Multifocal Lymphangioendotheliomatosis With Thrombocytopenia: Clinical Features and Response to Sirolimus

Catherine Droitcourt, MD; Olivia Boccara, MD; Sylvie Fraitag, MD; Géraldine Favrais, MD, PhD; Alain Dupuy, MD, PhD; Annabel Maruani, MD, PhD

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is a recently described glucose transporter 1–negative multifocal vascular disorder with significant morbidity and mortality. However, data are lacking on the clinical spectrum, long-term prognosis, and treatment of MLT. It is often confused with multifocal infantile hemangioma, but the conditions must be differentiated for appropriate assessment and therapeutic management. Treatments for MLT have been disappointing, and the treatments classically used for infantile hemangioma are often ineffective. We report 3 newborn cases featuring various clinical and biological phenotypes of MLT: 1 patient had severe brain involvement and died early; another had no thrombocytopenia; and the third had nearly no skin involvement.

Histologically, all were negative for glucose transporter 1 and positive for the lymphatic marker lymphatic vessel endothelial hyaluronan receptor 1 or D2-40 (∼38-kDa O-linked transmembrane sialoglycoprotein podoplanin). Two cases with severe gastrointestinal bleeding were treated with sirolimus 0.1 mg/kg per day, which was efficient after the first month of treatment. MLT clinically presents in various forms, and when complicated by widespread or severe extracutaneous involvement, initial aggressive therapeutic intervention is justified. The pathogenesis of MLT remains unclear, but lymphatic differentiation is widely acknowledged. Because of its antiangiogenic properties, including anti-lymphangiogenesis, sirolimus offers an adequate and targeted therapeutic approach for MLT.

abstract

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT), also called cutaneovisceral angiomatosis, was recently identified as a new congenital multifocal vascular disorder. The disease is characterized by multifocal cutaneous vascular lesions that are negative for glucose transporter 1 (GLUT-1), and it features thrombocytopenia and extracutaneous disease but mostly severe gastrointestinal involvement.1–5 The prognosis is grim, with high mortality often linked to gastrointestinal bleeding and unsatisfactory treatment.6 Because MLT is a recently described and rare condition,1 all facets of the disease are still unknown, and a treatment strategy remains to be established.

The present article describes 3 cases of MLT, all different clinical variants, identified in various pediatric dermatology departments in France. Two cases were treated with sirolimus, which was efficient.

PRESENTATION

Patient 1
A female infant was born at term by emergency cesarean delivery because of abnormal fetal heart rate. The pregnancy was uncomplicated. The infant presented...
with respiratory distress and hypotonia at birth. Physical examination revealed ~30 vascular skin lesions of 2 types: (1) red papulonodules, slightly indurated, 2 to 10 mm in diameter, on the face, arms, legs, and feet; and (2) blue nodules, 5 to 10 mm in diameter, on the palms, feet, and face.

The infant had thrombocytopenia (platelet count: $82 \times 10^3/\mu L$; normal range: $150-400 \times 10^3/\mu L$) with mild anemia (hemoglobin level: 10.2 g/dL; normal range: 13–20 g/dL) and normal coagulation status, with no evidence of disseminated intravascular coagulation (D-dimer level: $<500$ ng/mL; serum fibrinogen level: 1.66 g/L [normal range: 2–4 g/L]).

Cranial MRI revealed peri- and intracerebral vascular lesions (hyperintensity on T1-weighted images, mixed signal intensity on T2-weighted images with gadolinium enhancement). Two lesions (left frontal lobe and occipital region) were associated with hyperintense edema and a mass effect. Complementary investigations included a whole-body computed tomography scan, which revealed multiple vascular lesions of the liver, kidneys, bones (ribs, pelvis, and femoral epiphysis), and mucosal intestinal tract. Ophthalmologic examination revealed a vascular lesion on the right inferior temporal arcade.

Results of a vascular lesion skin biopsy revealed a proliferation of well-differentiated small vessels throughout the dermis with, for some, papillary intraluminal projections (Figs 1A and 1B), with hobnail endothelial cells frequently lining these vessels. Some vessels showed a thick hyalinized wall and/or papillary intraluminal projections. Immunohistochemical staining was negative for GLUT-1 and D2-40 (~38-kDa O-linked transmembrane sialoglycoprotein podoplanin) but positive for lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) (Fig 1D). The diagnosis of MLT was confirmed.

Propranolol at 2 mg/kg per day (and then 3 mg/kg per day), systemic intravenous corticosteroids at 3 mg/kg per day, and vincristine at 0.05 mg/kg (2 doses) failed to control the vascular lesions, and a ventriculoperitoneal shunt was required to treat the cerebral edema. Status epilepticus and multiple visceral failure developed. Palliative care was provided, and the infant died at age 5 weeks. An autopsy showed multiple similar vascular lesions in the liver, kidney, lungs, small intestine (Fig 1C), brain, and bones.

**Patient 2**

A male infant was born at term after an uncomplicated pregnancy. Gastrointestinal bleeding (melena) developed at age 4 months. Physical examination revealed only 1 telangiectatic macule, 3 mm in diameter, on the skin.

His platelet count was $58 \times 10^3/\mu L$ (normal range: $150-400 \times 10^3/\mu L$), and his hemoglobin level was 8 g/dL (normal range: 13–20 g/dL). The D-dimer level was elevated (6132 ng/mL; normal range: $<500$ ng/mL). Fibrinogen level, prothrombin time, and partial thromboplastin time were within normal limits. Upper gastrointestinal endoscopy and colonoscopy revealed multiple vascular nodules throughout the gastric mucosa. A computed tomography scan of the brain, chest, abdomen, and pelvis revealed multiple small lung nodules, with no lesions elsewhere.

Microscopy of a gastric mucosa sample revealed, in the lamina propria, multiple ectatic vessels lined by endothelial cells that focally formed intraluminal papillary projections (Fig 2A). Immunohistochemical staining was strongly positive for CD34, CD31, and erythroblast transformation-specific–related gene; slightly positive for D2-40 (Fig 2B); and negative for GLUT-1 and human...
herpesvirus 8. The infant was diagnosed with MLT, with gastric and probable lung involvement. Gastrointestinal bleeding, thrombocytopenia, and a hemoglobin level <7 g/dL necessitated weekly, and then daily, transfusions after the gastric biopsy was performed. When the infant was 5 months old, a multidisciplinary decision was made to introduce sirolimus (0.1 mg/kg per day), with the objective of increasing the serum sirolimus level from 5 to 10 ng/mL. A few days after sirolimus was started, transfusions were discontinued, and 2 repeated upper gastrointestinal endoscopies (with 1 month and 5 months of treatment) demonstrated no residual gastric bleeding but persistent vascular lesions. At the 14-month follow-up, the patient exhibited good tolerance to sirolimus but had 3 episodes of gastrointestinal bleeding (1 episode required blood transfusion) after 1 year of treatment, and an endoscopy performed at the same time revealed stability of the gastric vascular nodules. Sirolimus was increased to 0.2 mg/kg per day and was continued.

**Patient 3**

A male infant was born at term from a pregnancy achieved by in vitro fertilization. Physical examination at birth revealed multiple red-to-purple flat papules 1 to 3 mm in diameter associated with indurated nodules 5 to 15 mm in diameter distributed on the upper and lower limbs, feet, trunk, and scalp (Fig 3A). The infant was otherwise healthy. Results of initial laboratory investigations revealed normal values for platelet count (219 × 10^3/µL; normal range: 150–400 × 10^3/µL) and hemoglobin level (15.4 g/dL; normal range: 13–20 g/dL). At 4 days of age, the infant presented with gastrointestinal bleeding (melena); his hemoglobin level was 7.2 g/dL. Endoscopy revealed 2 mucosal vascular gastric lesions and 1 large vascular lesion in the cecum. From age 4 to 30 days, the infant experienced daily gastrointestinal bleeding that required erythrocyte transfusions once a week despite therapy with propranolol, 3 mg/kg per day (day 4); corticosteroids, 1 mg/kg per day (day 14); and octreotide, 1 µg/kg per hour (days 15–30). Endoscopic sclerotherapy was performed on the stomach and cecum lesions, but after a short time, the melena recurred (~2 times a week).

The patient’s coagulation status was normal. Ultrasonography revealed liver, spleen, and kidney involvement; cranial and spinal MRI showed right vascular extraparenchymal lesions with a mass effect and vascular lesions of the conus medullaris. Radiography revealed osteolytic bone lesions of the right femur, right tibia, and the T2, T3, and T4 vertebral peduncles. Echocardiography produced normal results, with normal fundus oculi. Results of the skin biopsy revealed a proliferation of well-differentiated dilated capillaries with thin walls throughout the dermis and superficial subcutis (Fig 3C). Some capillaries were lined with hobnail endothelial cells and focally formed intraluminal papillary projections. Endothelial cells were negative for GLUT-1 and D2-40 and focally positive for LYVE1 (Fig 3D). The diagnosis was MLT despite the lack of thrombocytopenia. At age 2 months, after multidisciplinary consultation, the
infant received sirolimus at 0.1 mg/kg per day; the objective was to increase the serum sirolimus level from 4 to 12 ng/mL.

During 13 months of treatment, the child had 1 mild incident of gastrointestinal bleeding, which did not require blood transfusion. Skin lesions were resolved (Fig 3B), with bone healing of the right femur and right tibia fractures; a decrease of 10% to 30% in the size of the kidney, liver, spleen, and brain vascular lesions (identical number); and resolution of the conus medullaris lesions. The treatment was well tolerated and continued.

DISCUSSION

We report 3 cases of MLT demonstrating the varying facets of the disease and that support sirolimus as a rapidly efficient treatment.

All patients had clinical and histologic features of MLT. MLT is typically characterized by congenital skin GLUT-1-negative vascular lesions and, commonly, thrombocytopenia and extracutaneous involvement, in particular frequent and diffuse gastrointestinal involvement resulting in severe bleeding; this bleeding is considered the major cause of morbidity and mortality in the first year of life. All of our patients had multifocal vascular lesions, particularly gastrointestinal involvement, which resulted in severe bleeding for patients 2 and 3. In addition, all patients had histologic features of MLT, with GLUT-1-negative thin-walled dilated vessels appearing like lymphatic vessels, sometimes lined with hobnail endothelial cells, and associated with intraluminal papillary projections (on skin biopsy specimens for patients 1 and 3 or on gastric biopsy specimens for patients 1 and 2). These vessels exhibited lymphatic vascular differentiation, expressing the lymphatic marker D2-40 or LYVE1 or both.

The differential diagnosis of MLT involves other multifocal vascular diseases, mainly diffuse neonatal hemangiomatosis (DNH); several reported MLT cases were misdiagnosed as DNH. In the systematic review by Glick et al, 17 of 73 cases of DNH were reclassified as MLT or probable MLT. Glick et al also proposed the name multifocal infantile hemangiomas (MIH) instead of DNH. MIH is recognized by positive immunohistochemical staining for GLUT-1, but gastrointestinal involvement is rare in MIH and if present, is usually associated with large segmental skin hemangiomas. These disorders must be distinguished for appropriate assessment and therapeutic management. Blue rubber bleb nevus syndrome is another rare multifocal vascular disorder featuring multiple skin lesions and gastrointestinal bleeding, but skin vascular lesions are blue, and, histologically, the lesions are composed of dilated venous channels. Other vascular entities with lymphatic marker staining (D2-40 or LYVE1) include kaposiform hemangioendothelioma, tufted angioma, Kaposi sarcoma, and lymphatic malformations, but the clinical features differ from multifocal vascular disorders such as MLT.

Although this multifocal vascular disorder of infancy has recently been described, data on MLT’s clinical features, long-term prognosis, and treatment are lacking. Our descriptions provide new insights into this entity. Each of our patients exhibited peculiar clinical features, characterized by the variable involvement of many different organs. Patients 1 and 3 exhibited widespread visceral involvement; patient 1 had extremely severe cerebral disease,
leading to death. Patient 1 exhibited severe MLT, despite the absence of gastrointestinal hemorrhage. In contrast, patient 2 had severe gastrointestinal bleeding but only 2 sites of visceral involvement (the gastric tract and lungs) and no skin lesions; the occurrence of MLT was not congenital. Finally, patient 3 did not have thrombocytopenia. However, neither platelet count within the normal range nor absence of skin lesions is classically reported.1 Biopsy specimens from patient 3 were negative for D2-40, with focal positivity for LYVE1. Negative staining for LYVE1 does not exclude the diagnosis of MLT because focal positivity might be missed on a small biopsy specimen. This patient did not have thrombocytopenia. Other vascular anomalies known to induce thrombocytopenia by trapping platelets and/or be associated with mucositis, edema, altered wound healing, male hypogonadism, and myelosuppression.9,14,15

Given the phenotype variation and rarity of MLT, the treatment strategy is not well established, and its results are disappointing. The various treatment attempts were based on drugs used for MIH with extracutaneous involvement (corticosteroids,1 vincristine,6 interferon alfa-2a,1,6 and propranolol6), but they produced limited success. Bevacizumab is a humanized monoclonal antibody that binds 5 isoforms of human vascular endothelial growth factor, and recent study results for this drug were encouraging in 2 cases of MLT.3,4 Sirolimus is a mammalian target of rapamycin inhibitor developed to prevent kidney allograft rejection in adults and children at least 13 years old but is commonly used in younger children.9 The drug also has antineoplastic activity and is being investigated in malignancies with overactivated mammalian target of rapamycin signaling.10 Sirolimus induces inhibition of angiogenesis, including lymphangiogenesis,11 as demonstrated in several models (surgical wound healing,12 embryogenesis development,11 and tumor formation and lymphatic metastasis13). This property was the basis of a clinical report of 6 patients with complicated lymphatic vascular anomalies treated with sirolimus (n = 4, diffuse microcystic lymphatic malformation; n = 1, capillary lymphatic-venous malformation; and n = 1, kaposiform hemangioendothelioma).14 Sirolimus reportedly has an acceptable safety profile in children. The main adverse effects include hyperlipidemia, mucositis, edema, altered wound healing, male hypogonadism, and myelosuppression.9,14,15 Sirolimus led to rapid and significant improvement of gastrointestinal bleeding in 2 of our patients, which allowed for the discontinuation of blood transfusions for patient 2 and a decrease in transfusions for patient 3. The latter patient also showed complete resolution of skin lesions and partial response in the other involved sites. Most reported cases display decreased severity of gastrointestinal bleeding after 2 or 3 years of age.1 Therefore, the clinical improvement in our patients, who received treatment early in life, may not be attributed to the natural history of the disease.

CONCLUSIONS

Our cases illustrate the phenotypic variation of MLT. The disease must be distinguished from MIH early because it is life-threatening and the therapy differs. Therefore, conducting a biopsy early is highly recommended. Because sirolimus had marked efficacy in both treated cases, it may be suggested as first-line treatment of MLT.

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ABBREVIATIONS

D2-40: ~38-kDa O-linked transmembrane sialoglycoprotein podoplanin
DNH: diffuse neonatal hemangiomatosis
GLUT-1: glucose transporter 1
LYVE1: lymphatic vessel endothelial hyaluronan receptor 1
MIH: multifocal infantile hemangiomas
MLT: multifocal lymphangioendotheliomatosis with thrombocytopenia

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