**Vascular Anomalies**

**Adams**

1. An infant is born with a 7 cm × 6 cm lesion over the upper extremity from the elbow to the shoulder. The lesion is indurated and purpuric, with some petechiae around the edges. No other areas of petechiae are noted on the skin. The infant is doing well without other systemic problems. Apgars were 9 and 9. You are called by the pediatric nurse practitioner to the NICU.



What is the most appropriate next step?

A. Do nothing because the infant is doing well and had good Apgars.

B. Obtain an ultrasound for more information about the lesion.

C. Obtain an MRI to assess the extent of the lesion.

D. Obtain labs, including a CBC with platelet count and fibrinogen.

**Explanation**

This appearance is that of a possible vascular tumor, but information is still needed to better define the lesion. Some of these lesions, such as a congenital hemangioma, are benign, but others are classified as an intermediate malignancy (kaposiform hemangioendothelioma) or a high-risk malignancy (angiosarcoma or a fibrosarcoma). The infant should have some intervention because this lesion is violaceous and has some petechiae, which can be a sign of thrombocytopenia. An ultrasound may help differentiate flow and makeup of the lesion but can be done after further investigation because an MRI may be necessary to determine the extent of the tumor. For an infant, an MRI can be done without sedation at most institutions. Several violaceous lesions can have coagulopathy, and this is the most immediate critical issue for this infant.

2. You are asked to see a 2-month-old boy admitted to the pediatric service with a history of hematemesis. He was seen by his pediatrician, who noted pallor on exam, tachycardia with a heart rate of 180, and tachypnea with a respiratory rate of 60. On history his parents point out several light blue flat lesions on his buttocks and legs (six total). The lesions were present at birth and have not changed. They were told the lesions were “hemangiomas” and that they would go away as he got older. His hemoglobin in the pediatrician’s office was 6.8 g/dL. A CBC in the hospital revealed a platelet count of 60,000 k/mL. Coagulation labs including fibrinogen are normal. Stool was positive for blood.

What is the most likely diagnosis?

A. Multifocal lymphangioendotheliomatosis (MLT)

B. Idiopathic thrombocytopenic purpura (ITP)

C. Infantile hemangioma (IH)

D. Kaposiform hemangioendothelioma (KHE)

**Explanation**

Neonatal ITP is very uncommon, and bleeding with ITP is uncommon. The skin lesions were present at birth, without petechiae or bruising. IHs are not present at birth, and the lesions grow over time and usually are not flat and blue in color. IHs can cause GI bleeding if associated with significant GI lesions. They are not associated with thrombocytopenia. KHE is not multifocal and usually does not cause GI bleeding. Furthermore, the fibrinogen was normal. MLT is associated with moderate thrombocytopenia. Platelets are thought to be trapped in the vascular lesions. Typically the diagnosis is seen in newborns. Areas of involvement include the skin, GI tract, lungs, and, rarely, other organs. The thrombocytopenia improves by 2 to 3 years of age. The skin lesions can lighten but do not go away completely. Limited research is available, and multiple treatments have been tried with mixed results. Sirolimus has recently been used with good results.

3. A 6-week-old infant is referred to you secondary to multiple raised vascular lesions. The lesions were noted at 3 weeks of age and have been growing. They are not causing any problems. The infant is doing well. In the pediatrician’s office, a slightly enlarged liver is noted. The spleen is normal, and there are no other abnormalities.



What is the most likely diagnosis?

A. Multiple infantile leukemia

B. Eczema

C. Multiple cutaneous infantile hemangiomas

D. Drug rash

**Explanation**

The lesions are small (millimeters), are circumferential, and were not present at birth. They are not dry and have no surrounding erythema, as is seen in eczema. Furthermore, the pediatrician did not mention any history of being on a medication to cause a drug rash, nor is the description consistent with this diagnosis. Leukemia cutis can be mistaken for vascular lesions, but the lesions are usually larger and do not have conformity of appearance. Most are purplish and irregular. Infantile hemangiomas are not present at birth but grow over days to weeks of age. Multiple lesions can present as small, round lesions that become slightly raised with proliferation. The term *hemangiomatosis* is an old term for the presentation of numerous cutaneous lesions; however, the term is no longer used. Infantile hemangiomas (more than 5 millimeters) can be associated with internal lesions.

4. A 6-week-old infant is referred to you secondary to multiple raised vascular lesions. The lesions were noted at 3 weeks of age and have been growing. They are not causing any problems. The infant is doing well. In the pediatrician’s office, a slightly enlarged liver is noted. The spleen is normal, and there are no other abnormalities.



What radiologic test would you order for this patient on the day of the appointment?

A. Abdominal X ray

B. Chest CT

C. MRI

D. Ultrasound of the abdomen

**Explanation**

Infants with multiple cutaneous hemangiomas are most likely to have involvement of the liver. With better technique, infantile hemangiomas can be identified on ultrasound. These lesions are usually circular, multiple or diffuse throughout the liver, with high flow. An ultrasound does not require sedation and can be used for follow-up evaluation of response to therapy. If there is need to quantify the lesions or rule out other liver tumors, an enhanced MRI can be performed, but it is usually not necessary, especially when an infant presents with cutaneous lesions. There is no reason to assess for lesions in other locations such as the CNS, lungs, or GI system because their presence in these areas is rare. The liver is the most common organ involved. The area must be assessed because problems such as compartment syndrome, heart failure, and liver failure can occur with continued growth of the hemangiomas.

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An ultrasound is performed, and the findings are consistent with diffuse vascular lesions throughout the liver, consistent with infantile hemangiomas.

What lab work is essential?

A. Thyroid function tests

B. CBC with platelets

C. PT

D. Liver function tests

**Explanation**

Liver function usually is normal in these patients unless they are left untreated. Patients are usually not anemic initially. Thyroid function evaluation is essential because the lesions can cause significant hypothyroidism, resulting in the overexpression of iodothyronine deiodinase. These patients can need a significant amount of thyroid replacement. If hypothyroidism is noted, an endocrinology consult is recommended.

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An ultrasound is performed, and the findings are consistent with diffuse vascular lesions throughout the liver, consistent with infantile hemangiomas. What is the best treatment for this patient?

A. Propranolol

B. Cytoxan

C. No treatment, because the lesions will go away

D. Vincristine

**Explanation**

Multiple liver infantile hemangiomas in the proliferative period can cause compartment syndrome, liver failure, heart failure, and hypothyroidism leading to developmental delays. Propranolol at 2 to 3 mg/kg/day is the treatment of choice. Propranolol, a nonselective beta-blocker, is the first-line therapy for infantile hemangiomas. Potential mechanisms of action include vasoconstriction or decreased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), leading to apoptosis. Specific mechanisms of action are under investigation. If hypothyroidism is noted, the response to propranolol can be measured in the improvement of the hypothyroidism. Cytoxan and vincristine have been used in the past to treat diffuse liver infantile hemangiomas, but this therapy is not necessary secondary to the effectiveness of the oral medication propranolol. If the lesions do not respond, other vascular lesion mimickers should be considered, such as angiosarcoma.

7. Propranolol is the first-line therapy for infantile hemangioma. It is well tolerated and can be started for patients older than 4 weeks in the outpatient setting. Which of the following side effects causes the most serious complications?

A. Sleep disturbances

B. Diarrhea

C. Constipation

D. Hypoglycemia

**Explanation**

Sleep disturbances are the most common side effect and can be improved by adjusting the dosing schedule or changing the preparation. GI problems (diarrhea and constipation) also are common. The most serious side effect that has occurred because of sleeping too long without feeding or because of use during illness is hypoglycemia. Education is essential. For infants younger than 4 months, it is recommended that they not go for more than 4 hours without feeding. Standards of practice have been published on propranolol use and will soon be updated.

8. A 16-year-old with a complicated vascular malformation is sent for a hematology consultation before a large debulking procedure. The patient has a large venous malformation over his entire upper extremity, from his hand to his upper chest and back. On X ray, multiple phleboliths are seen throughout the extremity. Osteopenia is noted in all bones of this extremity. He reports episodes of superficial phlebitis and pain throughout this lesion, with contracture at his elbow. He has had previous sclerotherapy, with significant anemia as a complication 48 hours after the procedure. No labs have ever been drawn except for a CBC before and after the procedures. You are asked to safely prepare him for surgery.

What labs should be obtained for this patient?

A. PT, PTT, fibrinogen, CBC, D-dimer

B. CBC with differential

C. Platelets and fibrinogen

D. von Willebrand panel

**Explanation**

The most concise set of labs includes a PT, PTT, fibrinogen, and CBC with platelets and D-dimer. Severe localized intravascular coagulopathy will cause significant hypofibrinogenemia (less than 60 mg/dL) and can cause decreased platelets, though not as low as in kaposiform hemangioendothelioma. Usually the platelet count is at least 80,000-90,000 k/mL. D-dimer is usually elevated, with high risk defined as 10 times the normal value. Patients can develop an acquired von Willebrand disease, but this is rare and not standard. There is limited information about the exact pathophysiology of the coagulopathy. Further investigation is needed.

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What medical regimen is used to prepare this patient for surgery?

A. Aspirin

B. Oral anticoagulants (direct oral anticoagulant [DOAC] or warfarin)

C. Low-molecular-weight heparin (LMWH)

D. Sirolimus

**Explanation**

Aspirin has been used to treat symptomatic pain, but there are no prospective or retrospective studies. DOACs are starting to be used, but there is reluctance without clinical trials because of the abnormal endothelium and possible increased bleeding risk. Warfarin has not been used with success. Sirolimus in recent clinical trials has improved localized intravascular coagulopathy (LIC) and pain but does not work right away and is needed over the long term. LMWH is considered the standard treatment. It is used 2 weeks before the procedure and 2 weeks afterward for high-risk patients. Decreased D-dimer is noted along with improvement in fibrinogen. A consensus statement should be published soon. High-risk patients are those with significant LIC and/or ectatic veins.

10. A 6-year-old girl is seen in your clinic with the following congenital conditions: lipomatous masses on her abdomen and back, extensive capillary malformations, large ectatic veins over her axilla, and large feet bilaterally with saddle foot deformity. Her diagnosis is congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal or spinal anomalies (CLOVES), and her parents are asking you about medical therapy and genomic evaluation.



If this patient does have CLOVES, what is the associated somatic mutation?

A. PIK3CA

B. RASA-1

C. MAP2K

D. AKT

**Explanation**

CLOVES is part of the PROS (PIK3CA related overgrowth syndromes). PIK3CA somatic mutations are seen in a large number of other phenotypes such as macrocephaly capillary malformation, lymphatic malformations, Klippel-Trenaunay syndrome, and fibro-adipose vascular anomalies. RASA-1 mutations are associated with Parkes Weber syndrome and other central collecting lymphatic anomalies. MAP2K mutations are found in non-CNS arterial venous malformations, and AKT mutations are found in Proteus syndrome.

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What procedure should be considered before any debulking?

A. Closure of anomalous veins

B. Laser therapy

C. Osteotomies

D. Laser therapy of the capillary malformation

**Explanation**

Patients with CLOVES syndrome have anomalous embryonic veins that are high risk for venous thrombosis and should be closed before any significant surgical procedure. The other procedures may be needed in the future but are not necessary before debulking. These patients need interdisciplinary consultations as part of their complete management.

12. What tumor should patients with congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal or spinal anomalies (CLOVES) syndrome be screened for?

A. Hepatoblastoma

B. Wilms tumor

C. Rhabdomyosarcoma

D. Lymphoma

**Explanation**

Patients with CLOVES syndrome have an elevated risk of Wilms tumor. Although it appears that this risk is higher in patients up to 3 years of age, routine Wilms tumor screening is recommended until 8 years of age because there is limited research. There is no increased risk for other tumors such as hepatoblastoma, as in other overgrowth syndromes.

13. A patient with multiple bone and liver lesions is on your clinic list. The patient is asymptomatic. A biopsy is performed, and histologically the lesions are characterized as epithelioid lesions arranged in nests, strands, and trabecular patterns, with infrequent vascular spaces. A *WWTR1-CAMTA1* gene fusion is found on further analysis.

What is the diagnosis?

A. Epithelioid hemangioendothelioma (EHE)

B. Pseudomyogenic hemangioendothelioma (PHM)

C. Angiosarcoma

D. Angiomatosis

**Explanation**

PHM is characterized by loose fascicles of plump spindle and epithelioid cells with abundant eosinophils, cytoplasm, and coexpression of keratins and endothelial markers. The etiology for this tumor is unclear, although a balanced translocation t(7;19) resulting in the *SERPINE1-FOSB* fusion gene has been reported in these patients. Angiosarcomas are largely aneuploid tumors. The rare cases of angiosarcoma that arise from benign lesions such as hemangiomas have a distinct pathway that must be investigated. *MYC* amplification is seen in radiation-induced angiosarcoma. *KDR-VEGFR2* mutations and *FLT4-VEGFR3* amplifications have been seen with a frequency of less than 50%. Ras mutations have also been noted in angiosarcomas, but no consistent somatic mutations have been identified. *Angiomatosis* is a vague term used for benign, ill-defined vascular anomalies. In EHE, a *WWTR1-CAMTA1* gene fusion has been found in a large percentage of patients; less commonly, a *YAP1-TFE3* gene fusion has been reported. These fusions are not directly targetable with current medicines. Monoclonality has been described in multiple liver lesions, suggesting a metastatic process.

14. A patient presents to your clinic with a lymphatic anomaly of the head and neck. The lesion is extensive, and imaging reveals a microcystic lesion that impinges on the airway. The patient has a tracheostomy. Treatment has included multiple sclerotherapy procedures with minimal results. A surgical procedure is being planned, but the surgeons are asking whether any medical therapy could be used.

What is the best present medical option for this patient?

A. Interferon

B. Sirolimus

C. Steroids

D. Vincristine

**Explanation**

There have been limited medical options for vascular malformations. Most have been treatment options used for other diagnoses, such as hemangiomas. Interferon was used initially to treat hemangiomas and has been used to treat lymphatic anomalies, mostly of the bone. Interferon causes spastic diplegia in infants and can have significant side effects with limited efficacy. Steroids are used in lymphatic anomalies and can decrease inflammation, but long-term efficacy is not seen. Vincristine has been used for vascular tumors but has limited use for true lymphatic malformations. A prospective study assessing the safety and efficacy of sirolimus for vascular anomalies noted an 85% partial response. No complete response was noted, but this was a very strict definition of complete response and was not expected for these congenital disorders. Many retrospective studies have reinforced these data.

15. Which of the following is *not* a common side effect of sirolimus?

A. Mouth sores

B. Headaches

C. Nausea

D. Effusions

**Explanation**

All these side effects are noted with sirolimus. The most common side effects in infants are GI disturbances and nausea, and in older children and young adults the most likely side effects are mouth sores and headaches. Effusion is a rare complication of sirolimus.