Kaposiform Lymphangiomatosis: A Distinct Aggressive Lymphatic Anomaly

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Objective To describe the clinical and imaging characteristics of a new lymphatic disorder with a unique histological pattern and poor prognosis.

Study design An observational, retrospective study identified and characterized 20 patients with distinct lymphatic histopathology referred to the Vascular Anomalies Center at Boston Children's Hospital between 1995 and 2011.

Results The median age at onset was 6.5 years (range, birth to 44 years). Clinical and radiologic findings suggested a generalized process. The most common presentations were respiratory symptoms (50%), hemostatic abnormalities (50%), and an enlarging, palpable mass (35%). All patients had mediastinal involvement; 19 patients developed pericardial (70%) and/or pleural effusions (85%). Extrathoracic disease manifested in bone and spleen and less frequently in abdominal viscera, peritoneum, integument, and extremities. Despite aggressive procedural and medical therapies, the 5-year survival was 51% and the overall survival was 34%. Mean interval between diagnosis and death was 2.75 years (range, 1-6.5 years).

Conclusions We describe a clinicopathologically distinct lymphatic anomaly. We propose the term kaposiform lymphangiomatosis (KLA) because of characteristic clusters or sheets of spindled lymphatic endothelial cells accompanying malformed lymphatic channels. The intrathoracic component is most commonly implicated in morbidity and mortality; however, extrathoracic disease is frequent, indicating that KLA is not restricted to pulmonary lymphatics. The mortality rate of KLA is high despite aggressive multimodal therapy. *(J Pediatr 2014;164:383-8)*.

The lymphatic vascular system is fundamental to interstitial circulation and immunity. Focal and generalized anomalies in the structure and function of lymphatic vasculature cause major morbidity through edema, effusion, and infection.[1-3] Complications vary by anatomic location and age at presentation as illustrated by intrathoracic lymphatic anomalies that range from fetal imaging abnormalities to acute or chronic pulmonary insufficiency in older children and young adults.[4-6] Intrathoracic lymphatic anomalies can be confined to the thoracic cavity, causing effusions, lymphatic reflux into air spaces, interstitial disease, and/or dilation of mediastinal and bronchopulmonary lymphatics,[5-7] or combined with systemic manifestations (splenic and osseous lesions, lymphedema, cutaneous changes, and chylous leak) as is observed with generalized lymphatic anomaly (GLA).[4,5,8] Microscopically, GLA is characterized by an anastomotic pattern of variably sized, thin-walled lymphatic channels lined by flattened endothelial cells. The presence of spindled endothelial cells amid the background of malformed lymphatic channels is not typical of GLA and, although reported in the pulmonary literature, has not been delineated as a separate entity.[4,6,9]

We describe a novel subtype of GLA, which is distinguished by histopathology, and highlight the presenting signs/symptoms, organ system involvement, clinical course, response to therapy, and outcome.

Methods

Patients referred to our Vascular Anomalies Center from 1995-2011 with various types of lymphatic anomalies were reviewed at an interdisciplinary conference. Twenty patients had a GLA with novel histopathology. The histologic hallmark was clusters or sheets of "kaposiform" hemosiderotic, spindled lymphatic endothelial cells oriented in parallel fashion amid abnormal and dilated lymphatic channels. These spindled cells were immunoreactive for lymphatic markers (D2-40, Lyve-1, and Prox-1). Mitoses and cellular atypia were rare. Interspersed red blood cells and hemorrhage were also frequently observed. Our Committee on Clinical Investigation approved a retrospective, observational study of these patients. No patients/guardians declined participation. Nine patients/

GLA	Generalized lymphatic anomaly
KHE	Kaposiform hemangioendothelioma
KLA	Kaposiform lymphangiomatosis
MRI	Magnetic resonance imaging

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guardians were successfully contacted and consented to a structured telephone interview and release of medical records to gather data missing from the initial referral. All patients had their medical records reviewed with attention to clinical history, laboratory data, and imaging reports.

Results

All patients had a distinctive histopathologic pattern,[10] characteristic imaging, and poor prognosis (Figure 1). They were often referred with a diagnosis of "lymphangiomatosis." Thoracic disease typically manifested as pleural and/or pericardial effusions. High-resolution computed tomography demonstrated interlobular septal thickening due to dilated lymphatic channels usually with a prominent soft tissue component in the mediastinal, paraspinal, or retroperitoneal region. On magnetic resonance imaging (MRI), this soft tissue component was heterogeneous and infiltrative in appearance with hyperintensity on fluid-weighted sequences. Numerous hypoechoic, round foci were identified in the spleen on sonography. Involvement of bony elements, evidenced by lucent lesions with cortical sparing, was also regularly observed on computed tomography scans or plain radiographs.

The median age at onset of signs and symptoms was 6.5 years (range, birth to 44 years); however, the median age at diagnosis of a lymphatic anomaly was 8.5 years (Figure 2, A). Several factors contributed to this interval, such as limited access to medical care and nonspecific findings, including thrombocytopenia with splenomegaly and indolent respiratory symptoms. There were 13 male and 7 female patients.

Presenting features included respiratory symptoms (50%), bleeding (50%), and subcutaneous mass (35%) (Figure 2, B). The most common respiratory complaints were cough and dyspnea. Five patients had an acute onset of cough and fever or dyspnea. Nonspecific respiratory problems developed in five patients and worsened over an average of 6.4 months (range, 1-12 months); parents recalled shortness of breath

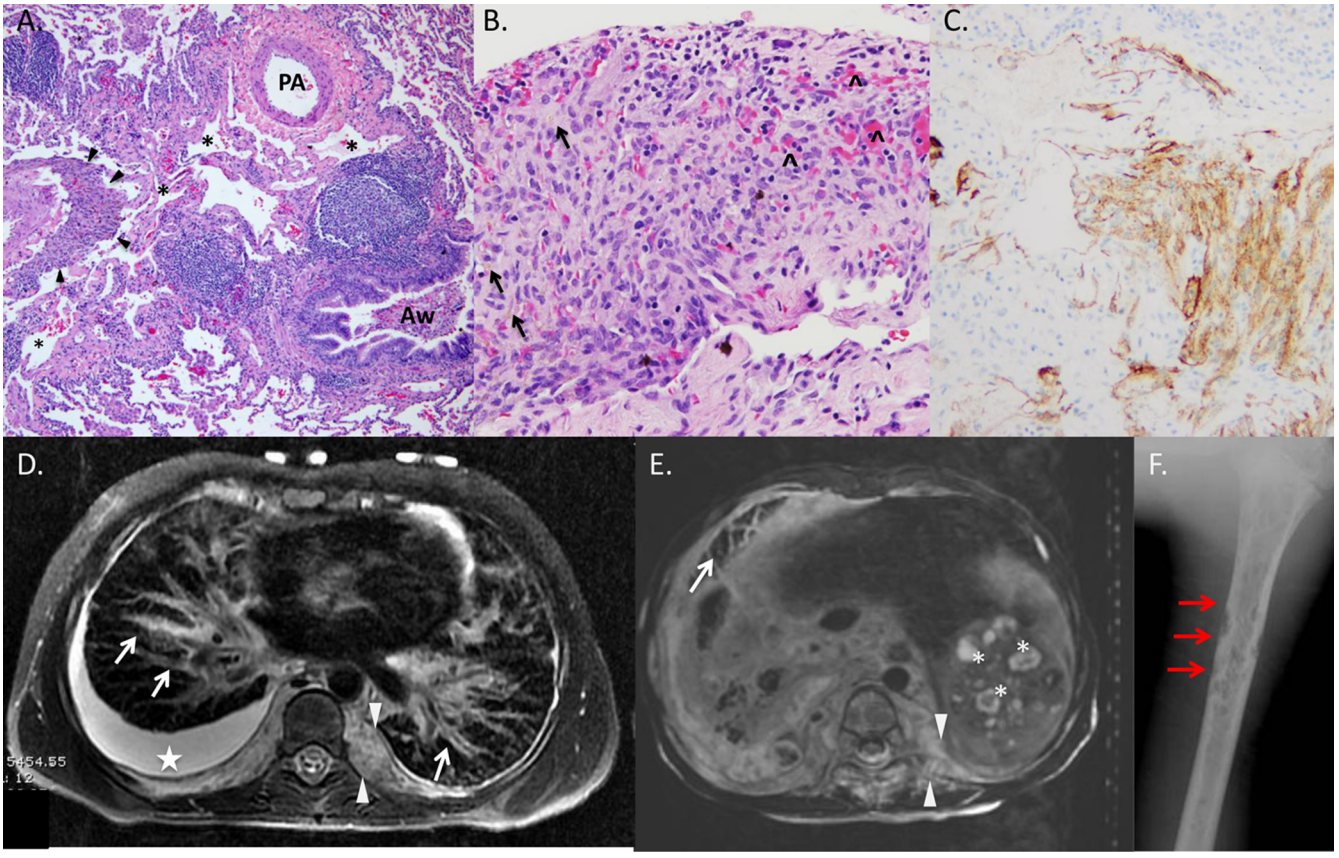

Figure 1. **A-C,** Histopathology, and **D-F,** radiologic, features of KLA. **A,** Pulmonary parenchyma with dilated lymphatic channels (*asterisks*), accompanying airway (Aw), pulmonary artery (PA), and focus of spindled cells (*arrowheads*) (H&E stain). **B,** Spindled cells with cytoplasmic hemosiderin granules (*black arrows*) and interspersed red blood cells (*black open arrowheads*). **C,** Spindled lymphatic endothelial cells immunopositive for D2-40. D, T2 axial thoracic MRI demonstrates pleural effusion (*star*), interlobular septal thickening (*white arrows*), and retroperitoneal soft tissue mass (*arrowheads*). **E,** T2 axial abdominal MRI shows heterogeneous, infiltrative, hyperintense retroperitoneal soft tissue mass (*arrowheads*), splenic cysts (*asterisks*), and pulmonary interlobular septal thickening (*white arrow*). **F,** Plain film illustrates multiple lucent lesions of the humerus (*red arrows*).