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CASE REPORT

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Complex lymphatic anomalies: Challenging diagnostic considerations

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Key Clinical Message

Diagnosis of complex lymphatic anomalies can be difficult, and biopsies can be associated with significant morbidity. Mediastinal masses with features such as osseous involvement warrant thorough noninvasive evaluation prior to biopsy.

KEYWORDS

cardiothoracic surgery, general medicine, radiology and imaging

1 | BACKGROUND

Complex lymphatic anomalies (CLA) refer to a heterogenous set of disease presentations involving lymphangiomas.[1] This includes diseases such as generalized lymphatic anomaly (GLA), Gorham-Stout disease (GSD), kaposiform lymphangiomatosis (KLA), and central conducting lymphatic anomaly (CCLA).[2] These conditions have overlapping findings with a few distinct characteristics. All CLAs can result in pleural and/or pericardial effusions, typically involving chylous fluid, varying degrees of multiorgan involvement as well as some form of osseous involvement.[1,2] Genetic testing may also assist in the diagnosis and differentiation of these conditions as each has been associated with specific mutations (Table 1).[3]

Patients with KLA usually present with cough or shortness of breath with pleural or pericardial effusions that are hemorrhagic and chylous.[1] KLA also tends to have more extensive thoracic involvement compared to the other CLAs and mediastinal disease is common.[4] The main distinguishing factor for GSD is that it specifically involves the loss of cortical bone.[1] The other CLAs typically involve the trabecular bone, but spare the cortical bone.[1] GLA more commonly presents with multiple sites of visceral involvement. Differentiation between CLAs can be difficult and usually requires a combination of imaging, lab work, and available genetic testing. However, obtaining tissue biopsies, especially near ribs, can be associated with a risk of worsening pleural effusions, pericardial effusions, ascites, and hemorrhagic complications.[1,2,4,5]

The management of complex lymphatic anomalies typically involves a multimodal treatment plan involving targeted medical therapy, endovascular therapies such as lymphangiography or lymphoscintigraphy and finally surgical intervention.[1] The goal of therapy is often focused on the prevention, reduction, and management of complications of complex lymphatic anomalies.[1] Supportive care in form of compression garments and lymphatic pumps also help to manage complications.[1] Medical therapy can involve mTOR inhibitors (e.g., sirolimus and everolimus), bisphosphonates, MAPK/MEK inhibitors (e.g., trametinib), vincristine, steroids, and interferon.[1,4,6] Table 1 lists some of the medications that have been used for each of the CLA subtypes.[1,4] However, there is no standard for when to start medications, dosing, or length of therapy.[1] Surgical interventions may include excision of lymphatic anomalies, thoracic duct embolization or ablation of lymphatic vesicles.[1] Interventional lymphangiography can be used to embolize lymphatic malformations or perform sclerotherapy and can be especially effective in CCLA.[1,4]

2 | CASE REPORT

A 35-year-old female presented to the emergency department with 3 months of cough and several weeks of dyspnea following COVID-19 infection. Work-up at that time included a CT angiogram which demonstrated infiltrative soft tissue throughout her mediastinum that was invading the anterior chest wall and pericardium with destruction of the left clavicle (Figure 1). Incidentally, multiple hypodense liver lesions were identified that appeared benign on follow-up abdominal MRI imaging. The patient was discharged from the ED and later underwent fine-needle aspiration with core biopsy of the mediastinal mass demonstrating nonspecific soft-tissue findings with mildly atypical vasculature. She presented again to the ED a week after the fine-needle aspiration with dyspnea and chest pain. Work-up was unremarkable and repeat CTA at that time was negative for pulmonary embolism and was unchanged from prior with regards to the mediastinal mass. A week after this ED visit, she underwent VATS procedure with biopsy which was notable for serosanguinous drainage after sampling of thin, trabeculated material in the anterior mediastinum, the gross appearance suggesting lymphatic malformation. Pathology report of the biopsy revealed benign fibroadipose tissue with chronic inflammation and flow cytometry of the fluid demonstrated no evidence of malignancy. The patient was stable after her VATS procedure and was discharged a day later. There was no specific treatment plan at this time due to a nonspecific biopsy result.

The patient then re-presented to the emergency department 3 days after the VATS procedure with chest pain, cough, and hemoptysis and was subsequently admitted. Bronchoscopy at time of admission suggested possible diffuse alveolar hemorrhage (DAH) as pulmonary lavage demonstrated bloody effluent from multiple sampled areas of the lungs. Repeat CTA at the time of bronchoscopy demonstrated a new right lower lobe pulmonary embolism and left-sided pleural effusion. Pleural fluid was noted to be serosanguinous with serous profile demonstrating a chylous effusion with triglycerides of 613 mg/dL. Review of prior chest radiography from 18 months prior to this admission also revealed radiolucency of the proximal clavicle. A week after admission, a rapid accumulation of the effusion and associated respiratory failure prompted chest tube drainage. Lymphangiogram was attempted at this time for thoracic duct ligation, but was unsuccessful due to small inguinal lymph node chains. After a month of continuous pleural drainage, a VATS thoracic duct ligation was performed with ligation of severely deformed lymphatic channels. The patient subsequently developed a pericardial effusion with tamponade physiology. TTE was notable for a 20 mm × 13 mm mobile echodensity in the pericardial space adjacent to the mid lateral wall of the left

TABLE 1 Characteristics and management of the different complex lymphatic anomalies 1.[1–4,6,7]

Type of CLA	Mediastinal involvement	Visceral involvement	Effusions	Osseous involvement	Histopathology	Genetic markers	Medical management	Comments
Generalized lymphatic anomaly	Yes	Yes	Chylous effusions	Medullary cavity resorption	Abnormal and dilated lymphatic vessels with endothelial cells	PIK3CA	mTOR inhibitors, interferon, bisphosphonates, MAPK/MEK inhibitors	
Central conducting lymphatic anomaly	Yes	Less Common	Chylous effusions	Less Common	Dilated lymphatic vessels that are not malformed but rather are dysfunctional or occluded	ARAF, EPHB4	mTOR inhibitors, MAPK/MEK inhibitors	
Kaposiform lymphangiomatosis	Yes	Yes	Hemorrhagic and chylous effusions	Medullary cavity resorption	Dysmorphic lymphatic channels, clusters of spindled, hemosiderotic lymphatic endothelial cells	NRAS	mTOR inhibitors, interferon, bisphosphonates, MAPK/MEK inhibitors, vincristine, steroids	Typically has hemorrhagic manifestations (with severe coagulopathy, low platelets, low fibrinogen) and elevated angiopoetin-2 levels
Gorham-Stout syndrome	Yes	Less Common	Chylous effusions	Cortical osteolysis	Abnormal and dilated lymphatic vessels with endothelial cells	KRAS	mTOR inhibitors, interferon, bisphosphonates, MAPK/MEK inhibitors	

ventricle. The patient was taken for emergent sternotomy with removal of the pericardial mass and a large right infraclavicular lymph node. Pathology specimen of the mass was nondiagnostic, only demonstrating inspissated mucus with acute inflammation. Of note, sternal wound closure was complicated due to brittle bones.

On postoperative day 2 of her sternotomy, the patient had to be intubated due to declining respiratory status secondary to mucus plugging. She remained intubated and 1 week later, she suffered a PEA cardiac arrest due to hypoxic respiratory failure. At that time, she was started on veno-venous extracorporeal membrane oxygenation (ECMO) and also continuous renal replacement therapy (CRRT) due to worsening acute kidney injury. The patient was also initiated on trametinib at 0.5 mg daily at this time. Over the next 2 weeks, she continued to require ECMO and CRRT. She was then transferred to an outside facility for continued care and possible interventional lymphangiography. Of note, further laboratory testing demonstrated markedly elevated serum angiopoietin-2 levels (15,706 pg/mL with normal range being 1434–4141 pg/mL). KRAS, NRAS, and PIK3CA gene mutations were not found on tissue analysis. DH-40 stains were also negative.

3 | OUTCOME AND FOLLOW-UP

At the outside facility, thoracic duct embolization was attempted again. However, she later suffered a PEA arrest and expired.

4 | RADIOGRAPHIC FINDINGS

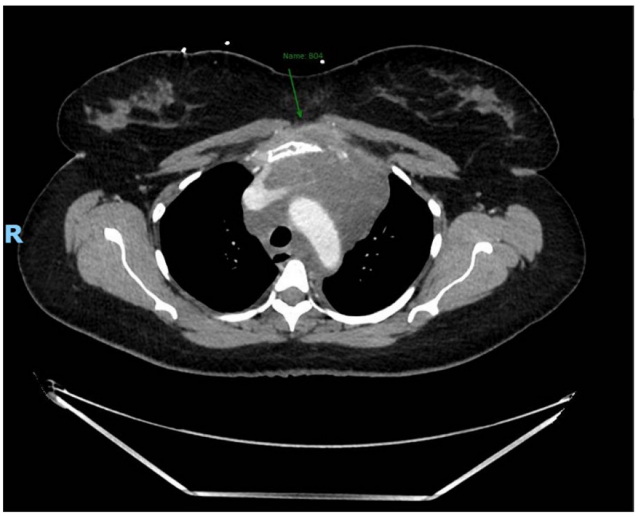

FIGURE 1 CT scan demonstrating anterior invasion of mediastinum.

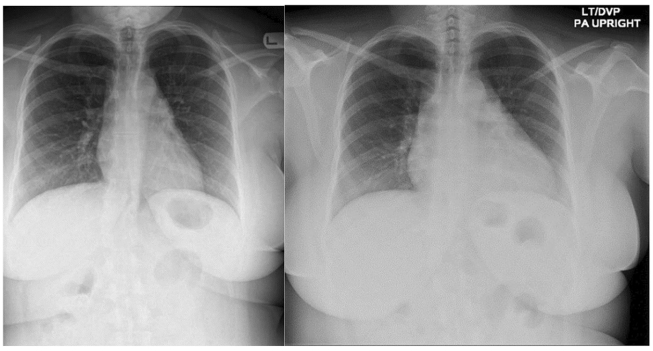

FIGURE 2 Chest X-ray on the left is from 2 years prior to presentation and chest X-ray on the right is at time of presentation. Both demonstrate left clavicular destruction.

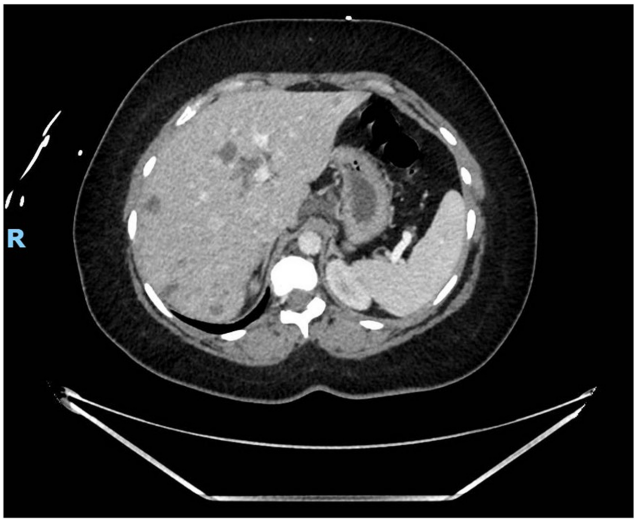

FIGURE 3 CT scan demonstrating multiple hepatic hypodensities.

5 | DISCUSSION

This patient's presentation had overlapping features of KLA and GLA as well as GSD. The mediastinal mass, the recurrent chylothorax and hemothorax as well as the numerous hepatic lesions are consistent with a CLA that has systemic involvement, which are typically KLA or GLA.[1,2] Figure 2 demonstrates evidence of lytic osseous involvement with cortical bone destruction which is consistent with GSD.[1,2] The lesions in the liver found on imaging are likely to be lymphangiomas (Figure 3). O'Sullivan et al describe a case with hepatic lymphangiomatosis that mimicked polycystic liver disease in a 53-year-old female patient.[8] The radiological findings of the aforementioned case report are more prominent than the images in our case, but they are similar in appearance.

Neither histopathology nor genetic analysis demonstrated findings associated with any of the four main

CLAs, which suggests potential sampling error or poor tissue quality; however, other reports have also demonstrated a similar lack of diagnostic pathological findings.[6] However, the patient did have elevated levels of serum angiopoietin-2 in addition to other features of KLA including hemorrhagic abnormalities such as the initial hemoptysis and suspected DAH.[1,9] Although it is difficult to clearly ascertain which of the CLAs this patient had, the elevated angiopoietin-2 and the hemorrhagic effusions make KLA more likely with possible contribution from GSD due to the cortical osteolysis found on imaging. This case emphasizes the difficulty of accurately classifying a CLA as the most commonly known distinctions may not be clearly evident and considerable overlap exists in findings; interestingly, a case series by Andreoti et al also described a patient with similar findings of both KLA and GSD.[7]

This case report is one of few that describe the post-biopsy decompensation of a patient with a CLA. This patient's underlying lymphatic disease may have been naturally progressing, but the biopsies likely exacerbated the condition. Thus, a valuable lesson from this case is the importance of a risk/benefit analysis in timing a diagnostic biopsy and the potential for complications associated with invasive procedures in this spectrum of diseases. Mediastinal masses are often clinically distinguished by the respective mediastinal compartment involved and are often biopsied due to concern for malignancy. Potential complications of biopsy in patients with CLAs have been described in prior literature and include prolonged lymphatic drainage leading to the development of chylothorax and ascites.[1,2,5] Patients with KLA can also develop significant bleeding and coagulopathy.[1] These complications tend to be associated with biopsy of bone lesions rather than soft tissue lesions and published guidelines have noted the ribs to be particularly concerning in terms of a biopsy location.[1,2,5]

When investigating pulmonary or mediastinal infiltrative lesions or effusions, clinical suspicion for CLA should arise as clinicians encounter associated findings such as unexplained bone loss or radiographic findings of distant visceral or soft tissue involvement. Additional imaging as well as focused laboratory evaluation (such as angiopoietin levels) may be sufficient for diagnosis in the appropriate clinical context,[4] avoiding morbidity that has been described with invasive biopsy. If a biopsy is deemed necessary due to lack of laboratory findings, it is important to consider the location of biopsy as certain regions such as the ribs are at higher risk for post-biopsy complications as per multidisciplinary guidelines.[2] If the diagnosis of CLA is sufficiently determined without biopsy, it may be appropriate to then initiate treatment with lymphatic embolization or medical management.

AUTHOR CONTRIBUTIONS

Venkatraman Kothandaraman: Methodology; visualization; writing – original draft; writing – review and editing. **John Wisener:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Paul W. Helgerson:** Conceptualization; methodology; project administration; supervision; visualization; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest or funding details to report (no fees, royalties, or grants related to this case report). This case report has approval from the IRB.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this case report in accordance with the journal's patient consent policy.

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