American Journal of Medical Case Reports, 2023, Vol. 11, No. 3, 55-59
Available online at http://pubs.sciepub.com/ajmcr/11/3/4
Published by Science and Education Publishing
DOI:10.12691/ajmcr-11-3-4

Essential Thrombocythemia Incidentally Discovered in 5-year-old Patient: A Case Report

Momen A. Zaid[1,*], Oadi N. Shrateh[2], Mariam Thalji[2], Yara Assaf[2]

[1]Research and Clinical Teaching Assistant, Faculty of Medicine, Al-Quds University, Jerusalem, Palestine
[2]Faculty of medicine, Al-Quds University, Jerusalem, Palestine
*Corresponding author: momen.a.zaid@gmail.com

Received January 19, 2023; Revised February 25, 2023; Accepted March 07, 2023

Abstract Essential thrombocythemia (ET) is considered a classic" BCR-ABL1-negative chronic myeloproliferative condition (MPD) that's characterized by thrombocytosis, bleeding, and/or thrombosis. It usually affects the megakaryocytic cell lineage. While the disease is most commonly observed in people between the ages of 50 and 60, ET is an extremely rare myeloproliferative disorder in the pediatric age group. In children under the age of 14, the annual incidence of ET is estimated to be 1 per 10 million, approximately 60 times lower than older ages. Most ET patients, especially children are asymptomatic and discovered incidentally while doing investigations for other reasons. Herein, we introduce a very rare case of essential thrombocythemia in a 5-year-old male patient that was detected incidentally following receiving the influenza vaccine. The patient had a persistent elevated platelet count over 450x109 /L. Bone marrow showed markedly increased megakaryocyte number. Genetic testing and bcr/abl rearrangement were unremarkable. The patient showed no symptoms during the period of follow-up.

Keywords: *essential thrombocythemia*

Cite This Article: Momen A. Zaid, Oadi N. Shrateh, Mariam Thalji, and Yara Assaf, "Essential Thrombocythemia Incidentally Discovered in 5-year-old Patient: A Case Report." *American Journal of Medical Case Reports*, vol. 11, no. 3 (2023): 55-59. doi: 10.12691/ajmcr-11-3-4.

1. Introduction

Essential thrombocythemia (ET) is a rare form of myeloproliferative disorder, that mainly targets the megakaryocytes lineage [1,2]. ET was first recognized by Emil Epstein and Alfred Goedel, two Austrian pathologists in 1934 [3]. Although the exact mechanism of the disease is still not fully understood, genetic mutations including JAK2 V617F, MPL, and CALR have been detected in a group of patients with ET. This genetic link is observed more in adult patients than in children given that only 25-40% of pediatric cases show one of these mutations. In fact, this may indicate another underlying mechanism for the clonal nature among different patients [4,5,6].

The clinical entity of essential thrombocythemia is rare in middle-aged adults, and it's far rarer in pediatrics with an estimated prevalence of 1 in 10 million [1]. The majority of pediatric ET cases are asymptomatic and discovered incidentally, while other patients may experience thrombosis's-related symptoms like headache, paresthesia, and abdominal pain. Furthermore, in cases of extremely high platelets level (up to 4500 × 109/L) patients may unexpectedly suffer from a serious bleeding disorder resulting from acquired von Willebrand syndrome (VW) [2,7].

Essential thrombocythemia is a diagnosis of exclusion, this emphasizes the great significance of proceeding with extensive workup and clinical investigations to rule out secondary causes such as infections, stress conditions (eg. Surgery), IDA, cancer, and post-splenectomy prior to confirming the diagnosis of ET [8].

In 2016, the World Health Organization (WHO) updated the diagnostic criteria for Essential thrombocythemia, which included four major and one minor criterion. The major criteria are as follows: (1) Platelet count ≥450 × 109/L, (2) Bone marrow biopsy showing megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with no significant increase in neutrophil granulopoiesis or erythropoiesis and, rarely, minor reticulin fibers (3) Not meeting WHO criteria for CML, polycythemia vera (PV), primary myelofibrosis, myelodysplastic syndromes, or other myeloid neoplasms. (4) Presence of JAK2, CALR, or MPL mutation. The minor criterion is the presence of a clonal marker or absence of evidence of reactive thrombocytosis (e.g., infection, inflammation, iron deficiency anemia) Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion [9]. Hereby, we present a rare case of essential thrombocythemia in a 5-year-old male patient that was discovered incidentally following receiving the influenza vaccine.

To use this template, you will need to (1) apply the embedded styles to each paragraph-level item in your manuscript or (2) use the specifications shown in Table 1 to format your manuscript, with this template as a visual guide. Information about paper submission is available from the Journal website.

2. Case Presentation

Table 1 shows the laboratory results of the patient

Laboratory parameter	The value
Complete blood count (CBC)	
Hb (z/dl)	9.24
PLT(*10^3Mul	7.6
WBC(*10^9)L	2.92
Neutrophil count/µl	800
Inflammatory markers	
CRP (mg/dl)	9
ESR (mm/hour)	10
PCT (ng/dl)	1.78
Ferritin (ng/dl)	60930
LDH (IU/L)	2400
Liver studies	
AST (U/L)	1451
ALT (UL)	178.3
Albumin (g/dl)	2.8
Kidney function	
UA(mg/d1)	23
CRE (mg/d1)	0.3
BUN (mg/dl)	5.4
Coagulation studies	
PT (seconds)	14.4
PIT (seconds)	**62.4**
Fibrinogen (mg/dl)	**130**

Hb: hemoglobin, PLT: platelet, WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PCT: procalcitonin, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRE: creatinine, BUN: blood urea nitrogen, UA: uric acid, PT: prothrombin time, PTT: partial thromboplastin

J.A., a 5-year- old Palestinian male child with a history of recurrent upper respiratory tract infections requiring hospitalization. The last one was in October 2021 following 10 days of influanza vaccine due to upper respiratory symptoms. At that time, complete blood count test showed an incidentally elevated platelet count approximately 1200 * $10^{\wedge 3}$/µl. CBC was repeated and revealed the same elevation in platelet count along with iron deficiency anemia measures. The patient was received the appropriate treatment for IDA with normalization of hemoglobin and iron parameters but without correction in the platelet count. On April 20, 2022 the patient was referred to the pediatric hematological department at Al-Istishari Arab Hospital, Ramallah, Palestine, for further evaluation and workup. The patient is a product of normal vaginal delivery of a spontaneous uneventful pregnancy and birth. Immunizations status was up to date and taking no medications. The child's parents are non-consanguineous and have no hematological issues. Past surgical history is significant for uncomplicated tonsillectomy 2 years ago. Physical assessment of the child was normal except for pallor and dyspnea. There is no visible skin rash, ecchymosis, mucosal bleeding, joint swelling and/or limping. Laboratory evaluation showed extreme thrombocytosis with platelet count of 1978 * $10^{\wedge 3}$/µl with elevated LDH of 351 u/l while RBCs, WBCs, Hb, ESR and CRP all were within the normal reference values (Table 1). Total body magnetic resonance imaging (MRI) with contrast under general anesthesia showed no significant findings. Bone marrow aspiration and biopsy were performed and disclosed an enlarged clustered megakaryocyte with bone marrow cellularity of 95%, decreased stainable iron, grade I reticulin fibrosis (figure 1). Essential thrombocythemia was suspected. Therefore, genetic analysis was done and myeloid panel was obtained which showed negative JAK-2, MPL and CALR gene mutations. According to the WHO 2016 diagnostic criteria, our patient was diagnosed with Essential thrombocythemia and causes of secondary thrombocytosis were ruled out. Saint Jude children's Research Hospital-Department of Hematology- was consulted for the management approach of this patient. Given (1) HB level >12 g/dL and normal WBCs (2) No splenomegaly (3) non-contributable family history (4) unlikelihood of myeloproliferative neoplasms at this age (5) the conclusive decision was to observe the patient with no need for medications along with close follow-up plan inflammatory markers (e.g., ESR) monitoring with repetition of genetic studying and bone marrow biopsy if abnormal changes in peripheral blood count seen.

3. Discussion

Essential thrombocythemia (ET), formerly known as hemorrhagic thrombocythemia, is one of the chronic myeloproliferative disorders characterized by persistent proliferation of megakaryocytes and a subsequent increase in circulating platelet count [10,11]. The myeloproliferative neoplasms (MPNs) are a family of chronic hematologic malignancies that share the same features on a molecular and clinical basis. They include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) [12,13]. All of these disorders share a common driving mutation and overlapping clinical features [14].

ET is the most common form of MPN [15]. MPN in general and ET in particular is an adult disease that is extremely rare in the pediatric age group. Limited data is available on incidence of ET in children, ET is estimated to be diagnosed in 1/1,000,000 children [16]. thus, we are reporting one of the very rare hematological diseases in pediatrics. Only 20% of cases are detected in patients younger than 40 years of age [17]. ET is 60 times more common in adults than in pediatric patients [18]. The incidence of ET is 1-2.5 cases per 100,000 per year. The incidence increases with age, and the average age at diagnosis is 60 years. In young adults, the disease is more common in women [19]. while in older adults, the incidence is the same in both sexes [10]. Although thrombocytosis is generally a common finding in pediatrics, the primary (even essential) cause is extremely rare [16]. The main problem in ET is the increased production of platelets by megakaryocytes in the bone marrow (thrombopoiesis). Current theories agree that thrombopoietin (TPO) plays an important role in the pathogenesis of ET. Thrombopoietin is a glycoprotein hormone produced by the liver and kidney and is an essential factor in stem cell differentiation and further maturation of megakaryocytes and platelet production [20-23].

The 3 most common mutations, also known as "driver" mutations, found in ET are: JAK 2 (Janus kinase 2), which is found in 50-60% of adults and in less than 30% of children [24,25]. This mutation is a gain of function that

results in permanent activation of the TPO receptor and continuous signal transduction, resulting in platelet overproduction [26,27]. MPL (myeloproliferative leukemia virus oncogene), This mutation is found in only 3-5% of children. The MPL gene encodes the TPO receptor protein, and the mutation results in receptor activation, leading to increased platelet proliferation and production [24]. CALR (endoplasmic reticulum-associated chaperone calreticulin) mutation found in 25% of adults. The mechanism by which this mutation leads to thrombocytosis is not fully understood [27]. Only 10-20% are triple negative (driver mutation negative) [24]. The proposed theories of molecular pathogenesis are relatively well understood and aligned in adults compared with children, who generally do not have any of the aforementioned mutations [25].

Since the incidence in children is very rare, there are no clear data yet on the clinical presentation in children. Our patient is considered to have an incidental diagnosis. In the comparison group (adults), only 25-30% of patients are asymptomatic and most of them have non-specific symptoms. The most common symptoms are headache, migraine, and dizziness [28]. Our patient was incidentally diagnosed after doing CBC test for another purpose.

Symptoms can generally be classified according to their mechanism: A microvascular occlusion occurring in the microcirculation of the toes, causing pain with a sensation of heat, known as erythromelalgia, and sometimes even affecting blood flow to the limbs, leading to gangrene. Thrombotic complications, which occur in 10-20% of affected patients [28]. Affecting small or large, arterial or venous vessels [14]. Bleeding complications that occur mainly in patients with extremely high platelet counts (> 1 million). The possible mechanism of this paradoxical complication is acquired von Willebrand disease [29]. The most common site for bleeding is the gastrointestinal tract [10]. 20-30% of the affected population present with constitutional symptoms.

Physical findings are generally unremarkable, with the exception of an enlarged spleen in 40-50% of patients and hepatomegaly in 20% [28,30]. To make the diagnosis ET, other causes of secondary (also known as reactive) thrombocytosis must be excluded [31]. In children, the two most common causes of increased platelet count are infections and iron deficiency anemia (IDA) [32,33]. Platelets are among the acute phase reactions. In the presence of infection or inflammatory state, IL-6 increases TPO mRNA expression and TPO levels, and this upregulation consequently leads to increased platelet production [34]. Recently, TPO levels were found to correlate with the well-known and commonly used C-reactive protein [35].

In iron deficiency anemia, increased EPO levels bind to TPO receptors (known as MPL) and result in a TPO-like effect leading to thrombopoiesis and platelet formation [36,37,38]. Other causes of secondary thrombocytosis that must be excluded are: inflammation [33], collagen disease [10], other causes of anemia (hemorrhage, hemolytic anemia) [31,33], Asplenia or decreased splenic function leading to platelet accumulation in the peripheral circulation, nephrotic syndrome [10].

Other less common causes include: Familial thrombocytosis, in which an enhancement infusion mutation leads to excessive production of TPO [39,40].This mutation can be inherited either autosomal dominant, recessive, or x-linked [10]. Other MPN, Considering the overlapping clinical presentations of myeloproliferative disorders, all CML, MDS, PV, primary myelofibrosis are important differential diagnoses [28,33].

Our patient was initially diagnosed and iron deficiency anemia, although it is uncommon for platelet counts to reach such high counts in IDA. After correcting the anemia, the platelet counts were still high, thus raising the suspicion of another differential diagnosis. Workup was done to rule out secondary causes, including CBC of both parents, excluding familial thrombocytosis, and eventually as ET diagnostic criteria were met, the diagnosis was confirmed.

Investigations should be performed to confirm the diagnosis and exclude secondary causes.

A CBC is mandatory, with a platelet count greater than 450. Other common findings include leukocytosis, erythrocytosis, and mild anemia [15]. Peripheral blood smear shows immature progenitor cells, platelets (large platelets), mild basophilia or eosinophilia [10]. Bone marrow biopsy showing in case of ET an increased cellularity in 90% of patients, especially increased proliferation of megakaryocytes [10]. Hyperplasia of granulocytes or reticulocyte precursor cells is a common finding. However, dysplasia in any of the progenitor cells is not a common finding, nor is bone marrow fibrosis [10]. Genetic testing for driver mutations. Other tests to rule out secondary causes include Acute phase reactants, iron and coagulation studies, platelet aggregation tests, in addition to U/S or Ct scan for organomegaly [41]. The Diagnosis of ET is made using the 2016 WHO criteria [9].

Unfortunately, there is no cure for ET, and the main purpose of treatment is to prevent vascular complications, namely thrombosis and bleeding [14,15,42]. These complications are the main causes of mortality and morbidity in ET patients [43]. There are no current guidelines for the treatment of children [42]. The proposed treatment approach in adults is based on risk stratification, in which patients are classified into different risk groups based on two main factors: Age and history of thrombotic events. The low-risk group is defined as individuals younger than 60 years with no history of thrombotic events. These patients receive a low dose of aspirin unless there is a contraindication [41]. In the pediatric age group, low-risk children are considered asymptomatic; these patients should be monitored and their blood count and platelet counts checked every 3-6 months. In adults, the high-risk group is considered to be those older than 60 years or with a history of thrombosis [14]. Recent studies consider mutation status as an independent risk factor for thrombotic events, namely the JAK -2 mutation. In high-risk patients, cytoreductive therapy aimed at lowering platelet counts should be initiated [30,44]. The first line of treatment is hydroxyurea, which reduces both platelet and white blood cell counts [12]. Other drug options include anagrelide which is considered the second line of treatment acting by inhibiting megakaryocyte and platelet differentiation [21,45], IFN-alpha [46], Busulfan [37], and Targeted therapy with ruxolitinib (JAK 1/ 2-inhibitor), which is FDA approved for MPD [47].

In children, the high-risk population is divided into the following groups: Intermediate-risk children who are

asymptomatic but at additional risk of thrombophilia (e.g., HSM, headache, erythromelalgia, CVS RF, thrombophilia, or bleeding). These children are treated with low-dose aspirin, although this is not recommended in children younger than 12 years [12,48], High-risk children are those in whom low- or intermediate-risk treatment has failed or who have developed a thrombosis or bleeding complication. These children must be treated with cytoreductive therapy [17]. There is no evidence of the effects of therapy on long-term complications such as leukemic transformation, the incidence of which over 15 years ranges from 2.1 to 5.3% of patients from ET [49], And fibrotic transformation of the bone marrow, which occurs in up to 11% of patients [46,49,50].

Acknowledgements

None.

References

[1] Aladily, T.N., et al., Essential thrombocythemia in a two-year-old child, responsive to hydroxyurea but not aspirin. Oman medical journal, 2017. 32(3): p. 243.

[2] Vafaie, M., et al., Asymtomatic essential thrombocythemia in a child: a rare case report. International Journal of Hematology-Oncology and Stem Cell Research, 2013. 7(2): p. 35.

[3] Epstein, E. and A. Goedel, Hemorrhagic thrombocythemia with a cascular, sclerotic spleen. Virchows Arch, 1934. 293: p. 233-248.

[4] Swerdlow, S.H., et al., WHO classification of tumours of haematopoietic and lymphoid tissues. Vol. 2. 2008: International agency for research on cancer Lyon.

[5] Fu, R., L. Zhang, and R. Yang, Paediatric essential thrombocythaemia: clinical and molecular features, diagnosis and treatment. British journal of haematology, 2013. 163(3): p. 295-302.

[6] Kucine, N., Myeloproliferative neoplasms in children, adolescents, and young adults. Current hematologic malignancy reports, 2020. 15(2): p. 141-148.

[7] Michiels, J.J., et al. The paradox of platelet activation and impaired function: platelet-von Willebrand factor interactions, and the etiology of thrombotic and hemorrhagic manifestations in essential thrombocythemia and polycythemia vera. in Seminars in thrombosis and hemostasis. 2006. Copyright© 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New ….

[8] Putti, M.C., I. Bertozzi, and M.L. Randi, Essential Thrombocythemia in Children and Adolescents. Cancers, 2021. 13(23): p. 6147.

[9] Arber, D.A., et al., The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood, The Journal of the American Society of Hematology, 2016. 127(20): p. 2391-2405.

[10] Tefferi, A. and A. Pardanani, Essential Thrombocythemia. N Engl J Med, 2019. 381(22): p. 2135-2144.

[11] Cervantes, F., Management of essential thrombocythemia. Hematology 2010, the American Society of Hematology Education Program Book, 2011. 2011(1): p. 215-221.

[12] Cervantes, F., Management of essential thrombocythemia. Hematology Am Soc Hematol Educ Program, 2011. 2011: p. 215-21.

[13] Barbui, T., et al., The 2016 revision of WHO classification of myeloproliferative neoplasms: Clinical and molecular advances. Blood Rev, 2016. 30(6): p. 453-459.

[14] Tefferi, A., A.M. Vannucchi, and T. Barbui, Essential thrombocythemia treatment algorithm 2018. Blood Cancer J, 2018. 8(1): p. 2.

[15] Ashorobi, D. and P. Gohari, Essential Thrombocytosis, in StatPearls. 2022: Treasure Island (FL).

[16] Cooper TM, H., Smith FO, In Pizzo PA, Poplack DG, Principle and practice of pediatric oncology. 2011, Philadelphia: Lippincott Williams &Wilkins: Lippincott Williams &Wilkins.

[17] Kucine, N., et al., Primary thrombocytosis in children. Haematologica, 2014. 99(4): p. 620-8.

[18] Dame, C. and A.H. Sutor, Primary and secondary thrombocytosis in childhood. Br J Haematol, 2005. 129(2): p. 165-77.

[19] Mehta, J., et al., Epidemiology of myeloproliferative neoplasms in the United States. Leuk Lymphoma, 2014. 55(3): p. 595-600.

[20] Sungaran, R., B. Markovic, and B.H. Chong, Localization and regulation of thrombopoietin mRNa expression in human kidney, liver, bone marrow, and spleen using in situ hybridization. Blood, 1997. 89(1): p. 101-7.

[21] Zeigler, F.C., et al., In vitro megakaryocytopoietic and thrombopoietic activity of c-mpl ligand (TPO) on purified murine hematopoietic stem cells. Blood, 1994. 84(12): p. 4045-52.

[22] Mehta, J., et al., Epidemiology of myeloproliferative neoplasms in the United States. Leukemia & lymphoma, 2014. 55(3): p. 595-600.

[23] Qian, S., et al., Primary role of the liver in thrombopoietin production shown by tissue-specific knockout. Blood, The Journal of the American Society of Hematology, 1998. 92(6): p. 2189-2191.

[24] Vannucchi, A.M. and P. Guglielmelli, What are the current treatment approaches for patients with polycythemia vera and essential thrombocythemia? Hematology Am Soc Hematol Educ Program, 2017. 2017(1): p. 480-488.

[25] Tefferi, A. and A. Pardanani, Essential thrombocythemia. New England Journal of Medicine, 2019. 381(22): p. 2135-2144.

[26] Tefferi, A. and A. Pardanani, Myeloproliferative Neoplasms: A Contemporary Review. JAMA Oncol, 2015. 1(1): p. 97-105.

[27] Vainchenker, W. and R. Kralovics, Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. Blood, 2017. 129(6): p. 667-679.

[28] Meier, B. and J.H. Burton, Myeloproliferative Disorders. Hematol Oncol Clin North Am, 2017. 31(6): p. 1029-1044.

[29] Barbui, T., M.C. Finazzi, and G. Finazzi, Front-line therapy in polycythemia vera and essential thrombocythemia. Blood Rev, 2012. 26(5): p. 205-11.

[30] Barbui, T., et al., Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J, 2015. 5: p. e369.

[31] Dror, Y. and V.S. Blanchette, Essential thrombocythaemia in children. Br J Haematol, 1999. 107(4): p. 691-8.

[32] Matsubara, K., et al., Age-dependent changes in the incidence and etiology of childhood thrombocytosis. Acta Haematol, 2004. 111(3): p. 132-7.

[33] Vora, A.J. and J.S. Lilleyman, Secondary thrombocytosis. Arch Dis Child, 1993. 68(1): p. 88-90.

[34] Wolber, E.M., et al., Hepatic thrombopoietin mRNA is increased in acute inflammation. Thromb Haemost, 2001. 86(6): p. 1421-4.

[35] Ishiguro, A., et al., Elevation of serum thrombopoietin precedes thrombocytosis in acute infections. Br J Haematol, 2002. 116(3): p. 612-8.

[36] Bilic, E. and E. Bilic, Amino acid sequence homology of thrombopoietin and erythropoietin may explain thrombocytosis in children with iron deficiency anemia. J Pediatr Hematol Oncol, 2003. 25(8): p. 675-6.

[37] Geddis, A.E. and K. Kaushansky, Cross-reactivity between erythropoietin and thrombopoietin at the level of Mpl does not account for the thrombocytosis seen in iron deficiency. J Pediatr Hematol Oncol, 2003. 25(11): p. 919-20; author reply 920.

[38] Matsubara, K., et al., Age-dependent changes in the incidence and etiology of childhood thrombocytosis. Acta haematologica, 2004. 111(3): p. 132-137.

[39] Ghilardi, N., et al., Hereditary thrombocythaemia in a Japanese family is caused by a novel point mutation in the thrombopoietin gene. Br J Haematol, 1999. 107(2): p. 310-6.

[40] Wiestner, A., et al., An activating splice donor mutation in the thrombopoietin gene causes hereditary thrombocythaemia. Nat Genet, 1998. 18(1): p. 49-52.

[41] Bleeker, J.S. and W.J. Hogan, Thrombocytosis: diagnostic evaluation, thrombotic risk stratification, and risk-based management strategies. Thrombosis, 2011. 2011: p. 536062.

[42] Barbui, T., How to manage children and young adults with myeloproliferative neoplasms. Leukemia, 2012. 26(7): p. 1452-7.

[43] Besses, C. and A. Alvarez-Larran, How to Treat Essential Thrombocythemia and Polycythemia Vera. Clin Lymphoma Myeloma Leuk, 2016. 16 Suppl: p. S114-23.

[44] Carobbio, A., et al., Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. Blood, 2011. 117(22): p. 5857-9.

[45] Tefferi, A., Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol, 2012. 87(3): p. 285-93.

[46] Posthuma, H.L., et al., Hereditary thrombocytosis not as innocent as thought? Development into acute leukemia and myelofibrosis. Blood, 2010. 116(17): p. 3375-6.

[47] Aruch, D. and J. Mascarenhas, Contemporary approach to essential thrombocythemia and polycythemia vera. Curr Opin Hematol, 2016. 23(2): p. 150-60.

[48] Barbui, T., et al., Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol, 2011. 29(6): p. 761-70.

[49] Cerquozzi, S. and A. Tefferi, Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. Blood Cancer J, 2015. 5: p. e366.

[50] Passamonti, F., et al., Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med, 2004. 117(10): p. 755-61.