Lymphatic Anomalies in Children: Update on Imaging Diagnosis, Genetics, and Treatment

Elizabeth J. Snyder, MD[1], Asha Sarma, MD[1], Alexandra J. Borst, MD[2], Aylin Tekes, MD[3]

Pediatric Imaging · Review

Keywords

lymphatic anomalies, MRI, vascular anomalies

Submitted: Dec 2, 2021
Revision requested: Dec 13, 2021
Revision received: Jan 7, 2022
Accepted: Jan 11, 2022
First published online: Jan 19, 2022

The authors declare that they have no disclosures relevant to the subject matter of this article.

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

Lymphatic anomalies comprise a spectrum of disorders ranging from common localized microcystic and macrocystic lymphatic malformations (LMs) to rare complex lymphatic anomalies, including generalized lymphatic anomaly, Kaposiform lymphangiomatosis, central conducting lymphatic anomaly, and Gorham-Stout disease. Imaging diagnosis of cystic LMs is generally straightforward, but complex lymphatic anomalies, particularly those with multiorgan involvement or diffuse disease, may be more challenging to diagnose. Complex lymphatic anomalies are rare but associated with high morbidity. Imaging plays an important role in their diagnosis, and radiologists may be the first clinicians to suggest the diagnosis. Furthermore, radiologists are regularly involved in management given the frequent need for image-guided interventions. For these reasons, it is crucial for radiologists to be familiar with the spectrum of entities comprising complex lymphatic anomalies and their typical imaging findings. In this article, we review the imaging findings of lymphatic anomalies, including LMs and complex lymphatic anomalies. We discuss characteristic imaging findings, multimodality imaging techniques used for evaluation, pearls and pitfalls in diagnosis, and potential complications. We also review recently discovered genetic changes underlying lymphatic anomaly development and the advent of new molecularly targeted therapies.

The lymphatic system is composed of an endothelium-lined unidirectional network of capillarylike structures that parallel the blood circulatory system. It has critical functions in the regulation of fluid balance, return of interstitial fluid from capillary beds to blood circulation, protein and cell transport, and trafficking of immune cells [1]. Lymphatic vessels are found in nearly every tissue in the body [2]. Peripheral lymphatic capillary vessels connect to larger lymphatic trunks, eventually emptying into central lymphatic vessels. Lymphatic drainage from most of the body enters the thoracic duct, whereas lymphatic vessels in the right upper extremity, right chest, and right side of the head and neck drain into the right thoracic duct.

Lymphatic anomalies are nonneoplastic lesions characterized by abnormally formed lymphatic channels. These lesions may present as localized lesions or as diffuse abnormalities affecting central conducting lymphatics (Table 1). Simple lymphatic malformations (LMs) are common and are typically subdivided into macrocystic, microcystic, and mixed types, as categorized by the International Society for the Study of Vascular Anomalies [3]. Lesions with cystic spaces greater than 1 cm are typically considered macrocystic, and those with cysts smaller than 1 cm are typically considered microcystic. In comparison, complex lymphatic anomalies (CLAs) are diffuse abnormalities and/or abnormalities involving the central conducting lymphatic channels; such disorders include generalized lymphatic anomaly (GLA), Kaposiform lymphangiomatosis (KLA), Gorham-Stout disease, and central conducting lymphatic anomaly (CCLA). LMs may also occur in conjunction with venous or capillary malformations. Finally, LMs may be components of overgrowth syndromes in the *PIK3CA*-related overgrowth spectrum (PROS), a group of disorders that includes Klippel-Trénaunay syndrome, CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies) syndrome, and macrocephaly-capillary malformation syndrome.

[1]Department of Radiology, Vanderbilt University Medical Center, Monroe Carell Jr. Children's Hospital at Vanderbilt, 2200 Children's Way, Nashville, TN 37232-9700. Address correspondence to E. Snyder (Elizabeth.snyder@vumc.org).

[2]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA.

[3]Department of Radiology, Division of Pediatric Radiology and Pediatric Neuroradiology, Johns Hopkins Hospital, Baltimore, MD.

doi.org/10.2214/AJR.21.27200
AJR 2022; 218:1089–1101
ISSN-L 0361–803X/22/2186–1089
© American Roentgen Ray Society

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

The aims of this article are to review the imaging criteria and differential diagnoses of LMs, ranging from common micro- and macrocystic LMs to rare complex disorders; multimodality imaging techniques used for evaluation of these disorders; and considerations pertaining to complications, treatment, and post-treatment follow-up of LMs. Given the increasing application of molecularly targeted therapies, we will also review the genetic basis for lymphatic anomalies.

Pathogenesis

Most LMs are caused by somatic mutations in genes that encode components of oncogenic growth factor signal transduction pathways (Fig. 1). Isolated LMs frequently harbor activating *PIK3CA* mutations [4–7]. *PIK3CA* encodes an upstream element of the PI3K/AKT/mTOR (phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin) pathway that is involved in the regulation of multiple functions, including cell proliferation, cell growth, and angiogenesis [6, 7]. Recently, specific genotypes in the *PIK3CA* gene have been linked to different phenotypes and severities of LMs [7]. PROS is caused by somatic gain-of-function mutations in *PIK3CA*, a gene that encodes a subunit of PI3K [8].

CLAs are associated with mutations in components of the RAS/MAPK (rat sarcoma–mitogen-activated protein kinase) pathway, although some *PI3KCA*-activating mutations, similar to those found in simple LMs, have also been found in patients with GLA [9–15]. Specifically, somatic activating mutations in *KRAS* have recently been found in Gorham-Stout disease, *EPHB4* and *ARAF* mutations have been identified in CCLA, and a somatic activating *NRAS* mutation has been associated with KLA and GLA [16]. The RAS/MAPK pathway is involved in regulating the cell cycle and cellular growth, as well as cell differentiation [17, 18]. Mutations in the RAS/MAPK pathway also cause syndromes including Noonan syndrome, Costello syndrome, neurofibromatosis type 1, capillary malformation-arteriovenous malformation syndrome, tuberous sclerosis, and other RASopathies [11, 17, 18].

In the era of precision medicine, knowledge of these genetic mutations has driven the creation and use of targeted therapies for several of these conditions, as discussed later in this review.

Clinical Presentation

Although the exact incidence of LMs has not been well established, the estimated prevalence is approximately 1 in 4000. Most LMs present within the first 2 years of life, although they may present at any age or may be diagnosed prenatally [19–22]. Simple LMs are most commonly found in the head and neck but may occur anywhere in the body [19, 20, 23]. On physical examination, simple LMs present as soft, partially compressible, nonpainful lesions. The overlying skin may appear normal, bluish, or with brownish vesicles. If complicated by infection or hemorrhage, they can present in the acute setting as a rapidly enlarging, potentially painful mass. Other potential complications of LMs include edema, disfigurement, and bone involvement with pain or pathologic fracture.

TABLE 1: Spectrum of Lymphatic Anomalies [3]

Category	Entities
Simple	Macrocystic Microcystic Mixed
Complex	Generalized lymphatic anomaly Kaposiform lymphangiomatosis Gorham-Stout (vanishing bone) disease Central conducting lymphatic anomaly *PIK3CA*-related overgrowth spectrum

HIGHLIGHTS

- *Lymphatic anomalies comprise a spectrum of disorders ranging from common localized LMs to rare CLAs that may exhibit multiorgan involvement or diffuse disease.*
- *Genetic changes underlying lymphatic anomaly development have been recently discovered and are enabling new molecularly targeted therapy.*
- *Radiologists play a critical role in the diagnosis, evaluation, and multidisciplinary management of patients with lymphatic anomalies, and knowledge of associated imaging findings is essential.*

CLAs typically present within the first 2 years of life, though they have a highly variable presentation. Furthermore, the clinical presentations of CLAs may overlap (Table 2). Typically, patients have lesions in multiple tissues or sites, including the spleen and bones. Lymph or chyle may leak into body cavities, potentially resulting in pleural effusions, pericardial effusions, and ascites [16, 24]. Intestinal lymphangiectasias may lead to protein-losing enteropathy or gastrointestinal bleeding. PROS may also present with a spectrum of symptoms that vary in extent and severity but always have an onset in utero, at birth, or in early childhood. Typical clinical findings of PROS include vascular malformations; overgrowth of adipose, muscle, and skeletal tissue; and, at times, epidermal nevi [25].

Role of Imaging and Imaging Modalities

Simple LMs can be diagnosed according to clinical appearance, and imaging may not be needed or indicated. Ultrasound (US) with Doppler is the first imaging modality of choice, is often sufficient for the diagnosis of superficial lesions, and has the added benefits of lack of ionizing radiation exposure or need for sedation. Advanced imaging (typically MRI) may be required to evaluate the extent of a lesion if it is atypical, large, or deep in location. CT is less often used for the diagnosis of LMs but may aid in the evaluation and diagnosis of bone involvement or in the identification of intraabdominal lesions. In certain cases, CT may be favored because of shorter imaging duration and lack of need for sedation.

In cases of suspected CLAs, whole-body MRI may be used to evaluate for multifocal lesions, including in cases with multifocal bone involvement or bone and soft-tissue abnormalities. MR lymphangiography is increasingly used in lieu of conventional lymphangiography or lymphoscintigraphy to assess patients with suspected CLAs and to evaluate the integrity of the central conducting lymphatics. It relies on heavily T2-weighted imaging to illustrate fluid-filled lymphatic channels and provide a detailed evaluation of the anatomy. Dynamic postcontrast images are also typically obtained after hand injection of gadolinium-based

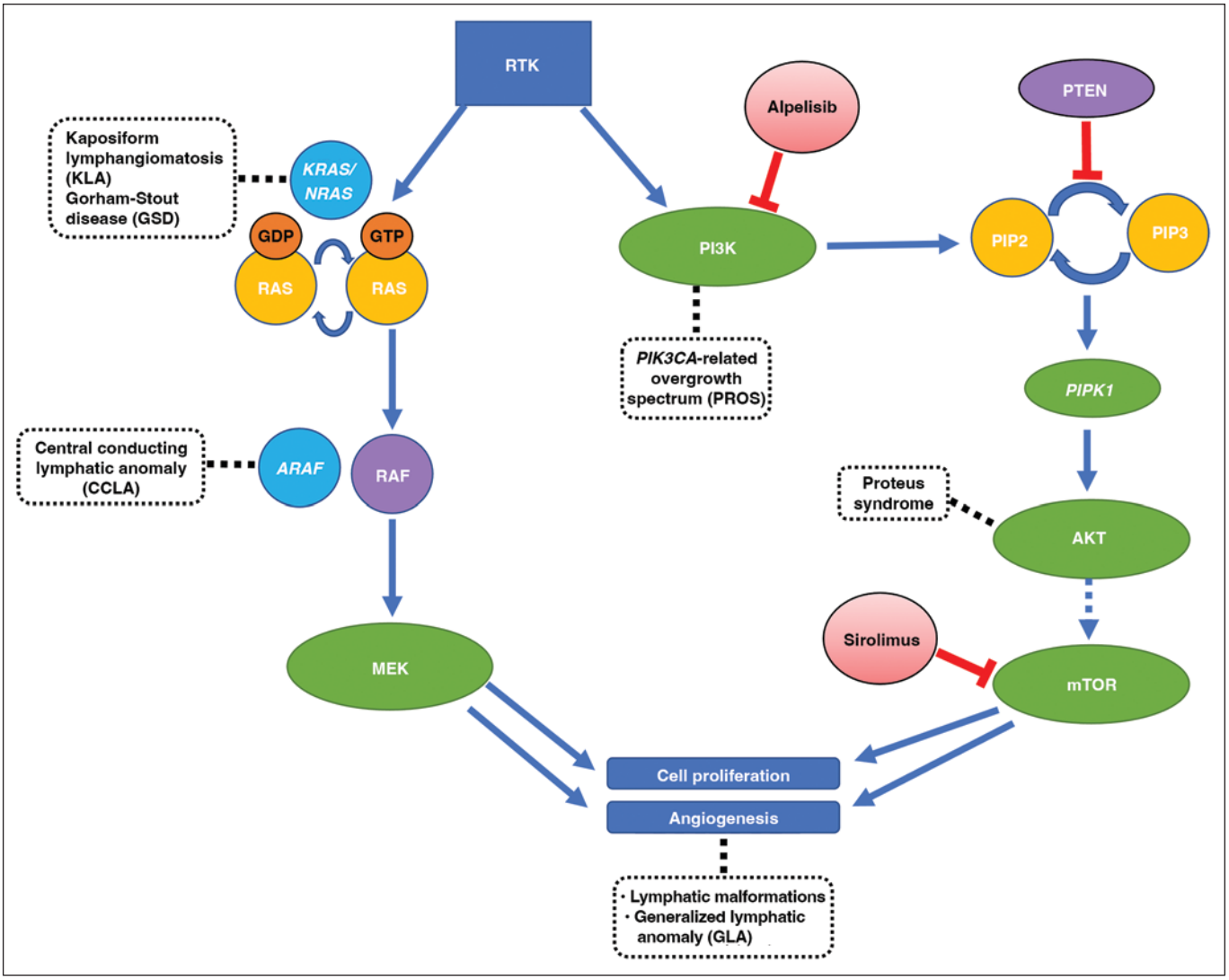


Fig. 1—Diagram of RAS/MAPK pathway and PI3K/AKT/mTOR pathway involved in pathogenesis of lymphatic anomalies [6, 17, 18, 25, 73]. RAS = rat sarcoma, MAPK = mitogen-activated protein kinase, PI3K = phosphoinositide 3-kinase, AKT = protein kinase B, mTOR = mechanistic target of rapamycin, RTK = receptor tyrosine kinase, PTEN = phosphatase and tensin homolog, GDP = guanosine diphosphate, GTP = guanosine triphosphate, PIP2 = phosphatidylinositol 4,5-bisphosphate, PIP3 = phosphatidylinositol (3,4,5)-triphosphate, RAF = rapidly accelerated fibrosarcoma, MEK = mitogen-activated protein kinase kinase.

TABLE 2: Clinical Findings in Complex Lymphatic Anomalies and *PIK3CA*-Related Overgrowth Spectrum (PROS)

Anomaly	Clinical Findings
Generalized lymphatic anomaly	Macrocystic and/or microcystic LMs affecting multiple sites; pleural effusions; splenic involvement; bone lesions involving medullary cavity
Kaposiform lymphangiomatosis	Mediastinal mass; pleural or pericardial effusions, possibly hemorrhagic; splenic lesions; bone lesions, especially of axial skeleton; consumptive coagulopathy and hemorrhage; spindle cells on biopsy
Gorham-Stout disease	Progressive osseous lesions with cortical destruction (vanishing bone); infiltrative soft-tissue masses; pathologic fracture
Central conducting lymphatic anomaly	Dilated central lymphatics with leakage; pleural or pericardial effusions; ascites; generalized edema; splenic lesions; abnormal MR lymphangiogram with disruption of central lymphatic channels
PROS	Bony, soft-tissue, or fatty overgrowth; possible vascular malformations (high-flow and/or low-flow); possible epidermal nevi

Note—LM = lymphatic malformation.

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

contrast material into inguinal lymph nodes. High-resolution T1-weighted images performed every minute after 15 minutes can be obtained [26]. Timing of first passage of contrast material through the central conducting lymphatics, including the cisterna chyli and the thoracic duct, as well as the anatomy of these structures, are assessed.

Correlation with physical examination findings or with documentation such as photographs in the medical record is often helpful to reach an appropriate radiologic diagnosis.

In addition to aiding in the diagnosis and initial evaluation of lymphatic anomalies, imaging may be necessary to evaluate potential complications of LMs. Simple LMs may rapidly increase in size in response to infection or internal hemorrhage; in these cases, imaging may be performed in the acute setting in the absence of a priori knowledge of an underlying LM. LMs may also cause mass effect on adjacent structures, and imaging may be required for evaluation. A notable example is the prenatal evaluation of cervical LMs, in which MRI is often required to evaluate for mass effect on the airway to facilitate delivery planning. Intraabdominal LMs may lead to intestinal obstruction, volvulus, or gastrointestinal hemorrhage, and imaging is frequently required to evaluate such complications [27].

MRI also plays an important role in posttreatment follow-up, particularly in cases of large or complex LMs [28, 29]. MR lymphangiography may help to direct therapeutic interventions in certain cases, such as when thoracic duct embolization is considered for a lymphatic leak, and can evaluate central lymphatic ducts after surgical or endovascular intervention [30, 31].

Imaging Findings of Lymphatic Malformations

Simple Lymphatic Anomalies

Macrocystic lymphatic malformations—The diagnosis of macrocystic LMs can typically be established on US, if imaging is indicated. A macrocystic LM typically appears on US as a lobulated cystic lesion with multiple thin septations. LMs frequently cross tissue planes, which is described as a transspatial or multispatial distribution. On US with Doppler, macrocystic LMs typically show no Doppler flow within cysts but possible flow in the septa. Although the cysts in macrocystic LMs characteristically appear anechoic on US, they frequently contain internal echoes or fluid-fluid levels because of proteinaceous content or associated infection or hemorrhage. The complexity of these lesions is typically best seen on US. MRI may better show the anatomic extent of a large macrocystic LM compared with US. On MRI, a macrocystic LM appears as a multiseptated hyperintense cystic lesion on T2-weighted imaging (Figs. 2 and 3). Internal cyst content may be hyperintense on T1-weighted imaging if it contains blood or protein (Figs. 2 and 4). Postcontrast images show enhancement restricted to septa (Figs. 2 and 4).

The differential diagnosis of macrocystic LMs includes congenital cystic lesions (e.g., branchial cleft cyst) and abscess, although patients with abscess commonly present with typical clinical findings of infection such as fever and redness. Follow-up imaging may be necessary when the diagnosis is not clear or when an infected congenital lesion is suspected (Fig. 5). Malignancies such as rhabdomyosarcoma or synovial sarcoma may simulate cysts on T2-weighted imaging but typically show more solid or nodular enhancement after contrast administration or features of high cellularity such as low diffusivity [32] (Fig. 6). Mesenteric macrocystic LMs can be confused with other intrabdominal cystic lesions such as enteric duplication cysts. However, LMs are more likely to be multilocular (rather than unilocular) and lack characteristic wall gut signature on US [33]. Cystic-appearing neoplasms of the abdomen, including large plexiform neurofibromas, Ewing sarcoma, and mesothelioma (although rare) may also mimic mesenteric macrocystic LMs. Compared with neoplasms, large mesenteric macrocystic LMs are more likely to appear soft, conforming to and insinuating among the abdominal organs with relatively little mass effect in consideration of the lesion's size.

Microcystic lymphatic malformations—Microcystic LMs may have subtle sonographic findings. Images may show tiny cystic spaces, but frequently the cysts are too small to distinguish and the lesions resemble nonspecific soft-tissue thickening or edema (Fig. 7). MRI may be helpful for troubleshooting. On MRI, microcystic LMs

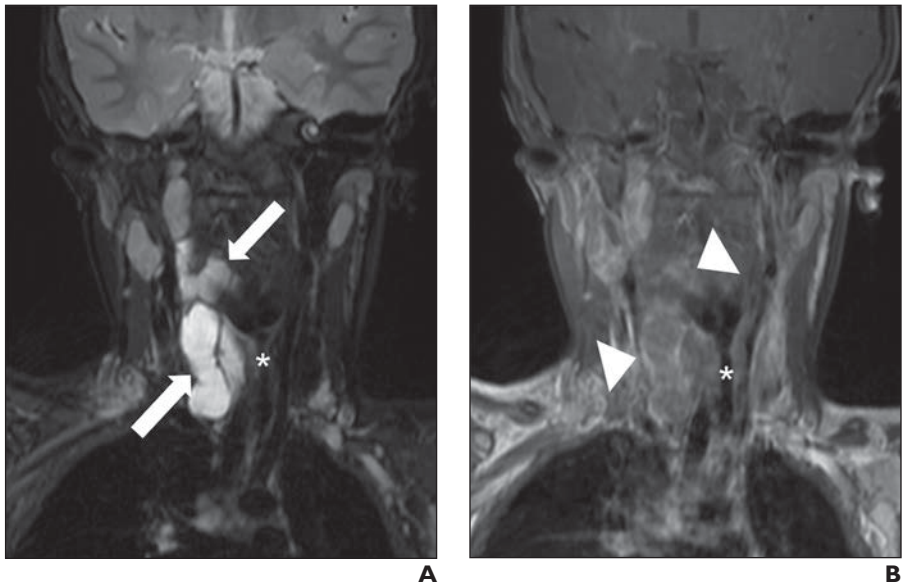


Fig. 2—2-year-old boy with neck swelling from macrocystic lymphatic malformation.
A and **B,** Coronal T2-weighted fat-saturated (**A**) and postcontrast T1-weighted fat-saturated (**B**) MR images of neck show hyperintense cystic spaces on T2-weighted imaging (*arrows*, **A**) crossing multiple tissue planes. Mild mass effect on adjacent esophagus (*asterisks*) is present. Septa show thin enhancement (*arrowheads*, **B**), but cystic cavities do not enhance.

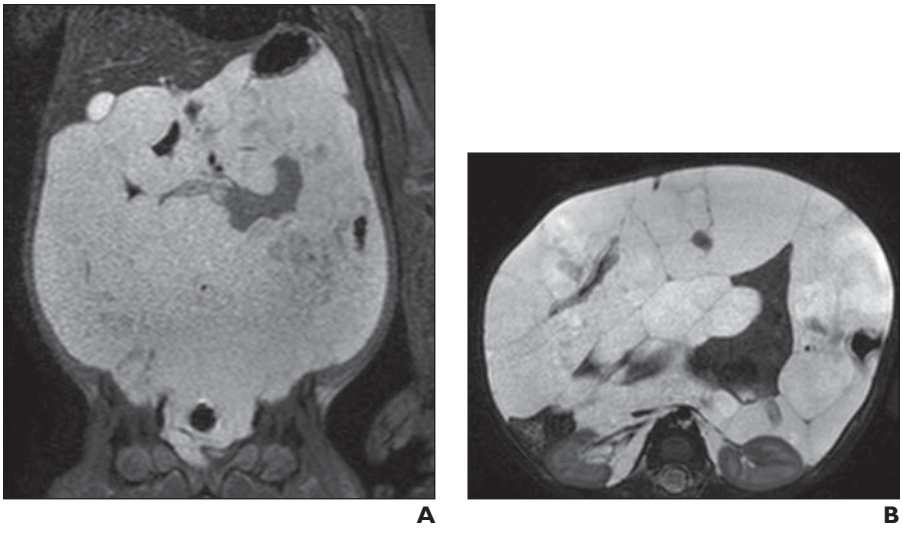


Fig. 3—15-month-old boy with abdominal swelling. **A** and **B,** Coronal (**A**) and axial (**B**) T2-weighted fat-saturated MR images show extensive hyperintense multiseptated mass with mass effect on liver, bowel, and kidneys, consistent with mesenteric and retroperitoneal lymphatic malformation.

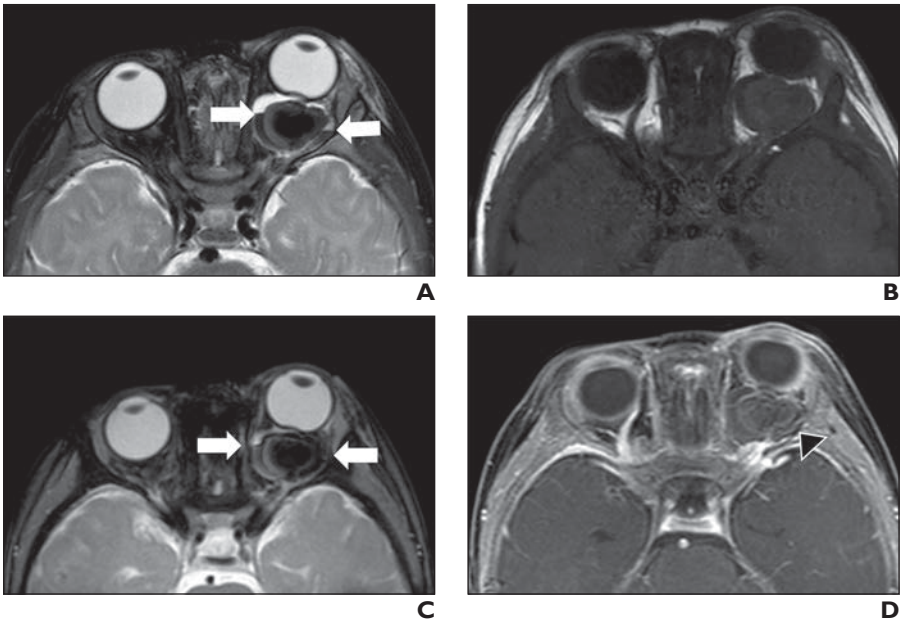


Fig. 4—8-month-old boy with acute proptosis because of intraorbital lymphatic malformation with acute hemorrhage.
A–D, Axial T2-weighted (**A**), T1-weighted (**B**), T2*-weighted (**C**), and postcontrast fat-saturated T1-weighted (**D**) images show macrocystic left intraconal orbital lesion (*arrows*, **A** and **C**) with internal hematocrit levels. Marked anterior globe displacement is present. Only thin septal enhancement is present (*arrowhead*, **D**) after contrast material administration.

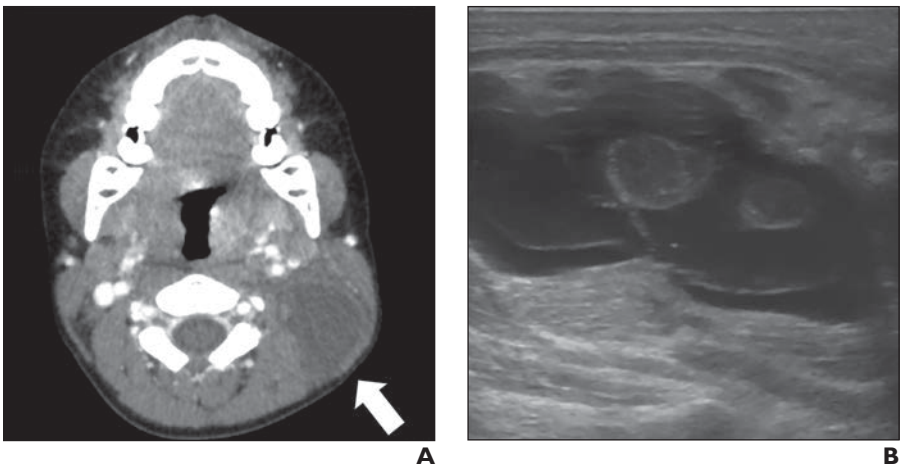


Fig. 5—7-year-old boy with acute tender neck swelling and dysphagia because of infected macrocystic lymphatic malformation (LM).
A, Axial contrast-enhanced CT shows left neck macrocystic lesion (*arrow*) with mass effect, rim enhancement, and adjacent fat stranding.
B, Gray-scale ultrasound image obtained 5 months later and after antibiotic treatment shows debris-containing multicystic collection. In acute setting, infected LM may be difficult to differentiate from branchial apparatus anomalies and nodal abscesses. However, multicystic presentation is unusual for branchial apparatus cysts, and nodal abscesses usually have surrounding lymphadenopathy. History of previously existing mass and follow-up may be helpful to establish correct diagnosis. Internal complexity of lesion is better shown by ultrasound than by CT.

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

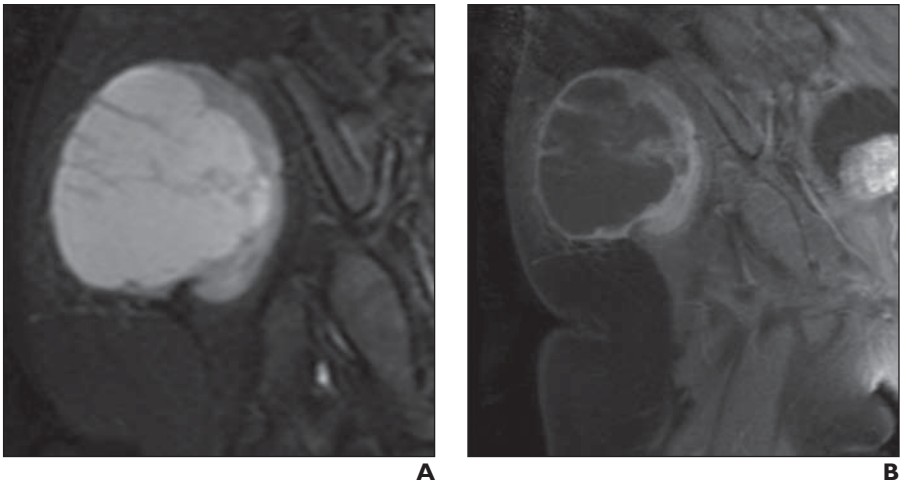


Fig. 6—6-month-old boy with enlarging right pelvic mass.
A and **B,** Coronal T2-weighted fat-saturated (**A**) and postcontrast T1-weighted fat-saturated (**B**) MR images show multiseptated mass that is hyperintense on T2-weighted imaging centered in right gluteus maximus muscle. Small solid component is present along medial aspect of lesion. On postcontrast image, septa also appear somewhat irregular, which would be atypical for lymphatic malformation. Biopsy of this lesion showed rhabdomyosarcoma.

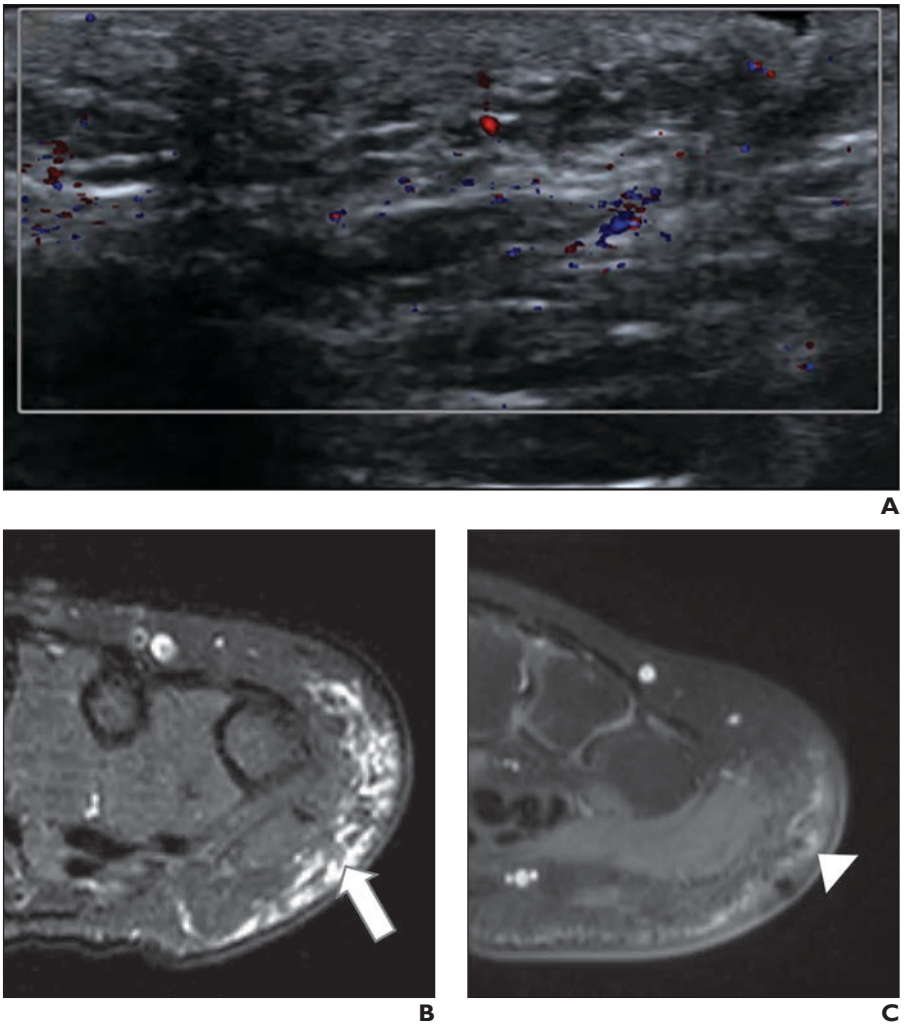


Fig. 7—7-year-old girl with hand swelling because of microcystic lymphatic malformation (LM).
A, Sagittal color Doppler ultrasound image of medial hand shows ill-defined soft-tissue thickening without associated vascularity. Tiny cystic spaces may be delineated.
B and **C,** Axial T2-weighted fat-saturated (**B**) and postcontrast T1-weighted fat-saturated (**C**) MR images show infiltrative, ill-defined T2-weighted hyperintensity (*arrow*, **B**) in subcutaneous compartment with associated mild ill-defined enhancement (*arrowhead*, **C**). No discrete cystic spaces are seen by MRI. Because of tiny cystic spaces and numerous contiguous cyst walls, microcystic LMs can show contrast enhancement and be confused with solid soft-tissue lesions.

appear as ill-defined infiltrative lesions that are hyperintense on T2-weighted imaging and that often do not enhance (Fig. 7). Careful comparison of pre- and postcontrast fat-saturated T1-weighted images and/or evaluation of subtraction images can be useful in differentiating between blood products or proteinaceous fluid and enhancing solid tissue. Because the septa may enhance on postcontrast images, these lesions can appear solid if the cysts are too small to be distinguished on imaging. Although the diagnosis can typically be established on imaging, the differential diagnosis also occasionally includes cellulitis or lymphedema.

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

Mixed lymphatic malformations—Mixed microcystic and macrocystic LMs contain both cysts over 1 cm and cysts under 1 cm in size (Fig. 8). Thus, US and MRI findings are similar to those previously described. As with microcystic LMs, the microcystic components of mixed LMs may appear solid with solid enhancement because of closely-packed septa. In the prenatal period, the differential diagnosis includes congenital teratoma, which typically shows more solid components and more mass effect compared with LM and often contains fat and/or calcifications.

Complex Lymphatic Anomalies

The diagnosis of CLA is typically established by a combination of clinical, laboratory, and imaging findings, and sometimes by biopsy. When clinical concern exists for a CLA, whole-body MRI is typically performed, because patients may have multifocal or anatomically extensive lesions [30, 34]. Typical sequences include coronal and axial STIR or fat-saturated T2-weighted and axial pre- and postcontrast T1-weighted images of the whole body, and sagittal STIR or fat-saturated T2-weighted images of the entire spine [34]. Sequence selection and use of IV contrast material may depend on the clinical context. Histopathologic and genetic analysis of lesions may also help to define potential pharmacologic management. If biopsy is required, imaging may be useful to identify a potential target for biopsy. Biopsy is typically preferred of soft-tissue lesions rather than of bone lesions. Biopsy should be performed judiciously, however, because potential complications include prolonged lymphatic leakage and worsening of chylothorax or chylous ascites [30, 34]. This concern particularly applies for biopsy of rib lesions [30, 34]. Differentiating among CLAs may be challenging given their overlapping clinical and imaging findings.

Generalized lymphatic anomaly—GLA is defined by multifocal LMs that are frequently intrathoracic and intraabdominal, as well as by bone and visceral lesions. Imaging, particularly MRI, is typically indicated for the evaluation of GLA [27]. Imaging may show multiorgan involvement by LMs, including involvement of the spleen, mediastinum, and bone, as well as pleural and pericardial effusions (Fig. 9). Vertebral body lesions are not infrequent. Bone lesions typically involve the medullary cavity, sparing the cortex (in contrast to Gorham-Stout disease), and are more likely to involve the appendicular skeleton [10, 27, 32, 33]. The diagnosis is typically established by clinical history and the distribution and extent of lesions [24, 27, 33, 35]. Clinical presentation and response vary greatly, but patients with more extensive and/or central involvement typically have higher morbidity and a worse prognosis. Patients with GLA are most commonly found to have pathogenic somatic mutations in *PIK3CA,* leading to overactivity in the PI3K/AKT/mTOR pathway and disrupted lymphatic development and growth [9, 36].

Functional imaging, particularly with MR lymphangiography, is important for the workup of patients with GLA [36]. If a specific site of leakage is found to be the cause of pulmonary lymphangiectasia, pleural effusions, or ascites, then targeted embolization with ethiodized oil (Lipiodol, Guerbet) can be performed [30]. Follow-up imaging can be performed to confirm resolution of the leak.

Central conducting lymphatic anomaly—CCLA refers to disorders of the central lymphatic channels, affecting either the thoracic duct or cisterna chyli. CCLA has been described as its own entity as well as a component of other CLAs. Poorly formed, atretic central lymphatic channels lead to chronic reflux of lymphatic fluid into the surrounding tissues. This results in reflux of lymph, with seepage of fluid into the lungs and abdomen causing pleural and pericardial effusions, ascites, and lymphedema, as seen on imaging [24, 27]. The diagnosis may be on the basis of clinical history and examination and imaging findings. MR lymphangiography is useful in the diagnosis of CCLA, showing disruption of central lymphatic channels [16, 37–39] (Fig. 9). Recently, investigators have identified mutations in *EPHB4* and *ARAF* in patients with CCLA, highlighting the role of altered RAS/MAPK pathway signaling in this disease [13, 40].

Gorham-Stout disease—Gorham-Stout disease is characterized by progressive osteolysis associated with proliferation of LMs within the bone. Radiography or CT shows lytic or lacelike lucent lesions in the affected bone, with associated cortical destruction and progressive bone loss [41–43] (Fig. 10). The progressive bone loss may lead to the appearance of vanishing bone disease or a "sucked candy" appearance of affected long bones, with the bone becoming tapered at one end [44]. The osteolysis can be profound and lead to complete dysfunction of an appendage or even spinal instability if vertebrae are involved. Associated pathologic fracture may occur. MRI may also show extension

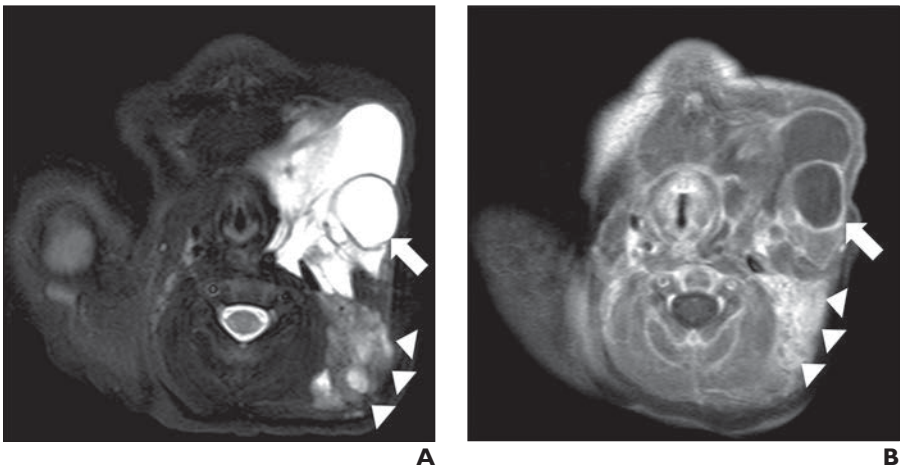


Fig. 8—2-month-old girl with neck swelling because of mixed macrocystic and microcystic lymphatic malformation.
A and **B,** Axial T2-weighted fat-saturated (**A**) and postcontrast T1-weighted fat-saturated (**B**) MR images show transspatial left neck mass, with both macrocystic anterior (*arrows*) and solid-appearing microcystic posterior (*arrowheads*) components.

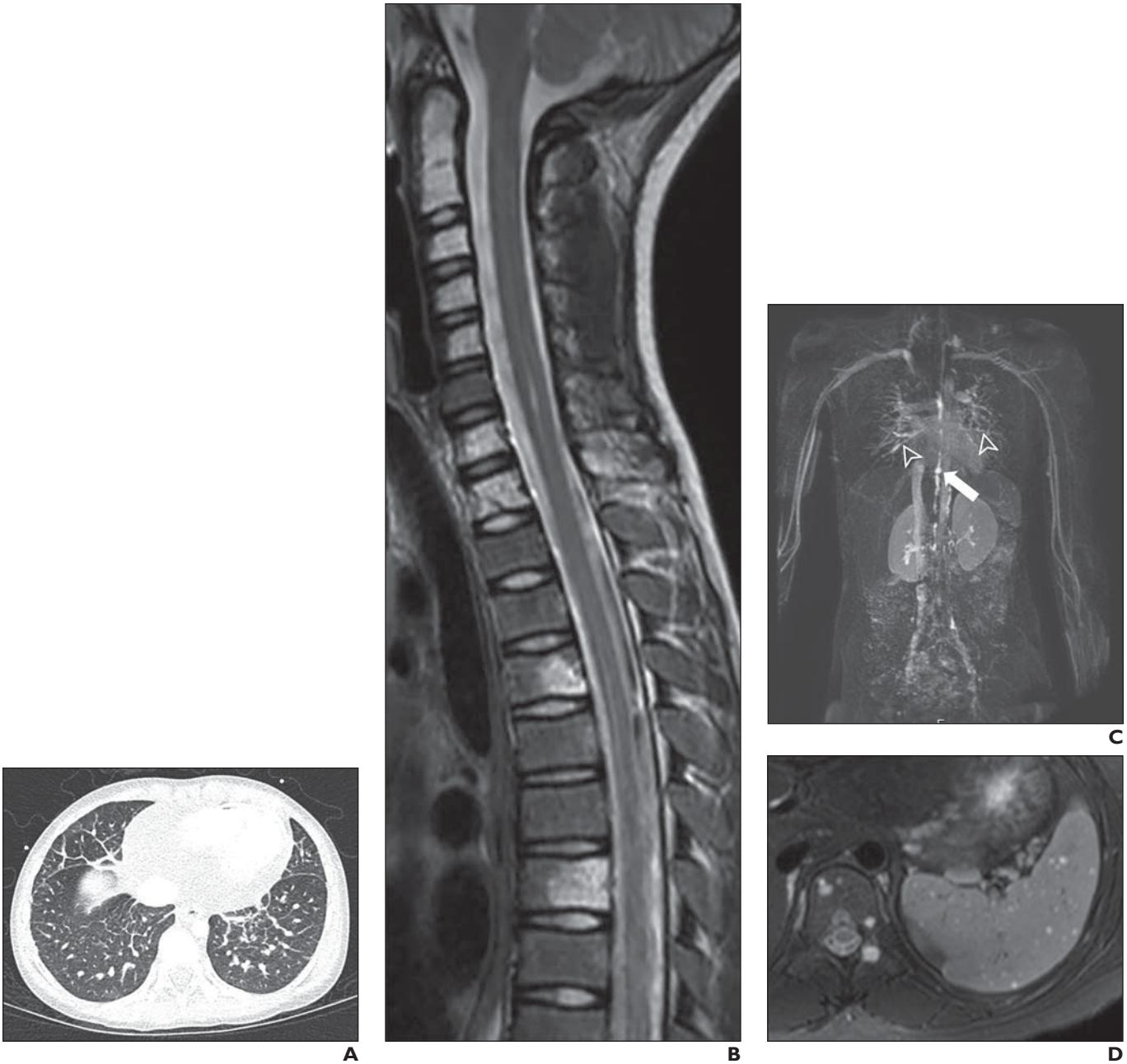


Fig. 9—Examples of complex lymphatic anomaly.
A–C, Axial chest CT (**A**) of 6-year-old girl who presented with chronic cough shows interstitial thickening, suggestive of lymphangiectasia. Sagittal T2-weighted MRI (**B**) of thoracic spine shows multiple hyperintense vertebral body lesions. Coronal maximum-intensity-projection postcontrast T1-weighted MR lymphangiogram (**C**) shows only mild dilatation of thoracic duct (*arrow*, **C**) and leakage of contrast material into peribronchial lymphatics (*arrowheads*, **C**), consistent with central conducting lymphatic anomaly (CCLA). Diagnosis of generalized lymphatic anomaly (GLA) and CCLA was established according to clinical and imaging findings.
D, Axial T2-weighted fat-saturated MRI of abdomen in 13-year-old boy with GLA shows multiple hyperintense cystic foci in spleen, compatible with splenic involvement of lymphatic malformation. Osseous lesions that are hyperintense on T2-weighted imaging are also present in adjacent vertebra.

of the LM into the soft tissue, which typically appears hyperintense on T2-weighted imaging and infiltrative, with associated enhancement, although the soft-tissue component may appear heterogeneous. Hypointense components on T2-weighted imaging may be present, attributed to increased fibrous tissue content [41, 43, 45, 46]. Patients may also have pleural effusions or splenic lesions, accounting for the clinical overlap with GLA. Relative to GLA, Gorham-Stout disease more commonly affects a single bone and more commonly affects the axial skeleton [36, 45]. The diagnosis can often be made on the basis of CT and/or MRI findings. Although typically not performed in these patients, MR lymphangiography results are normal [34]. Biopsy may show abnormally formed lymphatic channels in the soft tissue [30]. Certain recent molecular findings in patients with Gorham-Stout dis-

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

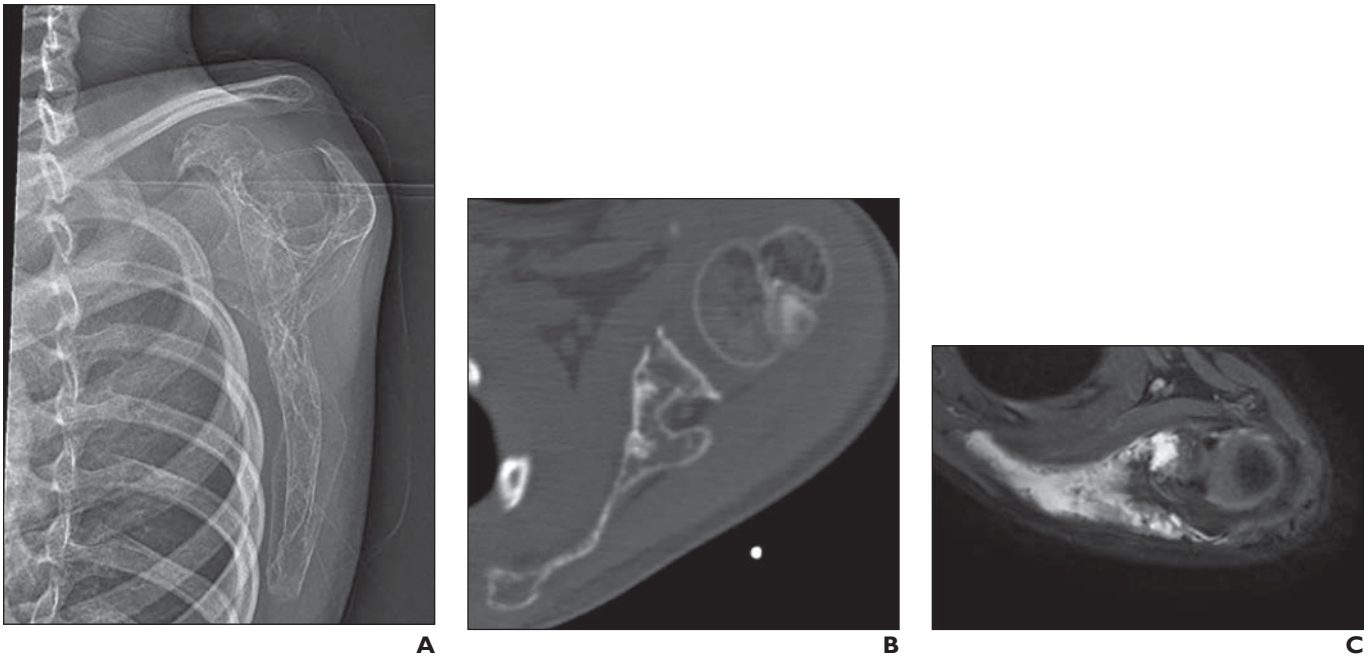


Fig. 10—9-year-old girl who initially presented with left shoulder pain from Gorham-Stout disease.
A and **B,** Radiograph (**A**) and axial CT (**B**) of left scapula show intramedullary lucent lesions with cortical thinning.
C, Axial T2-weighted fat-saturated MRI of scapula shows multiple lobulated foci that are hyperintense throughout scapula, with thinning of cortex.

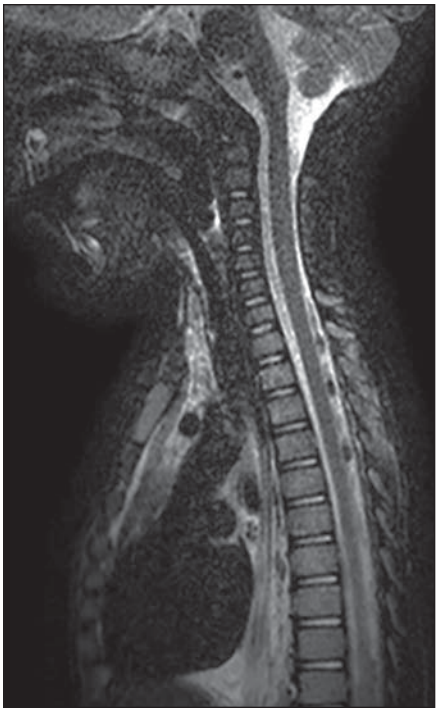
ease have suggested that somatic activating mutations in *KRAS* and dysfunction of the RAS/MAPK signaling pathway drive the pathogenesis [15, 47].

Kaposiform lymphangiomatosis—KLA is another diffuse lymphatic anomaly characterized histologically by the presence of spindle-shaped cells on biopsy [36, 48–52]. The clinical presentation overlaps substantially with GLA but is usually more severe and progressive, resulting in high morbidity and mortality [16, 30, 48, 50, 53]. As a key feature, KLA is distinguished from other CLAs by the frequent occurrence of consumptive coagulopathy characterized by thrombocytopenia and hypofibrinogenemia (i.e., Kasabach-Merritt syndrome), which can cause hemorrhagic complications [16, 36, 48, 49, 53, 54]. The imaging findings of KLA are similar to those in GLA, including pleural and/or pericardial effusions, retroperitoneal and intrathoracic involvement of hyperintense infiltrative soft tissue on T2-weighted imaging, and multifocal visceral involvement, but hemorrhagic pericardial and pleural effusions and ascites are more common in KLA [30, 36, 50, 55] (Fig. 11). Importantly, patients with KLA may have a component of CCLA, and functional imaging, such as with MR lymphangiography, may be warranted in some cases [16]. The thoracic spine is the most common site of osseous involvement [50]. Compared with GLA, infiltrative soft lesions in KLA are more commonly found adjacent to areas of osseous involvement and may show more contrast enhancement [16, 30, 50, 56]. Mediastinal and retroperitoneal involvement may also be more extensive. Somatic mutations in *KRAS* and *NRAS* have been recently identified in patients with KLA, again implicating the RAS/MAPK pathway in the pathogenesis of this disease [10, 11, 16].

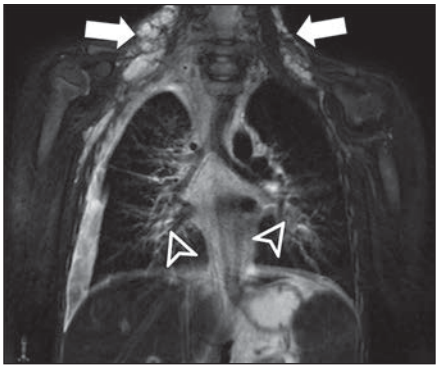
PIK3CA-*related overgrowth spectrum*—PROS refers to entities characterized by vascular anomalies associated with tissue overgrowth. The term encompasses a wide variety of clinical phenotypes, which have been recently found to be associated with activating mutations in *PIK3CA*. The group includes Klippel-Trénaunay syndrome, CLOVES, phosphatase and tensin homolog (PTEN)-associated hamartoma syndrome, and macrocephaly-capillary malformation syndrome [25, 57]. Closely related, but distinct, is proteus syndrome, which is a result of mutations in *AKT1* [58, 59]. Several different vascular anomalies may present in these patients, including high-flow, low-flow, and combined malformations, with imaging features dependent on the type of vessels involved in the malformation [8, 25, 60, 61] (Fig. 12). MRI is typically used in these patients for the evaluation of vascular anomalies, with dynamic time-resolved MRA useful for the differentiation of high-flow and low-flow malformations. Multistation MRI is often necessary for evaluation of patients with massive limb involvement. Whole-body MRI may be required in cases of truncal overgrowth or involvement [25]. Overgrowth may occur in organs, bones, fat, muscle, or vessels, and is well-characterized by imaging, particularly MRI. The discovery of the key role of *PIK3CA* mutation in these disease states has improved awareness of PROS and led to potential new therapeutic options such as *PI3K* inhibition [62].

Treatment

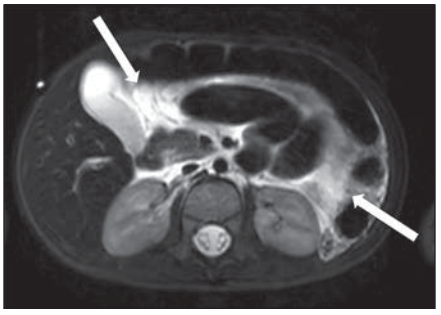
If therapy for simple LMs is indicated, percutaneous approach sclerotherapy is the mainstay of treatment [63–65]. Many sclerosing agents are available, including doxycycline, bleomycin, and sodium tetradecyl sulfate, among others. Bleomycin is often favored in cases in which postprocedural swelling should be avoided (e.g., when a LM is adjacent to the airway or another vital structure) [65–67]. Complex cases, frequently those involving microcystic or mixed LM, may require a multidisciplinary approach



A

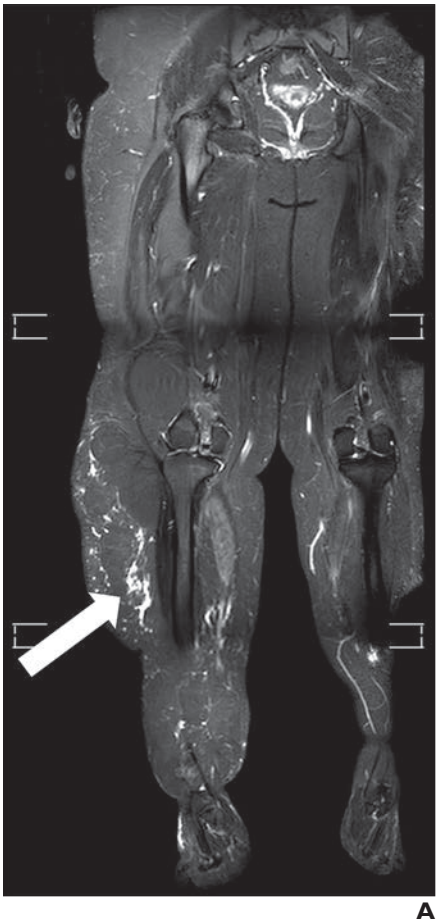


B

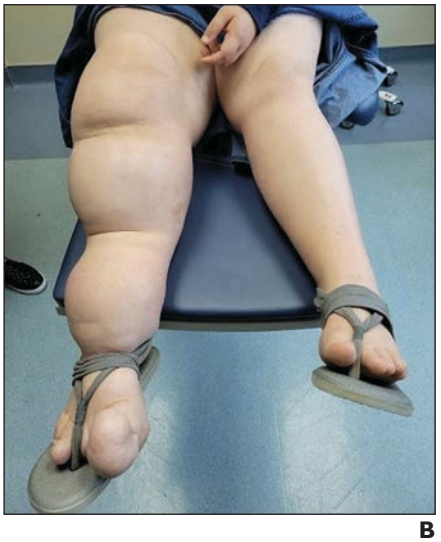


C

Fig. 11—2-year-old boy with cyanosis and coagulopathy resulting from Kaposiform lymphangiomatosis.
A, Sagittal T2-weighted fat-saturated MRI shows extensive marrow signal abnormality throughout thoracolumbar spine and posterior mediastinal involvement.
B, Coronal T2-weighted fat-saturated MRI shows paraspinal and mediastinal involvement, bilateral cervical lymphatic malformation (*arrows*), right pleural effusion, and parahilar interstitial thickening (*arrowheads*).
C, Axial T2-weighted fat-saturated MRI shows hyperintense extensive mesenteric (*arrows*) and retroperitoneal lymphatic malformation.



A



B

Fig. 12—14-year-old girl with *PIK3CA*-related overgrowth spectrum (PROS).
A, Stitched coronal STIR image of right lower extremity shows extensive soft-tissue overgrowth of entire lower extremity. Irregular serpiginous subcutaneous lesions that are hyperintense on T2-weighted imaging, best visualized along lateral aspect of extremity (*arrow*), are component of lymphatic malformation.
B, Photograph of lower extremity further shows degree of lower extremity overgrowth.

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

with a combination of sclerotherapy, surgery, and pharmacologic management.

Sirolimus, previously approved as an immune suppressant, is being increasingly used for the management of LMs. The drug is an inhibitor of mTOR, a serine-threonine kinase in the PI3K/AKT pathway, which is overactivated in most LMs and some CLAs as previously described. Sirolimus is an effective treatment for microcystic, macrocystic, and mixed LMs, as well as for CLAs [37, 65, 66–71].

Given recent advances in the genetic evaluation of LMs and CLAs, additional targeted therapies are being developed. For example, a *PI3K1* inhibitor (BLY719/alpelisib) has been shown to be effective in the management of PROS, reducing the size of vascular anomalies and decreasing tissue overgrowth [8, 62, 72]. Inhibitors of the RAS/MAPK pathway, which is frequently activated in CLAs, including the mitogen-activated protein kinase kinase (MEK)-inhibitors trametinib and selumetinib, have been shown to be effective in cases of KLA, CCLA, and GLA [13, 14]. Future therapeutics may target other components of the RAS/MAPK or PI3K/AKT pathways, and combination therapies may also prove to be effective [73] (Fig. 1).

Multimodal therapies are often needed to treat CLAs. In addition to the previously described medical therapies, interventional or surgical management can also be considered in specific cases. Targeted embolization of lymphatic channels with ethiodized oil (Lipiodol) can be performed at specific sites of leakage [30]. Sclerotherapy or surgical debulking of large lesions may be considered. Lymphaticovenous anastomosis can be attempted in cases of CCLA in which a site of lymphatic disruption is identified [31].

Additional therapies may be used in cases with lytic osseous lesions, particularly in Gorham-Stout disease. Interferon, bisphosphonates, and calcium and vitamin D have been used to treat these lesions and may be used in combination with surgical management [74–76]. Radiation has also been used successfully in some cases, although it is typically avoided in young patients [30, 74, 75].

KLA can be particularly difficult to treat given its typically progressive nature. In addition to sirolimus, combination medical therapies may be used, including steroids, vincristine chemotherapy, or interferon [30, 51, 55]. If bleeding complications occur, platelet transfusions or fresh frozen plasma may be administered [30, 49].

Medical, interventional, or surgical treatments are often used in combination in challenging cases.

Repeat imaging can be obtained after treatment for response evaluation, particularly in patients with large lesions or with CLAs. However, no guidelines currently exist to define the most appropriate timing of repeat imaging, which instead is typically decided on a case-by-case basis. Development of imaging treatment response criteria represents an active area of research [28, 29].

Conclusion

Lymphatic anomalies comprise a complex group of disorders and syndromes with substantial risk for morbidity and mortality. Knowledge of the range of imaging findings is essential for the radiologist, who plays a critical role in the diagnosis, evaluation, and multidisciplinary management of patients with these disorders.

References

1. Cueni LN, Detmar M. The lymphatic system in health and disease. *Lymphat Res Biol* 2008; 6:109–122
2. Breslin JW, Yang Y, Scallan JP, Sweat RS, Adderley SP, Murfee WL. Lymphatic vessel network structure and physiology. *Compre Physiol* 2018; 9:207–299
3. International Society for the Study of Vascular Anomalies website. ISSVA classification 2018. issva.org/classification. Accessed January 4, 2022
4. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr* 2015; 166:1048–1054.e5
5. Brouillard P, Schlögel MJ, Homayun Sepehr N, et al. Non-hotspot PIK3CA mutations are more frequent in CLOVES than in common or combined lymphatic malformations. *Orphanet J Rare Dis* 2021; 16:267
6. Mäkinen T, Boon LM, Vikkula M, Alitalo K. Lymphatic malformations: genetics, mechanisms and therapeutic strategies. *Circ Res* 2021; 129:136–154
7. Zenner K, Cheng CV, Jensen DM, et al. Genotype correlates with clinical severity in *PIK3CA*-associated lymphatic malformations. *JCI Insight* 2019; 4:129884
8. Pagliazzi A, Oranges T, Traficante G, et al. *PIK3CA*-related overgrowth spectrum from diagnosis to targeted therapy: a case of CLOVES syndrome treated with alpelisib. *Front Pediatr* 2021; 9:732836
9. Rodriguez-Laguna L, Agra N, Ibañez K, et al. Somatic activating mutations in *PIK3CA* cause generalized lymphatic anomaly. *J Exp Med* 2019; 216:407–418
10. Ozeki M, Aoki Y, Nozawa A, et al. Detection of *NRAS* mutation in cell-free DNA biological fluids from patients with kaposiform lymphangiomatosis. *Orphanet J Rare Dis* 2019; 14:215
11. Barclay SF, Inman KW, Luks VL, et al. A somatic activating *NRAS* variant associated with kaposiform lymphangiomatosis. *Genet Med* 2019; 21:1517–1524
12. Manevitz-Mendelson E, Leichner GS, Barel O, et al. Somatic NRAS mutation in patient with generalized lymphatic anomaly. *Angiogenesis* 2018; 21:287–298
13. Li D, March ME, Gutierrez-Uzquiza A, et al. *ARAF* recurrent mutation causes central conducting lymphatic anomaly treatable with a MEK inhibitor. *Nat Med* 2019; 25:1116–1122
14. Foster JB, Li D, March ME, et al. Kaposiform lymphangiomatosis effectively treated with MEK inhibition. *EMBO Mol Med* 2020; 12:e12324
15. Nozawa A, Ozeki M, Niihori T, Suzui N, Miyazaki T, Aoki Y. A somatic activating *KRAS* variant identified in an affected lesion of a patient with Gorham-Stout disease. *J Hum Genet* 2020; 65:995–1001
16. Ahlers CG, Baron CM, Sarma A, Borst AJ. Contrasting cases of complex lymphatic anomalies: case reports and review of the literature. *J Vasc Anom* 2021; 2:e007
17. Rauen KA. The RASopathies. *Annu Rev Genomics Hum Genet* 2013; 14:355–369
18. Aoki Y, Niihori T, Inoue S, Matsubara Y. Recent advances in RASopathies. *J Hum Genet* 2016; 61:33–39
19. Kronfli AP, McLaughlin CJ, Moroco AE, Grant CN. Lymphatic malformations: a 20-year single institution experience. *Pediatr Surg Int* 2021; 37:783–790
20. Hassanein AH, Mulliken JB, Fishman SJ, Quatrano NA, Zurakowski D, Greene AK. Lymphatic malformation: risk of progression during childhood and adolescence. *J Craniofac Surg* 2012; 23:149–152
21. Fevurly RD, Fishman SJ. Vascular anomalies in pediatrics. *Surg Clin North Am* 2012; 92:769–800, x
22. Hogeling M, Adams S, Law J, Wargon O. Lymphatic malformations: clinical course and management in 64 cases. *Australas J Dermatol* 2011; 52:186–190
23. Churchill P, Otal D, Pemberton J, Ali A, Flageole H, Walton JM. Sclerotherapy for lymphatic malformations in children: a scoping review. *J Pediatr Surg* 2011; 46:912–922

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved

24. Trenor CC 3rd, Chaudry G. Complex lymphatic anomalies. *Semin Pediatr Surg* 2014; 23:186–190
25. Keppler-Noreuil KM, Rios JJ, Parker VER, et al. *PIK3CA*-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A* 2015; 167A:287–295
26. Chavhan GB, Amaral JG, Temple M, Itkin M. MR lymphangiography in children: technique and potential applications. *RadioGraphics* 2017; 37:1775–1790
27. Lal A, Gupta P, Singhal M, et al. Abdominal lymphatic malformation: spectrum of imaging findings. *Indian J Radiol Imaging* 2016; 26:423–428
28. De Leacy R, Bageac DV, Manna S, et al. A radiologic grading system for assessing the radiographic outcome of treatment in lymphatic and lymphatic-venous malformations of the head and neck. *AJNR* 2021; 42:1859–1864
29. Durand R, Reid JR, Belasco JB, et al. MRI for response assessment of extensive lymphatic malformations in children treated with sirolimus. *AJR* 2021; 217:741–752
30. Ricci KW, Iacobas I. How we approach the diagnosis and management of complex lymphatic anomalies. *Pediatr Blood Cancer* 2021 Apr 12 [published online]
31. Taghinia AH, Upton J, Trenor CC 3rd, et al. Lymphaticovenous bypass of the thoracic duct for the treatment of chylous leak in central conducting lymphatic anomalies. *J Pediatr Surg* 2019; 54:562–568
32. White CL, Olivieri B, Restrepo R, McKeon B, Karakas SP, Lee EY. Low-flow vascular malformation pitfalls: from clinical examination to practical imaging evaluation—Part 1, lymphatic malformation mimickers. *AJR* 2016; 206:940–951
33. Francavilla ML, White CL, Oliveri B, Lee EY, Restrepo R. Intraabdominal lymphatic malformations: pearls and pitfalls of diagnosis and differential diagnoses in pediatric patients. *AJR* 2017; 208:637–649
34. Iacobas I, Adams DM, Pimpalwar S, et al. Multidisciplinary guidelines for initial evaluation of complicated lymphatic anomalies-expert opinion consensus. *Pediatr Blood Cancer* 2020; 67:e28036
35. Liu T, Basseri S, Mussari B, et al. Generalized lymphatic anomalies and review of the current management landscape: a case report and review of the literature. *J Med Case Reports* 2021; 15:398
36. Ozeki M, Fujino A, Matsuoka K, Nosaka S, Kuroda T, Fukao T. Clinical features and prognosis of generalized lymphatic anomaly, kaposiform lymphangiomatosis, and Gorham-Stout disease. *Pediatr Blood Cancer* 2016; 63:832–838
37. Ricci KW, Hammill AM, Mobberley-Schuman P, et al. Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease. *Pediatr Blood Cancer* 2019; 66:e27614
38. Bordonaro V, Ciancarella P, Ciliberti P, et al. Dynamic contrast-enhanced magnetic resonance lymphangiography in pediatric patients with central lymphatic system disorders. *Radiol Med* 2021; 126:737–743
39. 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
40. Li D, Wenger TL, Seiler C, et al. Pathogenic variant in *EPHB4* results in central conducting lymphatic anomaly. *Hum Mol Genet* 2018; 27:3233–3245
41. Kotecha R, Mascarenhas L, Jackson HA, Venkatramani R. Radiological features of Gorham's disease. *Clin Radiol* 2012; 67:782–788
42. Liu Y, Zhong DR, Zhou PR, et al. Gorham-Stout disease: radiological, histological, and clinical features of 12 cases and review of literature. *Clin Rheumatol* 2016; 35:813–823
43. Du CZ, Li S, Xu L, et al. Spinal Gorham-Stout syndrome: radiological changes and spinal deformities. *Quant Imaging Med Surg* 2019; 9:565–578
44. Kai B, Ryan A, Munk PL, Dunlop P. Gorham disease of bone: three cases and review of radiological features. *Clin Radiol* 2006; 61:1058–1064
45. Lala S, Mulliken JB, Alomari AI, Fishman SJ, Kozakewich HP, Chaudry G. Gorham-Stout disease and generalized lymphatic anomaly—clinical, radiologic, and histologic differentiation. *Skeletal Radiol* 2013; 42:917–924
46. Kim JH, Yoon DH, Kim KN, et al. Surgical management of Gorham-Stout disease in cervical compression fracture with cervicothoracic fusion: case report and review of literature. *World Neurosurg* 2019; 129:277–281
47. Homayun-Sepehr N, McCarter AL, Helaers R, et al. *KRAS*-driven model of Gorham-Stout disease effectively treated with trametinib. *JCI Insight* 2021; 6:149831
48. Croteau SE, Kozakewich HPW, Perez-Atayde AR, et al. Kaposiform lymphangiomatosis: a distinct aggressive lymphatic anomaly. *J Pediatr* 2014; 164:383–388
49. Fernandes VM, Fargo JH, Saini S, et al. Kaposiform lymphangiomatosis: unifying features of a heterogeneous disorder. *Pediatr Blood Cancer* 2015; 62:901–904
50. Goyal P, Alomari AI, Kozakewich HP, et al. Imaging features of kaposiform lymphangiomatosis. *Pediatr Radiol* 2016; 46:1282–1290
51. Ji Y, Chen S, Peng S, Xia C, Li L. Kaposiform lymphangiomatosis and kaposiform hemangioendothelioma: similarities and differences. *Orphanet J Rare Dis* 2019; 14:165
52. Nozawa A, Ozeki M, Yasue S, et al. Characterization of kaposiform lymphangiomatosis tissue-derived cells. *Pediatr Blood Cancer* 2021; 68:e29086
53. Eng W, Al-Sayegh H, Ma C, Adams D. Kaposiform lymphangiomatosis: update on outcomes and use of sirolimus as a therapeutic intervention. *Blood* 2018; 132(suppl 1):3734
54. Safi F, Gupta A, Adams D, Anandan V, McCormack FX, Assaly R. Kaposiform lymphangiomatosis, a newly characterized vascular anomaly presenting with hemoptysis in an adult woman. *Ann Am Thorac Soc* 2014; 11:92–95
55. Crane J, Manfredo J, Boscolo E, et al. Kaposiform lymphangiomatosis treated with multimodal therapy improves coagulopathy and reduces blood angiopoietin-2 levels. *Pediatr Blood Cancer* 2020; 67:e28529
56. Nakamura F, Kato H, Ozeki M, Matsuo M. CT and MRI findings of focal splenic lesions and ascites in generalized lymphatic anomaly, kaposiform lymphangiomatosis, and Gorham-Stout disease. *J Clin Imaging Sci* 2021; 11:44
57. Hughes M, Hao M, Luu M. PIK3CA vascular overgrowth syndromes: an update. *Curr Opin Pediatr* 2020; 32:539–546
58. Cohen MM Jr. Proteus syndrome review: molecular, clinical, and pathologic features. *Clin Genet* 2014; 85:111–119
59. Forde K, Resta N, Ranieri C, et al. Clinical experience with the AKT1 inhibitor miransertib in two children with PIK3CA-related overgrowth syndrome. *Orphanet J Rare Dis* 2021; 16:109
60. Bertino F, Braithwaite KA, Hawkins CM, et al. Congenital limb overgrowth syndromes associated with vascular anomalies. *RadioGraphics* 2019; 39:491–515
61. Mathew L, George R, Sudhakar S, Keshava SN, Fouzia NA. Clinical profile of overgrowth syndromes consistent with PROS (*PIK3CA*-related overgrowth syndromes)—a case series. *Indian Dermatol Online J* 2020; 11:738–746
62. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* 2018; 558:540–546
63. Bouwman FCM, Kooijman SS, Verhoeven BH, et al. Lymphatic malformations in children: treatment outcomes of sclerotherapy in a large cohort. *Eur J Pediatr* 2021; 180:959–966
64. Ardıçlı B, Karnak İ, Çiftçi AÖ, Tanyel FC, Şenocak ME. Sclerotherapy with bleomycin versus surgical excision for extracervical cystic lymphatic malformations in children. *Surg Today* 2016; 46:97–101
65. Kalwani NM, Rockson SG. Management of lymphatic vascular malformations: a systematic review of the literature. *J Vasc Surg Venous Lymphat Disord* 2021; 9:1077–1082
66. Cheng J. Doxycycline sclerotherapy in children with head and neck lym-

phatic malformations. *J Pediatr Surg* 2015; 50:2143–2146
67. Gallant SC, Chewning RH, Orbach DB, Trenor CC 3rd, Cunningham MJ. Contemporary management of vascular anomalies of the head and neck—part 1: vascular malformations: a review. *JAMA Otolaryngol Head Neck Surg* 2021; 147:197–206
68. Tian R, Liang Y, Zhang W, et al. Effectiveness of sirolimus in the treatment of complex lymphatic malformations: single center report of 56 cases. *J Pediatr Surg* 2020; 55:2454–2458
69. Wiegand S, Wichmann G, Dietz A. Treatment of lymphatic malformations with the mTOR inhibitor sirolimus: a systematic review. *Lymphat Res Biol* 2018; 16:330–339
70. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* 2011; 57:1018–1024
71. Hammer J, Seront E, Duez S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. *Orphanet J Rare Dis* 2018; 13:191
72. Garneau AP, Haydock L, Tremblay LE, Isenring P. Somatic non-cancerous PIK3CA-related overgrowth syndrome treated with alpelisib in North America. *J Mol Med (Berl)* 2021; 99:311–313
73. Queisser A, Seront E, Boon LM, Vikkula M. Genetic basis and therapies for vascular anomalies. *Circ Res* 2021; 129:155–173
74. Schneider KN, Masthoff M, Gosheger G, et al. Gorham-Stout disease: good results of bisphosphonate treatment in 6 of 7 patients. *Acta Orthop* 2020; 91:209–214
75. Ruggieri P, Montalti M, Angelini A, Alberghini M, Mercuri M. Gorham-Stout disease: the experience of the Rizzoli Institute and review of the literature. *Skeletal Radiol* 2011; 40:1391–1397
76. Ellati R, Attili A, Haddad H, Al-Hussaini M, Shehadeh A. Novel approach of treating Gorham-Stout disease in the humerus—case report and review of literature. *Eur Rev Med Pharmacol Sci* 2016; 20:426–432

Editorial Comment: Key Concepts of Complex Lymphatic Malformations

The imaging findings of simple lymphatic malformations are well described in radiology textbooks, and radiologists are generally comfortable with the diagnosis of macrocystic, microcystic, and mixed-type lymphatic malformations. However, in recent years, substantial progress has been made in the understanding of complex lymphatic anomalies, which present with variable and overlapping clinical features [1]. The authors of this article provide an overview of the range of phenotypes of complex lymphatic anomalies and underlying genetic anomalies, including mutations in the PIK3/AKT/mTOR (phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin) pathway and the RAS/MAPK (rat sarcoma–mitogen-activated protein kinase) pathway. The approach for performing imaging in this difficult-to-treat patient population, and the associated spectrum of imaging findings, are beautifully illustrated.

Complex lymphatic anomalies include generalized lymphatic anomaly (GLA), Gorham-Stout disease, channel-type lymphatic anomaly (i.e., central conducting lymphatic anomaly), and lymphatic malformations associated with *PIK3CA*-related overgrowth spectrum (PROS) [2]. Patients with GLA have anomalous lymphatic vessels that involve multiple structures including the lung, mediastinum, spleen, and medullary bone. Kaposiform lymphangiomatosis is a subtype of GLA typically associated with severe coagulopathy resulting in hemorrhagic pericardial or pleural effusions. Intraosseous lymphatic malformation with cortical bone resorption and osteolysis are typical of Gorham-Stout disease [3]. Clinical manifestations of channel-type lymphatic anomaly vary, depending on the involved organs.

A multidisciplinary team including diagnostic radiologists, interventional radiologists, dermatologists, hematologic oncologists, plastic surgeons, and other specialists is needed for the management of this patient population. Although unenhanced MRI sequences such as fat-saturated T2-weighted images can show the extent of organ involvement, dynamic contrast-enhanced MR lymphangiography performed with intranodal injection of gadolinium facilitates the identification of abnormal lymphatic channels and sites of lymphatic leak.

The authors also provide an overview of new molecularly targeted therapies such as sirolimus that, along with image-guided interventions, have become integral to the management of complex lymphatic anomalies.

Geetika Khanna, MD, MS
Emory University
Children's Healthcare of Atlanta
Atlanta, GA
Geetika.khanna@emory.edu

The author declares that there are no disclosures relevant to the subject matter of this article.

doi.org/10.2214/AJR.22.27426

References

1. Mäkinen T, Boon LM, Vikkula M, Alitalo K. Lymphatic malformations: genetics, mechanisms and therapeutic strategies. *Circ Res* 2021; 129:136–154
2. Ozeki M, Fukao T. Generalized lymphatic anomaly and Gorham-Stout disease: overview and recent insights. *Adv Wound Care (New Rochelle)* 2019; 8:230–245
3. Lala S, Mulliken JB, Alomari AI, Fishman SJ, Kozakewich HP, Chaudry G. Gorham-Stout disease and generalized lymphatic anomaly—clinical, radiologic, and histologic differentiation. *Skeletal Radiol* 2013; 42:917–924

Downloaded from www.ajronline.org by 88.24.154.111 on 08/21/23 from IP address 88.24.154.111. Copyright ARRS. For personal use only; all rights reserved