Contrasting Cases of Complex Lymphatic Anomalies: Case Reports and Review of the Literature
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Abstract
Complex lymphatic anomalies (CLAs) are rare, pediatric developmental lymphatic anomalies that include a spectrum of overlapping clinical presentations, imaging findings, and symptoms. Owing to their rarity, diagnosis and treatment can be challenging. CLAs have significant risk of morbidity and mortality and require multimodal, comprehensive management. New molecular insights into the pathogenesis of CLAs will likely change classification and therapeutic options in the future. We describe herein 2 children with CLAs with distinct presentations and clinical courses but with some overlapping features. These cases highlight the spectrum of disease presentation in CLAs as well as the need for continued use of molecular data to drive diagnosis, classification, and management of these rare disorders.

Keywords: Complex lymphatic anomalies, Generalized lymphatic anomaly, Kaposiform lymphangiomatosis, coagulopathy

Introduction
Complex lymphatic anomalies (CLAs) are rare disorders of embryonic lymphatic system development.\textsuperscript{1–3} The anomalous lymphatic vessels and malformations are present at birth but typically become clinically apparent within the first 2 decades of life. The term “complex lymphatic anomalies” includes generalized lymphatic anomaly (GLA), Kaposiform lymphangiomatosis (KLA), Gorham-Stout disease (GSD), and central conducting lymphatic anomaly (CCLA).\textsuperscript{1,3–5} These disorders encompass a variety of clinical subtypes with both distinct and overlapping features. Many medical and interventional therapies have been tried in CLAs, but owing to their rarity, optimal treatment is unknown.\textsuperscript{6,7} Recent research has identified a molecular basis for some CLAs, which will likely drive future therapeutic options, as well as inform our current classification system.\textsuperscript{5,8–12} Here, we present 2 children with complex lymphatic anomalies with distinct presentations and clinical courses but with some overlapping features.

Case 1
A 27-month-old healthy male presented to the emergency department with a 2-week history of episodes of perioral cyanosis and altered responsiveness. Laboratory studies were notable for microcytic anemia (hemoglobin 9.2 gm/dL) and thrombocytopenia (platelet count 57,000/µL). Chest computed tomography (CT) showed a large right pleural effusion, cervical adenopathy, splenomegaly, diffuse heterogeneity of the bones, and a suprarenal mass (Figure 1A). Initial concern was for metastatic neuroblastoma, but the CT showed features atypical for neuroblastoma, including pleural enhancement with interlobular septal thickening and marked right chest wall edema. The patient underwent thoracotomy with chest tube placement in addition to bone marrow and cervical lymph node biopsy. After drainage of 1.5 L of pleural fluid, the patient became hypotensive and severely coagulopathic with prolonged prothrombin time and partial thromboplastin time, thrombocytopenia, and hypofibrinogenemia. The patient was admitted to the pediatric intensive care unit for resuscitation. The patient had persistent pleural effusion with initial chest tube output of approximately 150–400 mL/kg/d. Whole body MRI revealed an extensive multicompartamental lesion involving the bilateral cervical, bilateral supraclavicular, and right axillary soft tissues, as well as the retroperitoneum and mesentery. The MRI also showed diffuse asymmetric
interlobular septal thickening suggesting dilated lymphatic channels, fluid isointense lesions involving the T12-L3 vertebral bodies, hepatosplenomegaly, and bilateral pleural effusions (Figure 1B). These findings were suggestive of a complex lymphatic anomaly. Lymphangiography showed abnormal retrograde flow in the pelvic and right paralumbar/thoracic lymphatics with outflow through right intercostal lymphatics. Additionally, although there appeared to be filling of a central structure in the location of the cisterna chyli, no thoracic duct or central lymphatic flow was demonstrated (Figure 1C). This suggested a possible central conducting lymphatic anomaly (CCLA).

Surgical pathology from the right cervical mass showed fibroadipose tissue associated with an interconnected vascular network (with positive immunostaining for ERG and D2-40), consistent with lymphatic anomaly. The walls of the vascular channels showed low cellularity with no definite spindle cell proliferation. Pleural fluid was serosanguinous, but with lymphocytic infiltration and increased pleural:serum ratios of lactate dehydrogenase and protein, concerning for a chylous component. Triglyceride testing was not done on the pleural fluid. Both cervical mass and bone marrow biopsy were negative for malignancy. Genetic testing from the cervical biopsy showed a somatic gain of function mutation in NRAS (c.182A>G) with a variant allele frequency of 2.3% (Tempus xT panel, uses hybrid capture next-generation sequencing to interrogate a custom panel of 648 genes, limit of detection is 5% variant allele fraction).

A presumptive clinical diagnosis of Kaposiform lymphangiomatosis (KLA) was made based on the imaging findings, biopsy results, massive hemorrhagic pleural effusion, and severe coagulopathy. This was supported by the finding of NRAS mutation, which has previously been reported in patients with KLA. The disruption of central lymphatic vessels on lymphangiography did raise suspicion for CCLA, however, many patients with KLA have a component of central conducting lymphatic anomaly and there is overlap in this disease spectrum. The patient was treated with multi-modal therapy—vincristine, sirolimus, and steroids—due to the severity of disease presentation and prior reports of use of these drugs in KLA. Within 2 weeks, there was significant improvement in coagulopathy and symptoms. The chest tube was removed after week 3 of treatment, although the pleural effusion remained moderate in size. Three months into treatment, the patient developed recurrent coagulopathy while on sirolimus and vincristine. Given the known

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Figure 1. Imaging from case 1. A. Contrast-enhanced coronal computed tomography of the chest and abdomen demonstrates a large right pleural effusion (white asterisk), prominent left peribronchial soft tissue (white arrow), suprarenal mass representing lymphatic anomaly (black arrow), and splenomegaly (black asterisk). B, Coronal STIR MRI of the chest following right thoracentesis shows increased peribronchial lymphatics (white arrow) and extensive abnormal hyperintense intraperitoneal and chest wall soft tissue (black arrows). C, Lymphangiographic images of the chest, abdomen, and pelvis show that most lymphatic flow terminates in the right paravertebral region (arrows) rather than continuing into central lymphatics. The thoracic duct (not shown) remained unopacified. MRI indicates magnetic resonance imaging; STIR, short tau inversion recovery.
NRAS mutation and recent successful reports of MEK inhibition in KLA,\textsuperscript{15} sirolimus was stopped and the patient was started on a MEK inhibitor (Trametinib). Vincristine was overlapped with Trametinib for 3 weeks and then subsequently discontinued. The patient continues to do well on Trametinib monotherapy, now 2 months into treatment. Platelet count, D-dimer, and fibrinogen have normalized, and the patient's Angiopoietin-2 level (a potential biomarker for KLA)\textsuperscript{16,17} decreased from 24,376 pg/mL to 2185 pg/mL after 4 weeks of Trametinib therapy. Recent whole-body MRI demonstrated complete resolution of pleural effusions and bony vertebral lesions, and significant improvement in the mediastinal and abdominal disease.

**Case 2**

A 5-year-old female with a 3-month history of cough presented to the emergency department with moderate to large pericardial effusion. She underwent pericardiocentesis, which revealed 300 mL of serosanguinous fluid. Infectious and pericardial effusion. She underwent pericardiocentesis, which presented to the emergency department with moderate to large pleural effusion. Her partial thromboplastin time and prothrombin time were normal. Fevers resolved after drainage requiring chest tube placement. Drainage was chylous at that time. She remained without thrombocytopenia or coagulopathy. She was treated with diuretics and colchicine, but the effusion recurred, necessitating creation of a pericardial window 1 month later. The patient was readmitted 2 months later with fatigue and low-grade fevers and found to have a large right pleural effusion requiring chest tube placement. Drainage was chylous at that time. She remained without thrombocytopenia or hypofibrinogenemia, and her partial thromboplastin time and prothrombin time were normal. Fevers resolved after drainage of the effusion. Chest CT revealed multifocal lucencies in the thoracic spine and manubrium (Figure 2A). Subsequent spinal MRI revealed multiple fat-isointense, nonenhancing lesions involving the skull base, manubrium, and multiple cervical, thoracic and lumbar vertebrae (Figure 2B). Our hematology-oncology team was consulted at that time due to concern for possible malignancy or vascular anomaly. In retrospect, pleural effusion may have been mistaken for elevated right hemidiaphragm on initial chest x-ray. MR lymphangiogram was recommended and revealed some disruption to central conducting lymphatics with evidence of alternative lymphatic pathways, including increased left peribronchial lymphatics and cervical supraclavicular lymphatics (Figure 2C). These findings were suggestive of a complex lymphatic anomaly.

A presumptive clinical diagnosis of GLA was favored given the presence of bony and vertebral lesions and absence of coagulopathy. However, a biopsy was not pursued due to concern for precipitating increased lymphatic drainage and the overlap with CCLA was noted. Cell-free DNA from the peripheral blood was sent for genomic analysis but did not reveal any mutations (Tempus xF panel, a next-generation sequencing cell-free DNA liquid biopsy tumor profiling assay to interrogate a custom panel of 105 genes). Genetic testing on the pleural fluid was unable to be performed at our institution. The patient was started on sirolimus for control of the pleural effusion, and her chest tube was removed after 4 weeks. She also began bisphosphonate therapy with zolendronic acid for the vertebral lesions. The patient’s effusion slowly resolved on sirolimus therapy. However, on surveillance imaging 6 months after initiation of sirolimus, she had recurrence of a large right pleural effusion and soon after developed symptoms of plastic bronchitis. This was not precipitated by any known infection, and she was afebrile and remained without coagulopathy. She underwent thoracentry for drainage of effusion but unfortunately a large chylous effusion recurred within 3 days. She continues to be clinically well on a regimen of sirolimus and strict pulmonary hygiene, but future interventional procedure such as thoracic duct embolization is under consideration. Additionally, we have discussed reattempt at genetic testing and possible future use of a MEK or PIK3CA inhibitor. She continues to be closely monitored without any evidence for hemorrhage or coagulopathy.

**Discussion**

Complex lymphatic anomalies (CLAs) are rare diseases characterized by abnormal growth and development of lymphatic vessels.\textsuperscript{1} CLAs include a spectrum of disease including GLA, KLA, GSD, and CCLA. These disorders have significant overlapping anatomic, symptomatic, and imaging features, frequently contributing to difficulty with diagnosis and classification.\textsuperscript{2} Sites of disease can include bone, lung, spleen, and mediastinum. Patients can also have soft tissue involvement and chylous leaks.\textsuperscript{13} While patients with KLA

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**Figure 2.** Imaging from case 2. Sagittal bone window chest computed tomography (CT) image (A), sagittal T1-weighted (B), and STIR (C) MRI reveal multifocal vertebral (white arrows) and sternal (black arrows) lesions that are lucent on CT and predominantly follow fat signal intensity on MRI. D, Coronal maximum intensity projection MR lymphangiographic image obtained 11 minutes after inguinal lymph node gadolinium injection shows notable backflow into peribronchial and left cervical lymphatics (arrows). MRI indicates magnetic resonance imaging; STIR, short tau inversion recovery.
and GLA may both present with pleural or pericardial effusions and multorgan involvement, patients with KLA typically exhibit more severe features, such as hemorrhagic pericardial or pleural effusion, extensive retroperitoneal or mediastinal involvement, and hematologic abnormalities. Patients with KLA frequently present with a consumptive coagulopathy characterized by severe hypofibrinogenemia and thrombocytopenia with risk of hemorrhage. This is similar to the Kasabach-Merritt phenomenon described in Kaposiform hemangioendothelioma, a rare vascular tumor. KLA is associated with high morbidity and mortality and affected patients typically have worse outcomes than those with GLA. KLA has been classified as a subtype of GLA, but there are clear distinct features and recent molecular data suggests that it may be a separate disease process entirely.

Historically, procedural interventions for CLAs such as pleural and pericardial drainage and thoracic duct ligation have provided transient improvement but symptoms tend to recur. Newer interventional procedures may be able to improve these outcomes in the future. Surgical resection of lesions is neither recommended nor generally feasible due to the infiltrative nature of CLAs and potential for severe chylous leak with manipulation. Patients with osteosarcoma may be treated with bisphosphonates such as pamidronic acid or zoledronic acid to prevent bone resorption. Chemotherapeutic agents, including vincristine and the mTOR inhibitor sirolimus may be effective treatments for some CLAs, but there are some patients that fail to respond adequately.

In recent years, the landscape of vascular anomalies has changed dramatically with identification of many of the germline and somatic mutations that drive these malformations and tumors. Increased understanding of the genetic underpinnings of vascular anomalies may lead to identification of potential therapeutic targets that will ultimately lead to increased development of targeted therapies. A somatic activating NRAS variant has recently been identified in lesional tissue and pleural effusion fluid of patients with KLA and possibly GLA. PIK3CA mutations have been identified in isolated lymphatic malformations and GLA, and EPHB4 and ARAF mutations have been identified in CCLA. The mTOR inhibitor sirolimus has been used in the treatment of complex lymphatic anomalies. With the identification of other molecular mutations, additional therapeutic agents, such as PIK3CA and MEK inhibitors, may provide additional therapeutic options.

We present 2 cases of complex lymphatic anomaly, diagnosed clinically as KLA and GLA, but with some overlapping features. The patient in case 1 was given the clinical diagnosis of KLA based on clinical presentation with pleural effusion and severe coagulopathy as well as presence of somatic gain of function NRAS mutation. However, it should be noted that he did have presence of some central conducting abnormality, and he did not have spindled endothelial cells on pathologic diagnosis. Likewise, the patient in case 2 was diagnosed presumptively as GLA, although it was noted that her presentation with both pericardial and pleural effusions is seen more commonly in KLA, and she has a clear central conducting lymphatic anomaly as well. The decision to treat with a MEK inhibitor in case 1 had a clear biologic basis, whereas unfortunately that data are lacking in case 2. The patient and her family are considering interventional procedures versus empiric therapy with MEK or PIK3CA inhibition, but additional modes of genetic testing are also under consideration. These 2 cases add to the known spectrum of disease in CLAs as well as highlight some of the important overlapping clinical features that can make diagnosis and management difficult. The NRAS mutation identified in case 1 adds to our evolving knowledge of Ras pathway mutations as molecular drivers for KLA and other CLAs. Our understanding of the molecular drivers of CLAs will improve our ability to understand disease pathophysiology, diagnose, classify, treat, and ultimately improve outcomes for children with these rare disorders.

Conclusions

We present 2 cases of complex lymphatic anomaly, diagnosed clinically as KLA and GLA, but with both distinct and overlapping clinical features. These cases highlight the spectrum of disease presentation in CLAs as well as the need for continued use of molecular data to drive diagnosis, classification, management, and ultimately outcomes in these rare disorders.

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