LECCIÓN
CONMEMORATIVA
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Introduction

Blood cell enumeration and differentiation have steadily become more automated. As a result there is less and less need for visual evaluation to report final results. There are problems, however, and thrombocytopenia is a case in point. Patients with giant platelet disorders (GPDs) are almost always thrombocytopenic, even though most individuals have a normal platelet mass in their circulating blood. The giant platelets are often larger than red blood cells and approach the volume of leukocytes. They are screened from the platelet count by gating techniques. Thus, the automated count may be considerably lower than the total number of platelets actually is. This is a clear signal to look at the peripheral blood smear, but may not always be done. Failure to recognize that the patient has a GPD, rather than just a low platelet count, may lead to misdiagnosis and inappropriate treatment.

Benign Giant Platelet Disorders

Mediterranean Macrothrombocytopenia

The GPDs represent a diverse group of conditions. Many are associated with abnormalities of other blood cells, physical conditions or syndromes. Seldom do we observe individuals in whom the only finding is enlarged platelets and thrombocytopenia. The closest is Mediterranean Macrothrombocytopenia (MMT). This disorder is found in high frequency among individuals from Greece, Italy and the Balkan peninsula. Despite the prevalence in these nations, MMT is rarely reported in individuals with a similar ethnic background living in other countries, such as the United States.

Pathological Platelet Disorders

Disorders with giant abnormal platelets are rare, but can be very serious.

Bernard Soulier Syndrome (BSS)

BSS is an autosomal, recessively inherited GPD described by Drs. Bernard and Soulier in 1948. Hemorrhagic symptoms are often severe, though they vary from patient to patient. Characteristic features include giant platelets (fig. 1) thrombocytopenia, prolonged bleeding times, serious morbidity and occasional mortality. BSS giant platelets are deficient in the surface membrane GPIb-IX-V complex which is the receptor for von Willebrand factor (vWF). As a result, they fail to adhere to vWF bound to collagen at the site of vascular injury. The GPIb portion of the GPIb-IX-V complex is also one of the thrombin receptors on platelets. Its absence reduces the giant platelet response to thrombin, and contributes to their failure to form hemostatic plugs that staunch prolonged bleeding.

Familial Macrothrombocytopenia with GPIV Abnormality

The disorder is rare. It has been described in just two families. Only one family had bleeding symptoms, though prolonged bleeding times were present in both. The giant platelets were deficient in GPIV, a receptor for collagen. However, deficiency of GPIV on normal sized platelets from other individuals is not associated with clinical bleeding. Deficiency of
other receptors on the giant platelets, together with decreased GPIV, could lead to bleeding, but such a combination has not been reported.

Montreal Platelet Syndrome (MPS)

MPS is a GPD found in three generations of a Canadian family, and appears to be inherited as an autosomal dominant condition. Characteristic features include giant platelets, profound thrombocytopenia, spontaneous platelet aggregation and prolonged bleeding times. Hemorrhagic symptoms are common. The large platelets from these patients undergo a hypervolumetric shape change when activated. This was believed to be due to excessive development of the open canalicular system (OCS) in their platelets. Ultrastructural studies, however, have suggested that the OCS in their large platelets is within normal limits. Thus the basis for hypervolumetric shape change remains unknown.

Giant Platelet Disorders associated with other blood cell abnormalities

GPD associated with other conditions are unassociated with excessive bleeding except in rare instances. Most are associated with other disorders having neutrophil inclusions and/or Alport’s syndrome.

May Hegglin Anomaly (MHA)

The disorder was originally reported by May in an asymptomatic patient with large neutrophil inclusions, and many years later by Hegglin in individuals with neutrophil inclusions, giant platelets (fig. 2) and thrombocytopenia. Hemorrhagic symptoms, if present at all, are limited to epistaxis and/or easy bruising. The most striking feature, besides giant platelets, are the neutrophil inclusions (fig. 3). Originally they were thought to be Dohle bodies which develop in the neutrophils of patients with long-term, severe infectious diseases. However, Dohle bodies are masses of rough endoplasmic reticulum (RER) that appear basophilic on Wright stained blood smears. MHA bodies are spindle shaped and maintained in that form by bundles of parallel-associated, intermediate filaments studded with clusters of ribosomes. The inclusions are basophilic and lie free in the cytoplasm of neutrophils and other granulocytes in circulating blood. They are not enclosed by membranes. Segments of RER lie nearby, but are not part of the structure. Patients with MHA are more common than other GPD.

Fechtner Platelet Syndrome (FPS), Sebastian Platelet Syndrome (SPS) and Sebastian Platelet Syndrome Variant (SPSV)

Three other giant platelet disorders also have neutrophil inclusions. Inclusions in polymorphonuclear leukocytes (PMN) of patients with FPS and SPS are identical (fig. 4). They are roughly spherical in form, and contain randomly dispersed intermediate filaments and single ribosomes or clusters. Segments of RER are often nearby, but the inclusions are not enclosed by membranes. Inclusions in neutrophils of patients with SPSV are different from those in PMN from individuals with FPS and SPS (fig. 5). They are rod-like in configuration or shaped like the letter “L”. Occasionally they appear spindle shaped, but do not resemble the inclusions found in PMN of patients with the MHA. The distinguishing feature of SPSV neutrophil inclusion is the presence of irregular cross strations produced by fragments of smooth endoplasmic reticulum (SER) studded with glycogen particles. Some of the inclusions are roughly spherical in form and are compartmentalized by segments of
SER studded with particles of glycogen. Patients with FPS also have Alport’s syndrome. This distinguishes them from those with SPS and SPSV who do not have features characteristic of Alport’s syndrome\textsuperscript{13}. Giant platelets in all three conditions are essentially the same. Except for their large size they are morphologically and functionally normal. The patients are thrombocytopenic but seldom have serious bleeding problems.

**Giant Platelets with Alport’s Syndrome**

**Epstein Syndrome (ES)**

Epstein Syndrome\textsuperscript{14} is another giant platelet disorder associated with Alport’s syndrome\textsuperscript{13}. The kidney disease may require renal transplantation. The giant platelets in the patients described by Epstein et al\textsuperscript{14} were reported to have defective responses to aggregating agents (fig. 6). A later report by Eckstein et al\textsuperscript{15} indicated the giant platelets in similar patients were functionally normal, and that has been the experience of others as well. Some individuals with ES, however, may have mild bleeding problems. The hemorrhagic symptoms are not of sufficient severity to prevent aggressive management of the renal disease.

**Giant Abnormal Platelet Disorder’s**

In some GPD the large platelets are morphologically abnormal, but white blood cells are normal. The best example of this is the Gray Platelet Syndrome.

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**Figure 4. Fechtner Platelet Syndrome (FPS) and Sebastian Platelet Syndrome (SPS).** Inclusions (I) in the polymorphonuclear leukocytes (PMN) of patients with FPS and SPS are essentially identical in appearance. They appear blue on Wright stained blood smear, but are not as intensely stained as MHA inclusions. Instead of a spindle shape the FPS-SPS inclusions are relatively spherical in form. Clusters of ribosomes and a few loosely organized intermediate filaments lie in an otherwise featureless matrix. The organelles are not enclosed by membranes, though segments of RER and smooth endoplasmic reticulum (SER) are often found nearby. Mag × 21,000.

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**Figure 5. Sebastian Platelet Syndrome (SPSV).** Inclusion in PMN from patients with the variant of SPS are usually rod or “L” shaped, though spherical forms have been identified. The striking feature of this inclusion are the frequent cross striations caused by fragments of SER studded with glycogen particles (↑). In all other respects the inclusions in SPSV neutrophils are the same as those in FPS and SPS PMN. Mag × 21,000.

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**Figure 6. Fechtner Platelet Syndrome (FPS).** Platelets from patients with FPS, as shown here, are essentially identical to those from individuals with SPS and SPSV. Mag × 11,000.

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**Gray Platelet Syndrome (GPS)**

The original patient with GPS was described by Raccuglia in 1971\textsuperscript{16}. He was evaluated for thrombocytopenia as a child and a splenectomy was carried out. However, the patient remained thrombocytopenic and was referred to Dr. Raccuglia for evaluation. His platelets were very large and on Wrights stained blood smears appeared almost devoid of granules (figs. 7, 8). This yielded a grayish appearance to the cells and, hence, the name: “Gray Platelet Syndrome” was coined. Many patients with GPS have subsequently been reported\textsuperscript{17}. The individuals have few bleeding symptoms, and are able to undergo major surgery without platelet transfusions. The giant platelets examined in the electron micro-
of those chosen. GPD such as the Enyeart anomaly, the Medich Giant Inclusion Disorder and acquired GPD have been discussed elsewhere\textsuperscript{1,12} or must await a later report\textsuperscript{19}. This presentation has emphasized the ultrastructural findings obtained in our laboratory, but did not mean to ignore the rapid developments coming from genetic analysis.

Recently, the genetic defects of the giant platelet syndromes: MHA, FPS, SPS and Epstein anomaly have been mapped to chromosome 22q11-13\textsuperscript{20-25}. Within this region the gene encoding nonmuscular myosin heavy chain-A (MYH9) is located. At present, nine different mutations have been found among patients with giant platelet syndromes\textsuperscript{25-28}.

For FPS two different mutations have been found. One of the mutations, R702C, is located close to the mutation found in patients with nonsyndromic hereditary deafness, R705H\textsuperscript{29}, which strongly links this region of nonmuscle myosin to a hearing dysfunction. The second mutation found in a FPS patient, D1424H, is also present in a family diagnosed with MHA/SPS, suggesting the need for a more stringent family characterization, and the necessity for a thorough phenotyping.

Presently, MHA and SPS are often linked as a collective diagnosis. However, the eight identified non-muscle myosin mutations may help to distinguish between MHA and SPS, as can be done at present only with the electron microscope. An interesting hypothesis is that different mutations in the MYH9 gene or other genes closely located on chromosome 22q11-13, e.g., fibulin 1D\textsuperscript{30} are responsible for the different morphologies of granulocyte inclusion bodies and for the different clinical presentations of these syndromes. Clearly genetic analysis of GPD is bearing fruit and will someday provide critical information for understanding the pathogenesis of these fascinating conditions.

References


