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The Role of Microscopy in the Classification of Macrothrombocytopenia

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Thrombocytopenia is a bleeding diathesis related to abnormally decreased platelet numbers (<150,000/ml) in the peripheral blood. The disorder has numerous etiologies, both acquired and congenital, including chronic blood loss, infections, chemotherapy, autoimmune conditions, genetic defects/mutations as well as unknown causes. It has been reported that at least 95% of all thrombocytopenia in both the pediatric and adult patient are due to an autoimmune process or drug-induced with most of these conditions presenting with small or normal sized platelets [1]. Thus, macrothrombocytopenia is a rare condition and is thought to be due to congenital defects with autosomal dominant inheritance. It that can readily be diagnosed by obtaining a routine complete blood count (CBC), including determination of the mean platelet volume (MPV), and evaluation of a peripheral blood smear (Fig. 1) but diagnosing the specific basis of this condition is not so simple. Macrothrombocytes are large platelets (ranging ~5-20μ) and the observation of abnormally large platelets (Fig. 2) in a patient with decreased numbers of circulating platelets defines the diagnosis. The "normal" platelet is approximately 1.5-2.5μ in greatest dimension and is discoid in shape. The normal range of circulating platelets is generally accepted to be 150-400,000/ml. The severity of thrombocytopenia may also be categorized as mild, moderate, or severe and often the platelets are normal sized, even smaller than normal.

There are at least 15-20 disorders including variations of specific classifications of macrothrombocytopenia that have been reported in the literature. A number of these can be classified by using clinical laboratory tests including flow cytometry to evaluate platelet surface receptors. The classic macrothrombocytopenic disorder, Bernard-Soulier Syndrome, is a condition characterized by a deficiency of the platelet receptor Ibα/Ibβ/IX/V which is the surface receptor for von Willebrands factor mediated aggregation [2]. A number of conditions that have been described with Döhle body leukocyte inclusions observed by light microscopic examination of peripheral blood smears including May-Hegglin Anomaly and Fechtner, Sebastian, Epstein, and Alport-like Syndromes have recently been shown to have a common mutation of the nonmuscle myosin heavy chain 9 gene (MYH9) [3]. Although these syndromes had been characterized as different disorders, principally by clinical features, it should not be surprising that the microscopic visualization of Döhle body inclusions in leukocytes (cytoplasmic "blue" bodies by light microscopy and paracrystalline inclusions by electron microscopy) might be a key predictor of a common inherited etiology.

The use of electron microscopy is still essential for classifying macrothrombocytopenia in conditions that manifest with specific abnormalities affecting organelles such as the alpha granule in Medich giant platelet disorder and White platelet disorder [4]. Another condition in which electron microscopy is essential to make a diagnosis is Swiss Cheese Giant Platelet Syndrome in which a highly dilated open canalicular system and the absence of the circumferential band of microtubules render the platelets with a "Swiss cheese" appearance (Fig. 3). The Swiss Cheese Giant Platelet Syndrome is thought to be congenital causing a defect of calcium mobilization in the platelet. There are other presentations of abnormal platelet morphologies in macrothrombocytopenia that have yet

to be defined (Fig. 4). This presentation will review macrothrombocytopenia in general with emphasis upon characteristic microscopic features that can be useful for accurately diagnosing these disorders.

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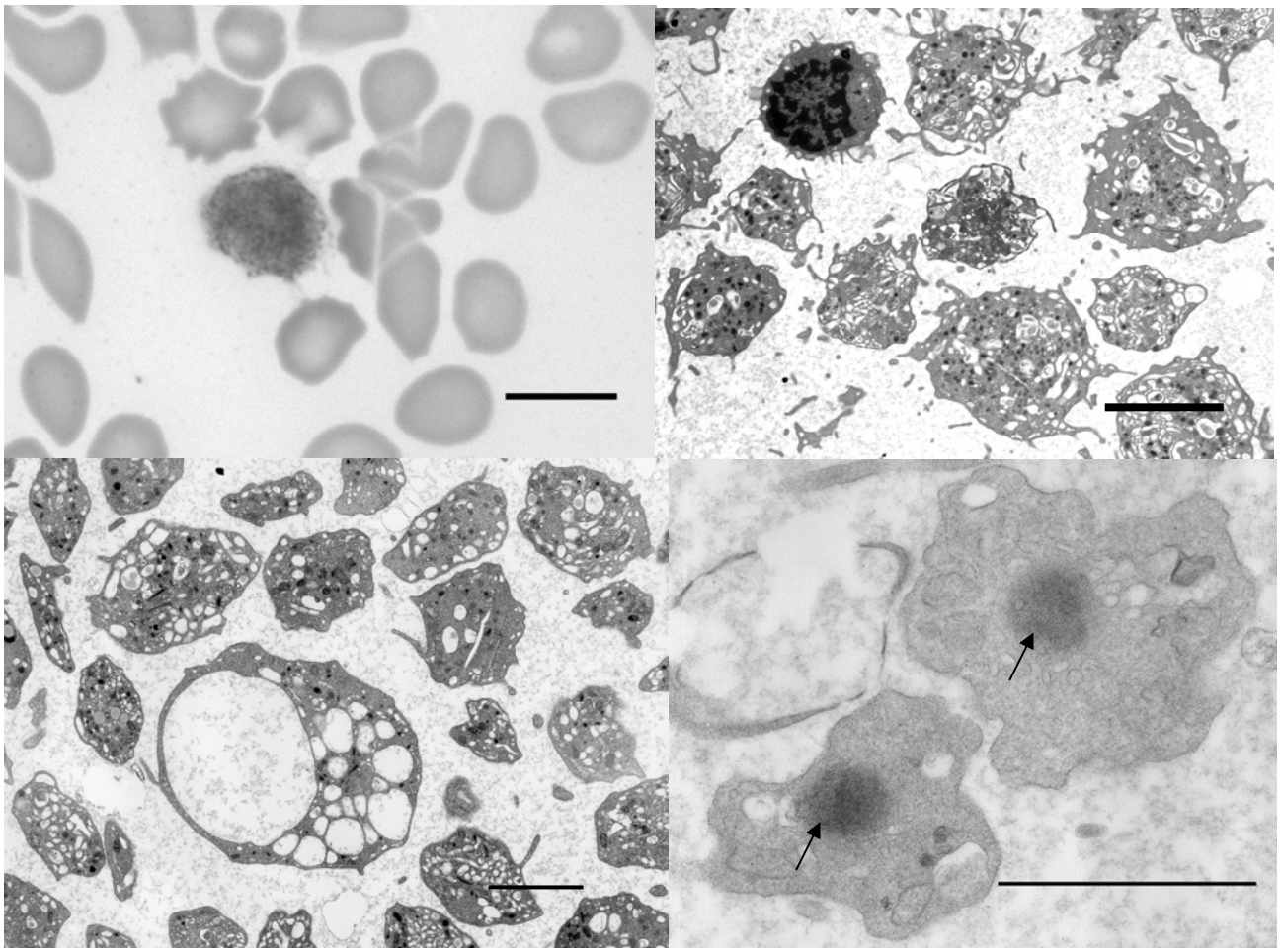

Fig. 1. This peripheral blood smear demonstrates unusually large platelets that in some cases are larger than white blood cells. Bar = 10μ

Fig. 2. This electron photomicrograph demonstrates large platelets in a buffy coat sample of peripheral blood (same as Fig 1). Platelets measure approximately 12-15μ in this field. Bar = 10μ

Fig. 3. The vacuolated platelet in this panel represents a disorder called "Swiss-Cheese" Macrothrombocytopenia Syndrome due to the extensive vacuolation of the giant platelets. Bar = 10μ

Fig. 4. The giant platelets in this photograph have a very large tangle of intermediate filaments (arrow) that are centrally located within the cell and are devoid of alpha granules. At the present time, the patient from which this sample was obtained has yet to be classified. Bar = 10μ

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