THROMBOCYTOSIS

TERM DEFINITION

Thrombocytosis refers to a platelet count platelet count greater than two standard deviations above normal, typically > 450 x 10^9/L*

PLATELET COUNT > 450 X 10^9/L

** Some use 400 x 10^9/L as their cutoff for thrombocytosis*

Extreme thrombocytosis is defined as a platelet count greater than 1,000 x 10^9/L, otherwise known as the "millionaire's club" (million platelets per uL)

CAUSES

In approaching a patient with an elevated platelet count, the clinician must first verify that the count is elevated consistently

PRIMARY*

- Essential thrombocythemia
- Other myeloproliferative neoplasms (MPN)
- Myelodysplasia (MDS)
- Familial

** Caused by defect intrinsic to hematopoietic progenitors*

SECONDARY (REACTIVE)

- Infection
- Malignancy
  (paraneoplastic thrombocytosis)
- Chronic inflammation
- Iron deficiency
- Hemolytic anemia
- Hemorrhage
- Post-splenectomy
  ("constitutive" thrombocytosis)
- Drugs
  (thrombopoietin (r-PO),r-PO agonists, vincristine, adrenalin)

CLINICAL PEARLS

Patients with primary, but not secondary, thrombocytosis are at increased risk for clotting

Post-splenectomy thrombocytosis peaks about 17 days after surgery, stabilizes after 45 days

Extreme thrombocytosis (≥ 1,000-1,500 × 10^9/L) in MPN may be associated with a paradoxical increased risk of bleeding due to acquired von Willebrand disease

Some have proposed that thrombocytosis in iron deficiency anemia may be an adaptive response to reduce continued blood loss

Treatment for thrombocytosis is rarely emergent unless extensive clotting

Familial thrombocytosis caused by germ-line mutations in thrombopoietin or its receptor

CLINICAL PRESENTATION

PRIMARY THROMBOCYTOSIS

- Often asymptomatic
- Vasomotor symptoms (e.g., changes in vision, headache, erythromelalgia)
- History of thrombosis or bleeding
- Splenomegaly

SECONDARY THROMBOCYTOSIS

- Patients rarely present with thrombotic or hemorrhagic symptoms, even at platelet count > 1,000 × 109/L
- Patients with thrombocytosis may present with symptoms referable to an underlying tumor or inflammatory condition

LABS

- CBC and differential
- Peripheral smear
- Iron studies
- CRP, other markers of inflammation
- Specific tests for systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD)
- If high suspicion for MPN, test for mutant JAK2, MPL or CALR
- If suspect splenomegaly, abdominal ultrasound
- If clinical history suggests possible solid tumor, consider appropriate imaging
- If signs of mucocutaneous bleeding and/or bruising, check von Willebrand factor antigen and activity

Because **secondary, or reactive, thrombocytosis** is not associated with an increased risk of thrombosis or hemorrhage, there is no indication to treat with anti-platelet agents or platelet-lowering[3] modalities. Management is targeted to the underlying condition, for example infection, inflammation or malignancy. Resolution of the underlying cause will lead to normalization of the platelet count.

In contrast, since **primary thrombocytosis** is associated with an increased risk of thrombosis and hemorrhage, treatment is usually indicated. Clinical practice guidelines are available to inform treatment decisions, including the use of aspirin, hydroxyurea and plateletpheresis. However, there is no evidence that the platelet count per se correlates with risk.

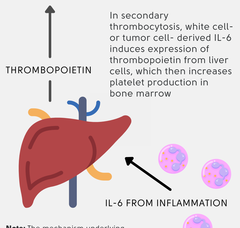
MANAGEMENT

If the **diagnosis is not certain** (i.e., primary vs. secondary thrombocytosis), and the patient is experiencing thrombo-hemorrhagic complications, then platelet-lowering therapies should be considered

PROXIMATE MECHANISMS

Platelets are produced by megakaryocytes in the bone marrow through a process called megakaryopoiesis

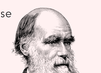
MEGAKAYOPOIESIS



In secondary thrombocytosis, white cell- or tumor cell- derived IL-6 induces expression of thrombopoietin from liver cells, which then increases platelet production in bone marrow

Note: The mechanism underlying thrombocytosis in iron deficiency is not well understood, but may involve increased commitment to megakaryocytic lineage

EVOLUTIONARY MECHANISMS



Why do platelets increase in secondary thrombocytosis? Is this an adaptive response that permits improved hemostasis in the setting of iron deficiency (which is almost always from blood loss), hemorrhage and inflammation? Or do platelets carry out other - poorly defined - functions such as hosts defense against microbial invasion, or participation in inflammatory and immune responses? And if so, do increased numbers of platelets translate into improved functions.

In the context of tumor cell evolution, it has been proposed that tumor-mediated activation of platelets during the metastatic cascade leads to the release of platelet-derived factors stored in their granules that then mediates the inflammatory, proliferative, and proangiogenic activities of platelets to promote tumor growth, tissue invasion, and metastasis. In other words, platelets become coopted during tumor growth to aid and abet tumor progression.

HISTORY OF MEDICINE

Platelets were first described as a formed element of the blood by Donne in 1842. 40 years later, their role in the blood clotting process was uncovered. In 1878, Haymen provided the first accurate counts of platelets. Over the next couple of decades, it was shown that the platelet count is not infrequently increased in a number of conditions including pyogenic infections, tuberculosis, malignancy, post-op state, post-splenectomy, CML and polycythemia vera. In the 1930s, there was increasing recognition of a chronic disorder variably termed **hemorrhagic thrombocythemia, essential thrombophilia and essential thrombocythemia** that was associated with isolated elevation in platelet count and an increased risk of hemorrhage and thrombosis. At that time:

Thrombocytosis = secondary elevation of platelet count
Thrombocythemia = primary elevation of platelet count

... just as leukocytosis differs from leukemia

NOTES

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