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PRACTICE

RATIONAL TESTING

Investigating thrombocytosis

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What you need to know

- Thrombocytosis is usually reactive or caused by clonal disorders
- Initial assessment includes repeat history and examination, a peripheral blood smear examination, and determination of iron and acute phase reactant status
- If no cause of inflammation is found, consider investigations for an occult malignancy or seek specialist advice for investigation of a clonal haematopoietic disorder

A 47 year old woman presents to her general practitioner complaining of feeling tired all the time. She is an ex-smoker and has a history of irritable bowel syndrome. Examination is normal. A full blood count is normal except for a platelet count of 725×10^9/L.

How common is thrombocytosis?

Thrombocytosis is defined as a platelet count elevated more than two standard deviations above the population mean, typically >400-450×10^9/L, and therefore includes 2.3% of the population.[1] Reference ranges usually do not account for variation in platelet counts dependent on age, sex, and ethnicity,[2 3] such that the upper limits of normal should be lower in older individuals and men.[4] Approximately 25% of the UK adult population attending primary care will have a full blood count (FBC) in any one year.[5] Thrombocytosis is a common incidental finding in 1.5% to 2.2% of the population aged >40 consulting primary care.[6]

What causes thrombocytosis?

The differential diagnosis for thrombocytosis is broad (table) and the diagnostic process can be challenging.[7] Rarely, non-platelet structures in peripheral blood can be erroneously counted as "platelets" in automated FBC counters, leading to a spurious thrombocytosis.[8] The two main classes of genuine thrombocytosis are secondary or reactive causes and primary or clonal causes (ie, haematological neoplasms) (box 1). In one cohort study of 732 people with an elevated platelet count, the thrombocytosis in 80-90% of patients was reactive to an underlying inflammatory cause.[9]

Box 1: Definitions

- **Reactive thrombocytosis**—proliferation of platelets is caused by a response to growth factors released from an underlying inflammatory or malignant condition, and is not due to a primary haematological disorder. The platelet count should normalise after resolution of the acute disease state
- **Clonal thrombocytosis**—caused by underlying myeloproliferative or myelodysplastic neoplasm. A growing number of acquired "driver" mutations causing autonomous proliferation through aberrantly activated cellular signalling pathways have been identified, most commonly JAK2 V617F

Reactive thrombocytosis

Reactive thrombocytoses are driven by thrombopoietic growth factors released in response to acute blood loss, iron deficiency, haemolysis, malignancy, infections, and acute or chronic inflammatory states, notably rheumatological conditions or tissue damage.[1] These factors, including thrombopoietin, regulate the differentiation and proliferation of the platelet "parent" cell, the megakaryocyte.

A large prospective cohort study[6] highlights the diagnostic importance of an incidental finding of thrombocytosis in general practice. The 12 month incidence of all cancers was higher in patients with thrombocytosis (11.6% in men, 6.2% in women) than in those without (4.1% in men, 2.2% in women). Paraneoplastic thrombocytosis is a poor prognostic feature in many solid tumours.[10]

Clonal thrombocytosis

Clonal thrombocytosis arises from an expansion of a mutated haematopoietic stem cell or myeloid progenitor cells, which give rise to megakaryocytes.[11] It is most characteristic of essential thrombocythaemia but is also seen in other myeloproliferative neoplasms (MPNs) such as polycythaemia vera, primary myelofibrosis, and chronic myeloid leukaemia,

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and in some myelodysplastic syndromes. Diagnostic criteria exist for MPNs[12] and they should be managed in conjunction with a haematologist or other specialist experienced in treating these conditions. Essential thrombocythaemia is associated with a relatively high risk of thrombotic complications, such as stroke and venous thromboembolism.[13] Risk scores based on patient and disease factors can help guide decisions on the use of prophylactic antiplatelet agents or cytoreductive therapies to reduce platelet counts.[7]

How to assess a patient with thrombocytosis

See fig 1.

History and examination

A thorough history and examination should identify most common reactive causes of thrombocytosis: underlying infection, chronic disease, malignancy, anaemia, previous splenectomy, or recent surgery (table). Most patients with clonal thrombocytosis are asymptomatic, but some experience vasomotor symptoms (headaches, visual changes, atypical chest pains, or distal limb pain), bleeding complications (due to acquired von Willebrand factor disease), and thrombotic complications.[14] Constitutional symptoms such as fatigue and pruritus are common in myeloproliferative disorders and can substantially impair quality of life.[15] Hepatosplenomegaly suggests a primary blood disorder. No clear correlation exists between symptoms and platelet counts: while control of the underlying MPN generally leads to the disappearance of vasomotor symptoms,[14] patients with platelet counts $>1000\times10^9$/L due to reactive thrombocytoses are usually asymptomatic.[7] Symptoms thus likely reflect underlying qualitative platelet abnormalities seen in MPNs.

Initial investigations

The British Society for Haematology guidelines for investigating thrombocytosis recommend three initial investigations[7]:

• *Peripheral blood smear*—This is an inexpensive means to confirm genuine thrombocytosis and exclude spurious causes. It may also help differentiate between causes such as acute infection (neutrophilia or "left shift"), iron deficiency (hypochromia or microcytosis, pencil poikilocytosis), hyposplenism (Howell-Jolly bodies), or myelofibrosis (tear drop poikilocytes and a leucoerythroblastic film). Abnormal platelet morphology can be helpful, for example large platelets can be seen in essential thrombocythaemia (fig 2). An accompanying polycythaemia or leucocytosis (particularly basophilia or eosinophilia) may also suggest a clonal disorder.

• *Acute phase reactants*—Raised inflammatory markers such as c-reactive protein or erythrocyte sedimentation rate support a diagnosis of reactive thrombocytosis, although normal values do not exclude inflammation or malignancy. Similarly, elevated levels do not exclude the possibility of a clonal cause.

• *Iron status*—Iron deficiency anaemia (IDA), causing microcytic anaemia, occurs in around 2% to 5% of adults.[16] It is a potentially treatable cause of reactive thrombocytosis. A low serum ferritin confirms IDA with a specificity close to 100%.[17] Interpretation of iron studies can be complicated by intercurrent inflammation raising ferritin levels; other means of determining iron status may be required.[17] Investigate confirmed IDA and manage according to standard guidelines.[16]

What other investigations could be considered?

Repeat FBC

A repeat FBC might be requested according to clinical judgment to check either resolution or persistence of the thrombocytosis. If a reactive cause is suspected at presentation, repeat testing should confirm the thrombocytosis has resolved following appropriate management. No standard definition exists for "persistent thrombocytosis," but for practical purposes it could be thrombocytosis for more than three months from initial assessment. In an Italian cohort of 10 000 asymptomatic individuals, <10% of patients with an initial incidental thrombocytosis had persistently raised platelet counts on repeat testing at eight months.[18] In the same study, only two patients were diagnosed with polycythaemia vera and three patients with essential thrombocythaemia at follow-up.

Investigating for occult malignancy

In most patients, a comprehensive clinical assessment will identify the underlying cause of any thrombocytosis. However, subclinical disorders may cause a reactive thrombocytosis, potentially facilitating the earlier detection of a serious underlying malignancy. In one prospective study, one third of the 1200 patients under 40 with thrombocytosis subsequently diagnosed with lung or colorectal cancer had no symptoms that met current referral criteria.[6]

In the UK, national guidelines recommend cancer investigations and referrals at a 3% positive predictive value (PPV) threshold, with investigations guided by accompanying symptoms and risk factors.[19] While the PPV of *asymptomatic* thrombocytosis for finding any cancer is not known, subsequent investigation should be based on clinical assessment.[6] Thrombocytosis is associated with increased risk of a malignant diagnosis in various sites (particularly lung, endometrial, gastro-oesophageal, colorectal, renal, and ovarian cancers) but not breast cancer.[20] Current UK guidance recommends that patients ≥40 with thrombocytosis should be considered for a chest radiograph within two weeks (lung cancer), and women ≥55 with thrombocytosis and unexplained vaginal discharge or macroscopic haematuria should be considered for a pelvic ultrasound (endometrial cancer).[18] Clinicians may consider faecal immunochemical testing (colorectal cancer).[21] Beyond this, there is limited evidence on how to investigate for occult malignancy.[20] While cancer incidence rises with increasing platelet counts,[6 22] there is no clear cut-off value at which malignancy becomes more likely. Further work is needed before recommendations can be made based on platelet count alone,[7 22] and clinical judgment should be used.

Specialist haematology investigations

Specialist investigations are required in patients with persistent unexplained thrombocytosis and in those with thrombotic complications or features of primary haematological disorders. Haematological investigations may include molecular testing for known driver mutations (such as *JAK2 V617F, MPL, BCR-ABL,* and *CALR* mutations*)* and often cytogenetics and bone marrow aspirate and trephine.[7]

Outcome

In our patient, repeat platelet counts remained elevated and no evidence of inflammation or occult solid organ malignancy was identified. Chest radiograph was normal. A diagnosis of essential

thrombocythaemia was made by haematologists based on a persistently elevated platelet count, abnormal bone marrow biopsy, and the presence of a driver *JAK2 V617F* mutation. Owing to her age and platelet count, she was classified as intermediate risk for thrombotic complications.[7] She was started on aspirin and screened for cardiovascular risk factors. Cytoreductive therapy in the form of hydroxycarbamide was not indicated.[7]

How patients were involved in the creation of this article

The vignette in this article is fictitious. No patients were involved in the creation of this article.

Education into practice

- What baseline tests are required for investigating an incidental finding of thrombocytosis?
- What other features of a blood count suggest a clonal disorder?
- When might you contact specialist teams for further investigations in patients with thrombocytosis?

How this article was made

We synthesised specialist national guidelines on assessing and managing thrombocytosis with recent research on investigating incidental platelet counts as a marker of underlying malignancy for the generalist audience. We searched PubMed for relevant articles on “thrombocytosis” and “malignancy”

Contributors AM wrote the first draft and all authors reviewed and contributed to the writing of the article.

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Table

Table 1| Causes of thrombocytosis

Reactive thrombocytosis/acute phase responses
Iron deficiency
Infection (typically bacterial in adults, less specific and commoner in children)
Rheumatological disorders
Inflammation
Recent surgery or trauma
Malignancy
Hyposplenism/ previous splenectomy
Others, eg, acute bleeding and drugs
Clonal thrombocytosis
Myeloproliferative neoplasms (essential thrombocythaemia, polycythaemia vera, primary myelofibrosis, chronic myeloid leukaemia)
Other primary marrow disorders, eg, chronic myelomonocytic leukaemia, myelodysplasia and overlap syndromes
Other causes
Spurious thrombocytosis, eg, red cell abnormalities (microspherocytes, fragments, etc)
Hereditary thrombocytosis

Figures

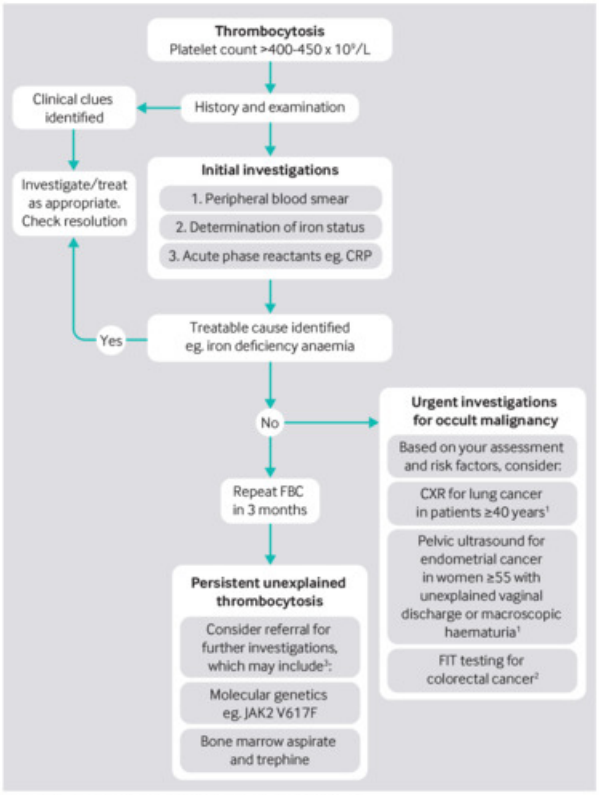

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Fig 1 Algorithm for investigating thrombocytosis

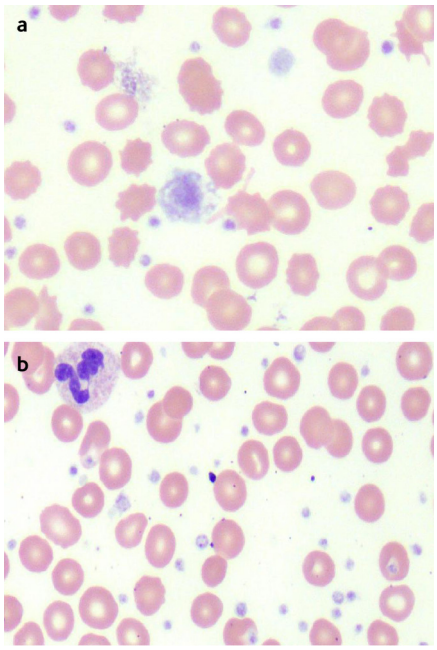

Fig 2 Blood films in a patient with a myeloproliferative neoplasm (a) and in a patient with a reactive thrombocytosis (b). In (a) the platelets are abnormally large, but in (b) the platelets appear normal