Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry

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Abstract
Purpose: Hepatic hemangiomas, though histologically benign, may be associated with significant morbidity and mortality in afflicted infants. The literature presents much confusion regarding the natural history and treatment options for hepatic hemangiomas. Clinical manifestations range from asymptomatic self-limiting lesions to congestive heart failure associated with high-volume vascular shunting to fulminant hepatic failure with hypothyroidism, abdominal compartment syndrome, and death. There has been little rationale to choose among observation, corticosteroid, other pharmacologic agents, arterial embolization, hepatic artery ligation, resection, or liver transplantation for any given patient.
Methods: We analyzed several recent retrospective radiologic analyses and pathologic studies to determine whether hepatic hemangiomas could be categorized, allowing prediction of their natural history and rational choice of therapies based upon their clinical presentation and radiographic appearance.
Results: We propose that hepatic hemangiomas do not represent a single entity but, rather, 3 principle categories of lesions: focal, multifocal, and diffuse. Because these 2 categories represent different anatomical and physiologic variants, so, too, may they respond differently to previously anecdotally applied treatment regimens. With input from international multidisciplinary authorities on hemangiomas, we developed and proposed a clinical practice algorithm for the evaluation and management of hepatic hemangiomas. Toward that end, we propose a plan to institute a web-based international hepatic hemangioma registry. Participants in the registry could obtain no-cost centralized review of imaging studies (and histology if available) and guidance regarding the management algorithm from an established multidisciplinary team. In exchange, the registry will facilitate the acquisition of systematic clinical and imaging information.
Conclusion: Longitudinal observation of response to more directed treatment protocols may contribute greatly to the understanding of these potentially fatal tumors.
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1. Purpose

Infantile hemangioma (IH) is the most common pediatric tumor, affecting 4% to 5% of white infants. It is a benign endothelial cell neoplasm that exhibits rapid postnatal growth followed by slow involution during childhood. Nevertheless, approximately 10% to 20% of IHs cause vision-threatening, life-threatening, or disfiguring complications [1]. The life cycle evolves in 3 stages: (1) a proliferating phase of rapid growth, beginning shortly after birth and lasting approximately 9 to 12 months; (2) an involuting phase, lasting 5 to 7 years, during which apoptosis predominates over mitosis and loose stromal tissue replaces the rapidly dividing endothelial cells, myeloid cells, and pericytes that characterize the initial stage; and (3) an involuted phase characterized by the lasting replacement of the original lesion with fibrofatty tissue. Although most IHs are cutaneous, visceral involvement also occurs, often in the setting of multiple lesions (hemangiomatosis).

Infantile hepatic hemangiomas (IHHs) share the same patterns of growth and regression as their more common cutaneous counterparts. It is probable that most hepatic hemangiomas are clinically silent and, therefore, remain undetected. Some hemangiomas, however, are discovered on routine prenatal imaging or postnatal imaging indicated for other causes. Another subset become symptomatic, manifesting as cardiac failure secondary to high volume shunting, hypothyroidism secondary to overproduction of type III iodothyronine deiodinase, fulminant hepatic failure, and/or abdominal compartment syndrome [2-8].

The field of vascular anomalies has emerged over the past 20 years as clinical, pathologic, and radiologic evidence has facilitated clarification of terminology. The behavior of true IHHs must be distinguished from commonly misnamed *hemangiomas* of adulthood [9,10] that are venous malformations and from *epithelioid hemangioendothelioma*, a malignant tumor with metastatic potential [11]. Unfortunately, IHH has also been called *hemangioendothelioma*, particularly in the histopathologic literature. Infantile hepatic hemangioma has also been confused with hepatic arteriovenous malformations because both exhibit rapid flow, shunting, and cardiac consequences. This confusion has made the diagnosis (and therapy) of IHHs haphazard with seemingly little rationale for choosing between pharmacologic treatments (corticosteroid, interferon alfa-2a, or vincristine), embolization, surgical resection, hepatic artery ligation, and even hepatic transplantation [12-19].

We reviewed evidence that might simplify the understanding of IHH, allowing improved predictability of outcome with rationale among therapeutic options. Furthermore, we hope to gather longitudinal data to validate a novel classification scheme and treatment algorithm by creating a web-based interactive registry for patients with IHH.

2. Methods

We performed a Pubmed search with keywords *hepatic hemangioma*, *liver hemangioma*, *visceral hemangioma*, and *hemangioma screening*, limiting the inquiry to publications over the past decade (1995-2005) that correctly identified hepatic hemangiomas. These publications, chiefly composed of retrospective radiographic, dematologic, and histopathologic analyses as well as case reports, were critically reviewed to elucidate patterns of physiologic and radiographic presentation that might allow more accurate characterization and prognostication of hepatic hemangiomas. Two articles were identified from our institution attempting to correlate angiographic and/or radiographic imaging patterns of IHH with features such as biologic behavior, prognosis, and response to treatment [14,15]. In aggregate, these studies provided detailed radiographic and clinical information on 55 children referred for evaluation of hepatic hemangiomas at 2 North American pediatric vascular anomaly programs between 1981 and 2000 [14,15]. These patients had been identified from computerized logs kept by the 2 institutions and supplemented by a keyword search from radiologic reports. Clinical information culled from these reviews included age at presentation, sex, presence of high output cardiac failure, hypothyroidism, decision to treat, type of treatment, and final clinical condition. Imaging studies had been reviewed by 4 independent radiologists with expertise in vascular anomalies. In discussion with the radiologists involved in the original publications, we reviewed the clinical, radiologic, and histologic findings (when available). We supplemented this critical review of these 2 studies with analysis of 5 histopathologic studies of liver tumors and hemangiomas and 2 studies investigating the correlation between cutaneous and extracutaneous hemangiomas to refine our understanding of our proposed categories [14,20-26]. Based on this analysis, we speculated that IHH comprised 3 subtypes: focal, multifocal, and diffuse, with each category demonstrating distinctive imaging, pathologic, and physiologic
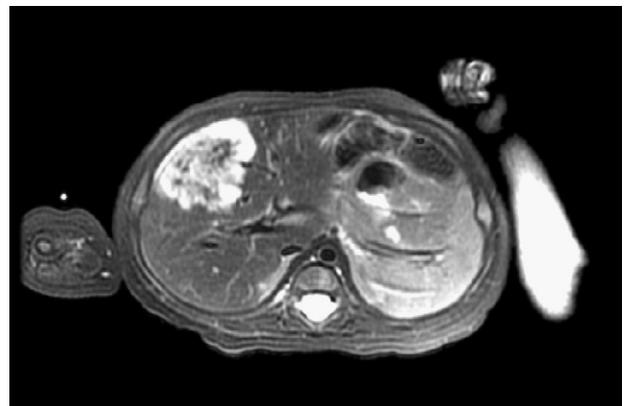
Fig. 1 Axial view of focal hepatic hemangioma demonstrating central thrombosis with centripetal hyperintense signal on T2 imaging.
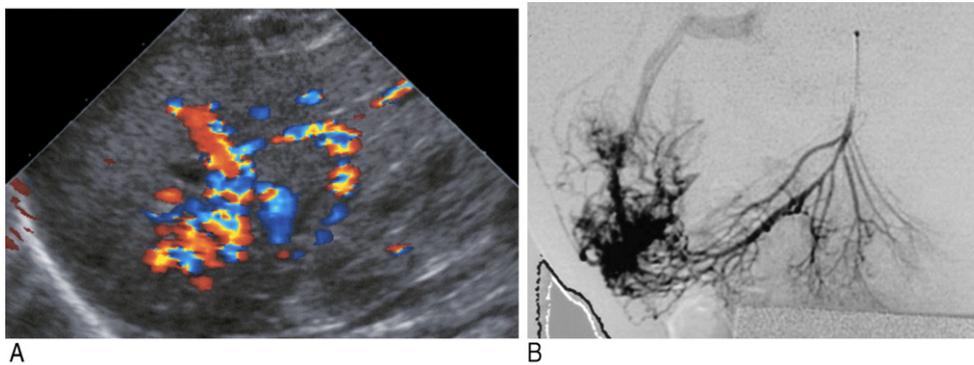
Fig. 2 A, Fast flow within hemangioma on color Doppler ultrasonography. B, Arteriovenous shunting within hemangioma by angiography.

features permitting prediction of its biologic behavior and natural history that could be used to guide management.

3. Results

3.1. Focal lesions

This type can be identified on magnetic resonance imaging (MRI) as a well-defined, solitary, spherical tumor that is hypointense relative to liver on T1-weighted sequences and hyperintense on T2-weighted sequences (Fig. 1). The typical tumor demonstrates centripetal enhancement on gadolinium sequences. Areas of central necrosis, thrombosis, or intralesional hemorrhage are heterogeneously enhanced. The solid nonthrombosed (non-involuted) areas of the lesion exhibit intense homogeneous enhancement. Most focal lesions are asymptomatic, and they are rarely, if ever, accompanied by cutaneous hemangiomas. In contrast to typical IHs that characteristically manifest in the first weeks of neonatal life, many focal lesions have been detected antenatally on routine prenatal ultrasonography. We believe that these focal tumors are the hepatic form of the cutaneous rapidly involuting congenital hemangioma, a hypervascular lesion most frequently located on the scalp or extremities and that regresses in an accelerated fashion by 12 to 14 months of age [27,28]. As in cutaneous rapidly involuting congenital hemangioma, focal hepatic hemangioma does not stain positive for Glut-1, a marker of common IHs [20-22,26]. Focal hemangioma variably demonstrates the presence of high-flow shunts (arteriovenous or portovenous) (Fig. 2). Some focal lesions are associated with a minor anemia or thrombocytopenia. Two reports in the literature document successful corticosteroid treatment of solitary fetal hepatic lesions detected during routine prenatal ultrasonography associated with in utero cardiac failure/cardiomegaly caused by intrahepatic shunts [18,29]. In retrospect, it is likely that these lesions would have undergone rapid spontaneous involution. It is unclear whether corticosteroid was responsible for accelerated involution.

3.2. Multifocal lesions

These IHHs present as homogeneously enhancing spherical tumors by MRI, hypointense relative to liver on T1 sequencing and hyperintense on T2-weighted sequencing. On computed tomography, they are hypodense lesions with uniform or centripetal enhancement (Fig. 3). Flow voids can be present in, or adjacent to, the lesions. These flow voids, along with enlarged hepatic arteries or veins or aortic tapering (distal to the origin of the celiac trunk), may
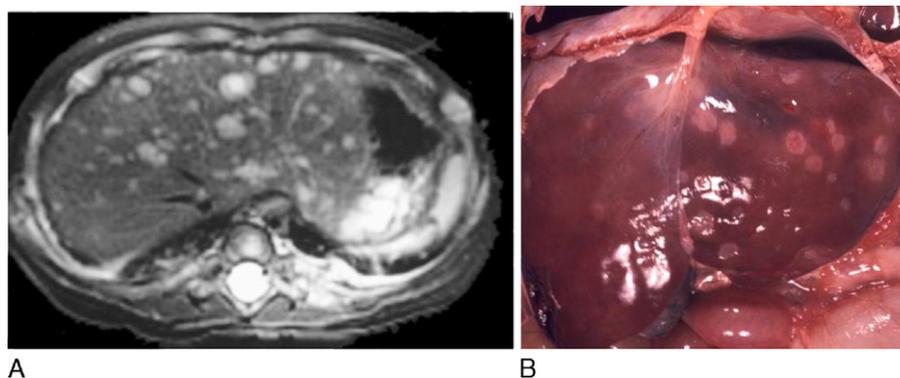
Fig. 3 A, Axial view of multifocal hepatic hemangioma demonstrating hyperintense homogenous signal on T2-weighted MRI. B, Postmortem view of liver with multifocal IHH.

Fig. 4   Aortic tapering on angiogram of patient with high-flow arteriovenous shunting.

indicate the presence of arteriovenous shunts (Fig. 4). Whereas many multifocal lesions are asymptomatic and are only detected upon postnatal screening imaging (because of the presence of multiple cutaneous hemangiomas, which may accompany visceral lesions), some are associated with high-output cardiac failure secondary to arteriovenous or porto-venous shunting. These lesions undergo the typical course of involution of cutaneous IHs. Like typical cutaneous IHs, multifocal hepatic hemangiomas demonstrate Glut-1 immunoreactivity [20-22,26].

3.3. Diffuse lesions

Some infants with hepatic hemangiomas present with extensive hepatic involvement and near-total replacement of the hepatic parenchyma with innumerable centripetally enhancing lesions (Fig. 5). These children are very likely to have a more serious clinical course than those patients diagnosed with solitary or multifocal tumors. Massive

hepatomegaly causes compression of the inferior vena cava and thoracic cavity, resulting in respiratory compromise. This mass effect can be so marked as to cause abdominal compartment syndrome and multiorgan system failure.

Another complication of diffuse IHH is severe hypothyroidism owing to the overproduction of type III iodothyronine deiodinase [8]. Hypothyroidism of this degree can cause cardiac failure (poor contractility with low output) and profound mental retardation in the developing infant. Review of imaging data revealed that, although some patients demonstrated high-flow lesions, dilation of hepatic veins was less than would be expected given the size of the lesion. Furthermore, despite the enormous tumor burden, no patients with diffuse involvement developed high output cardiac failure.

3.4. Formation of a database

We propose that these 3 subtypes of IHH, which demonstrate different radiographic appearance, pathologic features, and physiologic behavior, may also respond differently to various pharmacologic and invasive treatments. Nevertheless, hepatic hemangiomas are relatively rare, and the literature on the subject is a quagmire of colorful confusing terminology. Therefore, in an effort to better understand the presentation, behavior, risks, and response to treatment of IHH, we propose enrollment of patients in a web-based longitudinal data registry (www. LiverHemangioma.org). Participation in this registry will require regular updates on the patient's condition, and, in exchange, physicians worldwide will have access to rapid, centralized, and longitudinal review of clinical, radiographic, and any histologic findings by a multidisciplinary team of physicians associated with the Vascular Anomalies Center at Children's Hospital Boston, Boston, Mass. If desired by the enrolling physician, this team will also provide guidance regarding management. This treatment algorithm, first published herein (Fig. 6), was developed and refined after discussion at a National Institutes of Health research workshop on IHs and is discussed in more detail hereinafter [30]. The management algorithm will be subjected to continuous refinement because data are accrued. Final

Fig. 5   A, Axial view of diffuse hepatic hemangioma on computed tomography demonstrating massive involvement of parenchyma with innumerable lesions. B, Massive hepatomegaly causing abdominal compartment syndrome and respiratory compromise.

LIVER HEMANGIOMA MANAGEMENT ALGORITHM
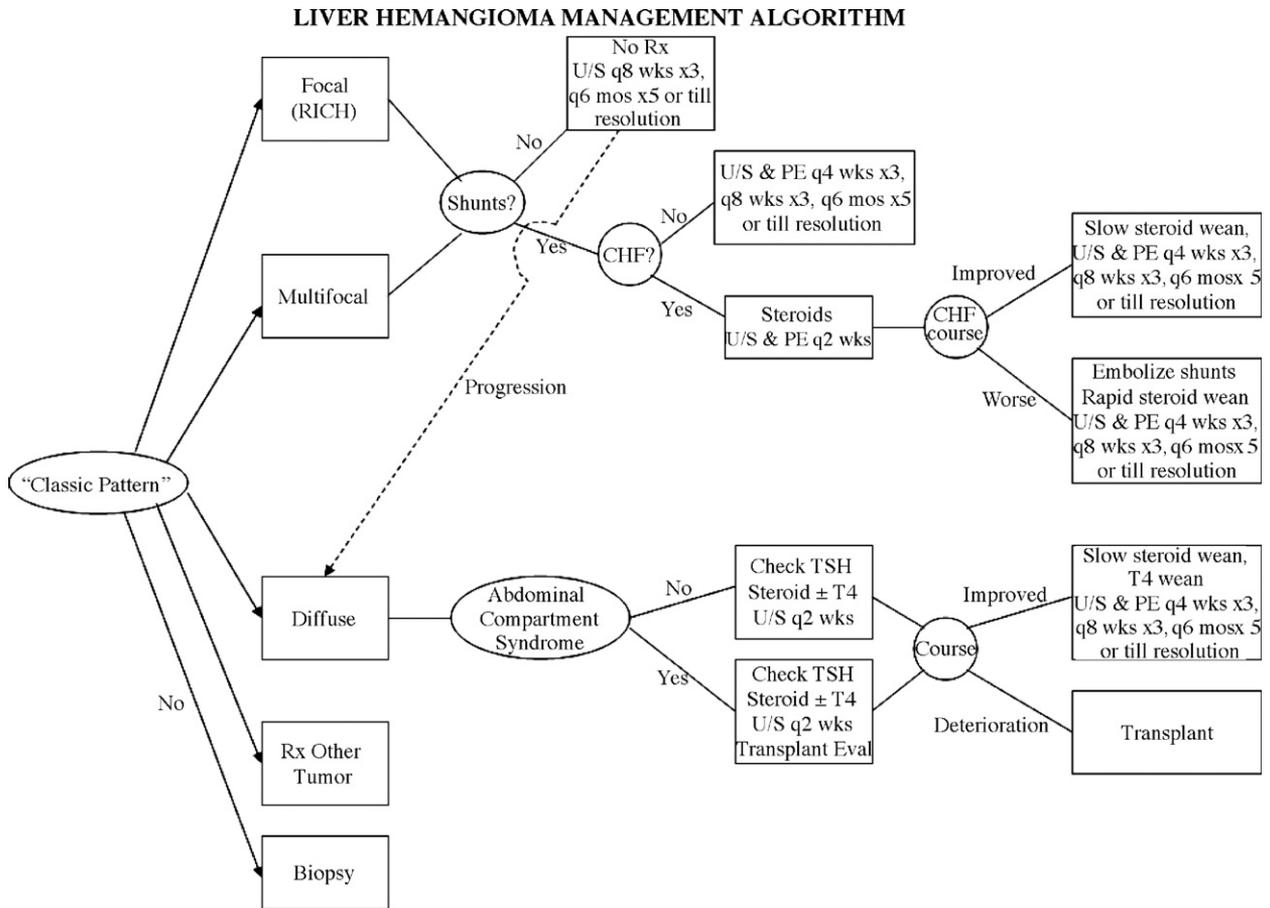
Fig. 6 Treatment algorithm for infants diagnosed with hepatic hemangioma. U/S indicates ultrasonography; PE, physical examination; TSH, thyroid stimulation hormone; CHF, congestive heart failure.

therapeutic decisions will be at the discretion of the treating physicians and patient's family.

The Infantile Hepatic Hemangioma Registry study design will include prospective and retrospective data collected from children diagnosed with IHH. We hope to enroll patients in the registry from institutions worldwide. All data will be recorded in a password-protected encrypted internet site for analysis by the study investigators. Pediatric specialists who enroll their patients in the IHH registry will be granted password-protected access to the web-based data entry forms. All data entered on these web-based forms will be encrypted. The study investigators will have password-protected access to the web-based registry. All participating physicians from outside hospitals will have password-protected access to only the data from children they have enrolled in the registry; that is, they will not have full access to the registry database. The consent form, approved by Children's Hospital Boston Committee on Clinical Investigation, will be made available to physicians from outside institutions on the password-protected Web site as a template for the informed consent process in their institution.

Based on cases of IHH in the Children's Hospital Boston Vascular Anomalies Center database, we propose an initial treatment algorithm (Fig. 6). Asymptomatic patients with focal or multifocal disease, without evidence of cardiac failure or hemodynamically significant shunting, should be observed with follow-up ultrasonography to document regression. Infants with hemodynamically significant shunting are candidates for corticosteroid therapy; they should also have close follow-up by a physician, including ultrasonography. We have observed that many shunts disappear with hemangioma regression. If pharmacologic therapy fails (approximately one third of patients in a published study by Kassarjian et al [15]), embolization should be considered as the next step. Large shunts in an infant presenting with cardiac failure should be considered candidates for early embolization, although this procedure may not have an effect on the underlying hemangioma per se. Rarely, if ever, is resection necessary. An infant with diffuse hepatic hemangioma is at greatest risk for death. Management includes aggressive pharmacotherapy and thyroid hormone monitoring and replacement. Because of the absence of high-flow shunts, embolization is not generally effective. These infants often respond poorly to pharmacologic therapy alone and may be the only patients with IHH who might benefit from hepatic transplantation.

4. Conclusion

Infantile hepatic hemangiomas represent a clinically diverse spectrum of benign hepatic tumors. A novel systematic classification scheme encompassing clinical presentation, radiographic appearance, pathologic features, physiologic behavior, and natural (untreated) and treated history is presented along with a proposed therapeutic algorithm. A registry for prospective data collection has been established with the goal of validating and refining current understanding and management of hepatic hemangiomas.

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Discussion

Paper No. APSA 2006-10: "Hepatic Hemangiomas: Subtype Classification and Development of a Clinical Practice Algorithm and Registry." Presented by Emily Christison-Lagay, MD, Boston, Mass. (Applause.)

APSA 2006-10: "Hepatic Hemangiomas: Subtype Classification and Development of a Clinical Practice Algorithm and Registry." Discussion by Rebecka Meyers, MD, Salt Lake City, UT.

Dr Meyers: I have 2 questions. The first involves interferon and I am wondering where that fits in your protocol. It has been in the past anecdotally used for steroid failures as a medical treatment arm and I am wondering if that is something that you still look at and/or recommend. My second question is on your slide; you didn't show what your radiographic follow-up would be for those people who were observed. We and others rarely but unfortunately the incidence is not zero—rarely there can be sarcomatous malignant degeneration of these tumors. In the child that we treated that was a 4 years of age and I am wondering if you have a follow-up treatment protocol

that you would recommend for those that are observed. Thanks.

Dr Christison-Lagay: The first question concerns the use of interferon. Interferon has been used with great success in the treatment of cutaneous lesions refractory to steroid treatment. We have recently become reluctant to use it due to the incidence of spastic diplegia in the young population which is upwards of 10% and because these children are not yet fully myelinated. We at this point prefer to avoid interferon therapy, although it may have a future role. I believe there is an Italian team, which suggests that the risk of spastic diplegia may be associated with concomitant or preexisting use of corticosteroid therapy. I think that is something that remains to be investigated. In terms of radiographic follow-up, this is something still in evolution. Certainly there have been some case reports of angiosarcomas occurring preexisting hepatic angiomas. I think that to begin with we would like to use ultrasound follow-up every 4-6 weeks depending on the severity of the lesion and whether there is any associated presentation, CHF or other problem. I don't think we have enough information at this point to recommend long term studies in terms of years but certainly since these hemangiomas undergo regression over the course of 5-7 years we may be at a point at which point we should do about yearly ultrasound until they reach year five or so.

APSA 2006-10: "Hepatic Hemangiomas: Subtype Classification and Development of a Clinical Practice Algorithm and Registry." Discussion by Phil Guzetta, MD, Washington, DC

Dr Guzetta: This is a wonderful use of all your experience, and it's a great model of how to do something like this. My question really is kind of an extension of Dr Meyers'. The way you have done this, if you have a symptomatic baby who has diffuse disease, really what you are recommending is that they be evaluated early for transplant rather than if they don't respond to the steroids as those of us who have dealt with these patients, you have a very short time to get all of this done because they get sick very quickly. So is that what you are recommending, if you have a patient who is profoundly symptomatic, has diffuse disease, that they be seen early for organ transplantation?

Dr Christison-Lagay: Yes, that is in fact what we are recommending. For patients with diffuse disease they really need to be referred into the transplant system. There are reported cases of diffuse disease presenting with severe hypothyroidism that have regressed with medical management but certainly the transplantation option should be available because these patients have a very short course and can be catastrophically ill and have a very high mortality rate associated with the diffuse lesions.

APSA 2006-10: "Hepatic Hemangiomas: Subtype Classification and Development of a Clinical Practice Algorithm and Registry." Discussion by Stephan Shochat, MD, Memphis, Tenn.

Dr Shochat: I think this is a very significant paper and I just wonder about the localized patients. Do you recommend, or would you not recommend, biopsy to confirm that patients have hemangioma? That's the first question. The second question, is there any indication for resection of a localized hemangioma?

Dr Christison-Lagay: Thank you, Dr. Shochat. I think that radiologists who are very specialized in looking at various vascular lesions feel comfortable in many cases saying that something is a hemangioma versus another tumor based upon its categorization, its radiographic presentation. For instance, angiosarcomas seem to have central enhancement rather than centrifugal enhancement. Hepatoblastomas tend to be heterogeneous on T2-weighted imaging, and so with radiologists who are very expert in looking at vascular anomalies, they seem to be pretty comfortable in looking at a subset of these lesions that present in a classic pattern. What I didn't show on this algorithm is that there are some lesions that do not present in a classic pattern, and if there is any question about the diagnosis, we would recommend a biopsy. The second question about surgical resection. Typically we would like to avoid surgical resection for asymptomatic lesions. For symptomatic lesions, this is always a little bit at the discretion of the patient's individual physician. If there is concern that it is symptomatic by on the basis of CHF, I think medical therapy is the first line of treatment. If embolization is available, then that's another line of treatment. Unfortunately, many interventional vascular radiologists are not necessarily very easily available so that a surgical resection may be considered if these is a problem getting somebody who can effectively address the disease less invasively.