Hemophagocytic lymphohistiocytosis in a neonate with cutis marmorata telangiectatica congenita

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ABSTRACT

In this case report we describe the first case of hemophagocytic lymphohistiocytosis with concurrent cutis marmorata telangiectatica congenita. She had pancytopenia and hepatosplenomegaly, hemophagocytic cells in spleen necropsy, and she died with respiratory failure and pseudomonas induced septicemia.

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Cutis marmorata telangiectatica congenita (CMTC) is a rare skin disorder, and its association or coincidence with hemophagocytic lymphohistiocytosis (HLH) was hardly ever noticed. Hemophagocytic lymphohistiocytosis is a rare and potentially fatal disease. Cutaneous involvement reported in 65% of cases of HLH, however, these presentations including erythroderma, morbilliform eruptions and purpuric macules, and papules were mostly nonspecific.[1,2] In this report, we described a case of familial HLH, who had typical skin presentations of CMTC.

Case Report. A febrile 2-month-old Iranian girl, admitted to the Emergency Department of Children Medical Center. She was severely pale and ill looking with respiratory distress. She had been delivered at 38th weeks of gestation from a 23-year-old primipara mother and had birth weight of 3300 g. Her parents were cousins and have had Rh negative blood types with normal blood cell count profiles. Her parents gave us the history of 2 other episodes of sepsis since the first week of their infant's life, and she did not recovered completely after her second bout of sepsis. We also found pancytopenia on all her complete blood cell count examinations. However, on admission date, her blood cultures were negative (**Table 1**). Physical examination showed a 4400 g infant with open fontanels. We observed a persistent pattern of reticular phlebectasia all over her trunk and limbs. Reticular marbled skin lesions were fixed in size without any reaction to cold and heat. There were also a few petechiae over her limbs (**Figure 1**). We also noticed splenomegaly, 2 cm below umbilical level, and hepatomegaly of about 3 cm below the costal margin. Laboratory test results were summarized in **Tables 1 and 2** and revealed a very high level of serum ferritin, which is the common finding in HLH. Abdominal ultrasonogram were normal except for the findings of hepatomegaly and splenomegaly.

Bone marrow aspiration and biopsy samples were sent to 2 separate expert pathologists, one of which reported hypo cellular marrow, while the other

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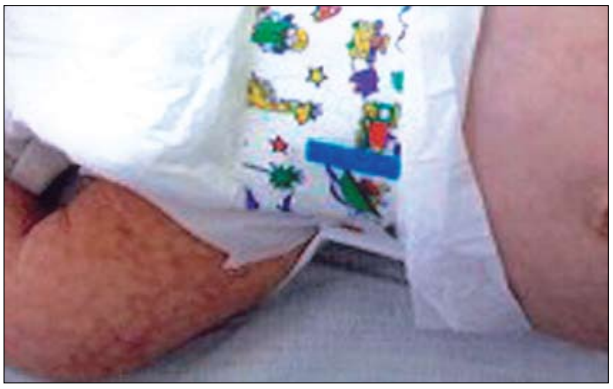

Figure 1 - Red and white marbled appearance of the skin in the patient with cutis marmorata telangiectatica congenita.

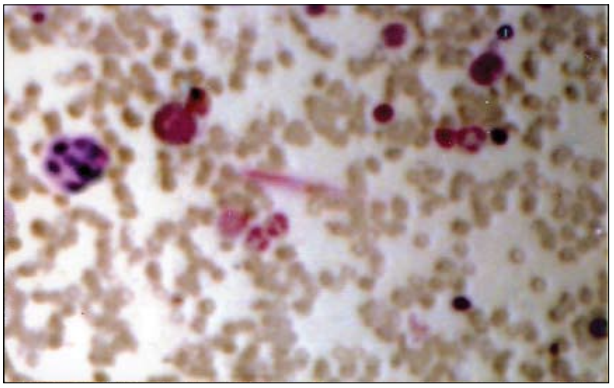

Figure 2 - Gram stained bone marrow aspiration, shows a hemophagocytic cell (middle left).

pathologist detected few typical hemophagocytic cells beside a hypo cellular bone marrow. Chromosomal study on bone marrow cells showed that she was normal. During hospitalization, multiple platelet and packed cell infusions were administered in order to keep the normal levels of platelet and red cell count. She also received multiple intravenous doses of wide spectrum antibiotics (ceftriaxone and vancomycin) and one dose of Etoposide (VP16) (150 mg/m^2) in accordance to the protocol advised by the HLH study group (HLH-2004). On the 12th day of admission, her respiratory condition worsened. She was intubated and blood culture which later showed growth of *pseudomonas aeruginosa,* was carried out. She died on the 15th day of hospitalization due to respiratory failure. Post mortem studies of spleen, revealed hemophagocytic cells on slides, which was confirmed by both pathologists. Skin biopsy was also compatible with the mild phlebectasia and normal overlying skin consistent with CMTC.

Table 1 - Hematologic laboratory values

Complete Blood Count	Results (normal ranges)		
	Day 1	Day 5	Day 12
White blood cell (cc)	3300	700	2900
Red blood cell (cc)	2.8 x 10^6	1.8 x 10^6	2.1 x 10^6
Hemoglobin (g/dl)	7 g/dl	4.4	5.1
Hematocrit (%)	22	13.9	14.7
Platelet	6000	1000	5000
Mean corpuscular volume (fl)	74	74.7	75

Table 2 - Serologic and bio-chemistry laboratory values.

Variables	Results (normal ranges)
Urine analysis	Normal
Venereal disease research laboratory	Negative
Rubella IgM	Negative
Anti herpes simplex virus type 1 IgM	Negative
Toxoplasmosis IgM	Negative
Cytomegalovirus IgM	Negative
Herpes simplex virus type 2 IgM	Negative
Epstein Barr virus specific ELISA	Negative
HIV-ELISA	Negative
Prothrombin time	22.5 second (13)
Partial thromboplastin time	62 second (30)
Ferritin (ng/ml)	>8000 (10-200)
Plasma glucose (mg/dl)	260
Creatinine (mg/dl)	0.25 (<1)
Urea (mg/dl)	8 (10-20)
Serum sodium (meq/liter)	132 (136-145)
Bilirubin total (mg/dl)	1.5 (0.3-1)
Serum calcium (mmol/liter)	8 (9 10)
Serum Potassium (meq/liter)	4.4 (3.5-5)
Immunoglobulin E level (arbitrary units)	2.8 (0.08-6.12)
Immunoglobulin A level (arbitrary units)	113 (2.8-47)
Immunoglobulin M level (arbitrary units)	275 (17 105)
Triglycerides (mg/dl)	660
Fibrinogen	Not assessed

ELISA - enzyme-linked immunosorbent assay,
HIV - human immunodeficiency virus.

Discussion. This case displays the clinical and hematological features of a group of disorders known as HLH. The signs and symptoms was either persistent or intermittent fever with hepatosplenomegaly, thrombocytopenia, and anemia that often evolve to severe pancytopenia, coagulation abnormalities, hypertriglyceridemia, and hepatic dysfunction.[3] These features were also compatible with the diagnostic criteria advised by the histiocyte society.[4] In this case, she also had typical skin presentation of CMTC, which was characterized by the reticular purplish phlebectasia and none resolving marbled skin appearance, as well as few bruises produced by minor traumas. Cutis marmorata

telangiectatica congenita, has been associated with various skeletal and vascular anomalies such as port wine stain, macrocephaly, and cleft palate.[5,6] But, there is no evidence in medical literature, which the co-occurrence of CMTC and HLH. However, one should also consider the other important differential diagnosis, such as, Chediak-Higashi syndrome, Griscelli syndrome, X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, Kasabach-Merritt syndrome, IL-12 receptor beta 1 deficiency, ectodermal dysplasia with immunodeficiency, and lymphohistiocytosis induced by herpes and Epstein Barr virus.[2,4] Since we did not detect any malignant transformation, hypopigmentation, hemangioma, or serologic evidence of viral infections, these diagnosis were ruled out. Complete gene analysis for detecting of suspected mutations in Iran was unavailable, and lack of these findings could be an important shortcoming of our study.

In conclusion, parents' consanguinity, severe recurrent infections, presence of hemophagocytic cells, and other laboratory findings were highly suggestive for the diagnosis of familial type of HLH syndrome, and we suggest that it will be of interest to assess the actual correlation of the CMTC and HLH, plus thorough evaluation of other interfering environmental or genetic factors.

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