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Symptomatic Severe Bradycardia during Pazopanib Treatment

Pazopanib Tedavisi Sırasında Semptomatik Şiddetli Bradikardi

ABSTRACT

Pazopanib, a tyrosine kinase inhibitor that targets growth factor receptors, is associated with various side effects, including bradycardia. We report a severe case of symptomatic bradycardia, with a heart rate dropping to 28 beats per minute, in a patient with cardiac angiosarcoma treated with 800 mg/day of pazopanib. Reducing the dosage to 600 mg/day improved the heart rate to 53 beats per minute. This case highlights the risk of severe bradycardia associated with pazopanib, emphasizing the need for vigilant heart rate monitoring.

Keywords: Angiosarcoma, cardiotoxicity, pazopanib, permissive cardiotoxicity

ÖZET

Pazopanib, büyüme faktörü reseptörlerini hedef alan ve bradikardi dahil çeşitli yan etkilere sahip olan bir tirozin kinaz inhibitörüdür. Biz, günde 800 mg pazopanib alan bir kardiyak anjiyosarkoma hastasında semptomatik ciddi bradikardi olgusu (28/dakika) sunuyoruz. Pazopanib dozunu günde 600 mg'a düşürmek, kalp hızının dakikada 53'e dönmesi için yeterli oldu. Bu olguda, pazopanib nedeniyle oluşabilecek ciddi bradikardi potansiyelini ve kalp hızını daha dikkatli takip etmenin gerekli olduğunu vurguladık.

Anahtar Kelimeler: Anjiyosarkom, kardiyotoksisite, pazopanib, izin verilen kardiyotoksisite

CASE REPORT
OLGU SUNUMU

Angiosarcomas are rare, highly vascular, and aggressive malignancies originating from endothelial cells lining the blood or lymphatic vessels. They are responsive to anti-angiogenic therapies.[1] Pazopanib, a tyrosine kinase inhibitor, targets various growth factor receptors, including vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and c-kit. By inhibiting vascular endothelial growth factor receptors, pazopanib may restrict tumor growth by limiting blood supply, potentially making it a valuable therapeutic agent for diseases characterized by abnormal angiogenesis or cellular proliferation.[1-3]

Originally approved for renal cell carcinoma and certain soft tissue sarcomas, pazopanib's mechanism of inhibiting vascular endothelial growth factor receptor inhibition could make it a promising treatment for angiosarcomas. In rare cancers like angiosarcoma, where standard treatments may fail or be unsuitable, the consideration of pazopanib for angiosarcoma treatment necessitates an understanding of its side effect profile, which includes hypertension, liver toxicity, and, less commonly, bradycardia. Ongoing monitoring and patient cooperation are essential for successful treatment with this drug.[3-4]

Case Report

A 25-year-old non-smoking, non-diabetic, normotensive female patient, previously diagnosed with Poland Syndrome, received a left breast implant for aesthetic purposes. She underwent heart surgery two years earlier at another hospital due to a sudden onset of shortness of breath caused by a pericardial effusion from primary angiosarcoma in the right atrium. Post-operation, she was administered three cycles of doxorubicin but did not achieve a sufficient clinical response. Consequently, she underwent six cycles of radiation therapy (RT) alongside paclitaxel and gemcitabine. She had Coronavirus Disease 2019 (COVID-19) seven months prior to this diagnosis but was unvaccinated and received no treatment.

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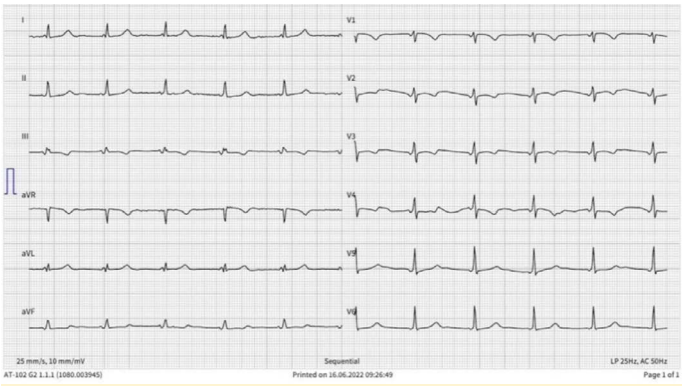

Figure 1. An ECG taken prior to pazopanib treatment displayed heart rate of 63 bpm with corrected QT interval using the Fridericia formula (QTcF) of 461 ms.

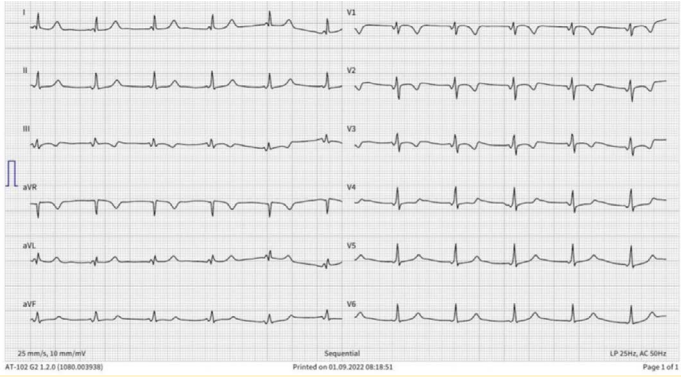

Figure 2. An ECG taken during pazopanib treatment displayed heart rate of 64 bpm with corrected QT interval using the Fridericia formula (QTcF) of 454 ms.

Approximately six months after the operation, when positron emission tomography-computed tomography (PET-CT) scans revealed recurrence and lung lesions, treatment with 800 mg/day of pazopanib was initiated. Two electrocardiograms (ECGs) from her routine CardioOncology follow-ups showed sinus rhythm, with heart rates of 63 and 64 beats per minute (bpm), respectively (Figures 1-2). At about the third month, the patient was symptom-free, and her ECG showed sinus rhythm at 54 bpm (Figure 3).

After about eigth months on pazopanib, the patient presented to the cardio-oncology department with symptoms of lightheadedness and episodes of fatigue. Neither peripheral edema nor pulmonary rales were observed during the physical examination. The body mass index was 24.2 kg/m^2, blood pressure was 101/62 mmHg, and her resting heart rate was 36 bpm, as per ECG (Figure 4). Left ventricular ejection fraction was 51%, and no wall motion abnormalities were detected on transthoracic echocardiography. On the same day, a 24-hour

ABBREVIATIONS

COVID-19	Coronavirus Disease 2019
ECGs	Electrocardiograms
PET-CT	Positron emission tomography-computed tomography
RT	Radiation therapy

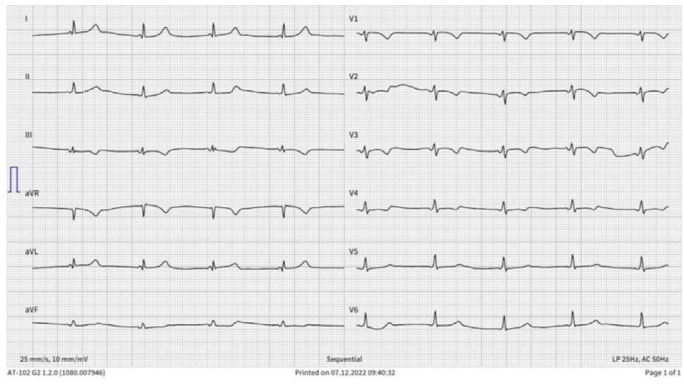

Figure 3. An ECG taken three months post-initiation of pazopanib at a dosage of 800 mg/day, showing a heart rate of 54 bpm. The patient was asymptomatic at this stage.

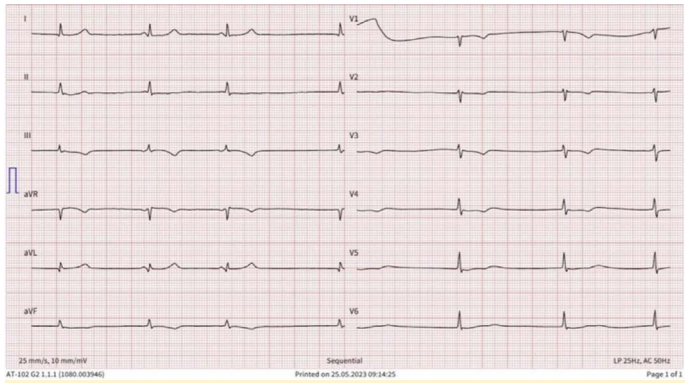

Figure 4. After about eight months pazopanib treatment, the patient reported episodes of fatigue. ECG revealed sinus bradycardia at 36 bpm and incomplete right bundle branch block (RBBB) with a QTcF of 460 ms.

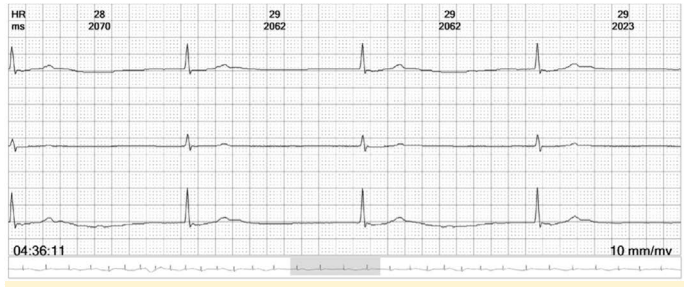

Figure 5. A frame from a Holter recording taken during the treatment phase, showing sinus bradycardia at 28 bpm with a normal QRS complex.

Holter monitor was performed, detecting bradycardia that reached 28 bpm during sleep hours (Figure 5).

No other cause of bradycardia, such as medications and/or comorbidities, was identified in the patient. The relevant oncologist was consulted, and the pazopanib dose was reduced to 600 mg/day. Subsequently, a control ECG showed the patient's resting heart rate had normalized to 53 bpm (Figure 6), allowing for the continuation of pazopanib treatment without interruption.

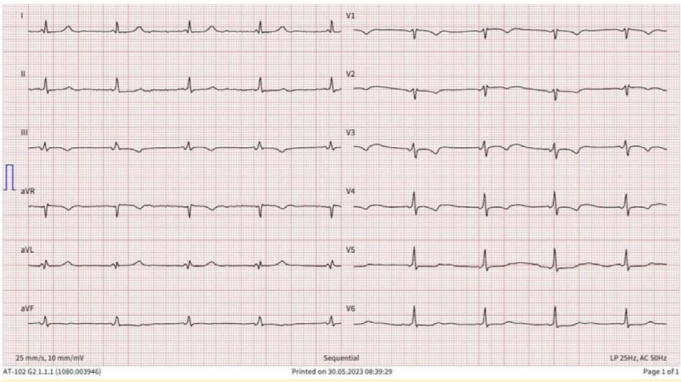

Figure 6. An ECG recorded four days after reducing the pazopanib dose to 600 mg/day, showing a heart rate of 53 bpm and a QTcF of 456 ms.

Discussion

Several cases of primary angiosarcoma have been previously published in conjunction with Poland Syndrome.[5-6] However, this case report focuses solely on severe symptomatic bradycardia that emerged during pazopanib treatment for primary angiosarcoma and its management. Pazopanib-induced bradycardia has been reported previously with rates reaching as low as 35 bpm.[7] While the Poland Syndrome previously identified in the patient is not the focus of this report, it is worth noting that the patient's cancer progressed even after surgery and treatment with doxorubicin, gemcitabine, paclitaxel, and radiotherapy. Given this progression, oncologists deemed pazopanib an appropriate next step.

In this instance, after detecting symptomatic bradycardia as low as 28 bpm, considered a grade 3 side effect,[8] consulted oncology team decided it was appropriate to continue pazopanib, which they believed offered significant clinical benefits. However, they opted to reduce the dosage rather than discontinuing or switching to another drug. The consensus was to closely monitor the patient, who then continued with pazopanib at a reduced dose of 600 mg/day. Previously, the patient had undergone resection of a right atrial mass and received three cycles of doxorubicin followed by six cycles of a combination of gemcitabine and paclitaxel, and had undergone radiotherapy with no history of bradycardia symptoms or documentation. Symptoms such as fatigue, lightheadedness, and bradycardia emerged only after initiating pazopanib at 800 mg/day. Four days after reducing the dose to 600 mg/day, symptoms improved, and were attributed to the most recent medication change.

Conclusion

In conclusion, the use of pazopanib for treating cardiac angiosarcomas represents an intriguing area of exploration, given its anti-angiogenic properties. While it may offer important therapeutic benefits, more robust clinical studies are needed to establish its efficacy and safety in this specific patient population. Until then, its application should be considered on a case-by-case basis, especially in settings where standard therapies have failed or are unsuitable. This report exemplifies the concept of "permissive cardiotoxicity,"[2] where a dose reduction of pazopanib was chosen over discontinuing this life-saving treatment. Effective implementation would require collaboration with a multidisciplinary team and diligent patient monitoring.

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