

Review

Reactive Thrombocytosis in Pediatric Pathology

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REZUMAT

Trombocitoza reactivă în patologia pediatrică

Trombocitele sunt considerate reactanți de fază acută. Prin urmare, ele cresc ca răspuns la diverși stimuli. Trombocitoza este clasificată ca fiind fie primară (clonală) sau secundară (reactivă). Trombocitoza primară este cauzată de producția autonomă de trombocite (nereglementate de mecanismul de feedback fiziologic). Trombocitoza reactivă apare la pacienții care au o afecțiune medicală sau chirurgicală și care se normalizează după rezolvarea cauzei. Trombocitoza reactivă este considerată o formă benignă de trombocitoză. Citokinele proinflamatorii, interleukinele 6, 11 și 1 beta, factorul de necroză tumorală, factorul de stimulare al coloniilor de granulocite, macrofagele și trombopoietina pot regla numărul de trombocite.

Cuvinte cheie: trombocitoza primară, trombocitoza secundară, trombocite, citokine

ABSTRACT

Platelets are considered acute-phase reactants. Therefore, they increase in response to various stimuli. Thrombocytosis is classified as either primary (clonal) or secondary (reactive). Primary thrombocytosis is caused by increase of autonomous production of platelets (unregulated by the physiologic feedback mechanism). Reactive thrombocytosis appears in patients who have a medical or surgical condition and who normalize after resolution of primary cause. Reactive thrombocytosis is considered to be a benign form of thrombocytosis. Inflammatory cytokines such as interleukins 6, 11 and 1 beta, tumor necrosis factor, granulocyte-monocyte colony-stimulating factor, and thrombopoietin can regulate platelet numbers.

Key words: primary thrombocytosis, reactive thrombocytosis, platelets, cytokines

Thrombocytosis (over 500.000/mm³) is classified as primary (clonal) or secondary (reactive). Increasing the number of platelets as response to various stimuli (inflammatory diseases, acute and recurrent bleeding, systemic infections or various types of malignancies) are considered to be reactive thrombocytosis [1,2,3].

Clonal or primary thrombocytosis (PT) is an abnormality of platelets production caused by clonal expansion of hematopoietic progenitor cells. In primary thrombocytosis autonomous platelets production is not regulated by physiological feedback mechanisms to maintain platelets count normal.

Secondary or reactive thrombocytosis (RT) refers to the increase in the number of platelets in patients who have a medical or surgical condition, which normalizes after curing the underlying condition that caused it. TR is considered a benign form of thrombocytosis and has no propensity as the age [3,4]. It has been observed an increase in the number of platelets after ovulation and a decrease of platelets at menstruating in the case of girls.

Thrombocytosis is classified as:

A. Primary thrombocytosis: essential thrombocytosis, polycythemia vera, chronic myeloid leukemia, myeloid metaplasia with myelofibrosis, acute mega-karyoblastic leukemia, idiopathic sideroblastic anemia.

B. Reactive thrombocytosis occurs in inflammatory diseases: tuberculosis, osteomyelitis, chronic hepatitis, hepatic cirrhosis, inflammatory bowel disease - Crohn's disease, ulcerative colitis, sarcoidosis, immune diseases (Kawasaki syndrome, juvenile rheumatoid arthritis, polyarteritis nodosa), nephrotic syndrome, hemato-logical diseases (iron deficiency anemia, chronic hemolytic anemia, megaloblastic anemia - deficient of folic acid or vitamin B12, hemophilia), rebound after thrombocytopenia, size reactions of drugs (vinblastine, steroids, prolonged cures of epinephrine), malignant diseases (malignant lymphoma, neuroblastoma, solid tumors, histiocytosis X, carcinomas), other causes (surgery, pulmonary embolism, glycogenosis type II, severe bleeding, severe trauma, pancreatitis).

C. Thrombocytosis may appear in: surgical asplenia, congenital asplenia (Ivemark syndrome) and functional asplenia.

Mechanisms of reactive thrombocytosis are not exactly known. The reactive thrombocytosis may result from overproduction of cytokines that act on

megakaryocytes. The primary regulator of synthesis of megakaryocytes is thrombopoietin (TPO). Megakaryocytes have thrombopoietin receptors called c-mpl receptors. Thrombopoietin binds to c-mpl receptor on the surface of circulating platelets. Thrombopoietin remaining free in plasma is available to trigger proliferation of megakaryocytes. Thus, if the platelet count decreases, plasma levels of free thrombopoietin stimulate production of megakaryocytes. In some cases of RT, a basic stimulus that produces inflammation may increase the production of thrombopoietin from the liver. The literature indicates that serum levels of TPO can act as an acute phase reactant, but cannot differentiate RT from PT [7,8]. TPO may play an important role in clonal myeloproliferative disorders. This is supported by recent proof of marked reduction in the expression of the c-mpl receptor in platelets derived from polycythemia vera and idiopathic myelofibrosis [7].

Inflammatory cytokines that mediates acute phase response (for example illness with fever) increase erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and they also stimulate platelet production. Overproduction of cytokines has been shown to promote ("in vivo" and "in vitro") the production of megakaryocytes [6,7]. Many cytokines are involved in thrombocytosis: interleukins (IL-1 beta, IL-6 and IL-11), colony stimulating factor, granulocyte (G - CSF), colony stimulating factor and granulocyte - macrophage (GM - CSF) and factor tumor necrosis factor (TNF) [7,8].

Clinical studies demonstrate increasing levels of serum IL-6, ESR, CRP in reactive thrombocytosis [6,7]. Interleukin-6 may be a key mediator of increased synthesis of thrombopoietin. This interleukin plays an important role in acute phase response, and regulates the expression of the messenger RNA in the liver which increases the production of TPO.

In acute inflammation, IL-6 is increased prior to increasing the number of platelets. Interleukin IL-6 has been shown to be increased in paraneoplastic syndromes [9]. New data suggests that cytokines IL-1 β and TNF (which are known for their ability to regulate the inflammatory response in acute phase of diseases) can be crucial for the increase of the number of platelets. Increased TNF has been reported in both PT and RT. Level of megakaryocytes growth factors failed to make a distinction between RT and PT [9,10].

Clinical examination

There are no distinctive features of the physical examination. Most patients with RT are asymptomatic. Clinical manifestations characterize the underlying disease. The persistence of thrombocytosis may signify clonal thrombocytosis [11, 12].

Differential diagnosis

Before a disorder attributable to clonal thrombocytosis (myeloproliferative syndromes), which is a diagnosis of exclusion, the clinician must make sure that the large number of platelets is not due to another condition. The differential diagnosis may include: chronic lymphocytic leukemia, chronic myeloblastic leukemia, polycythemia vera, thrombotic thrombocytopenic disease [13].

Complications of reactive thrombocytosis.

Thrombotic or hemorrhagic complications that are commonly associated with PT are not usually found in RT, regardless of the increase in the number of platelets. Lack of complications in RT can be explained by the fact that the interaction of platelets with the vessel walls remains qualitatively normal [14].

Laboratory investigations

Laboratory tests do not provide clear distinctions between PT and RT. Giant platelets are often found on peripheral smear in PT, but not in RT. A variety of platelet functional abnormalities have been described in RT, also in the form of secondary thrombocytosis. These abnormalities may include von Willebrand disease, syndrome of lack of platelet aggregation induced by epinephrine.

Examination of bone marrow aspirate and bone marrow biopsy revealed megakaryocytes increase in both forms of thrombocytosis, but there may be significant differences in morphological characteristics. Megakaryocytes in RT appear normal, but in PT may have dysplastic giant forms with increased ploidy. Thrombopoietin and IL-11 are not useful as laboratory parameters to distinguish RT from PT. Increased TPO levels may play a role in clonal myeloid disorders. Immunological staining demonstrated that c-mpl receptor expression decreased at bone marrow aspirates in essential thrombocytosis, and not in samples from patients with reactive thrombocytosis.

Abdominal ultrasound can detect splenomegaly in some cases [13, 14].

Laboratory investigations of the RT include the following: ESR, CRP, serum iron, total iron-binding capacity, serum ferritin, alkaline phosphatase leukocyte, nuclear antibodies, rheumatoid factor, serum levels of vitamin B12, peripheral blood smear, cytogenetic studies. If clinical examination and laboratory examinations do not distinguish clearly between RT and PT, cytogenetic testing may be indicated to confirm the diagnosis of PT (for example the Philadelphia chromosome).

Essential thrombocytosis is a diagnosis of exclusion, based on the following criteria adapted R. Hoffman [14]. Patients who meet the criteria from 1 to 5 and more than three criteria from the criteria 6-11 are considered to be essential thrombocytosis. The criteria are: 1. Platelet count greater than 600,000 / mm³ (highlighted twice every month); 2. The absence of identifiable causes of reactive thrombocytosis; 3. Normal number of red blood cells; 4. The absence of substantial bone marrow fibrosis; 5. The absence of Philadelphia chromosome (Ph) and absence of BCL-ABL fusion; 6. Splenomegaly on physical or ultrasound exam; 7. Megakaryocytes hyperplasia; 8. The presence of abnormal cells in the hematopoietic progenitors bone marrow by endogenous erythroid cell growth and / or megakaryocyte colony with increased sensitivity to IL-3; 9. Normal levels of CRP and IL-6; 10. The absence of iron deficiency anemia or normal serum ferritin level; 11. At females, demonstrating clonal hematopoiesis by presence of fragments with polymorphism in the genes of X chromosome [14].

Treatment of TR.

Conditions that cause PT may require therapy with cytotoxic drugs, while RT resolves with treatment of the underlying cause. The treatment of the underlying condition should normalize platelet count in RT. In general, no special treatment is necessary to directly reduce the platelet count. For patients with a platelets count greater than one million per ml, aspirin at dose of 65 mg per day may be used to minimize the development of rare stroke or thrombosis in different locations [14]. At patients with RT which was not identified causal factor, it requires careful clinical monitoring and laboratory tests to exclude the possibility of developing a clonal disorder.

Persistent thrombocytosis represents both in children and adults a hematological sign, a syndrome or a disease itself.

Regarding reactive thrombocytosis in children compared with adult reveals a higher frequency in children, because of the specific pediatric pathology (infectious and inflammatory diseases, iron deficiency anemia etc.). It was noted that primary thrombocytosis is more common in adults (myelodysplastic syndromes, polycythemia vera etc.) [15].

Also to be mentioned pseudo thrombocytosis or false thrombocytosis that occur both in adults and in children: Pappenheimer bodies, fragments of erythrocytes, leukocytes and bacteria [5,6], micro-spherocytes (appear in severe burns), cryoglobulinaemia, neoplastic cell cytoplasmic fragments, schistocytes, Heinz bodies, parasites (malaria), Howell-Jolly bodies (appear in: radiation therapy involving the spleen, severe hemolytic anemia, megaloblastic anemia, hereditary spherocytosis, and myelodysplastic syndrome).

Reactive thrombocytosis may have a role in signaling the presence of acute and potentially severe disease (sepsis, chronic inflammatory disease etc.), therefore it should be carefully monitored.

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