Commentary

A Short Note on Generalized Lymphatic Anomaly: A Lymphatic Disorder

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ABSTRACT

Lymphatic disorders may be challenging to diagnose because of the limited number of cases and diversity of symptoms. Along with the clarification of pathogenesis, advancements in diagnostic nomenclature and scrutinized internationally standardized classifications have been observed. Several causal genes have been elucidated and included in the classification system. The International Society for the Study of Vascular Anomalies (ISSVA) has established a classification of lymphatic disorders. For example, simple vascular malformations (IIa) or Lymphatic Malformations (LMs) include Generalized Lymphatic Anomaly (GLA), Kaposiform Lymphangiomatosis (KLA), and Gorham–Stout Disease (GSD). Morbidity and mortality of LMs are induced by infection or significant compression of the circulatory, respiratory, and digestive organs. To relieve symptoms, pleurodesis and sclerotherapy may be effective in providing local control. However, complete surgical extirpation of all lesions is considered risky due to adhesions around vital organs, such as the lung and mediastinal large vessels. Thus, the role of surgery remains unclear. In patients with GLA, the disease-causing genes identified from endothelial cells have a somatic mutation in neuroblastoma RAS. Other genes such as PIK3CAm were advocated as causal genes of another subset of LMs. Therapeutic agents are being developed based on these germlines and somatic mutations.

Key Words: Generalized lymphatic anomaly, Lymphatic malformation, Neuroblastoma RAS, ISSVA

Abbreviations: CT: Computed Tomography; DPL: Diffuse Pulmonary Lymphangiomatosis; GLA: Generalized Lymphatic Anomaly; GSD: Gorham-Stout Disease; KLA: Kaposi form Lymphangiomatosis; LMS: Lymphatic Malformations; MRI: Magnetic Resonance Imaging; mTOR: mammalian Target of Rapamycin; NRAS: Neuroblastoma RAS; PIK3: Phosphatidylinositol-3 Kinase; VATS: Video-Assisted Thoracic Surgery; VEGFR: Vascular Endothelial Growth Factor Receptor.

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ABOUT THE STUDY

Generalized Lymphatic Anomaly (GLA), previously termed as lymphangiomatosis, presents as a subset of multifocal Lymphatic Malformations (LMs) that involve the skin, neck, abdomen, and thorax [1-5]. We previously reported a case of an adult female patient with GLA and bacteremia [5]. She was successfully treated with an antibacterial drug and Video-Assisted Thoracic Surgery (VATS) debridement and drainage. Only palliative care was administered to the patient. To date, no fundamental treatment for GLA has been determined [4].

Etiology and genetics

The lymphatics form a delicate plexus of vessels that connect to the main lymphatic channels, including the cisterna chyli and thoracic duct. A disruption in this plexus of vessels may induce a variety of LMs. However, the exact etiology of LMs remains unclear.

Endothelial cells express Vascular Endothelial Growth Factor Receptors (VEGFRs). VEGF-C is considered to play an important role in lymphangiogenesis [4,6-11]. In patients with GLA, the disease-causing genes identified from endothelial cells have a somatic mutation in neuroblastoma RAS [7,12]. This mutation was proven to take part in the development of the lymphatic system. Other genes such as PIK3Cam were advocated as causative of LMs [12,13]. Therapeutic agents are being developed based on the germline and somatic mutations [8,10,12-14].

Symptoms and diagnostic investigations

LM symptoms vary depending on the site of occurrence and the LM subset. Patients with osteolytic bone diseases may present with pathologic fractures [2]. GLA and Gorham–Stout Disease (GSD) are congenital disorders that commonly involve the bones, thorax, spleen, and gastrointestinal tract. Osseous disease is observed in both subsets. Osteolytic lesions in patients with GLA frequently exhibit cortical bone sparing. In contrast, patients with GSD show aggressive lytic lesions with cortical bone loss [15].

Thoracic involvement includes chylous effusion, such as chylothorax, chyloptysis, chylopericardium, and chylous ascites, and is believed to be induced by leakage from the thoracic duct [2,14,15]. Diffuse Pulmonary Lymphangiomatosis (DPL) is a disease characterized by diffuse interstitial infiltration of lymphatic vessels in the lung, pleura, and mediastinum [2,14,16]. Chest Computed Tomography (CT) reveals peribronchovascular and interlobular septal thickening [16]. CT and Magnetic Resonance Imaging (MRI) lymphangiography reveal abnormal lymph flow around the thoracic duct [17]. Both chylothorax and DPL cause cough, wheezing, and dyspnea, subsequently leading to respiratory failure and death. Open biopsy may be recommended.

Treatments

Morbidity and mortality of LMs are induced by infection [2,3,18] or significant dysfunction of the circulatory, respiratory [19,20], and digestive organs [21-23] caused by the disruption in the lymphatic vessels. Cases in which bilateral lung transplant was successful for patients with DPL have been reported [24]. Generally, resection of organs may be difficult when the extent of the required resection is large. The role of surgery remains unclear because of the limited extirpation [5]. To relieve symptoms, pleurodesis and sclerotherapy may be effective in providing local control [25,26]. Our case had infection of several cysts of lymphangiomatosis along with bacteremia. We successfully performed debridement and irrigation of the lesions under VATS along with administration of an antibacterial drug, ultimately decreasing the cystic lesions and eradicating the infection [5]. This technique is sometimes performed for severe empyema thoracis [27-29]. Therapeutic decisions depend on the site of presentation and severity of the disease [23]. In our case, treatment was not initiated while the patient was asymptomatic [5].

The number of clinical drug trials evaluating the reduction of lymphatic proliferation has increased. Specifically, somatic mutations in genes encoding for the RAS/PI3K/mTOR signaling pathway have been identified as targets for drug development. Sirolimus, a mammalian target of rapamycin inhibitor, is used in the management of DPL [14,30].

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CONCLUSION

Lymphatic disorders are difficult to diagnose and treat. However, the classification and nomenclature of these disorders have improved because of advancements in the field of genetics and the accumulation of case reports. Genetic characteristics of subsets of LMs have been elucidated. Novel treatment modalities that impede LM pathogenesis should be developed in the future.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. International Society for the Study of Vascular Anomalies: ISSVA classification for Vascular Anomalies. 2018.
2. Trenor III CC, Chaudry G. Complex lymphatic anomalies. Semin Pediatr Surg 2014;23(4):186-90.
3. Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: Recommendations from the International Society for the Study of Vascular Anomalies. Pediatrics 2015;136(1):e203-14.
4. Liu X, Cheng C, Chen K, et al. Recent progress in lymphangioma. Front Pediatr. 2021.
5. Minakata T, Suzuki T, Kamio Y, et al. A case of lymphangiomatosis with infected lymphangiomas effectively treated by thoracoscopic debridement and drainage. Chest. 2020;158(5):221-224.
6. Lohela M, Bry M, Tammela T, et al. VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. Curr Opin Cell Biol. 2009;21(2):154-65.
7. Ozeki M, Fukao T. Generalized lymphatic anomaly and Gorham–Stout disease: Overview and recent insights. Adv Wound Care (New Rochelle). 2019;8(6):230-245.
8. Joukov V, Pajusola K, Kaipainen A, et al. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. EMBO J. 1996;15(2):290-298.
9. Hominick D, Silva A, Khurana N, et al. VEGF-C promotes the development of lymphatics in bone and bone loss. Elife. 2018.
10. Mäkinen T, Boon LM, Vikkula M, et al. Lymphatic malformations: Genetics, mechanisms and therapeutic strategies. Circ Res. 2021;129(1):136-154.
11. Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocr Rev. 2004;25(4):581-611.
12. Manevitz, Mendelson E, Leichner GS, et al. Somatic NRAS mutation in patient with generalized lymphatic anomaly. Angiogenesis. 2018;21(2):287-298.
13. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet A. 2015 Feb;167A(2):287-295.
14. Dimiene I, Bieksiene K, Zaveckiene J, et al. Effective initial treatment of diffuse pulmonary lymphangiomatosis with sirolimus and propranolol: A case report. Medicina. 2021;57(12): 1308.
15. Dellinger MT, Garg N, Olsen BR. Viewpoints on vessels and vanishing bones in Gorham–Stout disease. Bone. 2014;63:47-52.
16. Holden WE, Morris JF, Antonovic R, et al. Adult intrapulmonary and mediastinal lymphangioma causing haemoptysis. Thorax 1987;42(8):635-36.
17. Pimpalwar S, Chinnadurai P, Chau A, et al. Dynamic contrast enhanced magnetic resonance lymphangiography: Categorization of imaging findings and correlation with patient management. Eur J Radiol. 2018;101:129-135.
18. Ricca RJ. Infected mesenteric lymphangioma. N Y State J Med. 1991;91(8):359-361.
19. Nakagawa T, Koizumi T, Oiwa K. et al. Sudden death of a 14-year-old girl with lymphangiomatosis. Gen Thorac Cardiovasc Surg 2016;64(2):116-119.
20. Kadakia KC, Patel SM, Yi ES, et al. Diffuse pulmonary lymphangiomatosis. Can Respir J 2013;20(1):52-54.
21. Atalay E, Erdogdu HI, Tur BK. Intestinal lymphangiomatosis presenting with protein-losing enteropathy. Akademik Gastroenteroloji Dergisi. 2017;16:36-39.
22. Lawless ME, Lloyd KA, Swanson PE, et al. Lymphangiomatous lesions of the gastrointestinal tract: A clinicopathologic study and comparison between adults and children. Am J Clin Pathol. 2015;144(4):563-569.
23. Mimura H, Akita S, Fujino A, et al. Japanese clinical practice guidelines for vascular anomalies 2017. Jpn J Radiol. 2020;38(4):287-342.
24. Kinnier CV, Eu JP, Davis RD, et al. Successful bilateral lung transplantation for lymphangiomatosis. Am J Transplant. 2008;8(9):1946-1950.
25. Faul JL, Berry GJ, Colby TV, et al. Thoracic lymphangiomas, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. Am J Respir Crit Care Med. 2000;161(3):1037-1046.
26. Burrows PE, Mitri RK, Alomari A, et al. Percutaneous sclerotherapy of lymphatic malformations with doxycycline. Lymphat Res Biol. 2008;6(3-4):209-216.
27. Davies HE, Davies RJ, Davies CW. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;41-53.
28. Kern L, Robert J, Brutsche M. Management of parapneumonic effusion and empyema: Medical thoracoscopy and surgical approach. Respiration. 2011;82(2):193-196.
29. Suzuki T, Kitami A, Suzuki S, et al. Video-assisted thoracoscopic sterilization for exacerbation of chronic empyema thoracis. Chest. 2001;119(1):277-280.
30. Ozeki M, Nozawa A, Yasue S, et al. The impact of sirolimus therapy on lesion size, clinical symptoms, and quality of life of patients with lymphatic anomalies. Orphanet J Rare Dis. 2019;14(1):141.