sciendo Internal Medicine 2025 vol. XXII No. 1 - www.srmi.ro 85
10.2478/inmed-2025-0321

CARDIOVASCULAR RISK MANAGEMENT IN PATIENTS WITH POLYCYTHEMIA VERA

Florin Mitu[1,2,3,4], Ioana Țintilă[2], Diana Andreea Matianu[2], Corina Dima-Cozma[1,2], Alexandra Maștaleru[1,2*], Elena Andreea Moaleș[1,2], Maria-Magdalena Leon[1,2]
[1.] Department of Internal Medicine I, Faculty of Medicine, University of Medicine and Pharmacy "Grigore T. Popa", 700115 Iași, Romania
[2.] Department of Cardiovascular Rehabilitation, Clinical Rehabilitation Hospital, 700661 Iași, Romania
[3.] Academy of Romanian Scientists, 700050 Iași, Romania
[4.] Academy of Medical Sciences, 030167 Bucharest, Romania
Correspondent author: Alexandra Maștaleru Email: alexandra.mastaleru@umfiasi.ro

Rezumat

Prezentăm cazul unui pacient, în vârstă de 54 de ani, obez, de sex masculin, din mediul urban, fără antecedente personale patologice semnificative, fără medicație cronică, care se prezintă în regim de urgență pentru dizartrie și asimetrie facială, simptomatologie ce a debutat cu o zi anterior prezentării. Examenul clinic a evidențiat facies asimetric, eritroză generalizată, splenomegalie grad I, sindrom piramidal drept, pareză facială centrală dreaptă cu ștergerea șanțului nazogenian drept, coborârea comisurii bucale pe partea dreaptă, dizartrie, valori tensionale crescute. Electrocardiografic nu s-au decelat modificări semnificative, aspect observat și la ecocardiografia transtoracică. CT-ul cranio-cerebral nativ nu a obiectivat leziuni acute ale parenchimului cerebral, dar a evidențiat două lacune cronice la nivelul coroanei radiate drepte, respectiv la nivelul capsulei externe stângi, confirmându-se astfel diagnosticul de accident ischemic tranzitor stâng. Examenele de laborator au evidențiat eritrocitoză, leucocitoză cu neutrofilie, glicemie bazală modificată, dislipidemie tip IIa.

S-a inițiat tratament de prevenție secundară a accidentului cerebral vascular ischemic și tratament suportiv, cu remiterea simptomatologiei prezente la internare. S-a ridicat suspiciunea de poliglobulie, iar prin rezultatele testelor de biologie moleculară, nivelului scăzut al eritropoetinei, și creșterea hemoglobinei și hematocritului, s-a confirmat diagnosticul de sindrom mieloproliferativ cronic tip policitemie rubra vera.

S-a inițiat tratament citoreductor, iar pe parcursul internării s-au efectuat patru flebotomii terapeutice. Pacientul s-a externat cu recomandarea de a reveni pentru control și noi ședințe de flebotomie în regim ambulator. De asemenea, din cauza asocierii factorilor de risc cardiovascular și a atacului ischemic tranzitor din antecedente, pacientul necesită reevaluare cardiologică periodică.

Cuvinte cheie: *poliglobulie, atac ischemic tranzitor, policitemia vera, neoplasme mieloproliferative, flebotomie*

Internal Medicine

Clinical Cases

Abstract

We present the case of a 54-year-old male patient, obese, from an urban area, with no significant personal pathological history, no chronic medication, who presented in emergency room for dysarthria and facial asymmetry, with onset of symptoms the day before hospital admission. The clinical examination revealed asymmetric facies, generalized erythrosis, grade I splenomegaly, right pyramidal syndrome, right central facial paresis with flattening of the nasolabial fold, ptosis of the oral commissure on the right side, dysarthria, and increased blood pressure. Electrocardiographically, there were no significant changes, as confirmed by the transthoracic echocardiography. The native cranio-cerebral CT did not show acute lesions of the brain parenchyma, but identified two chronic lacunar infarcts located in the right corona radiata and the left external capsule, thus confirming the diagnosis of left transient ischemic attack.

Laboratory findings revealed erythrocytosis, leukocytosis with neutrophilia, altered basal glycemia, type IIa dyslipidemia. Secondary prevention of ischemic stroke and supportive treatment with improvement of the clinical symptoms was initiated. The suspicion of polycythemia was raised, and based on the results of molecular biology tests, low erythropoietin levels, and increased hemoglobin and hematocrit, the diagnosis of chronic myeloproliferative syndrome, specifically polycythemia vera, was confirmed.

Cytoreductive therapy was initiated and four therapeutic phlebotomies were performed during hospitalization. The pacient was discharged with a recommendation to return for follow-up and further outpatient phlebotomy sessions. Also, due to the association of cardiovascular risk factors and history of transient ischemic attack, the patient also requires regular cardiologic evaluation.

Keywords: *polycythemia, transient ischemic attack, polycythemia vera, myeloproliferative neoplasms, phlebotomy*

Introduction

Polycythemia vera is a type of myeloproliferative disorder linked to a mutation in the Janus kinase 2 (JAK2) gene, which leads to the abnormal proliferation of hematopoietic progenitor cells. This results in an increased production of red blood cells and secondary increased white blood cells and platelets. Complications of the disease are primarily due to the high viscosity of the blood, which can lead to thrombosis.

In patients with polycythemia vera, the bone marrow contains both normal stem cells and abnormal, clonal stem cells that inhibit the growth and maturation of the normal ones. The underlying cause of panmyelosis is uncontrolled neoplastic cell proliferation.

The mutation of the JAK2 kinase is believed to contribute to the signaling abnormalities that result in polycythemia vera. Specifically, a substitution of valine with phenylalanine at position 617 in the JAK2 gene (JAK2V617F) causes the cytokine receptors to remain continuously active[1].

At the time of diagnosis, patients with polycythemia vera may be asymptomatic or exhibit a range of symptoms. These can include microvascular complications such as headaches, dizziness, visual disturbances (e.g., blurred vision and scotoma), palpitations, chest pain, erythromelalgia, and tingling or numbness in the extremities. Other symptoms may include pruritus, discomfort in the spleen due to splenomegaly, superficial thrombophlebitis, mild mucocutaneous bleeding, or more severe thrombotic or hemorrhagic events[2].

The formal diagnostic criteria for polycythemia vera include three major criteria and one minor criterion. The major criteria are [1]: hemoglobin or hematocrit levels above 16.5 g/dL (49%) in men or 16 g/dL (48%) in women, or a red cell mass greater than 25% above the mean normal predicted value [2]; bone marrow morphology consistent with polycythemia vera and the presence of a JAK2V617F mutation or an exon 12 mutation. The minor criterion is a subnormal serum erythropoietin level. For a WHO-qualified diagnosis of polycythemia vera, a patient must meet either all three major criteria or the first two major criteria along with one minor criterion[3].

For low-risk polycythemia vera patients is recommended conservative management, which includes phlebotomy combined with once- or twice-daily aspirin therapy.For high-risk patients, cytoreductive therapy is recommended. First, second, and third line drugs of choice are hydroxyurea, pegylated interferon-α and busulfan, respectively.

Recent data on long-term survival have confirmed the positive outlook for patients with polycythemia vera, showing an estimated median survival of 24 years in individuals under 60 years of age [4].

Case presentation

A 54-year-old male patient, obese, with no significant personal pathological history is currently presenting as an emergency to the Neurology Department for dysarthria and facial asymmetry, with onset of symptoms one day ago. He was a non-smoker, denied chronic alcohol consumption and had no chronic treatment.

Clinical on examination admission revealed asymmetric facies, generalized erythrosis, grade I splenomegaly, right pyramidal syndrome (right Babinski sign), right central facial paresis with flattening of the nasolabial fold, ptosis of the oral commissure on the right side, dysarthric word articulation disorder, high blood pressure (BP=161/70 mmHg). The patient has a BMI of 30.1 kg/m^2.

Internal Medicine

Clinical Cases

Subsequent paraclinical examinations were conducted.

The electrocardiogram showed a sinus rhythm with a ventricular rate of 78 beats per minute, without significant morphological changes (Figure 1.) Laboratory blood tests revealed erythrocytosis (RBC= 9,57 10^6/uL), leukocytosis with neutrophilia (WBC= 15.88 10^3/uL, NEU= 11. 75 10^3/uL), altered basal glycemia (blood glucose= 115mg/dl, HbA1c= 7,3%), type IIa dyslipidemia (LDL-C= 124mg/dl), depicted in Table 1.

The native cranio-cerebral CT performed in the emergency room did not reveal acute lesions of the brain parenchyma, but showed two chronic lacunar infarcts, one in the right corona radiata and another in the left external capsule.

Minimal diffuse carotid atheromatosis with no hemodynamic significance was detected by doppler ultrasonography of cervical vessels. The internal medicine evaluation reveals generalized erythrosis, grade I splenomegaly, and blood pressure of 170/110 mmHg. Given that our patient suffered a transient ischemic attack and was diagnosed with stage 2 hypertension with very high additional risk, a cardiology examination was performed. The ABPM results revealed that the patient has a non-dipper profile. The average, highest, and lowest blood pressure readings over the 24-hour monitoring period were 193/88 mmHg, 167/75 mmHg, and 108/54 mmHg, respectively (Figure 2). Due to the higher incidence of atrial fibrillation in polycithemia vera, an EKG Holter monitor was recommended for our patient. The only findings from this investigation were 186 ventricular extrasystoles and 7 supraventricular extrasystoles (Figure 3).

For these values, the patient was prescribed an angiotensin receptor blocker (Candesartan 16 mg), an antiplatelet (Aspenter 75 mg) and a statin (Atorvastatin 40 mg). A peripheral blood smear, coagulation profile, hematological evaluation, and an abdominal-pelvic ultrasound were recommended.

The echocardiographic examination revealed an ejection fraction of about 55%, heart without segmental and global kinetic disorders. No space-occupying formations were detected during the examination (Figure 4, 5).

Secondary prevention of ischemic stroke and supportive treatment with remission of symptoms was initiated. The suspicion of polycythemia was raised and the patient was transferred to the Hematology Department. By correlating the clinical and paraclinical results, we established the final diagnosis as a left transient ischemic attack, multiple old lacunar infarcts, stage 2 hypertension with very high additional risk, type IIa dyslipidemia, polycythemia with unknown etiology. The patient was admitted to the Hematology Clinic, where further investigations were

Laboratory analysis	First evaluation	Second evaluation	Third evaluation
WBC NEU LYM MON EOS BAS	15,88 *10^3/ul 11,75 *10^3/ul 2,57 *10^3/ul 0,54 *10^3/ul 0,70 *10^3/ul 0,32 *10^3/ul	16,17 *10^3/ul 12,29 *10^3/ul 2,47 *10^3/ul 2,65 *10^3/ul 0,69 *10^3/ul 0,29 *10^3/ul	16,47 *10^3/ul 12,38 *10^3/ul 2,81 *10^3/ul 0,46 *10^3/ul 0,58 *10^3/ul 0,24 *10^3/ul
RBC	9,57 *10^6/ul	9,85 *10^6/ul	9,71 *10^6/ul
HGB	23,82 g/dl	24,57 g/dl	24,67 g/dl
HCT	77,6%	79,7%	78,9%
aptt	79,0 sec	-	79,7 sec
pt	14,8 sec	-	14,5 sec
INR	1,35	-	1,32
Blood glucose	115 mg/dl	-	-
HbA1c	-	7,3%	-
Morphologic examination of blood smear	-	-	neutrophil unsegmented 8%, neutrophil segmented 73%, eosinophil 6%, basophil 0%, monocyte 2%, lymphocyte 11%; erythrocyte

Table 1. *Laboratory analysis – evolution*

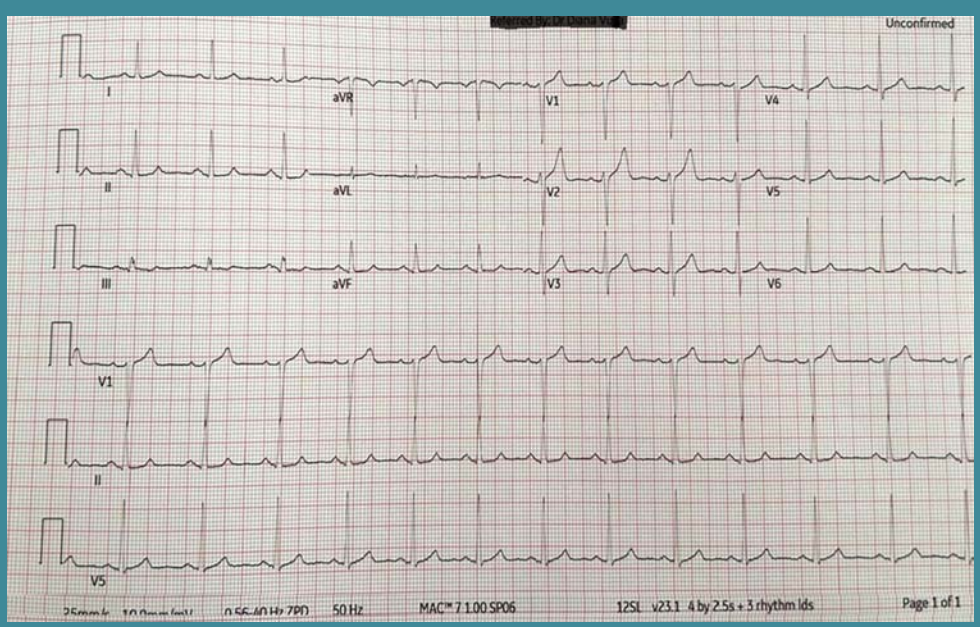

Figure 1. *Sinusal rhythm, ventricular rate of 78 beats per minute, without significant morphological changes*

carried out. Additional laboratory blood tests aside from those performed at the Neurology Department revealed low erythropoietin levels (3,5 mU/ml). The blood smear morphological examination revealed leukocytosis with neutrophilia, significant erythrocytosis with anisocytosis, occasional target cells, occasional macrothrombocytes.

The diagnosis of chronic myeloproliferative syndrome, type polycythemia rubra vera was confirmed by molecular biology tests which revealed the presence of JAK 2 kinase V617F mutation.

This finding was correlated with a low erythropoietin level (3.5 mU/ml), increased hemoglobin (22.80 g/dl) and hematocrit (72%), which is characteristic of chronic myeloproliferative syndrome, type polycythemia rubra vera. Differential diagnosis with other myelopro-liferative diseases such as essential thrombo-cythemia or secondary polycythemia was made on the basis of low erythropoietin levels and significant erythrocytosis. It was initiated cytoreductive therapy and four therapeutic phlebotomies were performed during hospitalization. The patient started a subcutaneous anticoagulant for 10 days (Enoxaparine 6000 UI/ 0,6 ml), followed by a direct oral anticoagulant (Apixaban 5 mg, twice daily). It has been decided to stop the antiplatelet therapy.

The patient was discharged and returned for periodically for follow-ups and further outpatient phlebotomy sessions. The laboratory values remained elevated, which is why the patient periodically returned for further investigations and adjustment of the treatment regimen. The patient's evolution was favorable under treatment, with therapeutic phlebotomy of 350 ml with 500 ml saline replacement and Hydroxycarbamide 4 tablets a day. The evolution of laboratory values during two months of treatment can be observed in Table 2.

Discussion

Myeloproliferative neoplasms are associated with an elevated cardiovascular risk, even in the absence of traditional cardiovascular risk factors. Identifying patients at elevated risk for fatal cardiovascular events is crucial for facilitating early intervention and care. Careful management of cardiovascular risk factors, combined with effective hematologic treatment, can significantly improve outcomes for patients with myeloproliferative neoplasms[5].

Elevated cardiovascular risk factors such as hypertension, arrhythmias, dyslipidemia, obesity, and smoking reduce survival rates in patients with polycythemia vera.

To minimize the risk of thrombosis, treatment should focus on normalizing hemoglobin, hematocrit, and white blood cell counts, while also addressing and modifying any existing

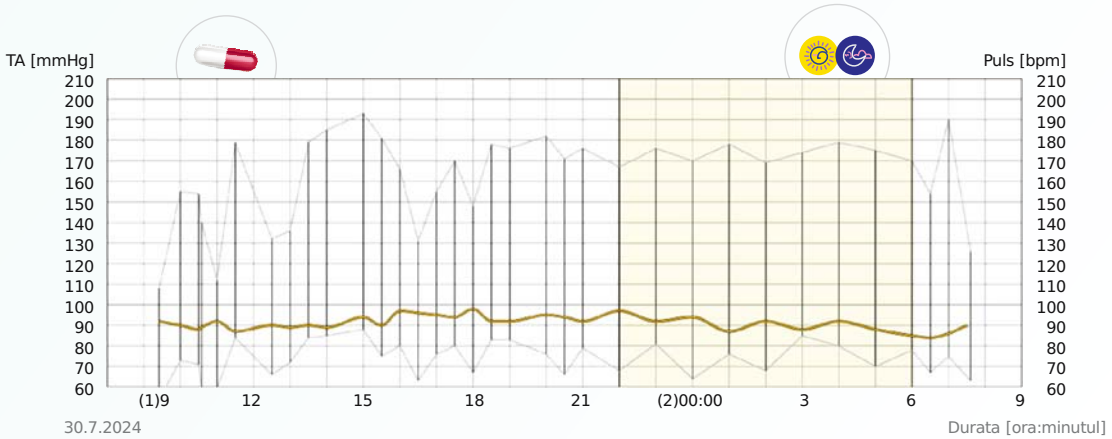

Figure 2. *Ambulatory blood pressure monitoring*

HEART RATE

Minimum HR-4 Intervals:	49 bpm at 5:27
Maximum HR-4 Intervals:	136 bpm at 10:50
Average HR-24 Hours:	73 bpm
Minimum HR-Hourly:	60 bpm at 1:00
Maximum HR-Hourly:	105 bpm at 9:00
Analyzed Beats:	105606
Analyzed Minutes:	1426
ECG Monitoring Period:	23 hours 46 minute

ST SEGMENT ANALYSIS

Total ST Minutes CH1:	0
Total ST Minutes CH2:	0
Total ST Minutes CH3:	0
Max Abs. ST Depression:	N/A
Max Abs. ST Elevation:	N/A
Max ST Episode:	N/A
Max HR In ST Episode:	0

VENTRICULAR ECTOPY

VE Total:	186
V-Pair Total:	0
V-Run Total:	0
Longest V-Run:	N/A
Maximum HR V-Run:	N/A
Minimum HR V-Run:	N/A
VE's per 1000/per Hour:	1.76/7.84
Ventricular R on T:	N/A

SUPRA VENTRICULAR ECTOPY

SVE Total:	7
SVE Pair Total:	0
SV-Run Total:	0
Longest SV-Run:	N/A
Maximum HR SV-Run:	N/A
SVE's per 1000/per hour:	0.07/0.30
Total Aberrant Beats/Runs:	0/0
Atrial Fib/Flutter:	0.0%

HEART RATE VARIABILITY

SDNN-24 Hour:	147
SDANN Index:	132
SDNN Index:	48
rMSSD:	18
pNN50:	1
Spectral Power-24 Hour:	2351.8
Min Spectral Power Hour:	951.4
Max Spectral Power Hour:	7737.1

PAUSES

Pauses in Excess of 2.50 sec:	0
Max Pause:	N/A

QT

Max QT:	515 ms (Ch. 1)
Max QTc:	515 ms
Time of Max QT:	at 14:51. HR 77 bpm.
IdioV	2

SIGNIFICANT ECG EVENTS

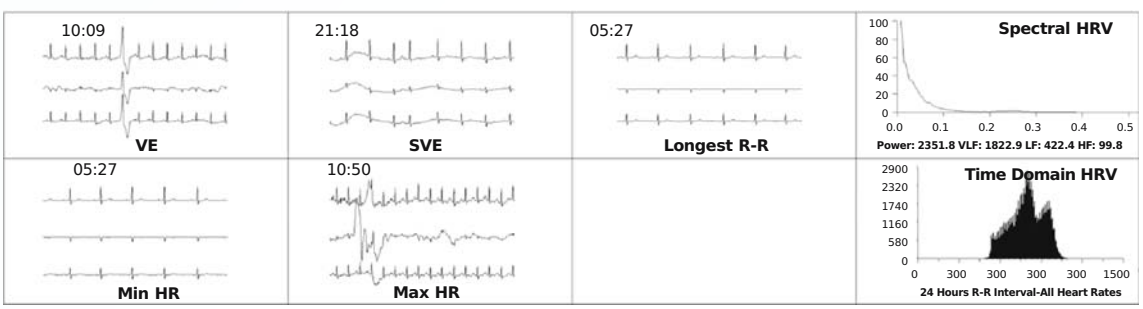

Figure 3. *Holter EKG*

cardiovascular risk factors [5-7]. In polycythemia vera, approximately 20% of patients experience thrombotic events, as observed in our case. Hypertensive patients with a nondipper profile are at risk of developing left ventricular hypertrophy, myocardial infarction, heart failure, renal failure and stroke[6].

A recent study involving 37,922 patients with polycythemia vera, identified through the National Inpatient Sample Database, found that the prevalence of atrial fibrillation in these patients was 18%, compared to 11% ($p<0.001$) in the general population[7].

The second most common cardiovascular risk factor in patients with myeloproliferative neoplasms is dyslipidemia, which can potentially lead to the development of acute coronary syndromes.

In our case, the patient presents with type IIa dyslipidemia, and doppler ultrasonography of cervical vessels revealed diffuse carotid atheromatosis. As a result, a high-potency statin was initiated. For most patients, the goal is to reduce LDL-C levels to below 100 mg/dL, while those at very high cardiovascular risk, as our patient, may require a more aggressive target of less than 55 mg/dL and a reduction of more that 50% of the initial values[8].

When examining the link between age and dyslipidemia, there is a notable gender difference in how the prevalence of dyslipidemia changes with age. In middle-aged men, the occurrence of dyslipidemia tends to decrease as they age, whereas, in middle-aged women, the prevalence of dyslipidemia generally increases with age [9].

In this case, the patient is considered to have high-risk polycythemia vera, so hydroxyurea is the first-line treatment. Multiple sessions of phlebotomy are also recommended.

This medication does not prevent thrombosis or increase survival.

Significant improvements have been noted in the rates of fatal and non-fatal cardiovascular events in patients treated with hydroxyurea compared to those undergoing phlebotomy or other treatments[10].

The patient's evolution was favorable under treatment, with a gradual improvement in his health. The latest laboratory results show a hemoglobin level of 16 g/dL and a hematocrit of 48%, representing significant improvement compared to his initial hospitalization.

Conclusions

Patients with myeloproliferative neoplasms, particularly polycythemia vera, face an elevated cardiovascular risk that extends beyond traditional risk factors, with thrombotic events, hypertension, arrhythmias, and dyslipidemia contributing significantly to unfavorable outcomes.

The identification of patients at particularly high cardiovascular risk is crucial for initiating

	Hemoglobin (g/dl)	Hematocrit (%)
First month	22.4	70%
	21.7	64%
	20.5	61.9%
	19.3	57.1%
	17	52%
	18	55%
Second month	16	48%
	17.8	53.7%
	16.6	49.9%

Table 2. *evolution of laboratory values during two months of treatment*

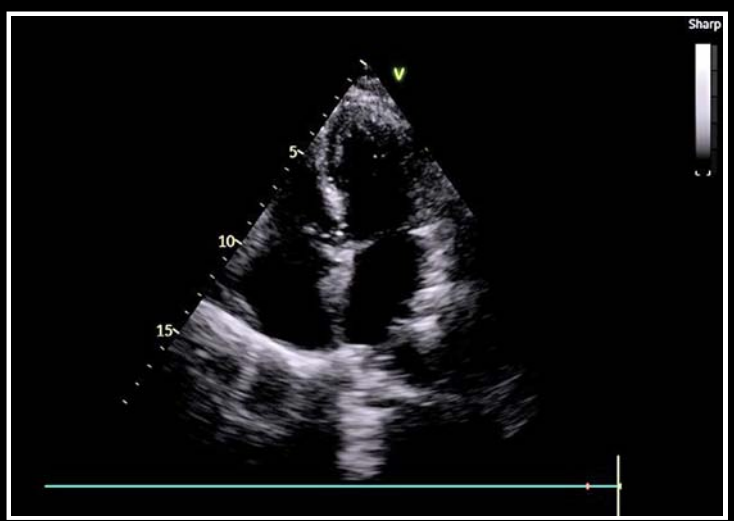

Figure 4. *Cardiac ultrasound – parasternal long axis*

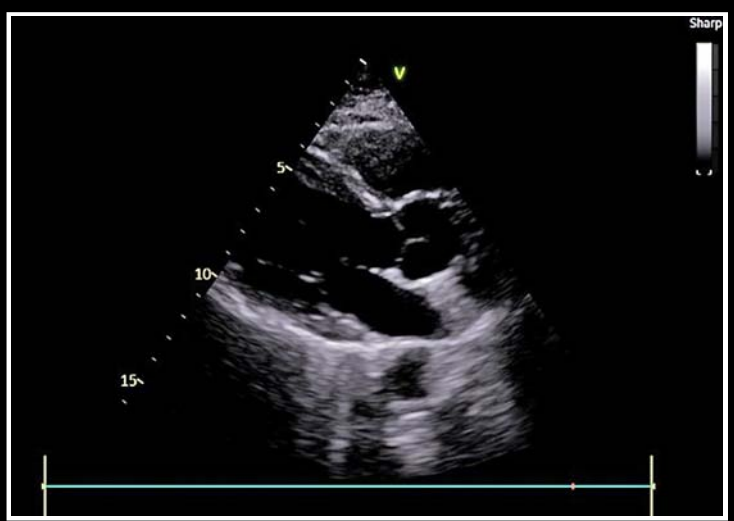

Figure 5. *Cardiac ultrasound – apical section*

INTERNAL MEDICINE
Clinical Cases

early, comprehensive management strategies aimed to reduce both hematological and cardiovascular complications.

In this case, a multidisciplinary approach, including optimal control of blood pressure, lipid levels, and hematological parameters, along with targeted pharmacological treatments has shown promise in improving patient outcomes.

Therefore, the importance of closely monitoring cardiovascular risk factors in polycythemia vera patients, particularly those with comorbidities, is highlighted. Ultimately, integrated care between hematologists and cardiologists is essential to mitigate the high cardiovascular burden associated with myeloproliferative neoplasms and to enhance overall patient prognosis.

References

1. Lu X, Chang R. Polycythemia Vera. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024; Available at: https://www.ncbi. nlm.nih.gov/books/NBK557660/

2. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023; 98(9): 1465-1487.

3. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera: historical oversights, diagnostic details, and therapeutic views. Leukemia. 2021; 35(12):3339-3351.

4. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera treatment algorithm 2018. Blood Cancer J. 2018; 8(1):3.

5. Benevolo G, Marchetti M, Melchio R et colab. Diagnosis and Management of Cardiovascular Risk in Patients with Polycythemia Vera. Vasc Health Risk Manag. 2023; 19:765-778.

6. Akdi A, Özeke Ö, Karanfil M et colab. Diurnal rhythm of blood pressure in patients with polycythemia vera. Blood Press Monit. 2020; 25(2):69-74.

7. Umer W, Umer N, Ali EA, Abubakar M, Yassin MA. Polycythemia Vera With Atrial Fibrillation: A Case Report and Review of the Literature. Cureus. 2022; 14(8):e28550.

8. Găman MA, Srichawla BS, Chen YF et colab. Overview of dyslipidemia and metabolic syndrome in myeloproliferative neoplasms. World J Clin Oncol. 2024; 15(6):717-729.

9. Wakabayashi I. Effects of age on polycythemia, cardiometabolic risk and their associations in middle-aged men. J Diabetes Metab Disord. 2022; 22(1):287-295.

10. Visweshwar N, Fletcher B, Jaglal M et colab. Impact of Phlebotomy on Quality of Life in Low-Risk Polycythemia Vera. J Clin Med. 2024; 13(16):4952.