Multifocal lymphangioendotheliomatosis with devastating intracranial hemorrhage

Case report

Christina Huang, B.S.C., Elias Rizk, M.D., Mark Iantosca, M.D., Andrea L. Zaenglein, M.D., Klaus F. Helm, M.D., Arabinda K. Choudhary, M.D., and Mark S. Dias, M.D.

Departments of 1Neurosurgery, 2Dermatology, 3Pediatrics, 4Pathology, and 5Radiology, Penn State University College of Medicine, Penn State Hershey Medical Center, Hershey, Pennsylvania

An in utero female was found to have a small hemorrhage at the foramen of Monro, hydrocephalus, and what was originally interpreted as a Dandy-Walker variant. At birth she had macrocephaly and numerous cutaneous, multifocal, red-pink blanchable macules. Postnatal MRI demonstrated a hemorrhagic soft-tissue mass involving the upper brainstem, thalamus, and basal ganglia most consistent with in utero complex multifocal intracranial hemorrhage. The skin lesions were thought to be consistent with multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT). The size and location of the hemorrhage precluded operative intervention, although the hydrocephalus was treated with a ventricular shunt. The child continues to have severe developmental delays. Multifocal lymphangioendotheliomatosis with thrombocytopenia is a multifocal vascular disorder most commonly involving the skin and gastrointestinal tract. Intracranial hemorrhages are rare in this context. This case is the third reported instance of MLT with associated intracranial hemorrhage and the only case described in the neurosurgical literature. The authors review the presenting features and pathophysiology of this condition.

(Please note: This article contains some figures that are displayed in color online but in black-and-white in the print edition.)

Abbreviations used in this paper: LYVE-1 = lymphatic vessel endothelial hyaluronan receptor-1; MLT = multifocal lymphangioendotheliomatosis with thrombocytopenia.

Key Words • multifocal lymphangioendotheliomatosis with thrombocytopenia • congenital cutaneovisceral angiomatosis with thrombocytopenia • intracranial hemorrhage • vascular disorders

Case Report

Prenatal Examination. Hydrocephalus and cerebellar hypoplasia interpreted as a Dandy-Walker variant were diagnosed in a female by using prenatal cranial ultrasound. Subsequent fetal MRI performed at 22 weeks’ gestation confirmed severe hydrocephalus of the lateral, third, and fourth ventricles. Hemosiderin staining of the brainstem and fourth ventricle was consistent with secondary obstruction of the fourth ventricular outlets by hemorrhage, resulting in hydrocephalus. Mass effect from the markedly dilated fourth ventricle led to flattening of the cerebellar hemispheres, but the posterior fossa was relatively small and the torcular herophili was not elevated; the diagnosis of a Dandy-Walker variant was not confirmed. A small hemorrhage was also identified in the left germinal matrix in the region of the caudothalamic notch (Fig. 1).

Postnatal Examination. The infant was delivered via...
cesarean section at 38 weeks’ gestation. At birth, the child was macrocephalic (head circumference 40.5 cm, > 98th percentile) with a full fontanelle and sutural diastasis; she had numerous cutaneous, blanchable red-pink macules and thin plaques on her head, neck, trunk, and extremities (Fig. 2). Apgar scores were 7 at 1 minute and 8 at 5 minutes, but shortly thereafter she began having seizures, for which she was treated with phenobarbital. There was no family history of genetic disorders, bleeding disorders, or brain tumors.

All laboratory values, including platelet count (242,000/μl), platelet morphology, prothrombin time, international normalized ratio, and fibrinogen, were normal at birth. Magnetic resonance imaging demonstrated a new large heterogeneous hematoma involving the midbrain, thalamus, and basal ganglia. The hematoma was multiloculated with both cystic and solid portions and contained blood in various stages of evolution with evidence of hemosiderin deposition, severe ventricular enlargement, and blood layering in both occipital horns (Fig. 3); there was no significant enhancement after the administration of Gd. The hemorrhage extended through the incisura with associated displacement of the cerebellum inferiorly and effacement of the fourth ventricle. A second hemorrhage involved the left frontoparietal paraventricular region with enhancement of the anterior component (Fig. 4). Magnetic resonance angiography showed prominent anterior and posterior choroidal arteries supplying the left lesion but no identifiable vascular malformation. The extent and location of the intracranial hemorrhage precluded any direct operative intervention, although a ventricular shunt was placed to control the hydrocephalus.

Biopsies of the skin lesions (Fig. 5) demonstrated superficial, dilated, blood-filled vascular channels consistent with the diagnosis of a vascular malformation or vascular neoplasm. There was no endothelial papillary hyperplasia or PAS-positive deposits. Immunohistochemical analysis was positive for CD31, and one biopsy site was positive for D2-40 (both markers previously described in MLT); however, all biopsies were negative for lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1), another common marker for MLT.

By 5 months of age the child demonstrated mild episistaxis that subsequently resolved. Laboratory studies at that time revealed moderate thrombocytopenia (84,000/μl) and anemia with a hemoglobin level of 8.4 mg/dl. Her cutaneous vascular lesions, while stable in number, evolved to more purplish-red patches and plaques with telangiectasia and hemorrhagic blebs, some of which required shave removal with cautery for chronic bleeding. Over the course of the next several months, her seizures remained controlled. Her thrombocytopenia persisted, ranging from 74,000–88,000/μl, but the anemia resolved. Stool guaiac tests have been repeatedly negative.

At 16 months of age, the child had severe developmental delays (estimated developmental age of approximately 4 months), a seizure disorder controlled with phenobarbital, and autonomic storms. Although there were no focal neurological deficits, she had increased tone with hyperreflexia and sustained bilateral clonus.
Multifocal lymphangioendotheliomatosis

Discussion

Multifocal lymphangioendotheliomatosis with thrombocytopenia is a congenital vascular disorder characterized by the presence of multiple cutaneous macules, papules, and plaques. The number and size of these lesions vary, but hundreds can be seen ranging in size from a few millimeters to several centimeters. Similar lesions can also be found in other organs, including the gastrointestinal tract most commonly, as well as the lung, synovium, muscle, bone, bone marrow, kidney, liver, spleen, and brain. The gastrointestinal lesions can be quite numerous and involve the esophagus to the sigmoid colon; recurrent life-threatening gastrointestinal bleeding can occur, often within weeks of birth.

Although platelet counts can be normal at birth, subsequent thrombocytopenia usually develops within the first few weeks of life. Thrombocytopenia is probably the result of platelet trapping and consumption within the abnormal dilated vascular channels of the lesions. It is often refractory to platelet transfusions, which are reserved only for active episodes of bleeding or severe thrombocytopenia. Accompanying anemia due to recurrent bleeding is also common. Although thrombocytopenia is an almost universal part of the MLT, one prior case report has documented normal platelet counts, which the authors proposed was due to limited extracutaneous involvement. 

Pathologically, the skin lesions in MLT are characterized by the presence of multiple, dilated thin-walled vessels involving both the reticular dermis and the subcutis. Hobnailed endothelial cells with intraluminal papillary projections line these vessels. Lesions in other organs contain similar thin-walled vessels with endothelial hyperplasia. The expression of immunohistochemical markers may be more variable than previously described. The lymphatic marker LYVE-1 was initially thought to be universally positive in MLT, based on a report of 3 patients, but the marker was absent in a subsequent report. Other reported markers may include CD31, D2-40 (both positive in this case), CD34, factor VIII, collagen IV, and vascular endothelial growth factor receptor-3. Although the immunohistochemical results in our case were not typical for MLT, 2 independent vascular disorders centers, which have previously published cases of MLT, conducted independent reviews of the clinical and histological features, and both confirmed the diagnosis.

Involvement of the CNS is rare. In fact, including the present case, only 5 such cases have been described (Table 1). Prasad et al. documented 2 cases: the first with a small frontal lobe hemorrhage that remained stable on follow-up, and a second with brainstem calcifications that remained stable at 4.7 years. Yeung et al. described a 1-month-old infant with multiple vascular lesions in the brain, lung, and gastrointestinal tract; the infant remained stable with no new lesions at the 6-month follow-up. Maronn et al. described an infant with numerous lesions involving skin, muscle, bone, lung, liver, and brain. The child had several intracranial hemorrhages that, over several months, increased in both size and number with extensive brainstem and cervical spinal cord involvement. The child demonstrated progressive opisthotonus and periods of apnea and died of respiratory failure at 8 months of age.

The present case is most similar to the case reported by Maronn et al. with an expanding and multiloculated hemorrhage consistent with recurrent intracerebral hemorrhages. Both infants demonstrated an expanding brainstem mass with a poor neurological prognosis. Although neither case has had pathological confirmation regarding the nature of the intracranial mass, the imaging characteristics are most consistent with repeated hemorrhage from an intracranial vascular lesion, similar to those confirmed on skin biopsies. Unlike the other cases, however, the patient in our case demonstrated intracranial hemorrhage in utero and without neonatal thrombocytopenia; this suggests that the organ malformations may bleed even in the absence of thrombocytopenia.

Treatment of MLT is difficult and often unsuccessful. A number of therapies aimed at controlling the progression of the vascular lesions and subsequent bleeding have...
been used with variable success. Treatments include systemic corticosteroids, vincristine, interferon α2A, thalidomide, and, most recently, bevacizumab (Avastin, Genentech Inc.).

The prognosis is poor with eventual death in nearly two-thirds of affected infants.

Conclusions

The patient featured in this case demonstrates an infrequently reported cause of prenatal intracranial hemorrhage—MLT. This case also highlights the unpredictable onset of thrombocytopenia in MLT and the evolving description of histopathological features, including negative LYVE-1 staining. In these very rare multiorgan vascular disorders, it is important to recognize the cutaneovisceral stigmata and remain watchful for varied presentations given that so few cases have been reported to establish accurate norms.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Dias, Rizk, Iantosca, Zaenglein. Acquisition of data: Dias, Huang, Rizk, Iantosca, Zaenglein. Analysis and interpretation of data: all authors. Drafting the article: Huang, Rizk, Zaenglein. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dias. Administrative/technical/material support: Helm. Study supervision: Dias, Zaenglein.

References


Table 1: Previously reported MLT cases with neurological involvement*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Description</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Prasad et al., 2005</td>
<td>frontal lobe hemorrhage due to thrombocytopenia brainstem calcifications</td>
<td>stable at 6 mos stable at 4.7 yrs</td>
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<tr>
<td>Yeung et al., 2006</td>
<td>multiple vascular lesions in brain, lung, &amp; GI tract</td>
<td>stable at 6 mos</td>
</tr>
<tr>
<td>Maronn et al., 2009</td>
<td>numerous intracranial lesions that, over several mos, increased in size &amp; number w/ extensive brainstem &amp; cervical spinal cord involvement</td>
<td>opisthotonus &amp; prolonged apneic periods; respiratory failure at 8 mos</td>
</tr>
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* GI = gastrointestinal.