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Case Report

Obstructive Sleep Apnea Does Not Exclude Polycythemia Vera: A Case Report

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Polycythemia vera · Secondary polycythemia · Sleep apnea · Myeloproliferative neoplasm · Janus Kinase 2 mutation

Abstract
Introduction: Polycythemia vera (PV) is one of the myeloproliferative neoplasms (MPN) diagnosed by World Health Organization (WHO) criteria 2016, which requires the presence of 3 major criteria: high hemoglobin/hematocrit, bone marrow findings, and Janus Kinase 2 (JAK2) mutation or two major and one minor criteria, including erythropoietin (EPO) level. However, in clinical practice, difficulties in diagnosis can arise as it may be masked by secondary causes for erythrocytosis such as smoking or obstructive sleep apnea (OSA). ***Case Presentation:*** Here, we report a 55-year-old gentleman, morbidly obese with OSA on home continuous positive airway pressure (CPAP) machine, who was incidentally found to have polycythemia. Further evaluation confirmed the diagnosis of PV. ***Conclusion:*** PV can be masked by the assumption of secondary polycythemia based on history. This underscores the importance of screening such cohort through JAK2 and EPO testing to avoid missing PV.

Introduction

Myeloproliferative neoplasms (MPN) are a group of hematopoietic stem cell disorders characterized by excess proliferation. They are classically described as Philadelphia-positive MPN (chronic myeloid leukemia) [1] and Philadelphia-negative MPN [2] which are classically

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categorized into polycythemia vera (PV, primary polycythemia), essential thrombocythemia, myelofibrosis (MF), and prefibrotic MF [3]. MPN can be acquired; however, familial cases have been described [4].

According to the 2016 diagnostic criteria from the World Health Organization (WHO), the diagnosis of PV is established if either all three major criteria are met or if two major criteria and the minor criterion are satisfied. The minor criterion involves a subnormal serum erythropoietin (EPO) level. The major criteria include the following [5]:

1. Elevated hemoglobin (Hgb) concentration (>16.5 g/dL in men; >16.0 g/dL in women) or elevated hematocrit (Hct) (>49% in men; >48% in women) or increased red blood cell mass (>25% above mean normal predicted value).
2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size).
3. Presence of Janus Kinase 2 (JAK2) mutation V617F or JAK2 exon 12 mutation.

PV is an indolent neoplasm, with an annual incidence ranging from 0.01 to 2.61 per 100,000 people [6]. PV median age at diagnosis is approximately 60 years. Most patients are discovered incidentally by the complete blood count test done for other reasons. While some patients may present with disease-related symptoms like pruritus, headache, and visual disturbances, others may manifest complications, including thrombotic or hemorrhagic events or transformation [7].

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder in which the patient experiences recurrent episodes of decreased breathing (hypopnea) or cessation (apnea). Additionally, intermittent hypoxia in OSA may lead to an increase in red cell mass and result in secondary polycythemia [8].

We report a case of a gentleman with OSA who was incidentally found to have high Hgb level. Initially, it was thought to be secondary polycythemia, but further evaluation established a diagnosis of PV. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535742).

Case Presentation

A 55-year-old gentleman was referred to the hematology clinic to evaluate high Hgb, which was incidentally noted before blood donation. He reports no specific symptoms related to the high Hgb. The patient is a nonsmoker, but he is morbidly obese, with a weight of 134 kg, a height of 171 cm, and a body mass index of 45.1.

His medical history includes controlled hypertension and type 2 diabetes mellitus. Additionally, he is being treated for OSA with a home continuous positive airway pressure (CPAP) machine. His complete blood count test revealed elevated Hgb and Hct as shown in Table 1.

The EPO level was 3.12 mIU/mL (2.59–18.5 mIU/mL) and JAK2 V617F mutation was positive. The bone marrow examination revealed a hypercellular marrow with panmyelosis and pleomorphic megakaryocytes, consistent with overall findings indicative of a JAK2-positive MPN.

The diagnosis of PV was established based on the WHO criteria 2016, fulfilling all the three major criteria. The patient was initiated on aspirin and hydroxyurea.

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Table 1. Initial complete blood count (CBC)

Laboratory parameters	Result	Reference range
Hgb	17.6 g/dL	13–17 g/dL
Hct	54.9%	40–50%
White blood cells (WBC)	8.4 × 10^3 cells/μL	4 × 10^3 –10 × 10^3 cells/μL
Absolute neutrophil count	6 × 10^3 cells/μL	2 × 10^3 –7 × 10^3 cells/μL
Lymphocyte	1.7 × 10^3 cells/μL	1×10^3 –3 × 10^3 cells/μL
Platelets	317 × 10^3 cells/μL	150×10^3 –400 × 10^3 cells/μL

Discussion

PV exerts a substantial negative impact on morbidity and mortality, manifesting as symptoms, thrombosis, bleeding, and the potential for progression to MF and leukemia. This underscores the burden of the disease and emphasizes the crucial role of early diagnosis [9].

The overall survival of treated PV patients is inferior to that of a matched normal population. It is estimated that untreated symptomatic PV patients have a median survival of 18 months, while treated patients can experience a significantly extended survival, reaching up to 13 years [10].

Up to now, there is no curative treatment for PV; the goal of treatment is to relieve symptoms and reduce the risk of thrombosis and bleeding events. In a large international study, arterial thrombotic complications, venous thrombosis, or major hemorrhage were noted prior to or at the time of diagnosis in 16%, 7%, and 4% of patients with PV. Unfortunately, no drugs have been shown to reduce the risk of hematologic transformation [11]. However, hydroxyurea and interferon have been used as cytoreductive therapies [12].

Similar to other causes of hypoxia, OSA can induce secondary polycythemia. A meta-analysis by Martelli et al. [8] estimated a polycythemia prevalence of 2% in OSA. However, it concluded that the prevalence is likely underestimated, as the majority of studies included used the WHO 2008 criteria for polycythemia. Further analysis showed a reduction in Hgb by 4 g/L and by 1% in Hct in OSA patients using CPAP.

It is important to establish an accurate diagnosis of polycythemia, whether it is primary or secondary, as the treatment approach and prognosis differ. Although secondary polycythemia is more common than primary polycythemia, it is important to keep in mind the possibility of primary polycythemia in patients with secondary causes, especially if polycythemia does not improve with the management of the underlying secondary causes or if polycythemia is accompanied by leukocytosis or thrombocytosis [8, 11, 13].

Secondary polycythemia results from rising EPO secretion, either appropriately in response to hypoxia or inappropriately in EPO secreting tumor [8]. An above-normal EPO suggests secondary polycythemia, while a low EPO is highly specific for PV [14]. However, some patients with PV have a normal or even elevated EPO [15].

On the other hand, the JAK2 mutation is not found in secondary polycythemia. Since the discovery of JAK2 V617F mutation in 2005, additional JAK2 mutations have been discovered, including exon 12 mutation. JAK2 mutations were assessed in PV, and virtually all patients with PV have a JAK2 mutation, with the majority of them harboring JAK2 V617F [2, 11].

Conclusion

In conclusion, the early discovery and accurate diagnosis of polycythemia are crucial to guide appropriate treatment and improve outcomes. Our report addresses a diagnostic dilemma in which OSA, an apparent secondary cause of polycythemia, is present but turns out to be PV. Moreover, the polycythemia did not improve with CPAP, and it was not associated with leukocytosis or thrombocytosis, as is typically seen in MPN. Medical knowledge and practice are dynamic, and reporting similar cases could change the diagnostic approach for patients with polycythemia to include the JAK2 assessment as a first step.

Statement of Ethics

This case was approved by the Hamad Medical Corporation's Medical Research Centre, under approval number MRC 04-23-138. Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflict of interest with regard to the writing and publication of this article.

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Author Contributions

Mohammad S. Afana contributed to writing the manuscript and literature review. Mohammad Abu-Tineh, Awni Alshurafa, Khalid Ahmed, and Mohammed Abdulgayoom contributed to literature review and final editing. Mohamed A. Yassin contributed to clinical follow-up, final editing, and final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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