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634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Polycythemia Vera with Elevated Erythropoietin Level: A Review

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According to the 2016 World Health Organization (WHO) recommendations, polycythemia vera (PV) should be suspected at hemoglobin levels of 16.5 gm/dl in males and 16 gm/dl in females.
Depending on the underlying driving factor, polycythemia is classified to primary and secondary. Secondary polycythemia is driven by erythropoietin (EPO), which can be released due to hypoxemia, as seen in people living at high altitudes, those with chronic lung diseases, obstructive sleep apnea (OSA) and smoking. It can also be directly released by an underlying EPO secreting tumor, such as renal cell carcinoma. On the other hand, primary polycythemia or polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) in which erythrocytosis is driven by an acquired activating mutation that increases sensitivity to EPO or causes EPO independent erythroid colony formation.
Manifestations of PV include fatigue, excessive itching, abdominal pain, weight loss, and fever. However, the most critical complications of PV, which impact survival, are thrombotic complications such as stroke and venous thromboembolism and leukemic transformation. The risk for leukemic transformation in patients with PV is about 2-5% over 15 years and is more common in individuals older than 60.
History and physical examination should focus on smoking history and signs and symptoms of cardiopulmonary diseases causing chronic or intermittent hypoxemia, as seen in OSA. On the other hand, findings of abdominal pain, early satiety, weight loss, erythromelalgia, and hepatosplenomegaly would be suggestive of PV. Laboratory workup classically starts with measuring EPO level which further directs workup toward PV or secondary polycythemia. If workup is suggestive of PV, the following steps would be testing for activating Janus Kinase 2 (JAK2) mutation (V617F), which has a sensitivity of 97% for PV, and bone marrow biopsy which shows hypercellularity with trilineage growth (panmyelosis) in cases of PV.
EPO measurement constitutes an essential step in polycythemia workup. It is widely accepted that elevated EPO levels are associated with secondary polycythemia; and suppressed EPO level was considered a criterion to diagnose PV, according to the WHO 2016 diagnostic criteria for PV.
We conducted a systematic review searching the entity of PV with elevated EPO to study the clinical significance and outcomes. Our search yielded 4 cases summarized in Table 1.
The cases were of three males and one female, with a mean age of 50. Two of them were healthy, with two with comorbid diseases, and as seen in the table; only one was a smoker. The most common symptom was headache, followed by erythromelalgia. Thrombotic phenomena happened in a single case in the form of Budd Chiari syndrome. Hepatosplenomegaly was found in a single case, and splenomegaly was found in two cases. The mean Hb level was 20.2 gm/dl, and the mean EPO level was 213.
EPO is a glycoprotein hormone that is mainly produced by the kidneys. However, it is also produced in small amounts in the liver, spleen, bone marrow, lungs, and brain. The primary regulator of EPO production is the partial pressure of oxygen (PaO2). Multiple case reports and case series suggested an association between PV with elevated EPO and Budd Chiari Syndrome. Thumures et al. described four patients that were diagnosed with Budd Chiari Syndrome with elevated red cell mass and were found to have elevated serum erythropoietin levels. PV was confirmed with JAK2 mutation assay and bone marrow biopsy examination. It is speculated that liver hypoxia with subsequent hepatocyte injury and necrosis caused by Budd Chiari Syndrome leads to EPO level elevation.
Accordingly, we assume that patients with PV and elevated EPO have some degree of organ injury that results in the release of EPO into circulation. This highlights the importance of a systematic approach in medicine, where signs and symptoms remain

the cornerstone in diagnosis and where lab tests should be taken in their appropriate clinical context. Thus, we recommend testing for JAK2 mutation in the proper clinical scenario regardless of the EPO levels.
It still remains to be clarified whether there are any prognostic importance of the elevated EPO level in these patients and whether it would alter the management.

Disclosures No relevant conflicts of interest to declare.

Case number	Age	Sex	Co-morbidities	Hepatomegaly/splenomegaly	Smoking history	Hb	HCT	Thrombosis	JAK-2 mutation
1	49	Male	None	Both	None	18 gm/dl	NA	No	Yes
2	64	Male	HTN, HLD, COPD	Splenomegaly	None	20 gm/dl	60%	No	Yes
3	58	Female	None	None	None	20 gm/dl	NA	Yes (Bud-chiari)	Yes
4	30	Female	Renal artery stenosis	Splenomegaly	None	22.5 gm/dl	67%	No	Yes

Figure 1

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