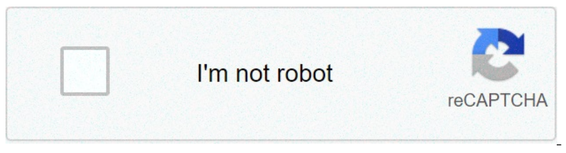


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# Iron deficiency anemia and thrombocytosis

Objective: Platelet count above 450,000mm3 is defined as thrombocytosis. It is called mild thrombocytosis if the platelet count is between 700,000–900,000mm3, and severe thrombocytosis between 900,000–1,000,000mm3. If the platelet count is over 1,000,000mm3, it is considered as very severe thrombocytosis. In this case report; we have showed that iron deficiency can also lead to very severe thrombocytosis by presenting the case of very severe thrombocytosis developing in an adolescent female patient.Case report: The 12-year-old girl was referred to our hospital for anemia (Hgb: 5.8g/dL) by an external clinic she applied due to her headache in the morning for the past month. The patient's history and family history were unremarkable. Her physical examination revealed that her general condition was moderate-poor, skin was pale, conjunctiva was extremely pale, peak heart rate: 130–140/min, TA: 90/50mm/Hg. Lymphadenopathy and hepatosplenomegaly were not detected. In the laboratory tests of the patient, the following findings were detected; the leukocytes count was: 14,900/mm3, neutrophil count: 11.9/mm3, Hgb: 4.8g/dL, Hct: 20%, MCV: 53fl, RBC: 3.7milyon/uL, MCH: 12.9pg (27–31), platelet count 2,629,000/mm3. Peripheral smear of the patient was analyzed. In eritrocytes, a high degree of hypochromic microcytes were detected and 80% neutrophils, 2% monocytes, 18% lymphocytes, abundant platelets were seen. Serum iron: 6.7uL/dL (50–120); iron binding capacity: 525uL/dL (155–355); ferritin: 0ng/mL; folate: 10.6ng/mL (0.3–24) and vitamin B12: 437ng/mL. There was no abnormality in other biochemical examinations. Iron replacement was started at a dose of 6mg/kg/day considering iron deficiency anemia and related thrombocytosis. Abdominal ultrasonography was evaluated within normal limits according to age. Since the patient had tachycardia, appropriate cross erythrocyte transfusion was performed. Viral serologies and autoantibodies of the patient were evaluated as normal. The control hgb level was 7.9g/dL and thrombocyte count was 1,875,000/mm3 after transfusion. In the bone marrow aspiration assessment, the myeloid and erythroid series in the normocellular bone marrow were seen as normal, blasts were not seen, megakaryocytes were increased. The patient had hgb: 10.4g/dL, platelet: 732,000/mm3 in the clinical examination performed in the second week. She is under the oral +2 valence iron treatment and had no clinical problem in her follow-up examinations.Methodology: Information was obtained from the patient file.Results: In childhood, thrombocytosis usually occurs due to secondary causes and thrombocytosis regresses by controlling the causing disease. Thrombocytosis due to iron deficiency is mostly seen in infancy period.Conclusion: The cause of thrombocytosis in iron deficiency is not fully understood. The fact that the increase in EPO stimulates TPO receptors (c-mpl) in iron deficiency is known to result in thrombocytosis. However, it is very important that children should be evaluated immediately for infection and iron deficiency before performing further examinations. Keywords: Thrombocytosis; iron deficiency; child. Thrombocytosis refers to having too many platelets in your blood. Platelets are blood cells in plasma that stop bleeding by sticking together to form a clot. Too many platelets can lead to certain conditions, including stroke, heart attack or a clot in the blood vessels. There are two types of thrombocytosis: primary and secondary. Primary thrombocytosis is a disease in which abnormal cells in the bone marrow cause an increase in platelets. It is also called essential thrombocythemia (or ET). The cause is unknown. It isn’t considered an inherited (genetic) condition even though certain gene mutations have been found in the blood or bone marrow. Secondary, or reactive, thrombocytosis is caused by another condition the patient may be suffering from, such as: ++Anemia++ due to iron deficiency. Cancer. Inflammation or infection, Surgery, especially splenectomy (removal of the spleen). Who gets thrombocytosis? The condition is found most often in older people. In fact, most people with the condition are diagnosed at about age 60. Most people with high platelet counts don’t have symptoms, at least at the beginning. If you do have symptoms, they can include: Skin bruising. Bleeding from places like the nose, mouth and gums. Bleeding in the stomach or intestinal tract.. Abnormal blood clotting can also occur, leading to stroke, heart attack and unusual clots in the blood vessels of the abdomen. Some patients with essential thrombocythemia develop erythromelalgia, a condition that causes pain, swelling and redness of your hands and feet. Numbness and tingling also occur. Finding the underlying condition (such as iron deficiency anemia, cancer or infection) can aid in the diagnosis and management of thrombocytosis. If no secondary cause is identified, it’s important to rule out essential thrombocythemia. Your healthcare provider may order a blood test for a specific gene, called JAK2, which is used to diagnose ET. However, it is positive in only about 50% of the cases. Other gene mutations are also tested, but are only positive in a low percentage of people. Your provider may suggest a bone marrow biopsy to help confirm the diagnosis. People who have no symptoms may remain stable and only require routine check-ups by their physician. Secondary forms of thrombocytosis rarely require treatment. For those with symptoms, a few treatment options are available. One is to treat the disease that is causing thrombocytosis. In some cases, you can take aspirin to help prevent blood clots. The low dose used for this purpose does not usually cause stomach upset or bleeding. In essential thrombocythemia, medications such as hydroxyurea or anagrelide are used to suppress platelet production by the bone marrow. These medications usually have to be taken indefinitely. Treatment with interferon is sometimes necessary but is associated with a greater number of side effects. Newer agents are now being developed in an effort to suppress the overproduction of platelets. In cases of severe life-threatening thrombocytosis, a procedure called plateletpheresis is performed to immediately lower the platelet count to safer levels. In this procedure, a special instrument is used to remove blood, separate and remove the platelets, and then return the other blood cells to the patient. Secondary thrombocytosis gets better when the underlying problem causing the high platelet count resolves. This could mean that your infection is treated or you recover from your surgery. Even though the platelet count is elevated for a short time (or even indefinitely after splenectomy), secondary thrombocytosis does not typically lead to abnormal blood clotting. Primary thrombocytosis, or essential thrombocythemia, can cause serious bleeding or clotting complications. These can usually be avoided by maintaining good control of the platelet count with medications. After many years of having the disease, however, bone marrow fibrosis (scarring) can develop. In a small percentage of patients, essential thrombocythemia can lead to leukemia. Cleveland Clinic is a non-profit academic medical center. Advertising on our site helps support our mission. We do not endorse non-Cleveland Clinic products or services. Policy Return to Article Details Study of iron deficiency anemia with thrombocytosis in association with serum erythropoietin levels What every physician needs to know: Thrombocytosis is defined as a platelet count greater than two standard deviations above normal, or above 400,000 per microliter in most clinical laboratories. In approaching a patient with an elevated platelet count, the clinician must first verify that the count is elevated consistently. Several transient reactive responses (for example, inflammation and certain infections) are known to increase platelet levels temporarily. Those responses are of little or no long-term consequence, except as determined by the underlying inciting event. If two measurements 3 months apart are clearly elevated, the clinician should determine the cause of the thrombocytosis. There are many causes of bone fide thrombocytosis, and one cause of “distributive” thrombocytosis (in which the asplenic patient redistributes [usually temporarily] the one third to one half of total body mass of platelets that normally pool in the spleen, into the peripheral blood stream). This “distributive” thrombocytosis is rarely of any consequence to the patient. In contrast, bone fide, consistent thrombocytosis is usually due either to a primary marrow disease of excess myeloproliferation, usually polycythemia vera (PV) or essential thrombocythemia (ET), or is far more commonly reactive, usually due to iron deficiency or chronic inflammation. In most individuals with thrombocytosis, treatment can await, if treatment is indicated at all, a specific causative diagnosis. It is very unusual that treatment for thrombocytosis is emergent; the only indication for the acute lowering of an elevated platelet count is ongoing arterial thrombosis (coronary, cerebral, peripheral), in which case platelet apheresis plus/minus platelet function inhibition is the treatment of choice. In nearly every case in which platelet apheresis is performed for thrombocytosis, the cause is a myeloproliferative neoplasm. In the chronic setting, treatment is usually indicated only for thrombocytosis due to a myeloproliferative neoplasm (see “What therapies should you initiate immediately and under what circumstances – even if root cause is unidentified?”). This is likely due to one of many functional abnormalities present in the blood cells of patients with ET or PV, in contrast to the functionally normal platelets and other blood cells produced in patients with reactive thrombocytosis. The diagnosis of a myeloproliferative neoplasm is usually made by a careful history (fevers, sweats, weight loss, early satiety, ruddy complexion), physical examination (splenomegaly, skin color), laboratory examination (complete blood count, including leukocyte differential), radiological evaluation (abdominal ultrasound), and, more recently, molecular testing for the acquired mutations (e.g. Jak2V617F, calreticulin or the thrombopoietin receptor [c-Mpl] missense mutations) that are commonly found in such patients. In addition to a definitive diagnosis, identification of one vs. two alleles of Jak2V617F may have some prognostic benefit in patients with PV, and identification of a mutation in calreticulin may reveal a more benign outcome for such patients than those with a mutation in Jak2. What features of the presentation will guide me toward possible causes and next treatment steps: World-wide, iron deficiency is the most common cause for reactive thrombocytosis. The symptoms of anemia are reduced energy, lethargy, exertional dyspnea, cardiac palpitations, and, when extreme, coronary insufficiency or other end organ ischemia. Iron deficiency presents like most other causes of anemia, although the peculiar symptoms of pica (craving for ice, clay, or other unusual “foods”), perioral cheilitis, and glossitis can occur when iron deficiency is severe or very long standing. The second major cause of reactive thrombocytosis is inflammation; usually, the symptoms and signs of rheumatoid arthritis, inflammatory bowel disease, and cancer, the leading causes of inflammation induced reactive thrombocytosis, are obvious. In such cases, treatment of the underlying disorder is called for, and if successful, almost always eliminates the thrombocytosis. In contrast, the presentation of a myeloproliferative neoplasm is usually subtle, or found upon routine blood testing. Occasionally, an acute thrombosis of the coronary arteries, cerebral arteries, or deep venous or hepatic vein thrombosis is the presenting feature of a myeloproliferative neoplasm such as PV or ET. It is in this setting, or thrombosis in a patient known to have ET, that emergent treatment with apheresis may be required. What laboratory studies should you order to help make the diagnosis and how should you interpret the results? The first diagnostic test is nearly always a complete blood count (CBC) with a differential leukocyte count. By definition, the platelet count is elevated in everyone with thrombocytosis, but the presence of abnormalities in other blood cell types will often lead one to the correct diagnosis. For example, an elevated leukocyte count could indicate inflammation, especially if neutrophilia is noted, or if basophilia and/or eosinophilia are noted, the likelihood of a primary myeloproliferative neoplasm rises substantially. An elevated red cell count could indicate PV, as inflammation and iron deficiency both cause anemia, and an examination of the red cell mean corpuscular volume (MCV) is important, as a patient with PV who is also iron deficient (such patients have an increased incidence of gastrointestinal bleeding) may present with normal or low red cell counts, and only with thrombocytosis. Once the CBC is evaluated, other laboratory tests that confirm specific diagnoses are appropriate. If inflammation is suspected, a C-reactive protein might confirm that suspicion, and more specific tests (evaluations for rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease) will usually confirm the diagnosis. If iron deficiency is suspected because of an appropriate patient history and low MCV, serum iron, iron binding capacity, and ferritin levels will nearly always establish the diagnosis. If a primary marrow disorder is suspected, the Jak2V617F test will establish a myeloproliferative neoplasm as causative, and while positive in nearly every person with PV, it is positive in only about 50% of patients with ET. A mutation in c-Mpl is found in an additional 5-10% of patients with ET, and mutation of the calreticulin gene is found in most of the remaining patients. A bone marrow exam can also strongly suggest a diagnosis of ET, marked by megakaryocytic hyperplasia, but occasionally, ET is a diagnosis of exclusion. What conditions can underlie thrombocytosis: The most common causes of thrombocytosis are iron deficiency, inflammation due to other conditions, and acute infections (for example, pneumonia, especially in children). Myeloproliferative neoplasms, ET and PV are not uncommon, each present in about 1 in 100,000 individuals in the population. Other rare causes are congenital, inheritance of a mutant form of the thrombopoietin or thrombopoietin receptor genes, or paraneoplastic production of a megakaryocyte active cytokine, such as interleukin 6 or thrombopoietin. When do you need to get more aggressive tests? If iron deficiency or inflammation is present, no further tests are warranted. If a primary myeloproliferative disease is suspected, a test for mutant Jak2 is warranted, as it establishes the diagnosis, and while still not absolutely certain, there is much evidence supporting the idea that gene dosage (one or two copies of the mutant gene) is prognostic for thrombotic complications A similar consideration exists for screening for mutations in c-Mpl receptor or calreticulin, especially since the various mutations predict prognosis in primary myelofibrosis (calreticulin=good, Mpl and Jak2=intermediate, and no mutations=poor). What imaging studies (if any) will be helpful? Occasionally, abdominal ultrasound can reveal a modest splenomegaly or hepatic or portal vein thrombosis, not obvious on physical examination, and point to either chronic inflammation (which is usually obvious), or a primary myeloproliferative neoplasm. What therapies should you initiate immediately and under what circumstances – even if root cause is unidentified? The only indication for emergent therapy of thrombocytosis per se (as opposed to emergent therapy for one of the inflammatory causes of thrombocytosis) is impending or ongoing thrombosis, either arterial or venous. Such circumstances are almost always found in the setting of a myeloproliferative neoplasm, PV, or ET. The platelet count should be reduced immediately by daily apheresis, and if/once a myeloproliferative neoplasm is confirmed, therapy with a cytoreductive agent (almost always hydroxyurea), and unless contraindicated (because of bleeding), an anti-platelet function agent should begin immediately. What other therapies are helpful for reducing complications? As for all acute thrombotic events, interventions aimed at restoring blood flow are paramount, and their effectiveness time limited. Thrombolytic therapy, percutaneous coronary intervention with stenting, cerebral vascular interventions, and bypass surgery are all appropriate for certain settings. Once out of the acute setting, anti-platelet agents to reduce thrombotic complications are usually indicated. More recently, Jak2 inhibitors have become available for the treatment of Jak2 mutation-positive primary myelofibrosis. This treatment is usually reserved for patients who have failed other modalities, but does reduce complications related to splenomegaly, and very recent studies suggest it can improve survival of patients with primary myelofibrosis (the third major myeloproliferative neoplasm). Whether Jak2 inhibitors will prove useful in patients with ET will require clinical trials, currently underway. What should you tell the patient and the family about prognosis? For most patients with thrombocytosis, the elevated platelet count is inconsequential, and the patient’s prognosis dependent entirely on the underlying cause of marrow reactivity (iron deficiency, inflammation). In patients with myeloproliferative neoplasms (PV, ET most common), prognosis is usually good, with minimal impact on long-term survival in most patients, especially since these disorders are more common in older individuals. In the past, several therapies that greatly increased the risk of transformation of PV and ET to acute leukemia were used (for example, radioactive phosphorus or alkylating agents), and this dictated prognosis. Today, with hydroxyurea as the primary therapy, and several anti-platelet agents to help reduce the risk of thrombosis, the prognosis has improved as only an occasional patient develops these complications. “What if” scenarios. Occasionally, a patient with bone fide myeloproliferative neoplasm induced thrombocytosis, who is at high risk for thrombosis, does not tolerate hydroxyurea. Alternate therapies include anagrelide, and interferon. Each have their drawbacks, but are occasionally useful to reduce platelet counts toward normal when indicated. Pathophysiology The pathophysiology of reactive thrombocytosis is becoming increasingly understood, at least for those patients in which inflammation is the causative mechanism. Interleukin (IL)-6 is a well known inflammatory mediator, released from leukocytes stimulated with bacterial or tissue breakdown products, which then acts on hepatocytes to stimulate the production and release of thrombopoietin, the primary regulator of platelet production. Some cases of cancer associated thrombocytosis are also due to either the inflammation evoked by the cancer, or by direct tumor production of IL-6. Far less understood is the cause of iron deficiency induced thrombocytosis. Initially, reports focused on erythropoietin as the thrombocytosis-inducing hormone, based on the hypothesis that the structural similarity of thrombopoietin and erythropoietin allows the latter, elevated in patients with iron deficiency anemia, to cross react with the thrombopoietin receptor, enhancing platelet production. However, this hypothesis does not account for the unique linkage between iron deficiency and thrombocytosis (erythropoietin is elevated in most patients with anemia but platelets are elevated only in iron deficiency anemia), or the fact that erythropoietin does not cross react with the thrombopoietin receptor. The pathophysiology of the myeloproliferative neoplasms is becoming increasingly well understood. Mutation of the pseudokinase domain of the signalling kinase Jak2 causes its activation, with subsequent activation of a number of downstream signalling pathways, for the most part identical to the binding of an activating growth factor. Mutation of the thrombopoietin receptor, c-Mpl, activates the receptor akin to binding thrombopoietin, again driving cell growth. Most recently, truncation mutations of the calreticulin gene, an endoplasmic reticulum (ER) chaperone and calcium buffering protein, has been shown to eliminate the ER tether, allowing the remainder of the protein to bind to c-Mpl and activate it. What other clinical manifestations may help me to diagnose thrombocytosis? Most patients with PV or ET are asymptomatic, but a ruddy complexion (in PV), early satiety (due to splenomegaly, in PV or ET), erythromelalgia (pain in the distal extremities, in PV), or pruritis (due to basophils, in PV or ET) can indicate a myeloproliferative disease. 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