Pathologic Quiz Case

Twin Neonates With Thrombocytopenia

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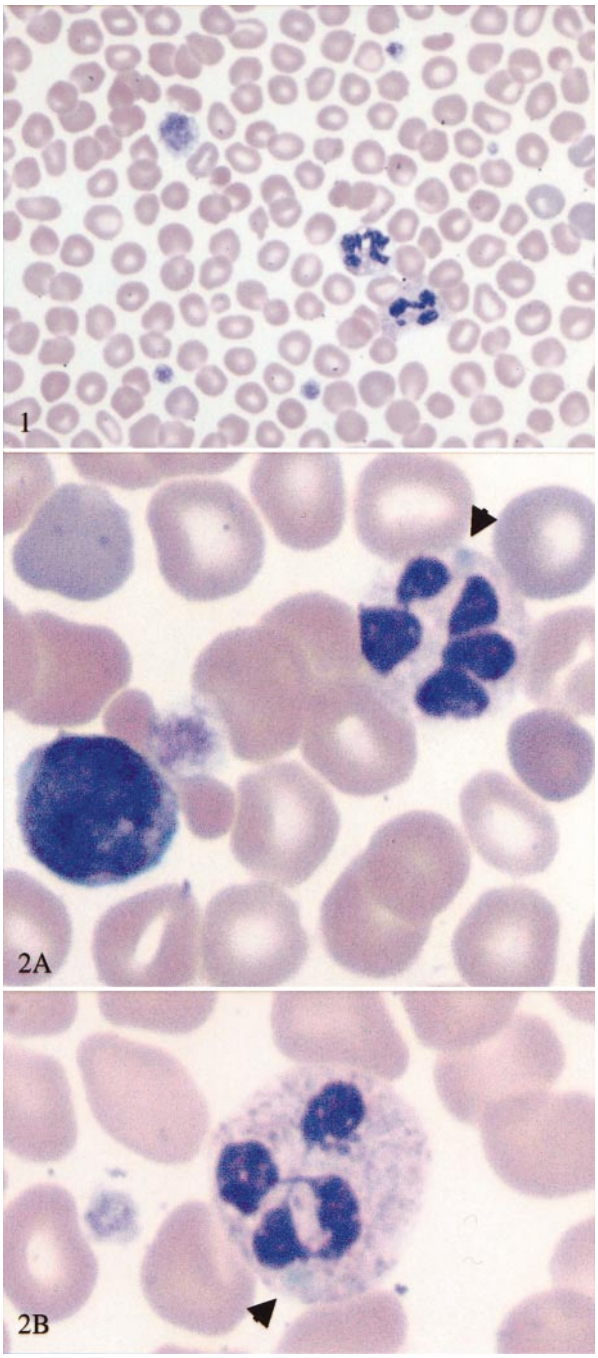
The 2 female patients are a product of a dizygotic (diamnionic, dichorionic) twin gestation and were born prematurely at 35 weeks with appropriate birth weight for gestational age. This was the first pregnancy for their 28-year-old mother, whose pregnancy was complicated by pregnancy-induced hypertension and type 2 diabetes mellitus. Labor was induced before the due date because of worsening pregnancy-induced hypertension. The twins were born by an uncomplicated vaginal delivery and required only routine resuscitation.

Initial laboratory investigation on the first day of life revealed similar hematologic findings in both twins. Twin A exhibited normal red blood cell indices (hemoglobin, 17.9 g/dL; hematocrit, 50.8%) with 9% nucleated red blood cells. The corrected white blood cell count was elevated to 20 100 $\times$ $10^3/\mu L$ with an age appropriate differential (31% neutrophils, 60% lymphocytes, 6% monocytes, 2% eosinophils, and 1% basophils). The platelet count was decreased at birth (90 000 $\times$ $10^3/\mu L$) and remained below 110 000 $\times$ $10^3/\mu L$ during the 7-day hospital admission. Twin B also had normal red blood cell indices (hemoglobin, 16.0 g/dL; hematocrit, 46.9%) with 6% nucleated red blood cells. The corrected white blood cell count for twin B was 16 100 $\times$ $10^3/\mu L$ with a normal differential (33% neutrophils, 54% lymphocytes, 10% monocytes, and 3% eosinophils). Twin B also exhibited thrombocytopenia at birth (platelets, 82 000 $\times$ $10^3/\mu L$) and never exceeded a platelet count of 98 000 $\times$ $10^3/\mu L$ during her 5-day admission. Hematopathology department consultation was requested on the third day of life for thrombocytopenia in both twins.

Examination of the peripheral blood smear confirmed the presence of thrombocytopenia with obvious large and giant platelet forms (Figure 1). In addition, single blue-gray cytoplasmic inclusions (arrows) were identified in the neutrophils of twin A (Figure 2, A) and twin B (Figure 2, B). Inclusions were not seen in other granulocytes. Toxic granulations were notably absent in the neutrophils. No red blood cell abnormalities were noted. The findings of thrombocytopenia, giant platelets, and neutrophil inclusions were seen in the peripheral blood smears from both twin A and twin B.

Clinically, the twins were asymptomatic and required treatment only for mild hyperbilirubinemia. Congenital malformations or abnormalities were not identified in either twin. Further questioning of the family history revealed that the patients' father and 2 paternal uncles had similar hematologic abnormalities.

What is your diagnosis?



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Pathologic Diagnosis: May-Hegglin Anomaly

May-Hegglin anomaly is a rare autosomal dominant disorder characterized by macrothrombocytopenia and the presence of Döhle-like inclusions in the white cells.[1,2] It is classically an isolated hereditary disorder. However, patients with concomitant congenital abnormalities have also been described. To the best of our knowledge, this is the first case report of May-Hegglin anomaly occurring in twins.

The granulocyte inclusions observed in May-Hegglin anomaly are typically seen as blue-gray, spindle-shaped bodies on light microscopy. Ultrastructurally, these Döhle-like bodies are shown to contain ribosomes and 10-nm filaments running along the long axis of the body.[3] This is in contrast to the Döhle bodies found in patients with reactive changes due to sepsis. In such cases, the Döhle bodies are composed of parallel strands of rough endoplasmic reticulum.

Genetic studies conducted on individuals with May-Hegglin anomaly have shown mutations in the *MYH9* gene located in chromosome 22q11.2. This gene codes for the nonmuscle myosin heavy chain IIA (MHCIIA).[4] Different types of mutations in the *MYH9* gene result in distinct phenotypic syndromes, which are allelic variants. This group of diseases is referred to as *MYH9*-related disorders or MHCIIA syndromes.

The *MYH9*-related disorders are a group of autosomal dominant disorders, which include May-Hegglin anomaly and Sebastian, Fechtner, and Epstein syndromes. At birth almost all are affected by platelet macrocytosis, thrombocytopenia, and leukocyte inclusion bodies. These inclusions are observed in 25% to 75% of circulating neutrophils. Other granulocytes, basophils, and eosinophils, as well as monocytes, may also exhibit similar inclusions. The usual number of inclusions is 1, although cells with more than 1 inclusion may be present. Interestingly, in Epstein syndrome, Döhle-like inclusions are typically absent.

In individuals with *MYH9*-related disorders, nonmuscle MHCIIA is distributed only within the inclusions, whereas it is uniformly distributed in normal cells.[5] In May-Hegglin anomaly the leukocyte inclusion is characterized as type 1, whereas in Sebastian and Fechtner syndromes the inclusions are type 2. In type 1 inclusions, the ribosomes are aligned along parallel filaments, and in type 2 the ribosomes are randomly distributed along highly dispersed filaments.[6]

In *MYH9*-related disorders, thrombocytopenia is due to ineffective thrombopoiesis and splenectomy fails to improve the platelet count. Platelets are increased in size. The basic defect of platelets in *MYH9*-related disorders is related to abnormality of the cytoskeleton. It is thought that the platelets are functionally abnormal. However, platelet aggregation and release reactions tested in vitro are usually normal. It has also been documented that the largest platelets have a significant reduction in GPIb/IX/V.[7]

Bleeding diathesis, hearing loss, renal involvement, and cataracts are, in descending order of frequency, the clinical features of *MYH9*-related disorders. Bleeding diathesis usually tends to be mild. However, life-threatening hemorrhages have been reported. Features of bleeding typically present in infancy, and severity does not change in later life. Kidney, hearing, and visual defects may appear in infancy or much later in adult life.

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