

A rare familial thrombocytopenia: May-Hegglin anomaly report of two cases and review of the literature

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ABSTRACT

May-Hegglin anomaly is a hereditary thrombocytopenia associated with giant platelets and large basophilic, cytoplasmic inclusion bodies (resembling Döhle bodies) in the granulocytes. Patients may experience easy bruising, recurrent epistaxis, gingival bleeding, menorrhagia and sometimes excessive bleeding associated with surgical procedures. Failure to appropriately diagnose May-Hegglin anomaly could result in inappropriate treatment. In states of chronic thrombocytopenia associated with large platelets, including chronic idiopathic thrombocytopenic purpura, May-Hegglin anomaly should be considered in the differential diagnosis. In this case report, we present a five-year-old girl previously followed as idiopathic thrombocytopenic purpura without bleeding symptoms and a 14-year-old boy who were diagnosed with May-Hegglin anomaly.

Key words: Thrombocytopenia, May-Hegglin

ÖZET

Nadir bir trombositopeni nedeni: May-Hegglin anomalili iki olgu sunusu ve literatür özeti

May-Hegglin anomalisi dev trombositler ve granülositik hücrelerde Döhle cisimciklerine benzer büyük bazofilik inklüzyon cisimciklerinin varlığıyla karakterize nadir bir kalıtsal trombositopenidir. Kolay morarma, tekrarlayan burun kanamaları, dişeti kanamaları, menoraji ve bazen özellikle cerrahi girişimler sırasında aşırı kanama gibi belirtiler verebilir. Doğru tanı konulamaması uygunsuz tedavilerin kullanılmasına yol açabilir. Dev trombositler ve kronik trombositopeni birlikteliğinde kronik idiopatik trombositopenik purpura yanısıra May-Hegglin anomalisi de ayrıncı tanıda düşünülmelidir. Bu olgu sunusunda; önceden kanama semptomları olmayan ancak idiopatik trombositopenik purpura tanısı konmuş 5 yaşında kız ve 14 yaşında erkek hasta sunulmaktadır.

Anahtar sözcükler: Trombositopeni, May-Hegglin

INTRODUCTION

May-Hegglin anomaly (MHA) is an autosomal dominant disorder characterized by varying degrees of thrombocytopenia that may be associated with purpura and bleeding, giant platelets containing few granules, and large (2-5 μm) basophilic, cytoplasmic inclusion bodies (resembling Döhle bodies) in the granulocytes (neutrophils, eosinophils, basophils and monocytes) ^[1,2,3].

The pathogenesis of MHA is poorly understood. Platelet life-span is usually normal. The thrombocytopenia is thought to be due to defective megakaryocyte maturation and fragmentation ^[4]. Failure of megakaryocyte fragmentation and a microtubular system abnormality may account for the production of large platelets and thrombocytopenia. The reason for leukocyte inclusions is unknown, but there is no evidence of increased susceptibility to infections observed in patients.

Although thrombocytopenia occurs in approximately 50% of patients, severe bleeding is unusual. Patients may experience easy bruising, recurrent epistaxis, gingival bleeding, menorrhagia and sometimes excessive bleeding associated with surgical procedures. Fatal bleeding has not been reported in this syndrome.

The gene responsible for MHA has been mapped to chromosome arm 22q12.3-q13.2 by linkage analysis in a single Japanese family ^[5]. The gene involved encoding non-muscle myosin heavy chain 9 (MYH9) was then identified ^[6-8].

In this case report, we present a five-year-old girl with no bleeding symptoms and a 14-year-old boy diagnosed as MHA accidentally.

CASE REPORT

Case 1

A five-year-old girl was admitted to the outpatient clinic with complaints of cough and sneezing two months previously. Although her physical findings were normal, blood cell count showed thrombocytopenia. She was diagnosed with idiopathic thrombocytopenic purpura (ITP). Her history revealed that she was the first child of healthy parents and had no bleeding abnormality. Laboratory examination revealed WBC: 9.56

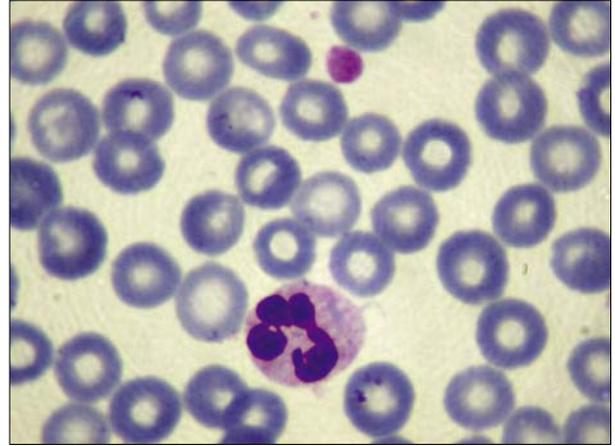


Figure 1. Cytoplasmic inclusion body in a granulocyte and macrothrombocyte (peripheral blood smear, x100, Giemsa stain).

$\times 10^9/\text{L}$, RBC: $4.94 \times 10^{12}/\text{L}$, Hb: 12.5 g/dl, Hct: 38%, MCV: 77 fL, MCH: 25.3 pg, MCHC: 32.9 g/dl, Plt: $35 \times 10^9/\text{L}$, and MPV: 18.1 fL. After this mistaken diagnosis of ITP, she was treated with high-dose methylprednisolone therapy (30 mg/kg/day for 3 days, 20 mg/kg/day for the next 3 days and 10 mg/kg/day for the last 3 days), but thrombocytopenia persisted (Plt: $32 \times 10^9/\text{L}$). In her follow-up in the hematology department, uniformly large, oval thrombocytes were very striking, and there were also intracytoplasmic, light basophilic inclusions in leukocytes (Figure 1). In family surveillance, her mother's hematological findings were similar (thrombocyte count $50 \times 10^9/\text{L}$, MPV: 21 fL, peripheral blood smear findings). The diagnosis was MHA characterized with autosomal-dominant inheritance.

Case 2

A 14-year-old boy was admitted to the outpatient clinic with complaints of easy bruising and recurrent epistaxis for five years. His physical findings were normal except for several ecchymoses on his extremities and right inguinal hernia. In his past and family history, his mother and brother had similar findings (easy bruising and mild thrombocytopenia). Laboratory examination revealed WBC: $4.62 \times 10^9/\text{L}$, RBC: $5.13 \times 10^{12}/\text{L}$, Hb: 13.1 g/dl, Hct: 40.4%, MCV: 78.7 fL, MCH: 25.6 pg, MCHC: 32.5 g/dl, Plt: $44 \times 10^9/\text{L}$, and MPV: 16.7 fL. In peripheral blood smear there were large, oval thrombocytes that could not cluster, and intracytoplasmic, light basophilic inclusions in leukocytes identical with MHA. In family surveillance, hematological findings of his mother and brother were also normal

except for mild thrombocytopenia in large diameters. In follow-up, six months after the diagnosis of MHA, he was readmitted to our hospital with complaints of fever and cough for four days. In his physical findings, there were rough rales in both lungs, and chest X-ray showed bilateral hilar infiltration; penicillin G 300,000 IU/kg/day was started. Since there was no clear response to therapy, chest tomography was obtained which showed conglomerated lymphadenopathy in both hilar regions. Abdomen tomography also showed multiple lymphadenopathies in different diameters ranging between 8 and 15 mm in pelvic and mesenteric areas. Bone marrow aspiration was normal. For tissue diagnosis, thoracoscopic lymph node biopsy was performed. Biopsy was concordant with sarcoidosis.

DISCUSSION

The most prevalent causes of isolated thrombocytopenia in childhood are acquired autoimmune disorders. The commonest form of these causes is ITP thought to be secondary to viral infections. Most ITP cases have severe thrombocytopenia and come with bleeding such as epistaxis and petechia-purpura, and it is sometimes life-threatening. However, in MHA, thrombocyte count changes, usually between $40 \times 10^9/L$ and $80 \times 10^9/L$, and severe bleeding are unusual. Furthermore, corticosteroids, as seen in this case, intravenous immunoglobulin (IVIG), and splenectomy are ineffective^[9]. In dif-

ferential diagnosis, platelet size and leukocyte inclusions are very important. The differential diagnosis for thrombocytopenia associated with large platelet size includes Bernard-Soulier syndrome, Montreal platelet syndrome, gray-platelet syndrome, Alport and Ebstein syndrome, Sebastian syndrome and ITP, and for leukocyte inclusions (Döhle bodies) includes septicemia, myeloproliferative disorders, and pregnancy^[1,10-12]. From these clinical situations, the conditions most resembling MHA are Sebastian syndrome and Fechtner syndrome. These disorders are characterized by thrombocytopenia associated with large platelet size, leukocyte inclusions, and autosomal dominant inheritance. However, some additional features, such as nephritis, deafness, and congenital cataract, may be seen in Fechtner syndrome, and the degree of thrombocytopenia is more severe than in MHA^[11]. On rare occasions of severe bleeding in MHA, platelet transfusions may be required. Prophylactic platelet transfusions prior to surgery and delivery may be warranted to prevent severe bleeding. Medications decreasing platelet functions must be avoided. Failure to appropriately diagnose MHA could result in inappropriate treatment. In states of chronic thrombocytopenia associated with large platelets, including chronic ITP, MHA should be considered in the differential diagnosis. It must be ruled out before considering medications with potentially toxic side effects and invasive procedures such as splenectomy.

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