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Case Report

A Chinese infant with multifocal lymphangioendotheliomatosis with thrombocytopaenia

一名中國籍嬰兒患有多灶性淋巴管內皮細胞瘤病與血小板減少症

Y Chan 陳湧, KH Yeung 楊國鴻, WY Lam 林永賢

Multifocal lymphangioendotheliomatosis with thrombocytopaenia (MLT) is a rare syndrome first described in 2004 that is characterised by multiple reddish-brown erythematous patches, gastrointestinal (GI) bleeding and thrombocytopaenia. The cause is still unknown. We report a Chinese infant who developed multiple congenital blanchable erythemas, GI bleeding and multiple internal organ involvement affecting the eyes, lungs and the brain. Skin biopsy was compatible with the diagnosis of MLT. Treatment with intravenous vincristine stabilised her platelet count. To the best of our knowledge, this is the first case of MLT reported in Chinese.

多灶性淋巴管內皮細胞瘤病與血小板減少症（MLT）是一種罕見的綜合症候群，在 2004 年首次被描述，症狀包括皮膚上出現多個紅褐色紅斑，腸胃道出血和血小板減少。其原因不明。我們報告一名中國籍嬰兒出現多個先天性紅斑，後來並發現腸胃道出血和多個器官，包括眼睛，肺部和大腦也受到影響。皮膚活檢與 MLT 吻合。長春新鹼靜脈注射治療穩定了她血小板的數量。據我們所知，這是第一個中國病人的 MLT 的病例報告。

Keywords: Multifocal lymphangioendotheliomatosis, thrombocytopaenia

關鍵詞：多灶性淋巴管內皮細胞瘤病，血小板減少症

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Introduction

Multiple cutaneous vascular lesions with visceral involvement are rare in infancy. Neonatal haemangiomatosis, blue rubber bleb naevus syndrome are more commonly described but thrombocytopaenia is not a feature. Multifocal lymphangioendotheliomatosis with thrombocytopaenia (MLT) is a rare vascular anomaly associated with thrombocytopaenia and gastrointestinal (GI) bleeding. Internal

visceral involvement affecting the brain and lung have been described. The aetiology is still unknown. In this report, we describe a Chinese infant with lesions compatible with MLT.

Case report

Our patient was a Chinese new-born baby girl with uneventful antenatal history. Her mother was a 33-year-old Chinese lady with two previous pregnancies, with the first one terminated and the second one ending in a spontaneous miscarriage. Our patient was delivered at 39+6 weeks of gestation by lower segment Caesarean section for failed induction after prolonged leakage. Her birth weight was 2.84 kg. At birth, there were already multiple well-defined blanchable erythematous papules, a few millimetres in size, over her limbs and genitalia (Figures 1 & 2). She had no family history of skin disease. On the first day of life, the platelet count was 80×10^9/L, haemoglobin was 16 g/dL. Then her platelet count dropped to 40×10^9/L at one week of age. The clotting profile, including prothrombin time (PT)/international normalised ratio (INR)/activated partial thromboplastin time (APTT), was normal at birth. Fibrinogen level was normal which excluded the possibility of congenital fibrinogen deficiency. A grossly raised D-dimer to 1944 ng/ml (normal <500 ng/ml) suggested a thrombotic event. At one month of age, our patient was found to have a grossly deranged clotting profile (INR 1.3, PT 14.3s, APTT 44.5s) which was compatible with consumptive coagulopathy. Concurrently, the patient was noted to pass fresh melaena with a drop of haemoglobin to the level of 3.4 g/dL. Several platelet transfusions were needed for resuscitation purpose during active GI bleeding and a lowish platelet count. There was no fever all along. Workup was done to exclude possible infections like cytomegalovirus (CMV) and parvovirus. Large platelets were noted in the blood smear. Bone marrow aspiration showed megakaryocytic hyperplasia which was compatible with peripheral consumption of platelets. Bilirubin

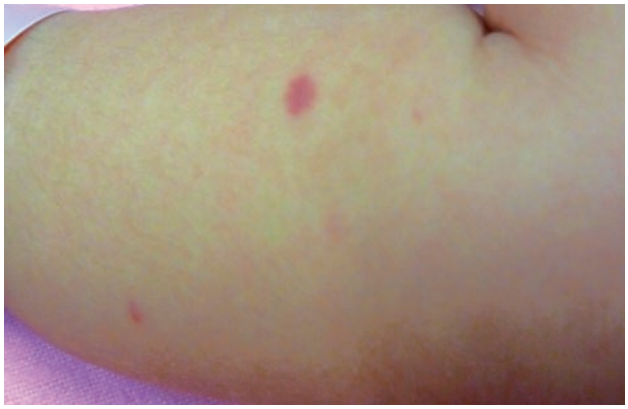

Figure 1. Erythematous macules over left leg.

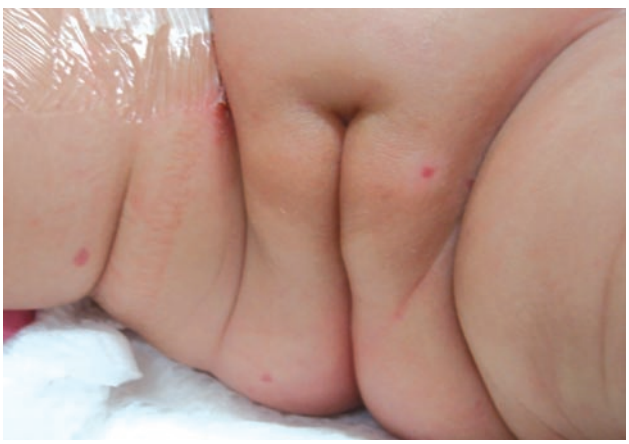

Figure 2. Erythematous macules over the genitalia.

was in the normal range which made haemolytic anaemia unlikely. Anti-platelet antibody and maternal autoimmune diseases screening were normal.

In order to look for any possible internal bleeding, various imaging studies were done. Ultrasonography of brain, abdomen and pelvis done at one month of age did not show any abnormality and the spleen was also found to be normal in size. However, on day 37, left hyphaema occurred and laser treatment was performed. A few days later, she was noted to have episodes of passing melaena; oesophagogastroduodenoscopy (OGD) revealed coffee ground material and multiple mucosal

telangiectatic lesions over the gastric body and antrum. At two months of age, computed tomography (CT) of the abdomen did not show any intra-abdominal lesion but there were multiple nodules over bilateral lung bases. Magnetic resonance imaging (MRI) of the brain showed intra-ventricular, subarachnoid and intra-ocular haemorrhage. CT thorax revealed multiple bilateral randomly distributed pulmonary nodules. The radiological differential diagnoses included metastasis and hemosiderin deposition.

An incisional skin biopsy was done on day 51 on her left leg lesion. Histologically, there was a circumscribed focus of ectatic irregular thin-walled vascular channels in the papillary dermis, superficial vascular plexus and reticular dermis lined with a single layer of endothelial cells (Figure 3). The endothelial cells reacted positively to immunohistochemical staining with anti-CD 31 (Figure 4) and factor 8. Specific lymphatic markers such as D2-40 or LYVE-1 were not available for study. There was no endothelial atypia. The histologic features were, however, compatible with an early lesion of microcystic lymphatic malformation and MLT though not pathognomonic.

Our patient had been treated with prednisolone and propranolol since day 43 with no clinical response. Therefore, weekly intravenous vincristine was added since day 50. Since then, the platelet count appeared to be stable at 170×10^9/L with haemoglobin level at around 11 g/dL. Platelet transfusion was not required after two months of age. When vincristine was tailed down to a biweekly dose, there was an increase in the severity of the haemangiomas on her skin and new vascular lesions in the left eye, so vincristine was continued weekly.

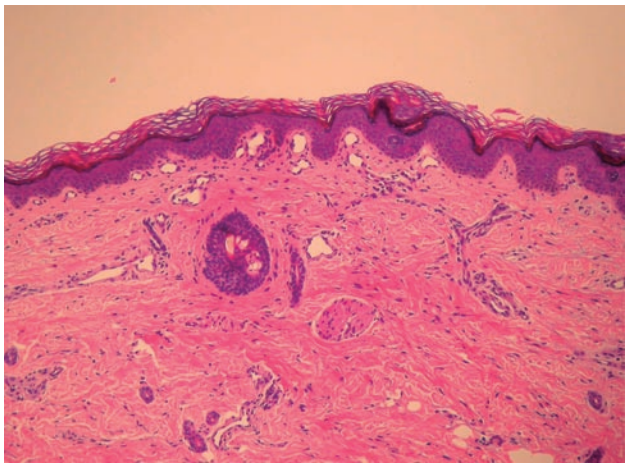

Figure 3. Beneath the epidermis in the papillary and reticular dermis are ectatic irregular thin-walled vasculature with flat endothelium.

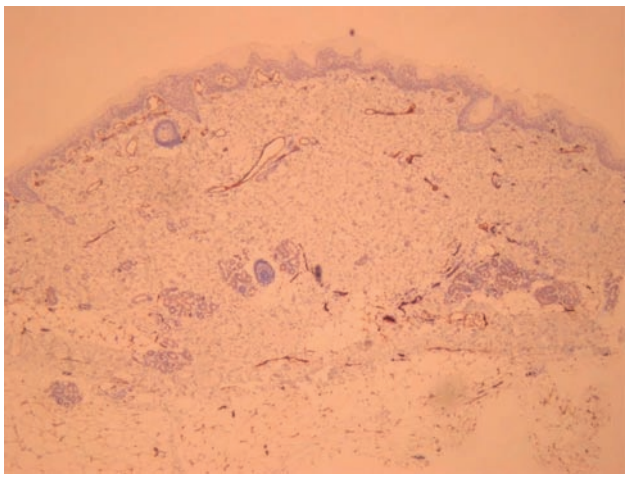

Figure 4. Immunostaining of the endothelial lining with anti-CD31 highlights the thin-walled vessels in this tiny malformation.

Discussion

Multifocal lymphangioendotheliomatosis was first described by North et al in 2004.[1] The author had a collection of three cases. Each one had hundreds of burgundy-coloured erythemas associated with GI bleeding and thrombocytopaenia. They shared similar histopathological features of an abnormal complement of small thin-walled vessels scattered throughout the reticular dermis and subcutis, lined by slightly hobnailed endothelial cells that focally formed intraluminal papillary projections. Positive CD31/LYVE-1 stain

suggested the vessels involved are lymphatic endothelial in origin. Prasad et al used the term cutaneovisceral angiomatosis with thrombocytopaenia to describe his collection of ten cases with similar features.[2] Since then, there have been a few case reports on this syndrome.[3,4]

Concerning the cutaneous lesions in our patient, there were multiple patches of well-defined blanchable cutaneous erythemas which suggested that the lesions were vascular in origin. The clinical differential diagnoses for multiple vascular lesions in infancy included haemangiomata (e.g. neonatal haemangiomatosis, Kaposiform haemangioendothelioma), venous malformations (e.g. blue rubber bleb naevus syndrome, glomuvenous malformations), arteriovenous malformations (e.g. hereditary haemorrhagic telangiectasia), and lymphangiomatous lesions (e.g. MLT). However, thrombocytopaenia is not a typical feature in these conditions except Kaposiform haemangioendothelioma and MLT. Also, the histology did not demonstrate the proliferative lesions of a haemangio-endothelioma. Neonatal lupus and idiopathic thrombocytopaenic purpura can also present with multiple cutaneous lesions with thrombocytopaenia but atrophic discoid lupus-like lesions and purpura are usually found in these entities respectively. The histology was not supportive of these conditions.

It is postulated that the thrombocytopaenia in MLT is due to platelet trapping in the lymphatic vessels.[1,5] Large platelets in the peripheral blood of the patient together with megakaryocytosis in the bone marrow suggested that it was a consumptive process. Immune-related thrombocytopaenia and infections caused by CMV/Parvovirus B19 may present with thrombocytopaenia in infancy but vascular lesions as noted in this case will not be found.

The histological features of MLT are similar to that of benign lymphangioendothelioma or acquired progressive lymphangioma (APL). APL is characterised by solitary lesions in adults with no associated GI lesions and thrombocytopaenia. North stressed on the essence of CD31 and LYVE-1 immunostaining in the diagnosis of this condition.[1] Positivity of these immunostains has also been reported in a few cases of MLT.[3,5] However, the significance of LYVE-1 has been questioned as it can be present in haemangioma as well.[2] In our case, LYVE-1 was not done because it was not available in our centre.

Like other cases reported in the literature, our patient had internal visceral involvement, namely the eyes, brain and lungs. Other reported visceral involvement included the muscle, liver, spleen, kidney, bone and synovium.[2]

There is still no consensus in the treatment of MLT. There are reports on the use of systemic steroid, vincristine (mitotic inhibitor), thalidomide (inhibits angiogenesis), bevacizumab (humanised monoclonal antibody that inhibits vascular endothelial growth factor A) with variable response. We demonstrated a case of MLT which was stabilised with the use of vincristine. However, a longer follow-up is needed to determine its long term outcome.

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