Multifocal lymphangioendotheliomatosis with thrombocytopenia: phenotypic variability and response to rapamycin

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ABSTRACT

Introduction. Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is characterized by multiple maculopapular lesions involving the stomach and the lungs, associated with thrombocytopenia as a result of platelet entrapment. Episodes of severe digestive bleeding, which are sometimes unmanageable, are one of its most frequent presentations and a cause of mortality. Our objective was to describe the various phenotypes, as well as our treatment experience.

Materials and methods. A retrospective analysis of patients diagnosed with MLT in our vascular abnormality unit from 2007 to 2018 was carried out. Epidemiological, clinical, and evolution data were analyzed, and a long-term follow-up was performed.

Results. Five patients (3 boys and 2 girls) had congenital macules and erythematous papules of various sizes. They were later associated with episodes of severe hematemesis along with thrombocytopenia, which required blood product transfusion. The most frequently involved areas were the stomach and the colon. In two patients, multiple bilateral pulmonary nodules were noted. The anatomical pathology examination showed extended vessels with a prominent, hobnail endothelium, as well as intraluminal papillary projections in the dermis. Immunohistochemical analysis was CD-31 positive and CD-34 positive in a characteristic manner. Two patients were treated with mTOR inhibitors (rapamycin), with a progressive decrease in extracutaneous involvement and platelet recovery, but with a poor response in dermal lesions. Two patients were treated with vincristine, with a reduction of digestive bleeding episodes. No deaths were reported in our series.

Conclusion. MLT is characterized by hematological and cutaneous involvement – sometimes minimal –, with potential lesions in other internal organs. Its heterogeneous presentation, which may start with severe digestive bleeding, makes this rare pathology difficult to diagnose. mTOR inhibitors have opened up new treatment possibilities.

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KEY WORDS: Multifocal Lymphangioendotheliomatosis; Cutaneovisceral Angiomatosis with Thrombocytopenia; Rapamycin; Sirolimus; Digestive Bleeding

LINFAGIOENDOTELIOMATOSIS MULTIFOCAL CON TROMBOPENIA: VARIABILIDAD FENOTÍPICA Y RESPUESTA A RAPAMICINA

RESUMEN

Introducción. La linfangioendoteliomatosis multifocal con trombopenia (LMT) es una anomalía, caracterizada por múltiples lesiones maculo-papulosas con afectación visceral gástrica y pulmonar, asociado a trombopenia por atrapamiento plaquetar. Una de sus presentaciones más frecuentes es en forma de episodios de hemorragia digestiva severa, en ocasiones inmanejable, y que es la responsable de su mortalidad. Nuestro objetivo es describir los diferentes fenotipos, así como nuestra experiencia en su tratamiento.

Material y métodos. Hemos realizado un análisis retrospectivo de los pacientes diagnósticos de LMT según las características histológicas típicas entre 2007 y 2018 en nuestra unidad de anomalías vasculares. Se analizaron datos epidemiológicos, clínicos y de evolución, así como seguimiento a largo plazo.

Resultados. Cinco pacientes (3 hombres y 2 mujeres) presentaron al nacimiento máculas y pápulas eritematosas de diferentes tamaños a los que más adelante se les asoció episodios de hematemesis graves junto a trombopenia, que llegaron a requerir transfusión de hemoderivados. Las regiones más afectadas fueron el estómago seguido del colon. En dos pacientes se detectaron múltiples nódulos pulmonares bilaterales. La anatomía patológica describió vasos alargados con endotelio prominente y en tachuela junto a proyecciones papilares intraluminales en dermis. La inmunohistoquímica fue positiva de forma característica para CD-31 y CD-34. Dos pacientes fueron tratados con inhibidores de mTOR (rapamicina) con disminución progresiva de la afectación extracutánea y recuperación plaquetar, pero con una pobre respuesta de las lesiones dérmicas. Dos pacientes fueron tratados con vincristina con reducción de los episodios de sangrado digestivo. No se registró ningún fallecimiento en nuestra serie.

Conclusión. La LMT se caracteriza por una afectación cutánea, a veces mínima, y hematológica que puede asociar lesiones en otros órganos internos. La presentación heterogénea, pudiendo debutar con hemorragias digestivas severas, hacen de esta entidad una patología de difícil diagnóstico. Los inhibidores de mTOR han abierto una nueva vía que arroja cierta esperanza para el tratamiento de esta patología tan poco frecuente.

Palabras Clave: Linfangioendoteliomatosis multifocal; Angiomatosis cutaneovisceral con trombocitopenia; Rapamicina; Sirolimus; Hemorragia digestiva.

INTRODUCTION

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) was simultaneously described by various groups in 2004[1,2]. They presented a similar first clinical description – multiple cutaneous lesions in the form of erythematous macules and papules at birth, with new lesions occurring during childhood. In addition, these patients had some unique characteristics, such as visceral involvement and severe thrombocytopenia. However, histological conclusions were diametrically opposed. North et al. claimed that MLT had a lymphatic histomorphology as a result of being LYVE-1 positive[1]. However, Prasad's research group concluded it had a blood vessel etiology, since cutaneous lesions became white when exerting pressure, showed enhancement at imaging tests, and had intravascular red blood cells[2]. Even though there is no clear evidence in terms of physiopathology, various treatments have been applied, with unequal results. Rapamycin is an m-TOR inhibitor with an antiangiogenic and immunosuppressive effect. Droitcourt et al. published a series of cases treated with rapamycin[3], which not only reduced the need for blood transfusion, but also allowed for total healing, with cutaneous and visceral lesions disappearing in one patient. Up until now, only eight cases describing MLT treatment with rapamycin have been published. We present our series of five patients with full phenotypes and vincristine and rapamycin responses, as well as an up-to-date literature review.

MATERIALS AND METHODS

A historic review of the cohort of patients histologically diagnosed with MLT from 2007 to 2018 was carried out. Demographic and clinical data, complementary tests, histology, and treatment response were collected. In addition, a bibliographic search of cases published in indexed journals since MLT was first described in 2004 was conducted in PubMed, EMBASE, and Science Direct medical databases. Search terms included "Multifocal Lymphangioendotheliomatosis", "Cutaneovisceral Angiomatosis", "Sirolimus", and "Rapamycin".

RESULTS

We present the cases of 5 patients (3 boys and 2 girls) with various cutaneous lesions at birth, from blueish and reddish macules to telangiectasic lesions, in the axial and head-neck skeleton, which can be undetectable. In the first 90 days of life, they all had severe digestive bleeding requiring blood transfusion. The digestive tract was assessed by means of endoscopic studies, which showed the stomach to be the most widely involved segment, followed by the duodenum and the colon. For extension study purposes, CT-scans were performed, demonstrating multiple bilateral nodular parenchymatous lesions in three patients. One patient had thymus and bone involvement. They all had thrombocytopenia, with 30,000/µl being the lowest level. Definitive diagnosis was achieved using cutaneous biopsies, and in some cases, gastric or pulmonary biopsies. In all patients, regardless of sample location, extended vessels with a prominent and hobnail endothelium were reported, with intraluminal papillary projections (Fig. 1). Immunohistochemical studies revealed CD31 (+), CD34 (+), D240 (+/-), WT-1 (-), and GLUT-1 (-). Endothelial cells were CD31 positive in all cases, and CD34 positive in those cases where it had been searched for. The study was GLUT-1 and WT-1 negative. Patients' genetic profile did not show mutations typically found in vascular abnormalities. Initial treatment was empirical, based on the experience and results from other research groups. At this stage, vincristine was the most widely applied treatment, with unequal results (improvement in digestive bleeding). Other treatments used included methylprednisolone and α-2A interferon. Four years ago, compassionate oral rapamycin treatment was initiated in two patients. The first one remained under treatment for 39 months, with fewer bleeding episodes, thrombocytopenia repair, and remission of pulmonary, thyroid, and eventually bone lesions. However, cutaneous lesions remained stable. The second patient was under treatment for 16 months. All lesions, including cutaneous lesions, remitted, but platelet count recovery was partial. None of the patients in our series died (Table 1).

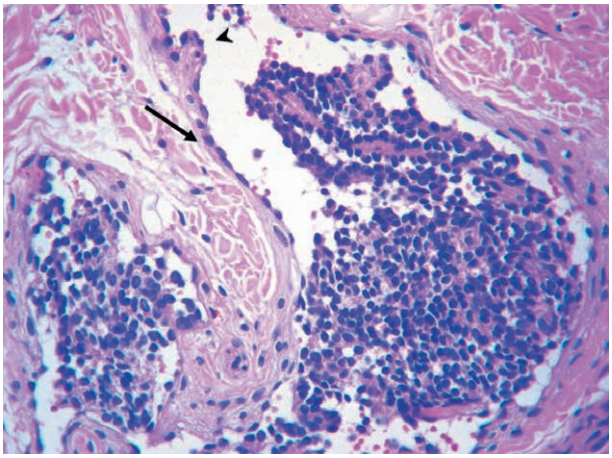

Figure 1. The dermis shows dilated thin vessels with a layer of hobnail endothelium, with many other endothelial cells in the lumen (arrow). Intraluminal papillary projections (arrow tip).

Table 1. Clinical characteristics, treatment, and follow-up.

Patients No.	*Sex*	*Cutaneous lesions*	*Digestive lesions*	*Other lesions*	*Treatment*	*Sirolimus*	*Follow-up*
1	Male	Blueish and reddish macules	Stomach	Lung, thymus, bone	Corticoids, vincristine, propranolol	Yes	7 years
2	Female	Purpuric lesions	Stomach	No	Corticoids, α-2A interferon, vincristine	No	13 years
3	Female	Blueish and reddish macules	Stomach	No	Corticoids, vincristine, propranolol	No	2 years
4	Male	Telangectasias	Stomach, duodenum, colon	Lung	No	Yes	2 years
5	Male	Blueish and reddish macules	Esophagus, stomach, colon	Lung	Bevacizumab, zoledronic acid	No	9 years

In the literature review, 35 scientific publications were found when applying the search terms. After screening and reviewing 25 publications, only 23 were included in the analysis. In order for all publications up to date to gain maximum representativeness, previous reviews, clinical case series, isolated clinical cases, and abstracts from international conferences were included (Fig. 2).

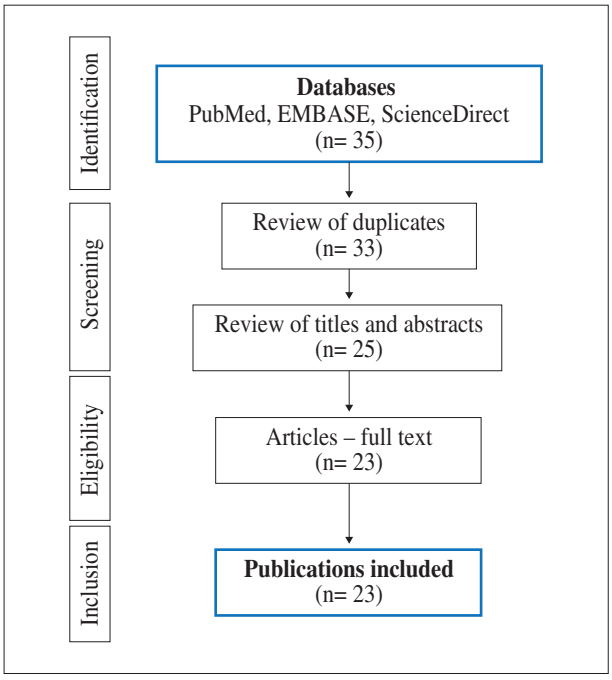

Figure 2. Flow diagram of publications reviewed.

DISCUSSION

MLT is a relatively new pathology pertaining to the so-called vascular multifocal disorder group. Diffuse hepatocutaneous hemangiomatosis in children or blue rubber bleb nevus syndrome are two representative examples of this type of condition. The first is the most frequent in this group, and it is characterized by multiple small reddish GLUT-1 positive lesions. The second is a rare venous malformation with gastrointestinal involvement stemming from a mutation in TEK gene (ONIM #600221), which causes TIE-2 protein hyperactivation. Other pathologies to be considered include glomuvenous malformations, Maffucci syndrome, and hereditary hemorrhagic telangiectasia. However, MLT has some unique clinical and histological characteristics which allow it to be distinguished from the other conditions. Visceral involvement tends to be more frequent in the bowel, where it causes severe digestive bleeding potentially requiring multiple transfusions.

Severe thrombocytopenia is a rare characteristic within vascular abnormalities. There are two groups with different prognoses. Venous malformations are characterized by large ectatic blood lakes favoring local coagulation activation and, under certain stimuli, dissemination, which is more dangerous. It implies an increase in D-dimer levels (as a result of fibrin degradation) and a decrease in coagulation factors[4,5]. On the other hand, in kaposiform hemangioendothelioma and tufted angioma, Kasabach-Merritt syndrome may occur[6-8]. It is characterized by platelet entrapment with a significant decrease in platelet count and fibrinogen, with increased D-dimer. Prothrombin times and partial thromboplastin times are slightly increased. According to North, this phenomenon is similar to that occurring in MLT, since they are both based on a lymph vessel disorder, with similar immunohistochemistries[9].

Since it was first described 15 years ago, a total of 44 MLT cases have been reported. The largest series was published by Prasad et al. in 2005, who coined the phrase "cutaneovisceral angiomatosis"[2] – however, this term fell into disuse as it caused confusion with "angioma". The review of this case series allows various conclusions to be drawn (Table 2):

Table 2. Table featuring the most significant data following a literature review.

Patients	44 (1987-2019)
Mean age	6 months
Sex	Male (17), female (14) (no data: 13)
Cutaneous lesions	Multiple congenital papules and macules 7 patients with occurrence of new lesions 8 patients without cutaneous lesions
Digestive involvement	Digestive bleeding (40) Stomach (26); Colon (14)
Pulmonary involvement	Hemoptysis (6) Radiological pulmonary nodules (10)
Brain involvement	5 patients
Diagnosis	Histology compatible with variable immunohistochemistry
Sirolimus	9 patients
Mortality	3 patients

1. Most cases were diagnosed in the first 6 months of life. They typically start with episodes of digestive bleeding in the context of severe thrombocytopenia. Cutaneous lesions tend to go unnoticed.
2. The phenotype is fully developed in most cases, but there are exceptions. Khamayasi et al. showed a patient with cutaneous involvement only[10]. Some series describe episodes of hemoptysis without cutaneous lesions or gastrointestinal tract involvement[11,12]. In our series, all patients developed the full phenotype. Pulmonary involvement was found at CT-scan in 4 out of the 5 patients, and none of the patients had episodes of hemoptysis.
3. After the gastrointestinal tract, the lung is the second most frequently involved organ, followed by the liver and the brain. In the literature, a tendency to only investigate the gastrointestinal tract has been detected, but the airways and the central nervous system may also be involved, with potentially fatal consequences[12]. Therefore, a chest and brain extension study is recommended in all patients. The CT-scan allows parenchymatous involvement to be detected, while nuclear magnetic resonance (NMR) allows the extension and local involvement of the lymphatic malformation to be established[13].
4. Histology is characteristic, but immunohistochemistry is variable. The primary markers used include CD31 (transmembrane glycoprotein of 135 KDa expressed in arteries, arterioles, venules, veins, non-sinusoidal capillaries, discontinuous endothelial cells of lymph vessels, macrophages, and platelets) and CD34 (sialomucin in endothelial cells, hematopoietic system precursor cells, and dendritic fibroblasts). Specific lymphatic markers include Lyve-1 or lymphatic endothelial nuclear transcription factor (a hyaluronidase receptor which is virtually only expressed in the lymphatic endothelium) and D2-40 (a transmembrane glycoprotein present in the lymphatic endothelium). Our cases were CD31 (+) and CD34 (+), with an irregular Lyve-1 positivity. The literature describes a wide immunohistochemical variability. Droitcourt published a series of 4 cases where 3 were CD34 (-), CD34 (-), and LYVE-1 (+). The other patient had opposite results, with CD34 (+), CD34 (+), and LYVE-1 (-) (3). Even though lymphatic markers are important for diagnosis, expression is variable within the malformation. However, consensus does exist around GLUT-1 negativity – since GLUT-1 is a hemangioma marker – and WT-1 negativity – since WT-1 has a strong expression in vascular tumors
5. Rapamycin is a safe and effective drug for MLT treatment. It inhibits the activation of T cells by blocking the transduction of calcium-dependent and calcium-independent intracellular signals while targeting the mTOR protein[14]. It has an antineoplastic effect, and it induces angiogenesis and lymphangiogenesis inhibition[15]. Given the rarity and phenotypical variation of MLT, the treatment strategy has never been adequately established, and the various empirical treatments applied have proved disappointing. In 2015, Droitcourt was the first to describe the use of rapamycin in MLT patients. He studied a series of 6 patients with complicated lymphatic malformations, which were effectively treated with rapamycin[16]. Digestive bleeding episodes ceased, while platelet count increased. Rapamycin has been used in few further series, with unequal cutaneous responses[17-20]. In our case series, response was highly adequate. Since this is one of the first indications of rapamycin, experience was not available yet in terms of dosage levels and target serum levels. Therefore, treatment monitoring was based on early side-effect detection and symptom reduction. Reliable markers are now being investigated for treatment monitoring purposes[21]. Serum and whole blood concentrations have demonstrated a wide pharmacokinetic variability among individuals – this means similar concentrations of the same drug have different effects in each patient. Most healthcare professionals start with a 0.5 mg/m^2 dose every 12 hours, with subsequent doses being reduced to 0.2-0.3 mg/m^2 every 12 hours so as to maintain blood levels between 5 and 15 ng/ml[22,23]. In our cohort of 7 patients with neonatal lymphatic malformations, dosage was started at 0.8 mg/m^{2}on day 15 of life and maintained for 12 months[24]. Plasma levels remained acceptable, between 4 and 12 ng/ml, but two patients had high levels of 22 and > 90 ng/ml. None of the patients had side-effects, and they all greatly improved, with a significant reduction of the mass. The experience acquired in our vascular abnormality unit over the past years has allowed us to confirm there

is high variability among individuals. Therefore, in a recent publication, we recommended a symptom-based dosage regimen, with blood levels being used to guide rapamycin dosage only. We believe rapamycin administration should be a factor of lymphatic malformation phenotype and extension, patient age, and especially symptoms[25]. The unequal effects rapamycin has on MLT demonstrate how little known molecular genetics and cell behavior are. Why identical histologic lesions have different immunohistochemical patterns, with unequal treatment responses, is still unknown.

Bevacizumab is a humanized monoclonal antibody that binds to the five isoforms of vascular endothelial growth factor (VEGF), thus impairing interaction with its receptor. By blocking this interaction, it effectively inhibits the survival, proliferation, and formation of new blood vessels in endothelial cells. It is approved by the US Food and Drug Administration for colorectal metastatic neoplasia, pulmonary neoplasia, cervical neoplasia, and glioblastoma. It was first used in 2008 in a 4-year-old patient diagnosed with MLT with histological confirmation and refractory to treatment with oral corticoids and intravenous vincristine. Owing to the concerns posed by the use of α-2 A interferon as a result of the patient's age, decision was made to initiate bevacizumab at a 10 mg/kg dose every 2 weeks. After the third dose, bleeding episodes were fully under control[26]. Based on this experience, other research teams have used bevacizumab as a rescue therapy, with all digestive bleeding episodes being under control[20,27,28].

6. Further studies are required to optimize treatment and learn about the genetic basis of MLT. Three deaths as a result of bleeding complications (digestive and cerebral) at 5, 7, and 8 months of life have been found in the literature[3,29,30]. Early detection and rapamycin treatment will allow for a better control and earlier intervention in acute bleeding cases.

In conclusion, MLT is a multifocal vascular malformation characterized by nodules and reddish papules of irregular distribution, with visceral involvement, (primarily the stomach and the colon, followed by the lung) and thrombocytopenia as a result of platelet entrapment. The presence of a prominent, hobnail endothelium with intraluminal papillary projections is unique and has variable lymphatic endothelial marker positivity. The phenotypic variability reported explains why no structured treatment has been made available yet, which in turn has brought about poor results with deadly cases. After 12 patients have been successfully treated by different research groups, and as a result of more than 5 years of experience in the use of rapamycin, rapamycin should be recommended as the first-line treatment for MLT. The other treatments applied throughout history lack evidence, have demonstrated inconsistent results, and should only be used as a second option in cases refractory to mTOR inhibitors.

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