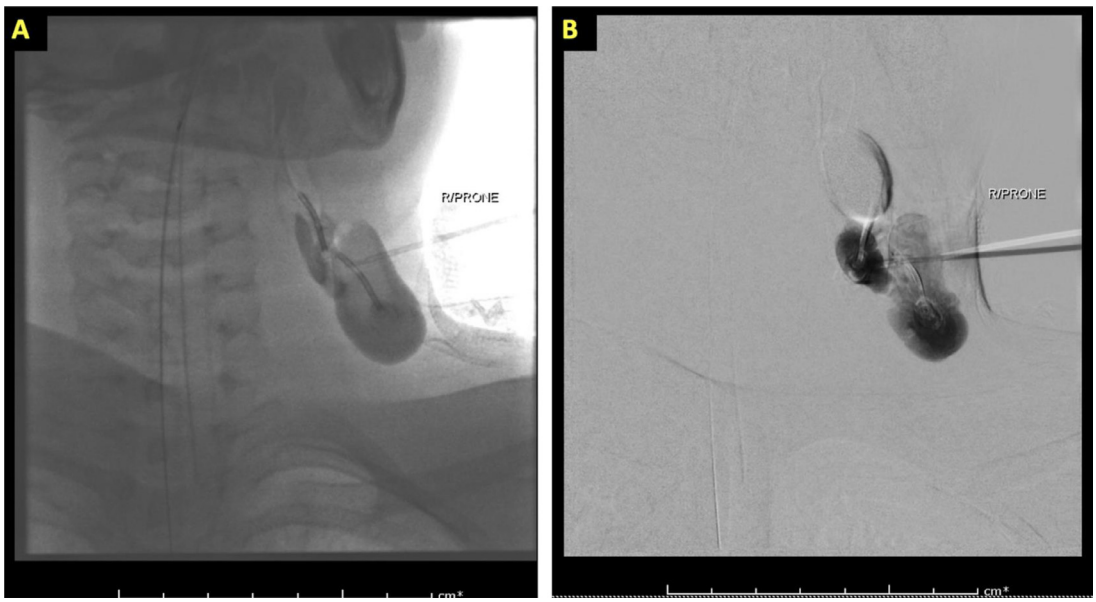

Fig. 5 – Interventional radiology conducted doxycycline sclerotherapy procedure under general anesthesia. The procedure involved fluoroscopic and ultrasound guidance for sclerotherapy of the lymphatic malformation as demonstrated in A and B.

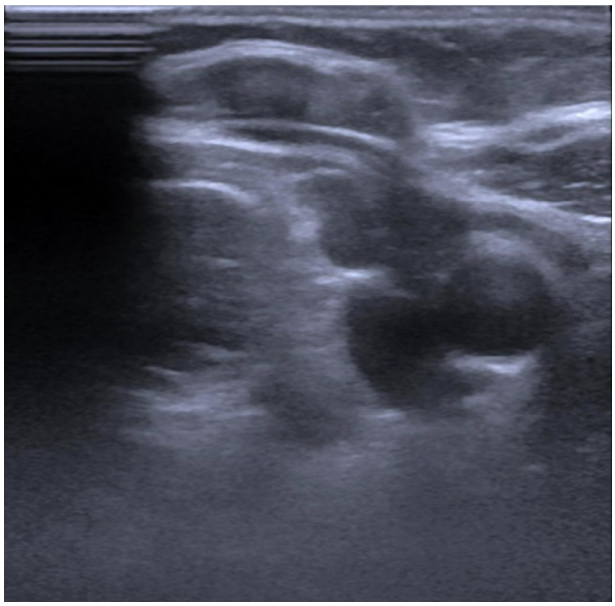

Fig 6 – Follow-up ultrasonography after treatment revealing mildly prominent lymph nodes within the right neck soft tissues, a single residual cyst measuring 12 x 3 mm, and other smaller cysts.

later in life. This case was unique in that this patient's malformation did not present until he was 8 years old.

Lymphatic malformations typically grow slowly over time and are nonemergent. There are even cases of spontaneous regression that occur, most often with macrocystic lymphatic malformations. The type of lymphatic malformation and the specific qualities of the lesion, such as the number of septa, can help in the determination of spontaneous regression. One study found that macrocystic lymphatic malformations with less than 5 septa can experience spontaneous lesion regression and the management of these types of lesions can be managed exclusively with observation [14,15].

Although lymphatic malformations typically exhibit slow, gradual growth, they can undergo sudden and pronounced expansion in the context of hemorrhage, infection, trauma, or puberty [16]. In this particular case, the patient presented with a large, nontender, nonerythematous mass at the right side of his neck. While he presented without symptoms, it is pertinent to acknowledge that rapid growth of lymphatic structures has the potential to cause obstruction of neighboring structures through mass effect. Such a scenario may lead to tracheal and esophageal compression, precipitating significant airway compromise and dysphagia, which can be life-threatening.

Unilateral macrocystic lymphatic malformations have been shown in some studies to be manageable through a conservative approach involving observation and nonintervention [15]. When considering a "wait and watch" approach, it is crucial to acknowledge the psychosocial ramifications for a child bearing a visible malformation on their neck or face. In the past, surgery served as the primary treatment modality, but sclerotherapy has gained prominence as one of the most frequently employed methods for managing lymphatic malformations in pediatric patients. However, the efficacy of sclerotherapy in this population may vary depending on the choice of sclerosant, with OK-432, bleomycin, Ethibloc, sirolimus, and doxycycline being the most commonly utilized agents. Surgical intervention carries the inherent risks of nerve injury, postoperative seroma or lymphocele formation, and heightened susceptibility to secondary infections. Additionally, the placement of a postoperative drain necessitates further follow-up, amplifies risks, and exacerbates the social impact on the child [17–19]. Following the diagnosis of

a macrocystic lymphatic malformation in our patient, treatment initially involved clindamycin, which seemed to halt the rapid growth, followed by doxycycline sclerotherapy, resulting in near-complete resolution of the lesion.

An intriguing aspect of this case revolves around the positive *streptococcus* test during the initial evaluation by his primary care pediatrician. Confirmation of strep throat typically relies on a rapid antigen detection test or throat culture, with the rapid antigen detection test in this case being positive [20]. Although, he was sent home with the appropriate dose of oral amoxicillin, 4 days later had an even larger mass on his neck. Notably, a research study involving 61 cases of macrocystic lymphatic malformations reported that all but 1 case was associated with a preceding local or upper respiratory infection that subsequently resolved [21]. Considering the possibility that this acute presentation of the lymphatic malformation was triggered by the confirmed infection, it raises the question of why the growth persisted even after 4 days of initiating the infection treatment [21].

Conclusion

Our case report of an 8-year-old with a sudden enlarging right-sided neck mass that was diagnosed as a lymphatic malformation and successfully treated with doxycycline sclerotherapy illustrates two important lessons. First, it adds to the growing body of literature that upper respiratory infections can trigger rapid expansion of previously asymptotic lymphatic malformations that have been present since birth. In this case, the patient tested positive for Group A *Streptococcus* infection and had concurrent enlargement of his lymphatic malformation, despite having no symptoms of *Streptococcal* pharyngitis, like sore throat, fever, or headache. Second, this case report demonstrates the utility of using a multidisciplinary team to diagnose and treat lymphatic malformations. In this case, prompt evaluation by his primary care pediatrician, as well as pediatric trained specialists in emergency medicine, hospital medicine, hematology/oncology, otolaryngology, and interventional radiology lead to timely diagnosis. Furthermore, it allowed for quick sclerotherapy treatment, which led to almost complete resolution of his condition.

Ethics approval

Case reports do not require formal Institutional Review Board (IRB) approval at any of the organizations associated with this project, and as such, was not obtained for this project.

Submission declaration and verification

This work has not been published previously and is not under consideration for publication elsewhere. All authors have approved the final product. If accepted, this report will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

Author's contributions

[JH, JB, and LR]: Data collection from the patient's medical record, retrieval and organization of all imaging, literature review, and writing and editing of the manuscript. [VR]: Supervision and manuscript revision. All authors read and approved the final manuscript.

Availability of data and materials

To maximize confidentiality and anonymity of pediatric protected health information, data used and analyzed from this case report are not available for outside use.

Patient consent

In accordance with the guidelines of this journal as well as the official policy of [Cook Children's Health Care System], informed consent was obtained from the patient's mother to use his anonymized information and images for dissemination in this article. After a comprehensive discussion, she signed a HIPAA authorization form and an image release form.

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