Case report

Case report: Therapeutic approach to secondary polycythemia vera in an adult with eisenmenger syndrome

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ABSTRACT

BACKGROUND: Secondary Polycythemia Vera due to Eisenmenger Syndrome remains a big challenge, and the reported cases regarding this condition are still scanty.

CASE: This was a case of a 22-year-old girl who, since childhood, had complaints of fatigue most of the time and thus showed more intolerance to heavy physical work. She had a history of a congenital heart defect, with lip and finger cyanosis that increased upon fatigue, and she had undergone Bi-directional Cavo-pulmonary Shunt. Physical examination showed cyanosis with clubbing of fingers with low oxygen saturation. Further diagnosis testing revealed this was a case of Eisenmenger Syndrome due to congenital heart abnormalities, with Polycythemia Vera: Secondary to the diagnosis. The patient also had a hemoglobin level of 21.1g/dL and a hematocrit level of 64.2%. Based on the diagnosis, treatment was given in the form of hydration therapy along with medications. Additionally, phlebotomy was performed. Because the patient improved clinically from the applied treatment, the patient was discharged after 5 days.

CONCLUSION: Early diagnosis, a multidisciplinary approach, and proper interventions are important in the management of Eisenmenger Syndrome and associated Polycythemia Vera to avoid complications and hence improve outcomes.

KEYWORDS: Eisenmenger syndrome; hyperviscosity; polycythemia vera; case report

INTRODUCTION

Polycythemia Vera originates from a somatic mutation in the JAK2 gene, leading to a myeloproliferative neoplasm marked by erythrocytosis—an excessive increase in red blood cells. This condition often coexists with leukocytosis, thrombocytosis, and splenomegaly and is accompanied by symptoms like itching, constitutional signs such as fever, weight loss, fatigue, circulatory issues, and a heightened risk of thrombosis.[1] Most complications in Polycythemia Vera are vascular and stem from increased blood viscosity, which can contribute to cardiovascular risks like heart attack or stroke.[2] The World Health Organization (WHO) establishes the diagnosis of Polycythemia Vera through specific major and minor criteria, provided that secondary causes are excluded first.[3] One secondary cause is Eisenmenger Syndrome, which develops from congenital heart defects and results in increased pulmonary pressure and abnormal blood flow, ultimately causing chronic hypoxemia. In response to prolonged hypoxemia, secondary Polycythemia Vera may occur,

featuring elevated hemoglobin, red blood cell, and hematocrit levels as the body adapts by increasing the oxygen-carrying capacity of red blood cells to oxygen-deprived peripheral tissues. This compensatory increase in erythrocytes aims to supply sufficient oxygen to tissues affected by hypoxemia-related circulatory issues, such as those present in Eisenmenger Syndrome.[4] However, while this response initially supports oxygen delivery, it may later increase blood viscosity, amplifying thrombosis risks and circulatory issues that worsen patient outcomes.[2] A comprehensive understanding of secondary Polycythemia Vera's pathophysiology is vital for effectively managing patients with Eisenmenger Syndrome and related congenital heart diseases.

Secondary Polycythemia Vera often develops in cases of Eisenmenger Syndrome. When the body encounters hypoxia, it compensates by producing more red blood cells, leading to secondary Polycythemia Vera. This condition can significantly impact the circulatory system, potentially causing severe complications such as thrombosis, bleeding, arrhythmias, and heart failure, which can further deteriorate the patient's health.[4] Effective management of secondary Polycythemia Vera in patients with Eisenmenger Syndrome requires a team-based approach, involving cardiology, hematology, and pulmonology experts.[4,5] From an epidemiological perspective, Polycythemia Vera occurs in about 22 people per 100,000. It has a higher incidence in Eastern Europe compared to Asia but is recognized globally. The male-to-female ratio for Polycythemia Vera is roughly 2:1, a trend seen across various races and ethnicities. The condition is most commonly found in those in their 60s, with a lower prevalence among younger individuals, especially those under 40.[6] However, in the context of cyanotic congenital heart disease, including Eisenmenger Syndrome, secondary Polycythemia Vera is more common in younger individuals, including children and young adults.[7] Despite its prevalence, secondary Polycythemia Vera related to Eisenmenger Syndrome is particularly challenging to diagnose and manage due to the lack of consensus on optimal treatment approaches. Management strategies such as medical therapy to lower hematocrit, phlebotomy, and managing associated heart and lung issues typically need to be customized based on the patient's unique clinical situation.[6] In this case report, we present a patient with both Polycythemia Vera and Eisenmenger Syndrome, aiming to provide insights that may help in managing secondary Polycythemia Vera, particularly for patients with Eisenmenger Syndrome.

CASE PRESENTATION

A 22-year-old female presented to our hospital with complaints of easy fatigue. This complaint was particularly felt during heavy activities and improved with rest. The patient had experienced this symptom since childhood. She denied having blurred vision, dizziness, or headaches. The patient is able to carry out daily activities independently. She was referred to our hospital due to laboratory results showing elevated hemoglobin and hematocrit levels for further examination and management. Regarding her medical history, the patient was diagnosed with congenital heart disease (a heart murmur) since birth, characterized by cyanosis of her lips and fingertips. The patient reported that her fingertips became more blue when she was fatigued. Since childhood, the patient frequently experienced prolonged coughs and colds, which developed into pneumonia requiring treatment. The patient then sought medical attention because of her cyanosis. Following examination, the patient was diagnosed with dextrocardia and a ventricular septal defect (VSD), and surgery was recommended. The patient then underwent a Bi-directional Cavo-pulmonary Shunt procedure, and her cyanosis improved. At that time, the patient was advised to undergo further surgery, as the doctor believed the

condition had not fully improved, but the family declined because the previous surgery had taken a long time.

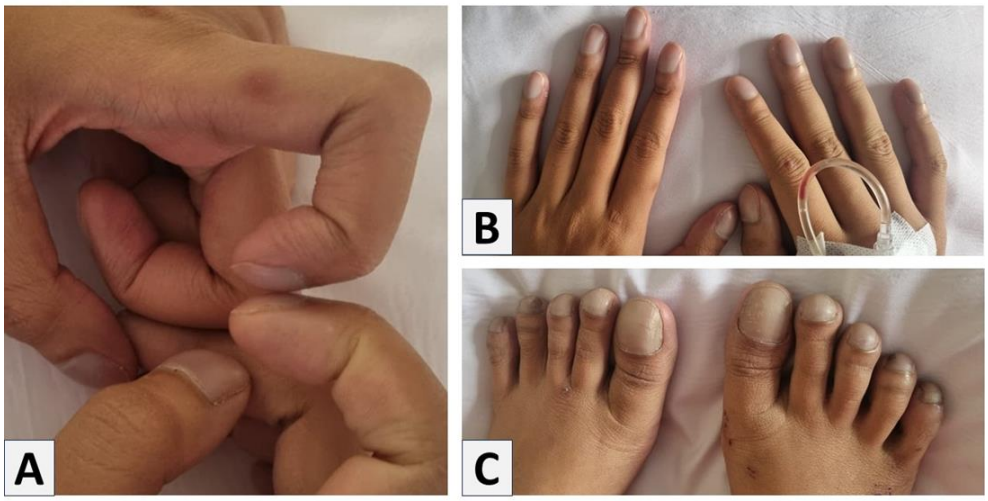

Figure 1. Clinical examination of digital regions in upper and lower limbs. (A). Positive clubbing observed in the fingers. (B). Cyanosis with accompanying clubbing in the hand digits. (C). Cyanosis with accompanying clubbing in the foot digits.

On physical examination, the patient showed cyanosis on the lips, a pansystolic murmur, cyanosis at the fingertips and toes, and clubbing fingers (Figure 1). Oxygen saturation in the extremities was 84% on the right hand, 83% on the left hand, 89% on the right foot, and 87% on the left foot. Chest X-ray examination revealed cardiomegaly (LAE and RVH) with associated increased vascular markings, likely due to a left-to-right shunt. Additionally, we also found widening of the mediastinum, which may be caused by an ascending aortic aneurysm. Echocardiography revealed dextrocardia with mesoposition, situs inversus, PA-VSD muscular inlet balanced shunt, a patent central shunt, and a McGoon ratio of 1.5 with a half-size of 14 mm. Blood tests showed Hb 21.1 g/dL and Hct 64.2%. Bone marrow aspiration revealed hypercellularity, increased erythropoiesis, and negative iron stores, with the conclusion of secondary polycythemia vera with iron depletion (Figure 2).

The patient was then diagnosed with Eisenmenger syndrome and secondary polycythemia vera due to congenital heart disease. The patient was subsequently given intravenous hydration therapy along with Ramipril 2.5 mg, Bisoprolol 2.5 mg, Hydroxyurea 2x500 mg, Acetylsalicylic acid 80 mg, Iron sulfate 1x200 mg, and phlebotomy 250–500 cc with fluid exchange therapy. In the following days, there was improvement in symptoms and laboratory data, with Hb at 18.5 g/dL and Hct at 54.3%. The patient's condition stabilized, and there was significant clinical improvement. The patient continued with conservative care and was discharged after 5 days of hospitalization.

DISCUSSION

In this article, we report a case of a 22-year-old woman with secondary polycythemia vera due to Eisenmenger syndrome. The patient has a history of congenital heart disease, which resulted in secondary polycythemia vera that persisted into adulthood and developed into Eisenmenger syndrome. Eisenmenger syndrome is characterized by chronic hypoxemia caused by a right-to-left shunt through anatomical damage to the heart wall. This condition physiologically leads to an increase in red blood cells (erythrocytosis) as a compensatory mechanism for oxygen deficiency, resulting in

elevated hematocrit and increased blood viscosity.[8] Polycythemia Vera is one of the four JAK2 mutations in Myeloproliferative Neoplasms (MPN), which also include Essential Thrombocytosis (ET), Primary Myelofibrosis (PMF), and Unclassifiable MPN (MPN-U). PV is classified as a hematologic malignancy due to the clonal ability to produce red blood cells. All diseases capable of clonality begin with changes in DNA structure within cells, leading to abnormal cells that mutate within the bone marrow.[9]

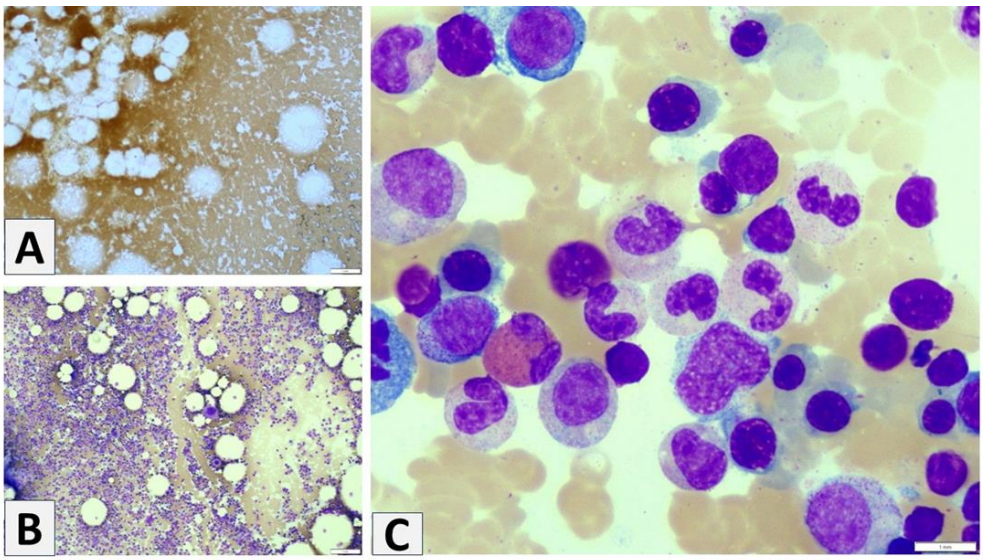

Figure 2. Bone marrow smear findings. (A). 10x magnification: hypercellularity observed with reduced iron stores. (B). 40x magnification: decreased iron stores observed, with well-maintained megakaryopoiesis. (C). 100x magnification: enhanced erythropoietic activity detected.

The patient underwent phlebotomy of 250-500 cc, along with fluid volume replacement using 250 cc of normal saline to avoid hemodynamic instability. After two phlebotomy sessions, the Hb level (18.5 g/dL) and Hct decreased. Symptomatic polycythemia can be treated with careful phlebotomy to reduce hematocrit to 55-65%, along with volume replacement using normal saline. However, compensated and asymptomatic polycythemia does not require phlebotomy, regardless of hematocrit levels.[6] Nevertheless, the phlebotomy procedure frequently performed on patients with cyanotic congenital heart disease and severe polycythemia has been found to have negative effects on the patient, as repeated phlebotomy can lead to iron deficiency. Recurrent phlebotomy in patients with cyanotic congenital heart disease and secondary erythrocytosis can increase the risk of cerebrovascular damage by causing chronic iron deficiency, which triggers microcytosis and increases blood viscosity.[7] The theoretical explanation for this is that iron deficiency increases viscosity and disrupts cerebral blood flow, as coagulation abnormalities occur in states of cyanosis. Severe cyanotic patients are more frequently subjected to aggressive phlebotomy, and poor cerebral oxygenation may be secondary to low Hb levels and reduced systemic oxygen transport.[10]

In this patient, we found that she had secondary polycythemia with iron depletion. This decrease in iron levels was caused by the compensatory mechanism of Eisenmenger syndrome, which increases hemoglobin production to capture oxygen for tissue oxygen supply.[4] Patients with cyanotic congenital heart disease and secondary erythrocytosis are divided into two groups: stable compensated erythrocytosis with adequate iron or ferrum stores and little or no hyperviscosity

symptoms, and decompensated erythrocytosis with iron deficiency (Fe) and microcytic erythrocytes, including those who undergo repeated phlebotomy.[7] Microcytic erythrocytes are those in which red blood cells experience shape defects, becoming stiff and resistant to high shear stress in the microcirculation, which increases the risk of hyperviscosity symptoms in adults and children with cyanotic congenital heart disease and secondary erythrocytosis. Dehydration and deficiency can trigger hyperviscosity symptoms and should be corrected before performing phlebotomy in cyanotic congenital heart disease patients with Hct levels > 65%, as failure to do so may suddenly reduce systemic blood flow, increasing the risk of sudden thrombotic stroke symptoms. Therefore, in cases of iron deficiency, a low dose of Ferrous Sulfate 1x200 mg is recommended.[11]

When iron deficiency has been diagnosed, iron supplementation must be given cautiously to replenish iron stores. Patients with Eisenmenger syndrome experience chronic hypoxia, which can trigger secondary erythrocytosis.[4] However, this response may be weakened due to iron deficiency. Studies show that patients with Eisenmenger syndrome have worse outcomes when they experience iron deficiency. These studies also indicate that iron deficiency occurs more frequently in patients who undergo venesection or receive anticoagulant therapy. Furthermore, other studies reveal that the preferred treatment approach for patients with Eisenmenger syndrome is to initiate iron supplementation.[12,13]

This study presents several valuable benefits and clinical implications. Firstly, it expands understanding of Eisenmenger Syndrome as a complication of congenital heart defects and explores the link between chronic hypoxia and secondary polycythemia development. This is underscored by the finding that early and accurate diagnosis—especially in patients with symptoms like fatigue and cyanosis—can direct effective treatment and help stabilize patients, thus preventing further complications. Secondly, the study demonstrates a treatment approach combining pharmacological options, such as Ramipril, Bisoprolol, and Hydroxyurea, alongside medical interventions like phlebotomy, to manage a case of Eisenmenger Syndrome with secondary polycythemia. Finally, the study underscores that suitable therapy can lead to significant symptom relief and improvement in lab results, while emphasizing conservative management's role in promoting long-term stability for patients facing such complex conditions.

CONCLUSION

This case highlights the complexity of the relationship between congenital heart disease, particularly Eisenmenger syndrome, and secondary polycythemia vera. Early diagnosis and appropriate management are crucial to improving patient outcomes, as evidenced by the significant clinical and laboratory improvements in this patient after initiating targeted therapy. The case also underscores the importance of a multidisciplinary approach that involves pharmacological treatment and procedural interventions, such as phlebotomy, to manage symptoms and prevent further complications. Additionally, this case demonstrates the importance of careful monitoring and tailored care for patients with congenital heart defects who develop secondary complications such as polycythemia. Timely intervention can lead to stabilization and significant clinical improvement, thereby enhancing the quality of life for patients with this challenging condition.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient has provided informed consent for the writing of this article.

CONFLICTS OF INTEREST
We have no conflict of interest

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AUTHOR CONTRIBUTION
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REFERENCES

1. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol 2023;98(9):1465-1487.doi: 10.1002/ajh.27002. PMID: 37357958
2. Benevolo G, Marchetti M, Melchio R, et al. Diagnosis and management of cardiovascular risk in patients with polycythemia vera. Vasc Health Risk Manag 2023;19(1):765-778.doi: 10.2147/VHRM.S429995. PMID: 38025519
3. Barbui T, Thiele J, Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J 2018;8(2):15.doi: 10.1038/s41408-018-0054-y. PMID: 29426921
4. Oechslin E, Mebus S, Schulze-Neick I, et al. The adult patient with eisenmenger syndrome: A medical update after dana point part iii: Specific management and surgical aspects. Curr Cardiol Rev 2010;6(4):363-372.doi: 10.2174/157340310793566127. PMID: 22043213
5. Diller GP, Lammers AE, Oechslin E. Treatment of adults with Eisenmenger syndrome-state of the art in the 21st century: a short overview. Cardiovasc Diagn Ther 2021;11(4):1190-1199.doi: 10.21037/cdt-21-135. PMID: 34527543
6. Raedler LA. Diagnosis and management of polycythemia vera: Proceedings from a multidisciplinary roundtable. Am Health Drug Benefits 2014;7(3):S36-47.doi. PMID: 26568781
7. Rose SS, Shah AA, Hoover DR, et al. Cyanotic congenital heart disease (CCHD) with symptomatic erythrocytosis. J Gen Intern Med 2007;22(12):1775-1777.doi: 10.1007/s11606-007-0356-4. PMID: 17917783
8. Kaemmerer H, Mebus S, Schulze-Neick I, et al. The adult patient with eisenmenger syndrome: a medical update after dana point part I: epidemiology, clinical aspects and diagnostic options. Curr Cardiol Rev 2010;6(4):343-355.doi: 10.2174/157340310793566154. PMID: 22043211
9. Tashkandi H, Younes IE. Advances in molecular understanding of polycythemia vera, essential thrombocythemia, and primary myelofibrosis: Towards precision medicine. Cancers (Basel) 2024;16(9):1679.doi: 10.3390/cancers16091679. PMID: 38730632
10. Broberg CS, Bax BE, Okonko DO, et al. Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease. J Am Coll Cardiol 2006;48(2):356-365.doi: 10.1016/j.jacc.2006.03.040. PMID: 16843187
11. DeFilippis AP, Law K, Curtin S, et al. Blood is thicker than water: the management of hyperviscosity in adults with cyanotic heart disease. Cardiol Rev 2007;15(1):31-34.doi: 10.1097/01.crd.0000214959.82120.97. PMID: 17172881
12. Van De Bruaene A, Delcroix M, Pasquet A, et al. Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J 2011;32(22):2790-2799.doi: 10.1093/eurheartj/ehr130. PMID: 21606083
13. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 2006;27(14):1737-1742.doi: 10.1093/eurheartj/ehl116. PMID: 16793921