PROFICIENCY TESTING SERVICE
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Q2-2018 Essential Thrombocytopenia

Chronic Myeloproliferative disorders (MPDs), are a group of heterogenous diseases that result from the clonal expansion of the multipotent hematopoietic stem cell. This group of disorders share molecular and cellular characteristics but differ in phenotype and clinical presentation. They include polycythemia vera (PV), idiopathic myelofibrosis (IMF) and chronic myelogenous leukemia (CML) and essential thrombocythemia (ET). In CML it is primarily granulocytes that are overproduced, in PV it is erythrocytes that are overproduced, IMF exhibits marrow fibrosis and extramedullary hematopoiesis in the liver and spleen and ET is characterized by abnormally increased platelet production.

This patient underwent extensive testing, that included a bone marrow exam, iron studies and cytogenetic studies, including Philadelphia chromosome and BCR-ABL assays. Once other identifiable causes of reactive thrombocytosis were ruled out, this patient was diagnosed as having essential thrombocythemia. ET is a rare but serious myeloproliferative neoplasm characterized by thrombocytosis with bone marrow megakaryocytic hyperplasia and a tendency to develop thrombotic and hemorrhagic complications.

The World Health Organization 2016 diagnostic criteria for ET requires that the patient exhibit either all 4 of the following major criteria or, alternatively, meets the first 3 major criteria and the minor criterion.

Major criteria:
- Platelet count ≥450 × 109/L (Note : The platelet count can be >1,000,000/µL)
- Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
- Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
- Presence of JAK2, CALR, or MPL mutation
- Minor criterion:
- Presence of clonal marker or absence of evidence for reactive thrombocytosis

With the widespread introduction of automated cell counters into the laboratory in the 1970s, there was a corresponding uptick in the numbers of ET cases being identified. Current data indicate that every year, in the United States, approximately 6000 patients are diagnosed with ET, making it the most frequently diagnosed MPD. Approximately two thirds of patients are asymptomatic at diagnosis, the remainder present with hemorrhagic and/or vaso-occlusive symptoms. Although occasionally diagnosed in older children, the median age at diagnosis is 60 and ET is diagnosed one and one half times more frequently in women. There is also a clearly identified peak occurring in women in the 30 to 50 year range. Between 71,000 and 88,000 people in the United States currently live with ET.

ET patients are at risk of microvascular occlusions (usually reversible), large vessel thrombosis or serious bleeding. Thrombosis may cause symptoms in the affected site, for example, leg pain, swelling, or both with lower extremity thrombosis and chest pain and dyspnea with pulmonary embolism. When thrombosis compromises cerebral blood flow (TIAs) the patients can experience a variety of symptoms including such headaches, dizziness, weakness or numbness on one side of body or slurred speech. Additional signs and symptoms associated with ET are weakness/fatigue, gout, ocular migrans, paresthesias of hands and feet, erythromelalgia (burning or throbbing pain in the feet), itching, sweating and/or and mild splenomegaly.
Bleeding is more likely with extreme thrombocytosis (ie, about 1.5 million platelets/µL); it is due to an acquired deficiency of von Willebrand factor caused because the platelets adsorb and proteolyze high molecular weight von Willebrand multimers. Although serious bleeding may occur in a small percentage of cases, more often bleeding is mild and manifests as epistaxis, easy bruisability, or GI bleeding.

The peripheral smear may show giant platelets and megakaryocyte fragments. Platelet function studies reveal a variety of abnormalities in some patients. Abnormal platelet aggregation to epinephrine, collagen ADP and ristocetin are quite common. Bleeding times can be either normal or abnormal. However these qualitative functional platelet abnormalities have proved to be insufficiently reproducible to be useful predictors of either thrombosis or hemorrhage. Additionally, repeated studies have documented that the severity of thrombocytosis does not necessarily correlate with the presence, absence or severity of symptoms.

Treatment of patients with ET is based on the patient's individual risk of developing either clotting or bleeding complications. Low-risk patients are considered to be those who are less than 60 year of age, have no history of thrombosis, no cardiovascular (CV) risk factors and whose platelet counts are less than 1,500 X 109. If they have no signs or symptoms, these patients are normally advised to take daily low dose aspirin and are monitored with routine regular check ups. However, in cases of surgery or childbirth, these normally low-risk patients may need a short period of treatment intended to temporarily reduce their platelet count and thus reduce their risk for clotting or bleeding complications.

Intermediate risk patients who are younger than age 60 years or who lack a history of thrombosis but have CV risk factors (eg, diabetes, hypertension, or tobacco use). Patients at high risk of developing these vaso-occlusive and/or hemorrhagic complications are those who have a combination of the following factors: older than 60, a prior history of thrombosis or bleeding, or

ET can also lead to complications in pregnant patients. These patients have been reported spontaneous abortion rates of 25% to 50%. Because anagrelide and hydroxyurea cross the placenta, they are not used during pregnancy; interferon alfa-2b can be used in pregnant women when necessary. Interferon is the safest therapy for migraine.

Platelet removal (plateletpheresis) is rarely necessary but, for a few rare patients with serious hemorrhage or recurrent thrombosis or, to immediately reduce the platelet count, may be useful. In addition, this therapy has been used prophylactically, even in those considered low risk, before emergency surgery or childbirth. However, it remains infrequently necessary and even when performed its effects are transient.

In some patients, particularly men with the JAK2V617F or CALR type 1 mutations, ET may transform to post-ET myelofibrosis. Leukemic transformation occurs in < 2% of patients.
Although ET remains an incurable disease, and symptoms are common, the course of the disease is often benign. ET patients have near normal life expectancy. Medical management of the disorder focuses primarily on the following areas; 1) avoiding first occurrence and/or recurrence of thrombotic and bleeding complications, 2) controlling systemic symptoms, 3) treating complications (thrombosis and hemorrhage) and 4) managing risk situations (eg, pregnancy, surgery).

Cell Identification

Specimen 1

Result	No.	Flag
Platelet, giant	242	
Platelet, normal	3	***
Abnormal Platelet, would refer	2	
Abnormal RBC, would refer	1	***
Basophilic Stippling	1	***
Megakaryocyte	1	***
Metamegakaryocytic Fragment	1	***

Total Population 251
Intended result: Platelet, giant

Specimen 2

Result	No.	Flag
Monocyte, any stage	217	
Monocyte, normal/any stage	33	
Immature Neutrophil	1	***
Lymphocyte; atypical, Downey, variant	1	***

Total Population 252
Intended result: Monocyte, any stage

Specimen 3

Result	No.	Flag
Eosinophil, any stage	245	
PMN with bacterial inclusion	2	***
Erythrocyte, normal RBC	1	***
Basophil, any stage	1	***
Segmented Neutrophil (PMN, poly)	1	***
PMN with Toxic Granulation/Vacuolization	1	***
Lymphocyte; atypical, Downey, variant	1	***

Total Population 252
Intended result: Eosinophil, any stage

Specimen 4

Result	No.	Flag
Erythrocyte, normal RBC	228	
Spherocyte	13	***
Macrocytic	6	***
Microcytic	3	***
Dimorphic RBC	1	***
Polychromatophilic RBC	1	***

Total Population 252
Intended result: Erythrocyte, normal RBC

Specimen 5

Result	No.	Flag
PMN with Degenerated Nucleus (pyknot	142	
Hypersegmentated Neutrophil	35	***
Abnormal, would refer	27	
Basophil, any stage	14	***
Abnormal Granulocyte, would refer	12	
PMN with bacterial inclusion	6	***
Parasite	3	***
Basophil, any stage	2	***
Basophilic Stippling	2	***
Segmented Neutrophil (PMN, poly)	2	***
Abnormal RBC, would refer	1	***
Basket/Smudge cell	1	***
Nucleated RBC, any stage	1	***
PMN with Toxic Granulation/Vacuolization	1	***
Metamegakaryocytic Fragment	1	***
Platelet Clumping	1	***
Platelet Satellitosis around PMN	1	***

Total Population 252
Intended result: pyknotic PMN
22 of 22 Referee Laboratories correctly identified the intended result of pyknotic PMN.

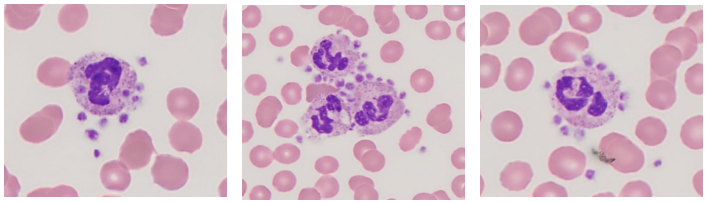
Correct responses are defined as those reflecting agreement among 80% or more of all participants or referees. Unacceptable responses are indicated by "*****" on the Flagging line of each specimen.

Cell Identification - Educational Challenge

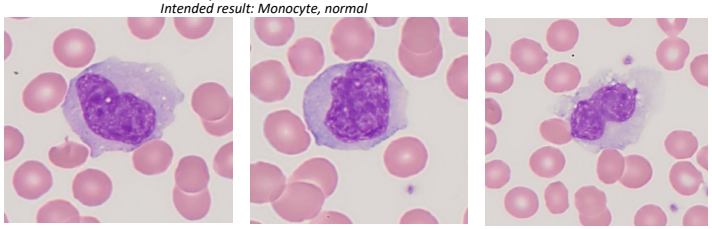
Specimen 1	No.
Platelet Satellitosis around PMN	152
Segmented Neutrophil (PMN, poly)	16
PMN with Toxic	3
Hypersegmentated Neutrophil	2
Abnormal Platelet, would refer	1
Eosinophil, any stage	1
Lymphocyte, normal	1
Platelet Clumping	1

Specimen 2	No.
Monocyte, any stage	131
Monocyte, normal	31
Lymphocyte; atypical, Downey, variant	5
Metamyelocyte	2
Lymphocyte, reactive	2
Immature WBC, would refer	1
Abnormal Lymphocyte, would	1
Hairy Cell	1
Plasma Cell, any stage	1
Platelet Satellitosis around PMN	1

Total Population: **177**
Intended result: Platelet



Total Population: **176**
Intended result: Monocyte, normal



*To see the original fullsized immages, please sign on to your data entry sheet at http://www.aab-pts.org

Sample 18Q2 - Clinical Discussion A 68-year-old man is seen by his primary physician with complaints of episodes of swelling and pain in his right knee. He has gained weight during the past year, but does not believe this is contributing to his discomfort, and states the pain "comes and goes". The swelling will then subside. He denies fever or chills. The patient also notes that his daughter and 4-year-old granddaughter recently moved in with him and his wife; his granddaughter gets frequent colds and ear infections. On physical examination, the patient is obese, afebrile, and has a blood pressure of 168/88. His right knee is mildly swollen and red; there is fluctuance and pain with movement. Arthocentesis (aspiration of joint fluid) is performed and the sample sent for culture and cell counts. CBC results on his peripheral blood are as follows: WBC 5.5 x 103 /µL, Hgb 15.5 g/dL, Hct 47.8%, Plts 99,000/µL.