Global Pediatric Health
Volume 3: 1–4
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DOI: 10.1177/2333794X16655255
gph.sagepub.com
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Lymphangiomatosis With Hemihypertrophy

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Received May 16, 2016. Accepted for publication May 18, 2016.

Case Report

A full-term white female with a weight that was appropriate for gestational age was delivered with the knowledge that a fetal ultrasound (US) and magnetic resonance imaging (MRI) had revealed a large multicystic intra-abdominal mass. A postnatal US (Figure 1) and MRI confirmed a large, predominately macrocystic lymphatic malformation involving the abdomen, pelvis, perineum, and the left gluteal and proximal leg soft tissues. The malformation within the abdomen was enveloping bowel, ureters, uterus, and vasculature, and was displacing other intra-abdominal structures (Figure 2), although there was no organomegaly. The lesion was noted to contain contents consistent with chyle. An US of a left neck mass revealed a similar but smaller cystic lesion with multiple internal septations beneath the sternocleidomastoid muscle. Echocardiography and X-rays did not reveal any pericardial or pleural effusions. A skin biopsy of the left leg lesion confirmed the suspicion of a lymphatic malformation. The perinatal course was also complicated by transient hypogammaglobulinemia and hypofibrinogenemia requiring intravenous gammaglobulin and cryoprecipitate. Although the patient did not manifest with a port wine stain, she was noted to have multiple, confluent nevus flammeus lesions on the anterolateral aspect of her left leg.

A variety of treatment options were considered, and over a number of weeks to months, she received 5 interventional radiologic treatments with sclerotherapy using doxycycline, ethanol, and 3% sodium tetradecyl sulfate (3% STS), which resulted in considerable size reduction of the majority of the treated cystic lesions. At 3 weeks of age, she was also started on oral rapamycin, which she has tolerated well without complications. She has remained on this medication for more than 1 year with no progression of her lesions. The follow-up US and MRI (Figure 3) confirmed generalized improvement of the abdominal mass and other lesions, but with the development of numerous cystic lesions within the spleen.

Although not noted initially, the infant was found to have left leg hypertrophy at the 4-month examination, which progressed modestly throughout the subsequent year. X-rays of the leg did not reveal any bony lesions, but by 12 months of age, the left leg, mid-thigh circumference was 2.5 cm greater than the right leg, and the left leg was 2.0 cm longer than the right leg (Figure 4).

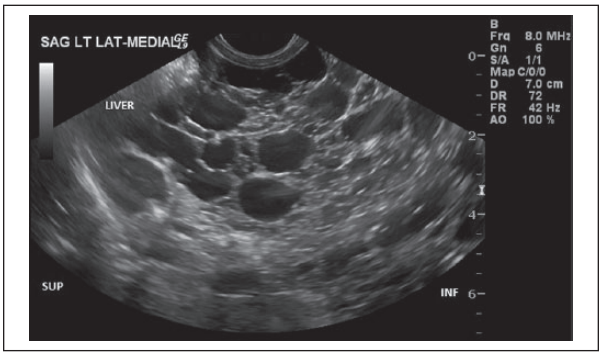

Figure 1. US of the abdomen demonstrating diffuse macrocystic lesions.

Discussion

A lymphangioma is a dilated mass of lymphatic tissue that is believed to be from an embryological developmental defect or from a primary malformation of the lymphatic vessels.[1,2] Most of these lesions (50% to 60%) are present at birth, and at least 90% are present by 2 years of age.[1] Although they can occur as a single lesion, they often occur as diffuse and multifocal, potentially occurring in any part of the body except for the central nervous system, since it is devoid of lymphatic vessels.[1,3] Congenital lymphangiomas are thought to be related to genetic defects, and they have also been associated with

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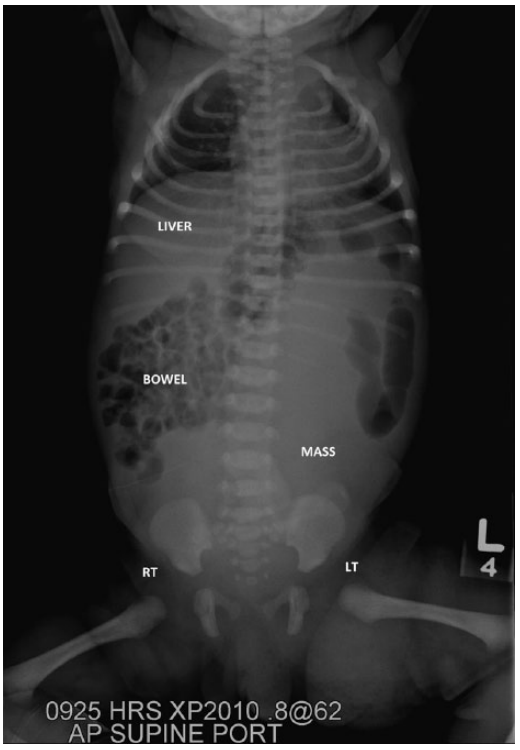

Figure 2. Plain film of the abdomen demonstrating the displacement effect of the fluid-filled mass in the left abdomen and pelvis.

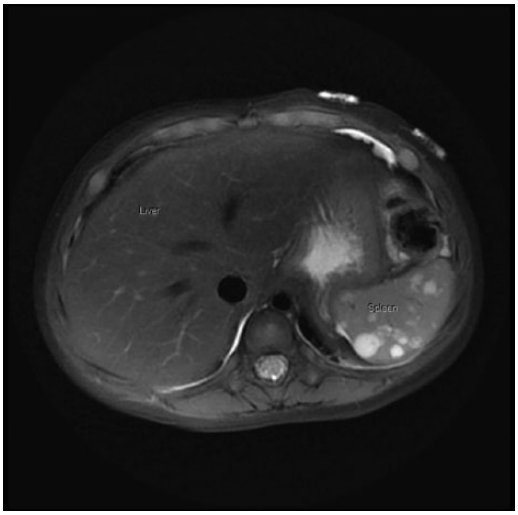

Figure 3. Follow-up upper abdominal MRI demonstrating a T2 weighted axial image with multiple bright, cystic lesions within the spleen.

chromosomal syndromes, such as Turner's syndrome and Klippel-Trenaunay syndrome (KTS).[1,2] The key to the lymphatic defects in these syndromes is related to lymphatic endothelial proliferation with resultant hyperplasia.[1] Vascular endothelial growth factors, such as a protein called VEGFR3, are known to affect the growth of lymphatic vessels.[3] Lymphangiomatosis is a rare condition that involves lymphangiomas occurring in a widespread or multifocal manner, involving many parts of the body,[1,3] and can involve solid organs, such as the liver or spleen, as occurred in our patient.

Hemihypertrophy (hemihyperplasia) is an overgrowth disorder that involves the asymmetrical excessive growth in the bone, soft tissue, or both of the affected body parts. This is often seen with overgrowth syndromes, such as Beckwith-Wiedermann syndrome, Proteus syndrome, Sotos syndrome, Perlman syndrome, and KTS.[4,5] KTS generally manifests in a single extremity, with 95% affecting a lower extremity.[2,4,5] Some KTS patients have shown genetic mutations of the VGFQ gene, which causes an enhanced effect of angiogenic growth proteins, such as VEGFR3.[2] Unlike other hemihypertrophy syndromes that have systemic signs of excess growth factors, the limb hypertrophy in KTS is secondary to a localized effect of the vascular malformation causing venous hypertension of the affected extremity, which results in the enlargement of the affected limb.[5] Thus, unlike the other overgrowth syndromes, KTS is not believed to be associated with an increased risk for embryonal tumors, such as Wilms tumor.[5]

There are multiple effects and complications of lymphangiomatosis, some of which can be from the compressive effect on the associated organs, such as bowel and other blood vessels, or from the abnormal function of the lymphatics, leading to edema, pleural or pericardial effusions, lymphopenia, hypogammaglobulinemia, and coagulopathies.[1] Our patient did experience some of these complications; however, they were transient and effectively treated. Due to these effects and complications, treatment of the lymphangiomas is generally indicated. However, there is still no universal definitive therapy, and it is usually individualized to the specific clinical scenario.[1] Because of the infiltrative nature of these lesions, surgery is often not an option, or is associated with potentially significant complications and recurrences.[6] Other treatment modalities have included corticosteroids, chemotherapy, radiotherapy, interferon-α, draining of pleural effusions, a restricted diet, amputation, and a variety of pneumatic pumps.[1,3,7]

Over the past 25 years, interventional radiologic sclerotherapy has been used with increasing success and has included varying agents, including bleomycin, doxycycline, ethanol, and STS 3%.[6] The procedure is performed

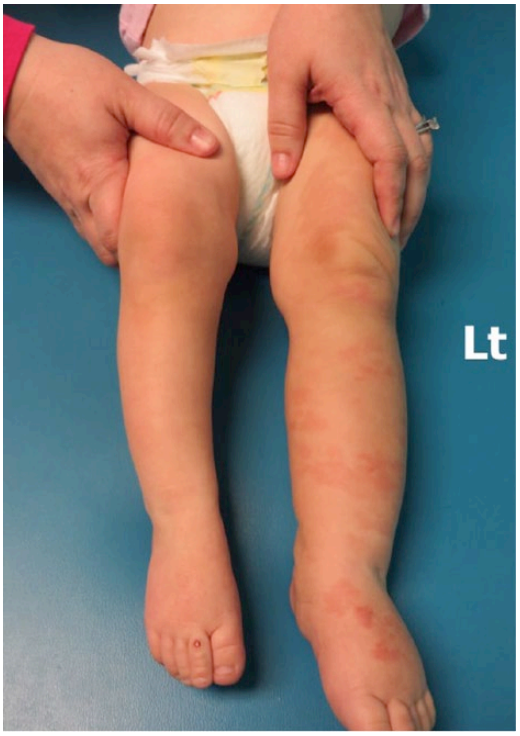

Figure 4. Photograph of the legs, demonstrating the hemihypertrophy with an increased length/volume of the left leg, along with the multiple nevus flammeus.

with a catheter and US guidance for macrocystic lesions, or with needle puncture for microcysts, with the majority of lesions responding after a single treatment.[6] Since the formation of lymphangiomas are believed to be influenced by angiogenic growth proteins, therapy to modulate the vessel growth and remodeling provides another therapeutic option.[2] Rapamycin has both immunosuppressant and antitumor properties, which are mediated by the specific inhibition of the mTOR protein kinase, which allows it to suppress tumor growth by inhibiting cell proliferation, inducing tumor cell apoptosis, and suppressing tumor angiogenesis.[8] Rapamycin has previously been reported to be very effective with no side effects in a newborn with diffuse lymphangiomatosis, with complete resolution of disease.[9] A more extensive experience in the use of rapamycin in the treatment of a variety of complicated vascular anomalies, including arterial, venous, and lymphatic malformations, also demonstrated it to be well tolerated and highly efficacious.[10] These published data reflect our experience with our patient with over a year of treatment.

KTS is a rare disorder with an incidence of approximately 1:100 000 live births, and it is traditionally characterized as a triad of capillary malformations (generally port wine stains, but may involve nevus flammeus lesions), venous and/or lymphatic abnormalities, and limb hypertrophy.[5,11,12] Most of the cases are sporadic with no predilection for race or gender.[12,13] However, since it was first described by Klippel and Trenaunay in 1900, variation in the phenotypic expression and in the severity of symptoms have been recognized.[13] This significant variation in presentation has contributed to the lack of a generalized accepted definition by the scientific community of KTS, although a proposed definition was published by Oduber et al in 2008.[13] The proposed definition of KTS incorporates 2 major features: congenital vascular malformations and disturbed (not generalized) growth.[13] The vascular malformations should include a capillary malformation, which generally is a port wine stain, and/or a venous malformation; however, lymphangiomas are also commonly described in patients with KTS.[2,11-14] The vascular malformations of KTS are typically "low flow volume" lesions, such as venous or lymphatic malformations, whereas Parkes Weber syndrome is characterized by "high flow volume" lesions with the presence of arteriovenous malformations.[12,13] The altered growth seen in KTS frequently manifests as hypertrophy of a limb, generally on the same side as the vascular malformation.[13] Although no definite etiologic gene has been identified, Oduber et al hypothesized that there could be the presence of several gene mutations, some of which control angiogenesis and others that control growth regulation.[13] This polygenic hypothesis could explain the extreme variability of the manifestations seen in KTS.[13]

Our patient, with lymphangiomatosis and a capillary malformation overlying the involved leg with hemihypertrophy, fulfills the diagnostic criteria for KTS. She did not have any dysmorphic features, and she does not have the characteristics seen with other similar syndromes, such as Proteus syndrome, Parkes Weber syndrome, CLOVES syndrome, or Sturge Weber syndrome. More recent developments for therapy, including sclerotherapy through interventional radiologic procedures, and the use of rapamycin, have been effective and safe, as was the experience in our patient, and prevented the sequelae of more conventional treatments, such as surgery. Some of our patient's early complications, such as hypogammaglobulinemia and hypofibrinogenemia are well described with lymphangiomatosis,[1] as is the involvement of splenic lesions.[3,7]

Author Contributions

JAW: Contributed to conception and design; contributed to acquisition and analysis; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DJM: Contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
ARW: Contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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