



Sticky platelet syndrome and thrombocythemia

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Platelets play an important role in hemostasis, thrombosis, and atherosclerosis. Most of our understanding of platelets is based on their function in hemostasis, as it relates to quantitative and qualitative bleeding disorders. In hemostasis, platelets perform two major functions. First, because of their ability to adhere and aggregate at sites of endothelial injury, they facilitate the initial arrest of bleeding, also called primary hemostasis. Second, on “activation” at the site of vessel injury, they provide the surfaces onto which the factors of the coagulation system can be bound, thus keeping clot formation localized. The physiology and biochemistry of platelets has been the subject of extensive reviews [1–4] and will not be discussed in this context.

Although the pathophysiology of the role of platelets in bleeding disorders is reasonably well understood, less is known about the involvement of platelets in thrombosis and atherosclerosis, though more patients have the latter than have bleeding problems. “Discovery of such abnormalities is the challenge of the future in platelet research” [2].

The role of platelets in the pathogenesis of arterial thrombosis in particular is relatively well known. Most arterial thrombotic events reside in clot formation at sites of atherosclerotic lesions, though other vascular diseases can also be involved. Ruptures at the base of the atherosclerotic plaques appear to precipitate thrombus formation [5,6]. As in normal hemostasis, platelets will adhere to exposed collagen fibers, aggregate, and initiate, together with tissue factor (TF), the activation of the coagulation system [7]. This leads to thrombus formation with temporary or permanent vascular occlusion. Atherosclerosis is the most prevalent reason for the development of acute myocardial infarction (AMI),

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angina pectoris, transient ischemic attack (TIA), acute cerebral ischemic insult (stroke), and transient or permanent peripheral arterial thrombotic occlusion.

Arterial thromboses are, however, also found in patients with no identifiable vascular lesions, and it is unclear at this time whether disturbances in the physiological antithrombotic posture of endothelial cell surfaces may contribute to thrombus formation [8]. Endothelial cells regulate platelet function, coagulation, and fibrinolysis through either cell surface located receptors or through the release of substances with anticoagulatory properties [9]. It is conceivable that disturbances in any of these regulatory mechanisms could lead to local activation of the hemostasis system with arterial or venous thrombosis.

It is known that a number of acquired or congenital dysregulations of the hemostasis system are associated with a higher risk for thromboembolic events. In addition, these hypercoagulable or prothrombotic conditions have been extensively reviewed [10–12].

Hyperaggregable platelets

Hyperaggregable platelets and their role in thrombogenesis are not well known at this time. Although abnormalities in the coagulation system associated with hypercoagulability have been studied extensively, little is published on “hyperactive” platelets, and what is documented is subject to controversy, apart from the fact that such conditions could be expected. The controversy and lack of information reside to a great extent in methodological problems assessing platelet function. There is as yet no screening test for hyperfunctioning, platelets and most test results published were obtained by platelet aggregometry. Platelet aggregometry, in platelet-rich plasma or in whole blood, is cumbersome, time consuming, and difficult to standardize. Quality control is difficult to perform. Moreover, platelet aggregation technologies were designed to assess platelet defects leading to bleeding and not to thromboses. Some technological improvements have been made [13], and flow cytometry has clearly added a new perspective with which information on hyperfunctioning platelets can potentially be obtained.

In spite of these problems, hyperaggregable platelets have been described with various techniques in association with several disease entities. Patients with diabetes mellitus appear to have hyperaggregable platelets [14–18] that are possibly linked to the diabetic vascular complications. Other conditions with hyperaggregable platelets are unstable angina and atrial fibrillation [19,20], thrombotic strokes [21], migraine headaches [22], anorexia nervosa [23], mitral valve prolapse [7], retinal artery occlusions [24], preeclampsia [25], arterial thromboembolism [26], and nephrotic syndrome [27]. In addition, some patients in intensive care units have been described with hyperaggregable platelets [28]. In some of these reports, platelet release proteins, such as β -thromboglobulin, platelet factor 4, and thromboxane A_2 , were also documented. Levels were frequently elevated, suggesting that in these patients' the platelets were activated

in vivo. It is difficult to establish whether platelet activation occurred as a consequence of underlying disease (thrombotic strokes, arterial thromboembolism) or whether platelet activation contributed to or caused the problems. There are, however, patients with hyperaggregable platelets whose platelet release protein levels are not elevated. In this context, reports on hyperaggregable platelets in response to stress or adrenaline release are of particular interest [29,30]. This also may be related to the well-recognized circadian variation in platelet function and its association with increased risk for myocardial infarctions [4,31,32].

Reports on an association between congenital platelet abnormalities and thromboembolic disorders are scarce, though they should be expected to exist. One report described defects in the prostaglandin pathway in relatively young patients who had no other risk factors but experienced thromboses, especially arterial [33]. These patients also did not have elevated platelet release protein levels. We have described a congenital platelet abnormality that was termed sticky platelet syndrome [34,35].

Sticky platelet syndrome

Sticky plate syndrome (SPS) was detected in 1982 in a then 24-year-old woman who had an acute myocardial infarction (AMI) while 7 months' pregnant. Coronary angiography revealed no evidence of atherosclerotic lesions. Her mother had an AMI during one of her pregnancies, and a brother, then 18 years old, had angina pectoris attacks without identifiable coronary artery disease; her father and a sister had no clinical symptoms. All factors of the hypercoagulability panel known at that time were normal. On platelet aggregometry in platelet-rich plasma, a high response (100%) was noted with adenosine diphosphate (ADP) and epinephrine as agonists; responses to thrombin, collagen, arachidonic acid, and ristocetin appeared normal. On dilution of the agonists, as described before [34,35], the patient's platelets aggregated to the fullest extent (Fig. 1), whereas platelets from healthy volunteers gave the expected dose-response patterns (Fig. 2). Identical aggregation patterns were found in the mother and brother, but not in the father and sister. We then studied the behavior of the patient's platelets in response to surface contact through a technique that uses electron microscopy [36]. The patient's platelets and her mother's and brother's platelets were hyperadhesive and hyperaggregable. Assays for platelet factor 4 and β -thromboglobulin were repeatedly normal. After treatment of these family members with aspirin (81 mg/day), the aggregation patterns became normal, but they became abnormal again when aspirin therapy was discontinued.

We concluded at that time that these patients had hyperaggregable platelets when challenged with ADP and epinephrine and had hyperadhesive and hyperaggregable platelets in response to surface contact but that the platelets appeared not to be circulating in an activated form. Moreover, we suspected that the problem was familial and potentially linked to the AMI experienced.

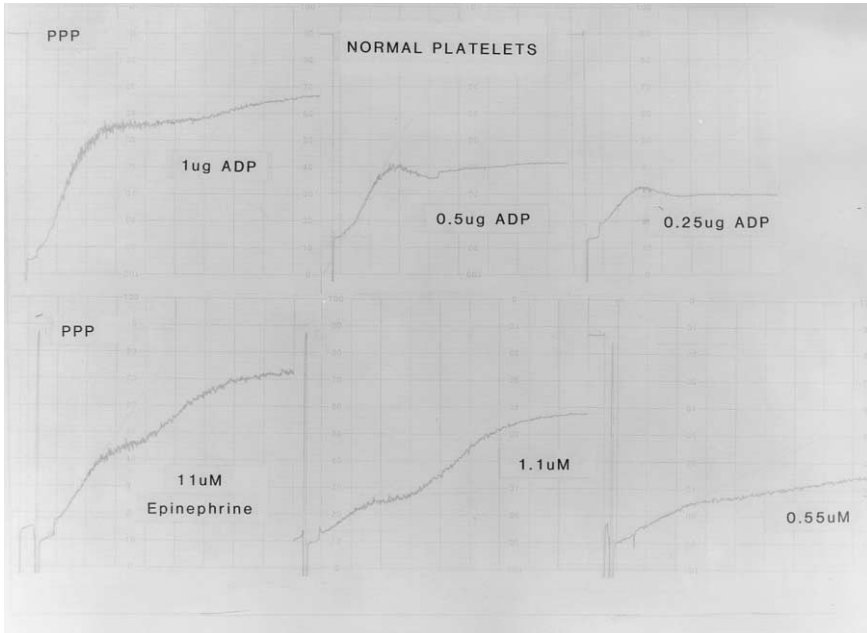


Fig. 1. Platelet aggregation patterns of a patient with type 1 SPS in response to different concentrations of ADP and epinephrine. Note the maximum aggregation response with all dilutions of the agonists. (From Mammen EF. Ten years' experience with the "sticky platelet syndrome." *Clin Appl Thromb Hemost* 1995;1:66–72; with permission.)

We next embarked on a study of other patients with AMI or angina pectoris but with angiographically normal coronary arteries. This patient group was compared with an age-, sex-, and ethnic origin-matched group of volunteers. The data revealed significant ($P < 0.001$) differences in aggregation patterns with ADP and epinephrine and equally significant differences in electron microscopic evaluation [37].

In cooperation with neurologists, we studied patients younger than 45 years of age who had had thrombotic strokes or TIAs [38]. They had no identifiable risk factors, and other factors known to be associated with hypercoagulability were normal. The same aggregation and electron microscopic patterns were seen, and a number of family members were tested on whom we could establish an autosomal dominant inheritance pattern.

A third study involving patients with idiopathic ischemic optic neuropathy, who had temporary or permanent vision loss, usually in one eye, was conducted. Again age-, sex-, and ethnic origin-matched volunteers were studied for comparison. Patients had significantly ($P < 0.0001$) higher aggregation patterns and responses to surface contact [34,39].

In the subsequent years we found well more than 200 patients with this syndrome, including children who had thrombotic strokes. Two patterns of the

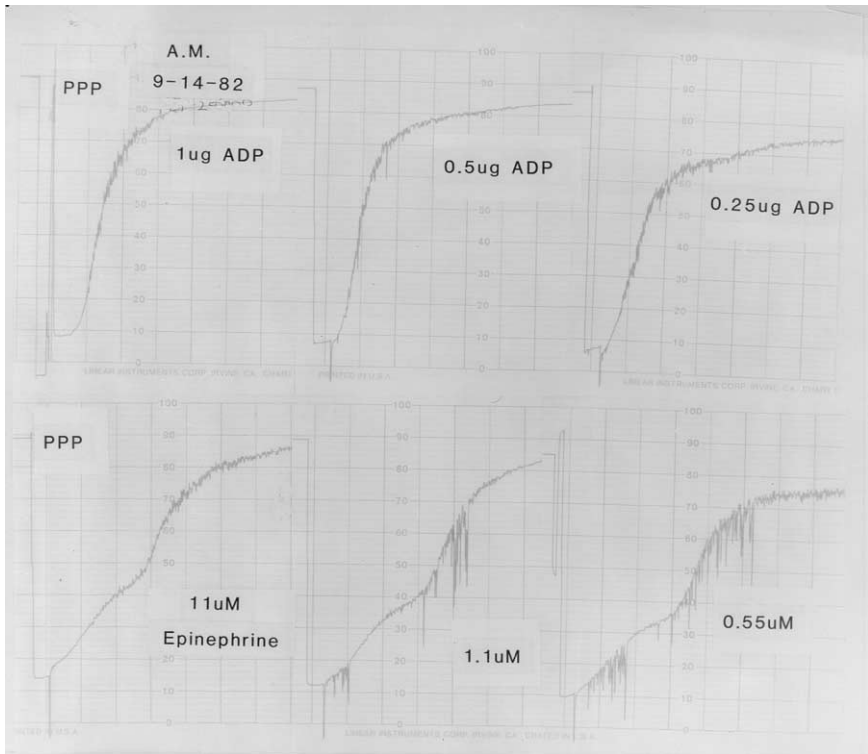


Fig. 2. Platelet aggregation patterns of a healthy volunteer in response to different concentrations of ADP and epinephrine. Note the dose-response with the dilutions of the agonists. (From Mammen EF. Ten years' experience with the "sticky platelet syndrome." Clin Appl Thromb Hemost 1995;1:66–72; with permission.

syndrome evolved, one in which platelets are hyperaggregable with ADP and epinephrine (termed type 1) and one in which platelets are hyperaggregable only with epinephrine (termed type 2). Most of the patients encountered arterial thromboembolic events, frequently triggered by stressful situations. Few patients with venous thrombosis who had recurrences while on oral anticoagulants had SPS. Laboratory studies were performed by several technologists using different aggregometers to exclude artifacts. Blood was drawn by one person only (E.F.M.). All patients were placed on aspirin treatment (81 mg/day), and most then became asymptomatic, both clinically and according to laboratory results. When patients decided not to take the aspirin, their aggregation again patterns became abnormal. All these experiences have been summarized in great detail [34]. In our experience as a reference laboratory and compared with other factors of the hypercoagulability panel, SPS appears to be prominent. Technical aspects obviously make general population studies impossible.

We are well aware of the technical difficulties with platelet aggregometry and have taken every precaution to rule out artifacts. We have used different

aggregometers, different technologists have performed the assays, and normal ranges were established for each agonist so that actual measurements of peak levels can be obtained. These procedures have to be followed by every laboratory that adopts our technology.

We assume that in patients with SPS, platelets aggregate *in vivo* in response to various stimuli, most notably stress. Small platelet aggregates may occlude vessels of similar size vessels. If the aggregates disperse spontaneously, TIAs result, especially in the coronary and cerebral circulations. If the aggregates do not disperse, permanent vascular occlusions ensue. We do not know at this time what actually facilitates hyperaggregability, but we assume the involvement of receptors on the surface of platelet membranes.

In the last few years other investigators, using our technique, have identified patients with the SPS. In one report [40], 153 patients with thromboses were studied over a 2-year period. Of these 21% had SPS and arterial forms of thrombosis (AMI, TIA, strokes, retinal thrombosis, peripheral arterial occlusions). Another 13.2% with SPS had venous thromboses. In this study a type 3I SPS was found—hyperaggregable platelets with only ADP. In the experience of that author, SPS was the second most common laboratory defect in patients with hypercoagulability, slightly less than activated protein C resistance (APC-R).

Another report [41] described 195 patients with hypercoagulability, of which 28% had SPS (15% APC-R). Eighteen of the patients had SPS and other congenital defects predisposing to thromboses.

In addition, case reports have been published in which SPS was identified in patients with thromboembolic disorders. One report describes two patients with cerebral thromboses and SPS [42], and another describes a patient who experienced bilateral strokes and had not only SPS but also protein S deficiency and homozygous APC-R [43].

Another article [44] described a patient with superior sagittal vein thrombosis and SPS but also reviewed the literature on this subject. The association of emotional stress and clinical events was highlighted.

Thrombocytosis and thrombocythemia

Thrombohemorrhagic clinical events have classically been related to increased platelet counts. The failure to consistently correlate specific increased numbers to a defined clinical risk has led to attempts to characterize the basis for such counts. We can now separate patients with elevated counts into three clinical categories: pseudothrombocytosis, reactive thrombocytosis, and thrombocythemia.

The term “pseudothrombocytosis” is now applied to an artifact of electronic counting wherein patients with any form of cryoglobulinemia may have their circulating protein precipitates misidentified as platelet-sized particles. Examination of a peripheral blood smear will correct this error. As expected, recognition of thrombohemorrhagic events in such patients does not correlate with the recognition or enumeration of such precipitates [45].

Thrombocytosis, commonly termed “reactive thrombocytosis,” defines patients with increased platelet counts who have an underlying clinical state that is commonly associated with such an increment [46]. Such circumstances are shown in Box 1.

In general, reactive thrombocytosis has not been associated with an increased incidence or risk for thrombohemorrhagic events, except in the presence of an underlying hematopoietic disease with prothrombotic features, clinically significant preexisting arterial lesions, or prolonged immobility [45,46].

The term “thrombocythemia” is applied to myeloproliferative states (eg, polycythemia vera, idiopathic myeloprolifibrosis, chronic myelogenous leukemia, and essential thrombocythemia) in which there is an autonomous drive to platelet production resulting in elevated platelet numbers. These lesions are the

Box 1. Clinical circumstances associated with thrombocytosis (reactive thrombocytosis)

- I. Acute and transient:
 - a. Persisting minutes to hours:
 1. Epinephrine
 2. Exercise
 - b. Persisting hours to a few days:
 1. Acute blood loss
 2. Recovery from acute infection
 3. Post (Rebound) thrombocytopenia:
 - a. Post-immune
 - b. Post-cytoreductive chemotherapy (esp. Methotrexate and Vinca Agents)
 - c. Post megaloblastic anemia
 - d. Post-alcohol associated thrombocytopenia
- II. Chronic:
 - a. Persisting for a significant duration:
 1. Chronic blood loss with iron deficiency
 2. Chronic inflammatory disease
 3. Chronic infectious disease
 4. Cancer
 5. Hemolytic anemia
 - b. Potentially life-long: post splenectomy (auto or surgical)

(From Rubenfire M, Blevins RD, Barnhart MI, et al. Platelet hyperaggregability in patients with chest pain and angiographically normal coronary arteries. *Am J Cardiol* 1986;57:657–60; with permission.)

result of clonal expansion of a multipotential stem cell and are noteworthy for transitions from one form to another during their clinical course [47]. The exact mechanisms for the specific lineage expression, amplification, and proliferation for each form, except chronic myelogenous leukemia, are still unclear.

Essential (primary) thrombocythemia

Thrombohemorrhagic events are the clinical hallmark of essential (primary) thrombocythemia (ET), the term commonly applied to these clonal lesions of megakaryocyte precursors in the United States and recently termed “thrombocythemia vera” in Europe [48].

Pathophysiology of thrombosis in ET

Thrombosis is a more common clinical event than bleeding in ET. The pathophysiologic mechanisms in thrombocythemia have been extensively explored, because thrombosis is an uncommon event in reactive thrombocytosis, suggesting that platelet numbers alone are not its basis. Although uncontrolled platelet counts are a risk factor for thrombosis [49–52], Regev et al [53] have shown that 70% of their patients had vascular symptoms or findings at platelet counts of less than 600,000/ μ L and that 50% had them at counts of less than 500,000/ μ L.

Alterations of platelet and megakaryocyte architecture with large abnormal platelet forms in the circulation are seen in ET. Nevertheless, studies have failed to relate these structural changes to an increased risk for thrombosis [45,54–57]. Similarly, studies of platelet function have largely failed to define correlative abnormalities that could be used to define the risk for thrombosis, until the recent application of whole blood lumiaggregometry, which identified significant in vitro platelet hyperactivity in patients with ET and a history of thrombosis [58]. This use of whole blood contrasts with conventional optical platelet aggregometry, which best defines platelet hypoactivity. Earlier evidence of platelet–endothelial interaction [59] and increased platelet factor 4 and β -thromboglobulin levels provide further support for excessive platelet activation in ET as an important mechanism for increased thrombosis [59–62]. Other attempts to examine endothelial-related parameters, such as homocysteine levels, have failed to show a relationship [63], though a recent derivation of a cell line from a patient with ET has demonstrated combined hematopoietic and endothelial features, indicating a close ontogenetic relationship between these lineages [47].

Diagnostic criteria of ET

The clinical-laboratory feature of ET is the recognition of an elevated platelet count. Therefore, the initial clinical consideration must ascertain that true

thrombocytopenia is present. The diagnostic criteria for primary thrombocytopenia have slowly evolved and continue to be refined as new biologic data have become available. The Polycythemia Vera Study Group (PVSG) developed criteria in 1975 that used platelet counts greater than 1 million per microliter as the essential diagnostic parameter [64–66]. As the disease process became better understood and the sometimes subtle thrombotic features were recognized, the specific criteria of a given platelet number was progressively modified downward, and the correlate clinical findings were better defined [45,56, 67–70,72,76].

Box 2 provides our current diagnostic criteria [45]. These are similar to the European criteria [71] and appropriately reflect the clinical view that an elevated platelet count is abnormal. Spontaneous megakaryocyte colony formation, a criterion enthusiastically endorsed in Europe [48], is infrequently evaluated in the United States and is associated with complex laboratory requirements.

Because differential diagnostic confusion does relate to those cases of thrombocytopenia associated with a myelodysplastic or other myeloproliferative state, these lesions must be eliminated from the diagnostic consideration by appropriate evaluation. Morphologic examination of the peripheral blood and bone marrow material has confirmed architectural changes that help define the disease. Abnormal platelet architecture and function are usually seen in the peripheral blood. Increased mature, often hyperploid, megakaryocytes are seen in the marrow. In the absence of a significant increase in fibrosis or proliferative erythroid or myeloid responses, these changes serve to add a diagnostic parameter. Evaluation of leukocyte alkaline phosphatase activity and the erythrocyte sedimentation rate, used by our European colleagues, have largely disappeared from clinical practice in the United States given that these are nonspecific parameters.

Box 2. Diagnostic criteria for primary (essential) thrombocytopenia)

Platelet count greater than 450,000 μL (confirmed on more than one occasion)

Absence of an identifiable cause for the increased platelet counts

Absence of a myelodysplastic syndrome or other myeloproliferative state

Bone marrow with:

Megakaryocytic hyperplasia

Fibrosis less than 1/3 of marrow cross-section

Ancillary supportive criteria:

1. Splenomegaly

2. In vitro: spontaneous megakaryocyte colony formation

Clinical features of ET

As many as one third of patients with ET have a clinically silent presentation, and the diagnosis is raised by the recognition of an elevated platelet count during evaluation for reasons unrelated to a projected clinical finding in ET. In addition to the absence of presenting symptoms or signs, many patients have a prolonged, stable, uneventful clinical course. These circumstances have resulted in significant hesitation in applying the diagnosis of ET in asymptomatic patients.

Age

The most common presentation is in those older than 50 years of age, though ET has been seen in children as young as 2 years, and at least 10% of the patients are younger than 40 [72]. The disease is more prevalent in women than in men, but firm demographic data are lacking.

Thrombotic lesions

Vascular occlusive lesions are the predominant clinical features of ET. These extend from transient ischemic episodes in the retina, central nervous system, and heart to the whole spectrum of symptoms secondary to decreased blood flow with defined vascular occlusions resulting in angina, myocardial infarction, cerebrovascular accident, and portal vein thrombosis. Heterogeneity of occurrence sites in the absence of other overt mechanisms for thrombosis should lead to consideration of the diagnosis of ET. Two special clinical aspects of the thrombotic lesions of ET help provide an understanding of the pathophysiologic events: erythromelalgia and microcirculatory thrombosis.

Erythromelalgia

Erythromelalgia is nearly a pathognomonic finding in patients with primary thrombocythemia, though the same findings do occur in polycythemia vera with associated thrombocythemia [73,74]. Erythromelalgia has a characteristic clinical pattern that often yields an immediate diagnosis simply through elicitation of the history. It commonly begins as acroparesthesias, or itching sensations of the feet. Promptly, the balls of the feet become painful and burning. Often the feet and toes appear red and congested. The pain can be severe and is sometimes precipitated by exercise or heat [73]. These episodes have occurred with even only marginal elevations in circulatory platelet numbers. Significant histopathologic changes have been identified, characterized by arteriolar vascular changes with swollen endothelial cells and fibromuscular internal proliferation [75]. It is clear from the extensive studies of Michaels et al [73–76] that erythromelalgia is caused by platelet-mediated acral inflammation and arteriolar thrombosis. The remarkable feature of this lesion is the prompt and immediate response of the entire symptom complex to the administration of aspirin [76,77].

Emphasis is merited on the terminology applicable to this pathophysiologic sequence. The extensive studies of Michaels et al [48,73,75,76] have provided a rationale for the restriction of the term erythromelalgia to circumstances of

thrombocytopenia in which the biology and therapy appear specific. By contrast, the term *erythromalgia* is more appropriately applied to the whole host of inflammatory and circulatory disturbances or neurologic disorders (eg, lupus, rheumatoid arthritis, endarteritis obliterans, diabetes) in which secondary vascular changes occur.

Microcirculatory thrombosis

Arterial and arteriolar occlusive lesions produce a wide array of symptoms that include transient ischemic episodes, visual abnormalities caused by retinal vessel occlusions, intermittent claudication, and even digital infarction [57,78]. These probably are the most frequent lesions in patients with thrombocytopenia. Because the vessels are often in relatively silent sites, their recognition is frequently difficult.

Historically, major vessel occlusions were considered uncommon in primary thrombocytopenia. As better understanding of this clinical entity has developed, it is clear that there is an increased incidence of cerebral and coronary artery occlusive disease. Even more impressive is the significant incidence of mesenteric venous occlusive lesions, and it may be the most common cause of Budd-Chiari syndrome. Griesshammer et al [76] reviewed 11 retrospective clinical studies of 809 patients and identified cerebral artery, portal venous (with associated Budd-Chiari syndrome), and coronary artery thrombosis in a surprisingly high number of cases. Thus, though the past focus was on changes in the microcirculation, it is clear that large vessel involvement occurs. One intermediate vessel bed thrombosis that does provide a special clinical presentation is priapism.

Bleeding

Although the term thrombohemorrhagic event has commonly been used to define the clinical features of ET, bleeding is less common than thrombosis, and it is generally not severe. A history of epistaxis, gingival bleeding, or mild gastrointestinal or genitourinary bleeding can usually be elicited. Ease of bruising with superficial ecchymosis, particularly of the extremities, is common. Unprovoked retinal hemorrhages can produce serious visual changes, and they represent a common and potentially severe complication [79]. It appears that bleeding is more common and more significant with thrombocytopenia in association with other myeloproliferative lesions than with primary thrombocytopenia, and it is most common in patients whose platelet counts more 1.5 million per microliter [67,80–83].

Pregnancy complications

A high incidence of obstetrical complications occurs in women with thrombocytopenia. Placental vessel thrombosis with infarction and related spontaneous abortions are common events. It is of note that spontaneous declines in platelet numbers often occur during the course of pregnancy, and these patients have successful term pregnancy. Similarly, in patients whose platelet aggregation is

controlled with aspirin and platelet numbers are reduced with interferon, successful pregnancies can be expected [84–87].

Interferon may have an important role for pregnant woman with known primary thrombocythemia. Although most patients can be managed through a successful pregnancy with aspirin, we use it for subsequent pregnancies for any patient who has had a prior fetal loss.

Splenomegaly

A slight degree (1–4 cm) of splenomegaly is now well recognized in nearly 70% of cases of primary thrombocythemia.

Hypertension

Elevated blood pressure is seen in approximately 30% of patients. It may be a comorbid condition that may result in an increased risk for an occlusive vascular lesion.

Pathophysiology of essential thrombocythemia

Several interesting pathophysiological events are seen in patients with primary thrombocythemia. First, and best established, is the evidence of endovascular changes in patients with erythromelalgia. These changes include swollen, large, nuclear lumen narrowing because of proliferation of smooth muscle cells with vacuolization and swelling of the cytoplasm, deposition of intercellular material, and fragmentation of the internal elastic lamina [73,75]. Second are identified changes in platelet architecture and function that have been related to clinical symptoms and the endothelial changes described. These changes include platelet size heterogeneity and ultrastructural changes, elevated levels of platelet-specific proteins, increased thromboxane generation, and the expression of activation-dependent epitopes on the platelet surface [83]. A third finding relates to recent observations in the familial form of primary thrombocythemia in which elevated levels of thrombopoietin were found in the affected members and a 1-bp deletion was found in the 5'-untranslated region of the thrombopoietin gene [81]. At least in the familial form, it appears that the genetic change is important in regulating thrombopoietin expression, and it is the basis of this familial form of thrombocythemia. Finally, an inverse relationship has been seen in patients with thrombocythemia between high platelet counts and large von Willebrand factor multimers. The increased platelets have been related to increased degradation of platelet-bound von Willebrand factor multimers [80]. These effects have been considered an additional factor for hemostatic problems in thrombocythemia.

Natural course of essential thrombocythemia

The characterization and description of the natural course of ET has been hampered by the lack of absolute agreement in the diagnostic criteria, population selection bias (ie, data from specific thrombosis units), serious differences about

the indications and parameters for therapy, and limited follow-up in a disease known to last decades.

In studies of small cohorts of patients, there has not been clear evidence of substantial differences in life expectancy between those with ET and an age- and sex-matched central group [88–91], and this has led to the view that ET is essentially a nondisease. Nevertheless, when one looks at subsets of patients with a defined presentation, this view needs reinterpretation. One of the very best studies is that by Bazan et al [89] from Turin, Italy, in which 187 consecutive patients were followed up. Fifty percent of patients had at least one thrombotic episode within 9 years of diagnosis. Thrombosis-free and overall survival curves were not significantly different for those younger or older than 50 years of age; and only 85% were alive 10 years after diagnosis. They demonstrated a relative rate of death four times greater in patients with ET than for healthy, age-matched controls. Interestingly other combined factors commonly expressed as confounding factors in addressing the effect of ET on cardiovascular risk (age at diagnosis, smoking, sex, hypercholesterolemia, hypertension, and diabetes) were not significant, nor was peak platelet numbers.

As a form of myeloproliferative syndrome it is not surprising that progression to defined polycythemia vera or idiopathic myelofibrosis is seen in up to 5% of patients with ET [82,89,90], though these numbers are derived from small studies. Progression to acute myeloid leukemia has been seen in 3% to 4% of patients [82], but virtually all had had previous exposure to potentially leukemogenic agents used to control their platelet numbers. An increased incidence of myelodysplastic syndromes and solid tumors has also been seen in patients treated with myelosuppressive (ie, busulphan or hydroxyurea) agents [92].

Therapy of essential thrombocythemia

The recognition of ET in otherwise healthy persons and the evidence that some simple maneuvers, such as the administration of aspirin, has led to a normal life expectancy free of thrombosis [85,93] and to the concept of risk stratification as a basis for therapy planning [49,50,52,71,85,93–95], and risk stratification has largely been related to factors that affect thrombohemorrhagic complications. In Box 3, Tefferi [95] depicts simple parameters for such stratification for therapy planning. The management of patients with ET has focused on the use of antiaggregating agents and the reduction of circulating platelet numbers.

Platelet antiaggregating agents

Traditionally, concern regarding the use of platelet antiaggregating agents has focused on the evidence that platelet dysfunction is commonly seen in primary thrombocythemia. Indeed, some of the hemorrhagic phenomena have been ascribed to such defective platelet function. These findings led to a fear of any agent that could further affect platelet function.

Box 3. Risk stratification in essential thrombocythemia

Low risk

- Age < 60 years, and
- No history of thrombosis, and
- Platelet count < 1.5 million/ μ L, and
- No cardiovascular risk factors (smoking, obesity)

Intermediate risk

- Neither high-risk nor low-risk

High risk

- Age \geq 60 years, or
- A previous history of thrombosis

(*Modified from Frenkel EP. The clinical spectrum of thrombocytosis and thrombocythemia. Am J Med Sci* 1991;301:69–80; with permission.)

This thesis was perturbed by evidence that aspirin could reverse vascular lesions and even incipient gangrene [78]. More recently, aspirin has been shown to improve neurologic function, even in the continued presence of increased platelet numbers [79]. It is now clear that aspirin is effective at reducing clinical symptoms and signs in patients with vascular occlusive lesions [76,77,96,97]. In addition, the use of aspirin has become an important therapeutic agent during pregnancy [56,85–87,96]. Aspirin has been effective in helping patients carry a pregnancy to successful term. At present, too little experience exists with the newer antiaggregating drugs to define their role in such patients.

Approaches to reduction of platelet numbers

Virtually every method capable of reducing platelet numbers has been used.

Platelet pheresis

Pheresis provides a rapid lowering of platelet numbers (in hours). Unfortunately, its effect is of short duration (hours to days). It is not commonly needed but has its major value either in rapidly evolving microvascular thrombotic lesions or in circumstances in which emergency surgery is required.

Myelosuppressive-cytoreductive drugs

Virtually every cytoreductive chemotherapeutic agent (phosphorous, alkylating agents, antimetabolites) has been used to reduce platelet numbers. These agents are successful and can reduce platelet numbers. Unfortunately, most also have leukemogenic potential; therefore, these have largely been abandoned in favor of hydroxyurea.

Hydroxyurea

Hydroxyurea has emerged as the cytoreductive agent of choice. This simple molecule was synthesized more than 100 years ago, but its entry into clinical medicine did not come until the 1960s, when it was shown to be a ribonucleotide reductase inhibitor [98,99]. Hydroxyurea is relatively nontoxic, and it has a broad dose-response range. It does induce megaloblastic changes, as one might expect from its biochemical site of action [100]. The enthusiasm for its use was the belief that it was nonleukemogenic; however, it should at best be considered an agent with uncertain carcinogenic potential because primary thrombocythemia conversion to acute leukemia has been linked to hydroxyurea therapy [101,102]. In daily oral doses of 500 to 1000 mg, most thrombocythemia patients will have a decrease in platelet values, and then drug dosage can be titrated to the desired circulating platelet number [45,49,103,104].

Interferon

Interferon has been shown to effectively lower platelet counts in patients with primary thrombocythemia and thrombocythemia associated with other types of myeloproliferative lesions [67,105–110]. Its mechanism of action appears to be mediated by the inhibitory effect of interferon on megakaryopoiesis, as discussed earlier. A common therapeutic dose is 3 million U subcutaneously given 3 times per week. As many as 80% to 90% of patients achieve a stable state of remission with interferon therapy. On cessation of the therapy, clinical and laboratory findings usually recur. Remission is sustained in only approximately 10% of patients.

Anagrelide

After almost a decade of clinical trials, anagrelide has become an important addition to the therapeutic armamentarium for patients with thrombocythemia regardless of the underlying form of myeloproliferative disease. It was originally introduced because it has anti-cyclic adenosine monophosphate phosphodiesterase activity that inhibits platelet aggregation [111]. Evidence of a dose-dependent reduction in platelet numbers in healthy controls [112] and in patients with thrombocythemia [70,113–117] has led to its use as an important therapeutic modality. The exact mechanism of action is not completely defined, but *in vitro* and *in vivo* studies have shown that it altered the maturation of megakaryocytes, with a resultant decrease in their size and morphologic abnormalities [117]. It is of note that other findings of platelet survival and proliferation of the megakaryocyte-committed progenitor pool were normal. In general, initial starting doses can be 0.5 to 1.0 mg given two to four times per day. A significant decline in platelet numbers is usually evident by 7 to 14 days, and dose adjustments can then be effected. In general, individual doses should not exceed 2 mg, and a maximum daily dose of 10 mg has been recommended [114]. It is rare to require more than 4 mg per day. Presently a long-acting form of anagrelide is in clinical trials, and that may help simplify treatment schedules.

Anagrelide does have a vasodilatory effect, and headaches, postural hypotension, fluid retention, and diarrhea have been seen as side effects. Palpitations and tachycardia are seen in nearly one quarter of patients; these seem to be significantly worse in patients who ingest close to a maximum dose of the drug. These symptoms generally disappear after 4 to 8 weeks of therapy. Although expensive, anagrelide has added an important therapeutic advance in the approach to thrombocythemia.

Summary

Platelets are intimately involved in the pathogenesis of thromboembolic disorders, especially arterial forms of thrombosis. Although most arterial thromboses develop on the basis of endothelial injuries, some do not. In these instances “hyperactive” platelets could be the cause. Hyperaggregable platelets have been described in association with a number of acquired disease entities whereby the cause-and-effect relationship is unclear. In contrast, the sticky platelet syndrome is a congenital, autosomal dominant disorder, characterized by hyperaggregable platelets in response to ADP, epinephrine, or both. Patients usually seek treatment for transient or permanent arterial vascular occlusions. These are often precipitated by stressful events. Treatment with low-dose aspirin (81 mg/day) reverses clinical symptoms and hyperaggregability in the laboratory.

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