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REACTIVE AND CLONAL THROMBOCYTOSIS: CYTOKINES AND ACUTE PHASE REACTANTS

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SUMMARY – Platelets are acute phase reactants that increase in response to various stimuli, including systemic infections, inflammatory conditions, bleeding, and tumors. This is called reactive or secondary thrombocytosis, which is a benign form of thrombocytosis. Clonal thrombocytosis is an unregulated abnormality of platelet production due to clonal expansion of bone marrow progenitor cells. Secondary thrombocytosis may be due to the overproduction of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and IL-11, which occurs in chronic inflammatory, infectious and malignant states. The presence of elevated IL-1, IL-6, C-reactive protein and granulocyte-macrophage colony-stimulating factor in individuals with this condition suggests that these cytokines may be involved in reactive thrombocytosis.

Key words: *Thrombocytosis – classification; Thrombocytosis – etiology; Thrombocytosis – blood; Thrombocytosis – diagnosis*

Introduction

Reactive thrombocytosis occurs in chronic infectious or inflammatory states, malignancy, iron deficiency anemia, and postsplenectomy states[1-3]. Clonal (or primary, or essential) thrombocytosis is a primary hematologic process that is seen in essential thrombocythemia and other myeloproliferative disorders such as chronic granulocytic leukemia, polycythemia vera, idiopathic myelofibrosis, and 5q-syndrome[3]. Conditions that cause clonal thrombocytosis may require therapy with cytotoxic drugs, whereas reactive thrombocytosis resolves with causal treatment.

Etiopathogenesis of Reactive Thrombocytosis

It may be clinically difficult to differentiate clonal thrombocytosis from reactive thrombocytosis in the absence of classic clinical signs (e.g., splenomegaly), absence of abnormalities of the granulocytic and erythroid lineage, and absence of the Philadelphia chromosome. Several cytokines, interleukin-1 (IL-1), IL-6, IL-11, granulocyte-macrophage colony-stimulating factor (GM-CSF), and thrombopoietin (TPO) can regulate platelet count and functions in humans[4-7]. IL-1ß, IL-6, and tumor necrosis factor (TNF-α) are proinflammatory cytokines that mediate the acute phase response associated with fever, elevated erythrocyte sedimentation rate (ESR), and elevated C-reactive protein (CRP) level[8]. Platelets, often considered acute phase reactants, may also be influenced by these cytokines. It has been previously shown that serum IL-6, ESR, and CRP are elevated in reactive thrombocytosis and clonal thrombocytosis[9-11]. Similarly, IL-6 has been shown to be elevated in patients with paraneoplastic thrombocytosis complicating mesothelioma[12-14]. IL-11 was not elevated in thrombocytosis in one study[15].

Data on circulating TPO levels in reactive thrombocytosis and clonal thrombocytosis are complex and indicate that serum TPO level is highly variable and can be elevated in both clonal and reactive thrombocytosis[15-20]. The lit-

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erature indicates that serum TPO level may function as an acute phase reactant and cannot be used to differentiate reactive from clonal thrombocytosis[21].

Diagnosis

A simple, reproducible test to differentiate the clinically aggressive clonal thrombocytosis from reactive thrombocytosis would be a useful tool in routine hematology practice[22]. A patient is diagnosed with essential thrombocytosis by exclusion of other myeloproliferative diseases, i.e. chronic myelogenous leukemia (CML), polycythemia vera, agnogenic myleoid metaplasia, and myelodysplastic syndrome (MDS), and exclusion of factors that could be responsible for reactive thrombocytosis[23]. The original set of diagnostic criteria provided by the Polycythemia Vera Study Group (Table 1)[24] have been revised to include patients with lower platelet counts (>400x10^9/L), and a number of additional laboratory investigations have recently been shown to be useful for refining the diagnosis (Table 2)[25,26].

Reactive thrombocytosis can be caused by a wide range of phenomena, including inflammatory diseases, infections, drugs, and even exercise[27]. The relatively high frequency with which extreme thrombocytosis is encountered as a reactive phenomenon in a general acute care hospital population indicates the need of caution before making a diagnosis of essential thrombocytosis[28]. Platelet counts in the range of 450 to 600x10^9/L are not uncommon in conditions associated with bleeding or in those associated with thrombosis when there is also necrosis and/or inflammation[29].

Essential thrombocytosis can usually be differentiated from reactive thrombocytosis by careful medical history and laboratory data to exclude underlying disorders. In many cases, the development of reactive thrombocytosis is believed to be related to high levels of IL-6, which are known to occur in a variety of infectious or inflammatory conditions[30].

There is also a positive correlation between IL-6 and CRP, and either or both of these have been shown to be increased in 81% of patients with reactive thrombocytosis but not in patients with uncomplicated essential thrombocytosis[30]. Spontaneous *in vitro* megakaryocyte and erythroid colony formation on culture of blood or bone marrow progenitor cells also confirms the diagnosis of essential thrombocytosis, which is not seen in tissues from patients with reactive thrombocytosis[31-32]. However, it does not occur in all essential thrombocytosis patients and cannot therefore be used as a sole diagnostic criterion. Similarly, whereas TPO levels, which are inversely correlated with platelet and megakaryocyte mass in healthy subjects, may be within the normal range or even slightly raised in essential thrombocytosis despite the increased megakaryocyte mass[33], this feature is not unique to essential thrombocytosis[23]. The increased levels of TPO may result from the marked reduction in TPO receptor (c-Mpl) expression in platelets and megakaryocytes seen in essential thrombocytosis[34,35], but low c-Mpl expression is not specific to essential thrombocytosis[23].

Table 1. Diagnostic criteria for essential thrombocytosis

I	Platelet count >600x10^9/L
II	Hemoglobin ≤13 g/100 ml or normal red cell mass (male <36 ml/kg, female <32 ml/kg)
III	Stainable iron in marrow or failure of iron trial (<1g/100 ml rise in hemoglobin after 1 month of iron therapy)
IV	No Philadelphia chromosome
V	Collagen fibrosis of marrow: (a) absent, or (b) <1/3 biopsy area without splenomegaly and leukoerythroblastic reaction
VI	No known cause for reactive thrombocytosis

From the Polycythemia Vera Study Group, 1982[24]

Table 2. Revised diagnostic criteria for essential thrombocytosis

A1	Platelet count >400x10^9/L and known cause of reactive thrombocytosis
A2	Increase in and clustering of mature giant megakaryocytes with hyperploid nuclei
A3	No preceding or allied other subtype of myeloproliferative disorder or myelodysplastic syndrome
B1	Normal or elevated LAP score, normal ESR, no fever
B2	Normal or slightly increased cellularity and no or minimal reticulin fibrosis
B3	Splenomegaly on palpation or spleen length >11cm on diagnostic imaging procedure
B4	Spontaneous erythroid colony and/or spontaneous meakaryocyte colony formation on bone marrow cultures

A criteria are diagnostic; B criteria are confirmative
From the Polycythemia Vera Study Group, 1999[25,26]
LAP, leukocyte alkaline phosphatase, ESR erythrocyte sedimentation rate

Case Report 1
Physiologic Utilization of Coagulation Factors and Reactive Thrombocytosis

A 63-year-old patient was hospitalized for invasive backpain followed by flaccid paraplegia. Computed tomography of the aorta revealed dissection of the abdominal and thoracic aorta. During hospital stay, neurologic symptoms gradually regressed, however, laboratory parameters of intravascular coagulopathy were observed. Twenty-four hours of admission, a significant decrease occurred in red blood count (E from 4.9 to 3.9 and Hb from 149 to 21 g/L) as well as in platelet count (Plt 94x10^9/L); prothrombin time up to 58%, fibrinogen 0.6 g/L with an increase of D-dimer up to 12.5. Other acute phase reactants showed the following findings: increased CRP that gradually declined from 393 to 28l, persistent leukocytosis of up to 20x10^9/L over the first few days, and 13x10^9/L on the last control. With normalization of coagulation parameters reactive thorombocytosis developed (Plt 718), with a rising tendency of platelet aggregation. On day 8, digital subtraction angiography (DSA) of the aorta confirmed De Backey I aortic dissection, with false lumen thrombosis up to the renal artery level (Plt 691). From then on, platelet count showed gradual decrease. At discharge from the hospital, platelet count was 248x10^9/L.

Case report 2
Tumor Necrotic Reactive Thrombocytosis

An 83-year-old man was admitted to the hospital for weakness, dizziness, weight loss, loss of consciousness, and vomiting a month before. On admission, his skin and visible mucosa were extremely pale. Initial laboratory results indicated severe microcytic anemia and thrombocytosis: E 2.2x10^{12}/L; Hb 34 g/L; MCV 54 fl, Plt 553x10^9/L; Fe 5.2 mmol/L; ferritin 21 ng/mL. Day 10: Plt 1044x10^9/L. Cecum colonoscopy revealed a 2-cm proliferation process and PHD indicated adenomatous colon carcinoma. The patient was transferred to the Department of Surgery, where he underwent hemicolectomy l. dex. and ileotransverse T-T anastomosis. On day 2 postoperatively, platelet count decreased from 1044 to 404x10^9/L.

Case Report 3
Inflammatory Reactive Thrombocytosis

A 28-year-old patient with a history of alcohol abuse presented for epigastric pain radiating to the back, followed by dizziness and vomiting. Laboratory results on admission showed elevated levels of amylase in serum (570U/L) and urine (1095U/L) indicating acute pancreatitis, and increased acute phase reactants (ESR 55, L 13x10^9/L, CRP 12, Plt 593x10^9/L). The diagnosis of acute pancreatitis of a mixed etiology (alcoholism, cholelithiasis) was confirmed by ultrasound finding of enlarged, hyperechogenic liver and gallbladder, with a large number of small concrements within the lumen and thin ascites mantle along the pancreas tail towards the spleen hilus. Laboratory results pointed to the presence of hyperlipidemia. During the second week of hospital stay, parenteral fluid and electrolyte replacement (0.9% F.O., 5% glucose), appropriate antibiotic (cefuroxime) and other symptomatic therapy (paracetamol) resulted in a gradual decrease in serum levels of transaminases and urine amylase, with normalization of laboratory parameters of acute inflammation. Platelet count declined from 593 to 122.

Case Report 4
Inflammatory Necrotic Reactive Thrombocytosis

A 69-year-old patient with a history of longlasting arterial hypertension and stroke was hospitalized at Angiology Department for moist gangrene of the big toe of his right foot. Duplex scan of arterial circulation in both lower extremities revealed subtotal stenosis of both popliteal arteries with occlusion of all knee band tract arteries bilaterally. The indication for angiography was set up (digital subtraction angiography of pelvic and lower extremity arteries with the use of a non-ionic contrast medium), which showed stenosis of the superficial femoral artery bilaterally, with significant bottle-neck shaped lumina in the middle segment of the arteries in the area of both popliteal arteries and knee band occlusion of all three main branches. According to vascular surgeons, amputation of the knee band was indicated. Pretherapeutically, platelet count was increased (555x10^9/L), which could, along with elevated levels of other laboratory parameters of acute inflammation, have pointed to reactive thrombocytosis.

Case Report 5
Essential Thrombocytosis

A 74-year-old patient was admitted for febrility, swollen ankle joints, and impossibility of standing and walking; longlasting hypertension; corticosteroid therapy for chronic obstructive pulmonary disease. In the status, Cushing's aspect predomianted (iatrogenic Cushing's syndrome), the skin on the extremities was thinner with many hematomas, crusts and perimaleolar edema bilaterally. Laboratory finding on admission: Plt 921x10^9/L. Cytolog-

ic biopsy of bone marrow showed abundant megakaryocytes, polymorphic etiology, and abundant mature granulocytopoiesis. The findings pointed to the diagnosis of a chronic myeloproliferative disorder. The patient responded favorably to parenteral therapy with an iron agent, and during the first week platelet count decreased from 921 to 620x10^9/L

Discussion

A simple, noninvasive test to distinguish between clonal thrombocytosis and reactive thrombocytosis will find application in routine hematology practice. The study results showed significantly elevated levels of the acute phase cytokines IL-6 , IL-1ß, and CRP in reactive thrombocytosis. Serum TPO measurements failed to differentiate reactive from clonal thrombocytosis, an observation similar to those previously reported[36-38]. Patients with reactive thrombocytosis also tended to have significantly higher levels of CRP than clonal thrombocytosis patients or healthy controlos.

The cytokines IL-1ß and TNF-α, which are well known for their ability to regulate the acute phase response, may be crucial to regulate platelet count in inflammatory and reactive states. Platelets can be considered as acute phase reactants. The cytokines TPO and IL-11 are essential for platelet formation in both reactive and clonal states, and may act in concert with the inflammatory cytokines in inducing thrombocytosis.

Thrombopoietin and IL-11 are not useful as laboratory parameters to distinguish clinically difficult cases of thrombocytosis.

Hence, thrombopoietin may have an additional critical role in the pathogenesis of clonal myeloproliferative disorders. This is supported by recent evidence of marked reduction in the expression of the TPO receptor, Mpl, in platelets derived from polycythemia vera and idiopathic myelofibrosis[39]. By immunohistochemichal staining, the expression of Mpl was shown to be decreased in bone marrow aspirate samples from polycythemia vera patients but not in samples obtained from patients with secondary erythrocytosis[40]. Hence, thrombopoietin may have an additional critical role in the pathogenesis of clonal myeloproliferative disorders[41].

Conclusion

Approximately a half of all essential thrombocytosis patients are asymptomatic at diagnosis, while the rest present with a variety of vasomotor, thrombotic, or hemorrhagic complications. Neither the degree of thrombocytosis nor the platelet function abnormalities consistently correlate with clinical presentations. An increased risk of thrombosis has been associated with age greater than 60 years and prior thrombosis. The risk of hemorrhage may increase with extreme thrombocytosis (>2,000x10^9/L). Recent advances in medical therapy have resulted in the availability of cytoreductive agents with fewer longterm side effects and, in particular, with a decreased risk of leukemic transformation.

The primary treatment should address the underlying cause of thrombocytosis. In general, no treatment is indicated to directly reduce platelet count. In patients with platelet counts in excess of 1,000,000 *per* mL, aspirin 65 mg daily may be considered to minimize the rare development of stroke or thrombosis[28].

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Sažetak

REAKTIVNA I KLONSKA TROMBOCITOZA: CITOKINI I REAKTANTI AKUTNE FAZE

Lj. Fodor-Alagić,V. Stančić, P. Gaćina, D. Čaržavec,V. Nikolić-Heitzler, D. Planinc, K. Štambuk, I. Bonić, B. Car, M. Solter, M. Vitezić-Misjak, B. Bečejac i V. Altabas

Trombociti su reaktanti akutne faze i njihov se broj povećava kao odgovor na različite podražaje, uključujući sistemske infekcije, upalna stanja, krvarenja i tumore. To se naziva reaktivnom ili sekundarnom trombocitozom, što je benigni oblik trombocitoze. Esencijalna trombocitoza je nenormalna proizvodnja trombocita uzrokovana klonskom ekspanzijom progenitorske stanice koštane srži. Sekundarna trombocitoza može biti uzrokovana prekomjernom proizvodnjom proupalnih citokina, kao što su interleukin-1 (IL-1), IL-6, IL-11, koji se javljaju u kroničnim upalnim, infektivnim i malignim stanjima. Prisutnost povišenih vrijednosti IL-1, IL-6, C-reaktivnog proteina i granulocitno-makrofagnog faktora stimulacije rasta u pojedinaca s ovim stanjem ukazuje kako bi ovi citokini mogli biti upleteni u reaktivnu trombocitozu.

Ključne riječi: *Trombocitoza – klasifikacija; Trombocitoza – etiologija; Trombocitoza – krv; Trombocitoza – dijagnostika*