

Acute Myocardial Infarction: An Unusual Presentation of Essential Thrombocytosis in a 17-Year-Old Man

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Primary thrombocytosis is extremely rare in childhood.¹ Thrombotic events are a recognized complication of clonal thrombocytosis and are predicted in childhood by a prior history of thrombotic events or a platelet count greater than $1,500 \times 10^9/L$. In adults, the same factors predict future thrombotic events, with the addition of cardiovascular risk factors and advanced age. Acute coronary syndrome associated with thrombocytosis is very uncommon in adults under the age of 40, with rare case reports.² We report the case of a 17-year-old male who presented with an acute ST segment–elevation myocardial infarction (MI) following a 3-year history of mild idiopathic thrombocytosis eventually attributed to essential thrombocytosis (ET).

Case Report

A 17-year-old man presented to our emergency room with a 6-hour history of acute substernal chest discomfort, rated a seven on a conventional ten-point scale, associated with diaphoresis and nausea. Admission electrocardiogram revealed ST-segment elevation in the anterolateral leads. He denied a history of recreational drug use, steroid abuse, or chest trauma. The patient had no risk factors for coronary artery disease. Three years prior to presentation, mild asymptomatic thrombocytosis (platelet count $600 \times 10^9/L$) had been detected on a routine screening examination. The patient's father was also reported to have a low-grade thrombocytosis ($600 \times 10^9/L$), with no history of thrombotic episodes. For 2 years prior to presentation in the emergency room, the patient had been followed by a local hematologist who performed screening tests



Figure 1. Coronary angiography demonstrating thrombus in mid-left anterior descending artery (LAD) and complete occlusion of the distal LAD.

for secondary causes of thrombocytosis, all of which were negative. His platelet count remained fairly stable, with a complete blood count performed 4 months prior to presentation showing a platelet count of $800 \times 10^9/L$. A bone marrow biopsy was not performed at that time due to the presumed benign nature of his disease and lack of risk factors for complications.

In the emergency room, the patient was treated with aspirin, clopidogrel, metoprolol, and abciximab and was taken immediately to the cardiac catheterization laboratory. Angiography showed a layered mid–left anterior descending thrombus with complete occlusion of the distal left anterior descending artery (Figure 1). The patient had no signs of underlying atherosclerotic disease. The distal left anterior descending thrombus was aspirated with a

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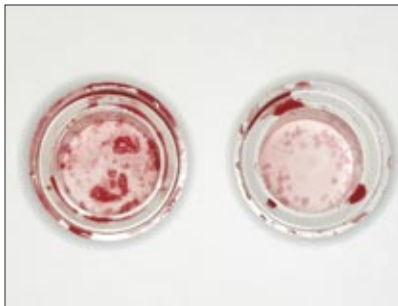


Figure 2. Aspirated thrombus.

Pronto (Vascular Solutions) extraction catheter, revealing a large amount of white thrombus consistent with platelet thrombus (Figure 2). A hematoxylin and eosin smear was performed on the thrombus confirming the primary platelet-rich composition (Figure 3). There was a vast improvement in clot burden postthrombectomy, with TIMI-3 flow into the distal left anterior descending artery and resolution of the patient's symptoms. After percutaneous coronary intervention, he was transferred to the coronary care unit with continued heparin and tirofiban treatment. Upon arrival at the coronary care unit he was started on hydroxyurea and emergent platelet pheresis, with a subsequent decrease in his platelet count from $917 \times 10^9/L$ to $459 \times 10^9/L$.

Additional evaluation revealed normal hemoglobin concentration, an elevated white cell count of $25.1 \times 10^9/L$ with a 90% neutrophil differential, and an elevated platelet count of $917 \times 10^9/L$. Peripheral blood smear showed normal red blood cell and platelet morphology with an overall elevated platelet count. Renal function was normal. A urinary drug screen was negative for cocaine or amphetamines. Chest radiograph was unremarkable. No splenomegaly was detected on either physical examination or computed tomography evaluation of the abdomen. Blood cultures drawn on admission were negative, and the patient remained afebrile during the entire admission, having no signs of active infection. Five days after undergoing cardiac catheterization, with a platelet count of $470 \times 10^9/L$, he was discharged on aspirin, clopidogrel, atorvastatin, lisinopril, metoprolol, and hydroxyurea.

Given the patient's high risk for future thrombosis, treatment with hydroxyurea continued after hospitalization with close monitoring. A platelet count of approximately $450 \times 10^9/L$ was maintained during treatment, with no sign or symptom to suggest new microvascular or macrovascular thrombosis or hemorrhage. A bone marrow examination, which was deferred on initial presenta-

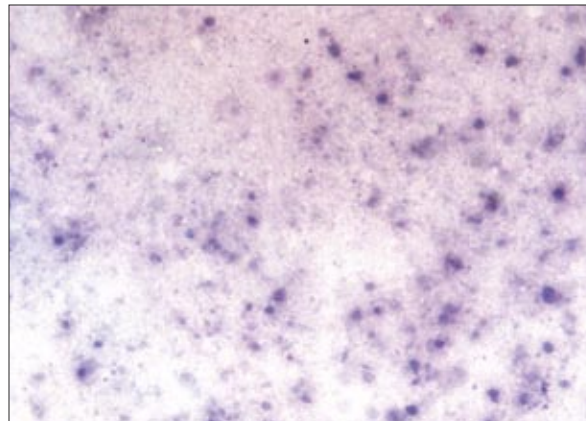


Figure 3. Hematoxylin and eosin stain of aspirated thrombus confirming platelet composition.

tion because of the high clinical acuity, was performed approximately 2 months after initiation of hydroxyurea treatment. Results showed a moderately hypocellular marrow, likely an effect of hydroxyurea, with trilinear maturation and no significant morphologic abnormalities. Iron and reticulin stains were normal as was chromosomal analysis. Fluorescence in situ hybridization for *BCR-ABL* and peripheral blood genomic DNA polymerase chain reaction analysis for the Janus kinase 2 (*JAK2*) *V617F* mutation were negative.

Follow-up echocardiography 6 months after the patient's acute MI showed a normal left ventricular ejection fraction with no residual wall motion abnormalities. Eight months after his acute MI, the patient has had no further cardiopulmonary complaints or signs or symptoms of thrombus or hemorrhage. His platelet count has remained adequately suppressed on hydroxyurea, which he continues without significant side effects.

Although the patient's bone marrow examination and evaluation for disease-specific cytogenetic markers were negative, revealing no evidence of an ongoing clonal process, the patient's history of idiopathic chronic thrombocytosis with acute coronary arterial platelet thrombosis is clinically most consistent with ET, alternatively representing an inherited form of the disease.

Discussion

Thrombocytosis, often found incidentally, is most commonly a reactive or secondary response to chronic inflammation, iron deficiency, active malignancy, infection, surgery, or trauma. In a small number of cases, however, thrombocytosis may be attributable to a clonal process,

such as one of the four well-described classic myeloproliferative disorders (MPDs): chronic myelogenous leukemia (CML), polycythemia vera (PV), agnogenic myeloid metaplasia (AMM), and ET. Rare cases of familial thrombocytosis, an autosomal dominant disorder caused by a gain-of-function mutation in the thrombopoietin gene, have been identified as well.^{3,4} Unfortunately, making the distinction between reactive and clonal thrombocytosis, although clinically important, is often difficult in practice due to the absence of definitive clinical or laboratory findings to differentiate the two entities. Attributing thrombocytosis to a clonal disorder, a decision with important therapeutic implications, requires a thorough evaluation to rule out the potentially treatable causes of reactive thrombocytosis.

To date, CML is the only condition of the classic MPDs with a disease-defining genetic mutation, the *BCR-ABL* rearrangement. The remainder of the classic MPDs, including ET, are currently classified as *BCR-ABL*-negative MPDs. A diagnosis of ET is entertained when persistent nonreactive thrombocytosis is present and the other MPDs are excluded. The primary feature of ET is an increase in megakaryocyte count and platelets, which likely has its roots in an acquired disruption of the signaling process involved in thrombopoiesis. The exact molecular cause of this disruption may be unique in different subsets of patients, creating disease heterogeneity. Rare cases of inherited forms of ET have been described as a result of gene defects in thrombopoietin and its receptor, *c-Mpl*.⁵

A mutation in the gene for *JAK2*, a cytoplasmic protein-tyrosine kinase, has recently been linked to a significant number of patients with ET, PV, and AMM.⁶⁻⁹ Although it is not specific for any particular MPD, this mutation, if present, does help to narrow the differential diagnosis of thrombocytosis, essentially eliminating CML and reactive causes from consideration. The *JAK2* mutation is described as occurring in 23–57% of patients with ET.¹⁰

Approximately 40–90% of patients with ET are symptomatic at presentation with vasomotor symptoms, thrombosis, and/or hemorrhage.¹¹ Thrombosis, when it occurs, is more common in the arterial vascular bed (75%) than in the venous circulation (25%).¹² Platelet-mediated vasomotor symptoms such as headache, lightheadedness, and transient visual disturbances mimicking migraine headaches, as well as syncope and focal neurologic deficits, are present in about 30–40% of patients.¹³⁻¹⁵ A large number of patients, however, remain asymptomatic.

Thrombosis and hemorrhage are the most common and feared complications of ET. Bleeding tends to occur spontaneously in superficial sites such as the skin and mucus membranes as well as the gastrointestinal or

respiratory tracts. In contrast to thrombosis, the degree of platelet elevation has a direct correlation with the risk of hemorrhage, with bleeding occurring more frequently when platelet counts reach levels greater than $1,500 \times 10^9/L$, likely a result of decreased circulating multimers of von Willebrand factor.¹⁶

The overall risk of thrombotic events in ET, which may include MI, stroke, pulmonary embolism, deep vein thrombosis, transient ischemic attack, retinal artery or venous occlusions, hepatic or portal vein thrombosis, and digital ischemia, has been found to be 6.6% per patient per year in comparison to 1.2% per patient per year in the control population.¹⁷ MI in adult patients with ET does not appear to be a commonly encountered problem, although the exact incidence is unknown given the small cohort of patients presented in the literature, generally in the form of case reports. MI appears to be exceedingly rare in children, with one case report in the Danish literature of a 17-year-old man.¹⁸

A recently published cohort study of patients diagnosed with ET at Mayo Clinic in Rochester, Minnesota, before 1992 suggests that patients diagnosed with ET can expect a normal life expectancy in the first decade after diagnosis, with mortality risk increasing in subsequent years (risk ratio, 2.21; 95% confidence interval, 1.74–2.76). Predictors of increased mortality risk include age greater than 60 years at diagnosis, leukocytosis, tobacco use, and diabetes. Predictors of major thrombotic events are a previous history of thrombosis, age greater than 60 years at time of diagnosis, and leukocytosis. Likewise, the risk of transformation to leukemia or other myeloproliferative disease has been noted to increase from time of diagnosis, with an overall risk of 24% and 58.5%, respectively, at 30 years.¹⁹ Although further research is needed to determine the impact of these data on treatment, it should be aimed at reducing all modifiable risk factors of poor outcomes, with an emphasis placed on prevention of thrombosis. These treatment goals become of heightened importance when the patient is a child and has a lifetime to accrue additional risk factors.

Essential thrombocytosis is extremely rare in the pediatric population, with only 25% of cases occurring in individuals younger than 40 years of age.²⁰ The overall incidence of clonal disorders of platelets is approximately 1 per 10 million in the pediatric population, a 60-fold lower incidence than in the adult population,^{21,22} with the median age at presentation being 11 years.²³ A notable feature of familial thrombocytosis, which has been reported as occurring in 75% of children with clonal thrombocytosis, is the absence of risk for thrombosis and hemorrhage. Otherwise, the presentation, pathogenesis, and disease findings of ET in children appear to be quite similar to those seen in the adult population.¹

Treatment of ET is typically dependent on the relative risk of thrombosis and transformation. Based on the data presented above, patients who are diagnosed after age 60 or who have a history of thrombosis can be considered at high risk. These patients should be treated with a cytoreductive agent such as hydroxyurea. Randomized controlled trials have documented the effectiveness and safety of hydroxyurea in the treatment of thrombocytosis associated with ET, both in comparison to control and in combination with aspirin or anagrelide and aspirin.^{24,25} These studies further suggest that anagrelide is associated with a higher risk of bleeding and transformation than hydroxyurea, which is generally considered the mainstay of treatment in nonpregnant patients with high-risk disease. In cases of hydroxyurea intolerance or pregnancy, interferon- α is considered a reasonable second-line treatment. Low-dose aspirin therapy is recommended for all intermediate- and low-risk patients who are not pregnant, have no history of platelet-related hemorrhage, and do not have a platelet count greater than $1,500 \times 10^9/L$, placing them at risk for significant bleeding events. In cases of intermediate risk with extreme thrombocytosis (platelet count $>1,500 \times 10^9/L$), the need for cytoreductive agents is generally supported, especially when there is a history of bleeding.

In conclusion, although molecular diagnostics did not confirm the diagnosis of ET in this case, our patient by exclusion is either among the 40–70% of patients with ET who do not carry the *JAK2V617F* mutation or is among an unidentified cohort of patients with familial thrombocytosis in which thrombosis does occur. Current literature suggests that familial history does not increase a risk of thrombosis. However, ET, one of the classic *BCR-ABL*-negative myeloproliferative disorders, carries a significant risk of arterial thrombosis and hemorrhage. Diagnosis of ET is dependent on eliminating reactive causes and other forms of MPD. Although it is a recognized occurrence in ET, MI is exceedingly rare, particularly in the pediatric ET population. Treatment, therefore, should be aimed at reducing all modifiable risk factors, mainly markers of cardiovascular disease, and decreasing the risk of future thrombotic and hemorrhagic events by controlling the platelet count with cytoreductive agents in at-risk members of the population.

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Review

Challenges in the Management of Thrombocytosis in Young Patients

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An elevated platelet count is an independent risk factor for poor outcome after myocardial infarction (MI). In a multivariate analysis of over 10,000 patients in the TIMI trials, higher platelet counts after adjusting for other risk factors were significantly associated with an increased risk of the combined endpoint of death, reinfarction, or congestive cardiac failure.¹ For those patients with platelet counts greater than $400 \times 10^9/L$, the multivariate odds ratio was 1.71 (95% confidence interval, 1.16–2.51). Similar findings were reported in the CADILLAC trial in an analysis of over 2,000 patients.²

This challenging case study presented by Kelly and colleagues of a 17-year-old with thrombocytosis who went on to suffer an MI highlights the complexities surrounding the diagnosis of thrombocytosis and appropriate management strategies.³ Three years prior to presentation in the emergency department, the patient, following a routine full blood count, was found to have mild, asymptomatic thrombocytosis with a platelet count of $600 \times 10^9/L$. A reactive thrombocytosis, which would be far more likely in this age group, was excluded. Interestingly, the father also had a platelet count of $600 \times 10^9/L$ but no history of thrombosis. This finding raises the possibility of a diagnosis of familial thrombocytosis (FT), which has probably not been fully excluded in this case. No bone marrow biopsy was performed at the time of the original diagnosis because of the presumed benign nature of the thrombocytosis; this may have represented a unique opportunity (prior to treatment) to be more certain of the diagnosis, whether FT or essential thrombocytosis (ET). Four months prior to presentation, the patient's platelet count had increased to $800 \times 10^9/L$. The development of a life-threatening platelet thrombosis at an early age is a remarkable feature of this case, particularly as the

father was asymptomatic. The natural history of FT is unclear and sometimes the condition is loosely described as inherited ET. In a number of families with FT, a unique genetic basis has been identified.^{4,5}

At present, the diagnostic criteria for ET and other myeloproliferative disorders (MPDs) are ever-changing in keeping with scientific advances in the field and should be radically reviewed following the description of *JAK2V617F* and *MPL W515L/K* mutations. This report most likely represents an evolving case of *JAK2V617F*-negative ET in view of the sustained thrombocytosis leading to an MI. Although FT cannot be ruled out as the morphologic assessment was not conclusive, this may be due to 8 weeks of treatment with hydroxyurea prior to the bone marrow biopsy, distorting the findings. Interestingly, in the *JAK2V617F* era, there are reports of a greater than previously appreciated familial tendency to develop MPDs, and in these families the *JAK2V617F* does not appear to be inherited as a constitutional abnormality nor is there always concordance for *JAK2V617F* status.⁶

Both the original⁷ and revised⁸ World Health Organization (WHO) diagnostic criteria for ET incorporate bone marrow morphology as a positive discriminatory test, unlike the original Polycythemia Vera Study Group diagnostic criteria. Such a strong emphasis on morphology in the diagnosis of ET has been debated, as megakaryocyte morphology is notoriously difficult to interpret, especially outside of specialized centres. A recent analysis of bone marrow trephines obtained in the large prospective Primary Thrombocythaemia 1 (PT-1) trials suggests that although the use of marrow morphology may supplement diagnosis, the further subclassification of ET into prefibrotic myelofibrosis cannot be reliably and robustly applied even by competent expert hemopathologists. Furthermore, no clinical differences in outcome for those patients with ET or putative prefibrotic myelofibrosis were identified.⁹ The revised WHO criteria also propose a reduced diagnostic platelet threshold of $450 \times 10^9/L$ and require molecular analysis for *JAK2V617F* or other clonal markers to confirm a diagnosis of ET. In contrast, criteria proposed by Campbell and Green¹⁰ suggest a platelet threshold remaining at $600 \times 10^9/L$ for a diagnosis of *JAK2V617F*-negative ET, given the difficulty in ruling out reactive thrombocytosis and the fact that 2.5% of persons without an MPD have a platelet count above the normal range. This case predated the discovery of the *JAK2V617F* mutation, and the polymerase chain reaction analysis for *JAK2V617F* was in fact negative post-MI. Interestingly, pediatric patients with ET are apparently mostly polyclonal and *JAK2V617F*-negative,¹¹ although when present the *JAK2V617F* and more recently described *MPL* mutations are helpful positive diagnostic factors. Therefore, for

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those patients lacking a suitable clonal marker there is still diagnostic dilemma and a bone marrow biopsy will be both necessary and useful in most cases.

Thrombosis is a major cause of morbidity in ET, and the dominant risk factors include a prior thrombosis and increasing age¹²; both leukocytosis^{13,14} and the presence of the *JAK2V617F* mutation¹⁵⁻¹⁷ have also been suggested as thrombotic risk factors. Young patients with an apparent diagnosis of ET are still, however, at risk of life-threatening thrombosis, and we urgently need better markers of thrombotic risk for such patients. Given the results of the ECLAP study in polycythemia vera,¹⁸ low-dose aspirin from the time of presentation in this patient might possibly have reduced the risk of the MI occurring.

At 17 years of age, the patient subsequently presented to the emergency room with an acute ST segment–elevation MI. Angiography revealed platelet thrombus aspirated by catheter and no evidence of underlying atherosclerotic disease. Follow-up echocardiogram showed normal left ventricular function with no residual wall abnormalities. The acute management of this case clearly reflects the successful outcome and highlights the necessity for interaction of both the cardiology and hematology teams. Management strategy is intriguing and open to debate as there are very few reports of MI in young ET patients. Following the initial treatment with aspirin, clopidogrel, metoprolol, abciximab, and angiographic intervention, the patient was transferred to the coronary care unit on heparin and tirofiban. On arrival, he commenced hydroxyurea and platelet pheresis, with a subsequent decrease in platelet count from 917 to $459 \times 10^9/L$. This dual approach combined standard cardiac management of antiplatelet agents and anticoagulant therapy with hydroxyurea and platelet pheresis to impair platelet function and acutely reduce the platelet count to within the normal range.

Therapeutic options for controlling the platelet count in young patients with ET include hydroxyurea, anagrelide, and interferon- α . The majority of ET patients at high risk of thrombosis will currently be receiving hydroxyurea in combination with low-dose aspirin on the basis of the MRC-PT-1 study, which demonstrated the superiority of hydroxyurea and aspirin when compared with anagrelide and aspirin.¹⁹ In that study the composite primary endpoint of major thrombohemorrhagic events/death occurred in 36 patients treated with hydroxyurea and aspirin versus 55 with anagrelide and aspirin. In addition, significantly fewer arterial thromboses (17 vs 37, respectively), major hemorrhage (8 vs 22), and transformation to myelofibrosis (5 vs 16) occurred in patients receiving hydroxyurea. It must be emphasized however that the overall number of events was small: 96% of hydroxyurea-treated patients and 91% of anagrelide-treated patients remained free from arterial thromboses.

In the long term, however, although hydroxyurea is associated with fewer arterial events the risk of leukemogenesis should not be overlooked, particularly in young patients where interferon- α and anagrelide are probably more attractive. Anagrelide inhibits cyclic AMP phosphodiesterase III and produces positive inotropic effects; side effects include palpitations, tachycardia, congestive cardiac failure, hypertension, arrhythmias, and chest pain. Side effects of interferon- α include hypotension, hypertension, and arrhythmias. The initial agent of choice in the case described would appear to be hydroxyurea in view of its swift mode of onset in reducing platelet count and the cardiac side effects described with the alternative agents. Following the 8-month review, at which there was no evidence of long-term myocardial damage, it might be prudent to consider the alternative use of anagrelide or interferon- α in place of hydroxyurea.

The prognosis for young ET patients is unclear and is being studied prospectively in the low-risk arm of the PT-1 trial (<http://www.ctsu.ox.ac.uk/projects/leuk/pt1/>). However, a recent case series of 126 ET patients age 5 to 40 years reported that, when compared with the normal population, these patients had a significant increase in risk of stroke and venous thrombosis. Thrombosis-free survival was 84% at 10 years.²⁰ It is a useful case series to impress upon young ET patients the importance of smoking cessation, as smoking was associated with a higher risk of thrombosis. Thirty-one thrombotic events were registered in 25 patients. The reported incidence rate for coronary artery disease (0.2 events per 100 patients/year) was not different when compared with the general population. An international registry of childhood cases of ET and indeed FT is most likely required to inform future treatment strategies for young patients with ET.

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