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Case Report

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Acute Cardiogenic Shock Secondary to Pazopanib with Recovery after Use of Impella Device

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1. Introduction

Cardiotoxicity is a potential side effect of some of the chemotherapeutic agents such as anthracyclines **[1]**, tyrosine kinase inhibitors (TKI) (Sunitinib, Sorafenib, Dasatinib, and Pazopanib), and tyrosine kinase antibodies (Trastuzumab, Bevacizumab) **[2,3]**for this reason patients on these drugs are monitored closely for any cardiac dysfunction. TKI have been approved for therapy of metastatic renal cell carcinoma and soft tissue sarcomas. Their mechanism of action is by inhibition of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). Among the most common cardiovascular effects from TKIinclude hypertension, congestive heart failure and arrhythmias **[4]**.

2. Summary

We present the case of a 57 year old female with a right parasternal muscle high grade undifferentiated pleomorphic sarcoma who developed acute cardiogenic shock after receiving 3 cycles of Pazopanib. Prior to starting her Pazopanib she had normal cardiac function and no cardiovascular risk factors other than exposure to Adriamycin one month earlier. Fortunately, her presentation was recognized promptly and she was placed on a percutaneous ventricular assist device with inotropic support resulting in improvement of her hemodynamic and cardiac function. This case is unique because it shows reversibility of cardiogenic shock with the use of Impella device.

3. Case

We present the case of a 57 year old female with a past medical history of high grade undifferentiated pleomorphic sarcoma of the right parasternal muscle diagnosed 2 years prior for which she underwent surgical resection and radiation. One year later she had recurrence of the disease with metastasis to the lung. At this time she was started on chemotherapy with Adriamycin, Ifosfamide, and Mesna for 6 cycles. At the completion of the chemotherapy she had an echocardiogram that showed Ejection Fraction (EF) of 62% with normal left ventricular (LV) and right ventricular function. One month later, after completion of the 6 cycles, the pulmonary nodules continued to increase in size and decision was made by her oncology team to be started on Pazopanib (600 mg/day) and topotecan (4 mg/day). LVEF was 60%. A week after receiving the third cycle of therapy, she presented to a local hospital with shortness of breath and decline in mentation with slight slurring of speech and was noted to have a decline in LVEF to 35%. Head CT and brain MRI showed no acute intracranial pathology. She was transferred to us 48 hours later because of worsening symptoms of shortness of breath. Her heart rate 110 beats-per-minute, blood

pressure 76/60 mmHg, respiratory rate 23 breaths-per-minute on 10 L of oxygen. On examination she looked ill, clammy, tachypneic, diaphoretic, with slow mentation but still able to answer questions properly without focal neurologic deficits, heart sounds were regular without any murmurs, lungs were clear to auscultation, no lower extremity edema, no jugular venous distention. Her laboratory white blood cell count 6.1 x 109/L, hemoglobin 11.5 g/dL, platelet 65 x 109/L, prothrombin time 20.5 seconds, international normalized ratio 1.8, sodium 136 mmol/L, potassium 4.5 mmol/L, bicarbonate 23 mmol/L, Creatinine 0.7 mg/dL, aspartate aminotransferase 1,785 U/L, alanine aminotransferase 1,189 U/L, brain natriuretic peptide 2,870pg/mL,lactic acid 4.3 mmol/L and troponin T 0.02 ng/ml. Hepatitis B and C negative. Chest computed tomography (CT) with contrast was negative for pulmonary embolism; showed pulmonary nodules consistent with metastasis with a small right sided pleural effusion. Electrocardiogram **(Figure 1)** showed sinus tachycardia with incomplete right bundle branch block (RBBB) and non-specific ST and T wave abnormalities.

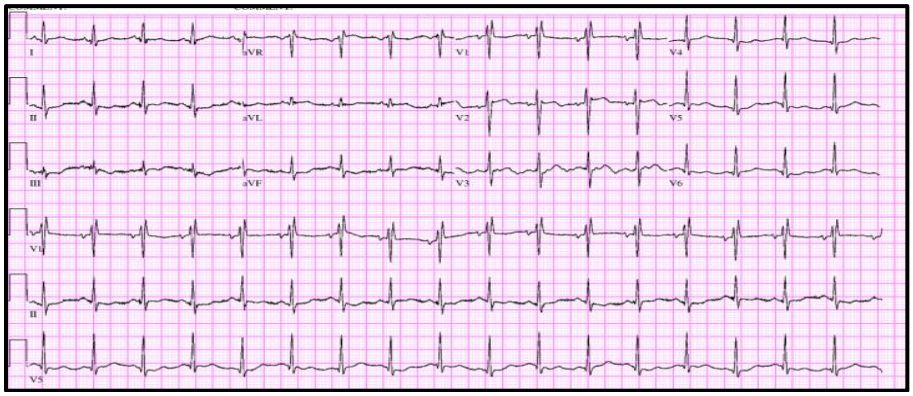

Figure 1: Sinus tachycardia with incomplete RBBB and non-specific ST and T wave abnormalities.

Repeat echocardiogram showed EF had decreased to 15% with global hypokinesis **(Figure 2).**

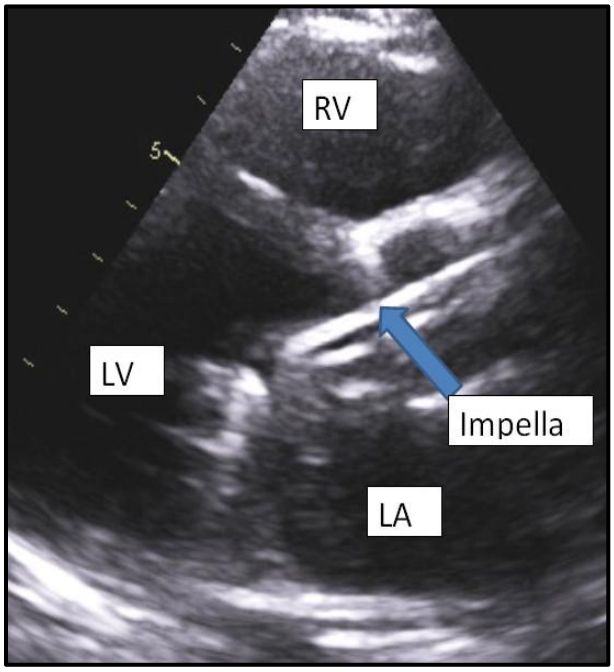

Figure 2: Echocardiogram showing right ventricle (RV), left ventricle (LV), left atrium (LA) and Impella device. LVEF= 15%.

A percutaneous ventricular assist device, Impella 3.5, was placed in the setting of acute cardiogenic shock for hemodynamic support for 3 days **(Figure 2 and Figure 3)** during which she was treated with Milrinone drip that was gradually weaned off within 1 week.

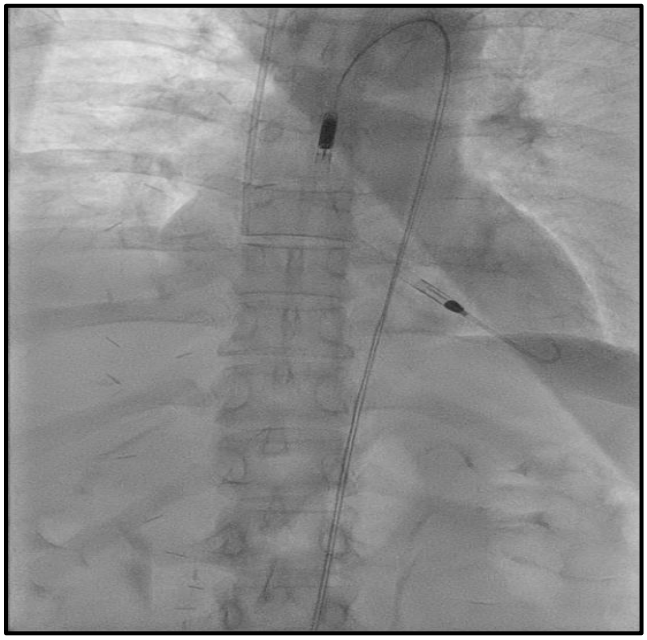

Figure 3: Impella – Percutaneous ventricular Assist Device.

Repeat echocardiogram a week later showed improvement in LVEF to 25%. However, she developed acute onset of aphasia and right sided weakness. Brain MRI and CTA demonstrated left middle cerebral artery infarction, M1 occlusion for which she underwent mechanical thrombectomy with some improvement. Patient was anticoagulated and had a repeat echocardiography prior to discharge that showed significant improvement in LVEF to 35-40% **(Figure 4).**

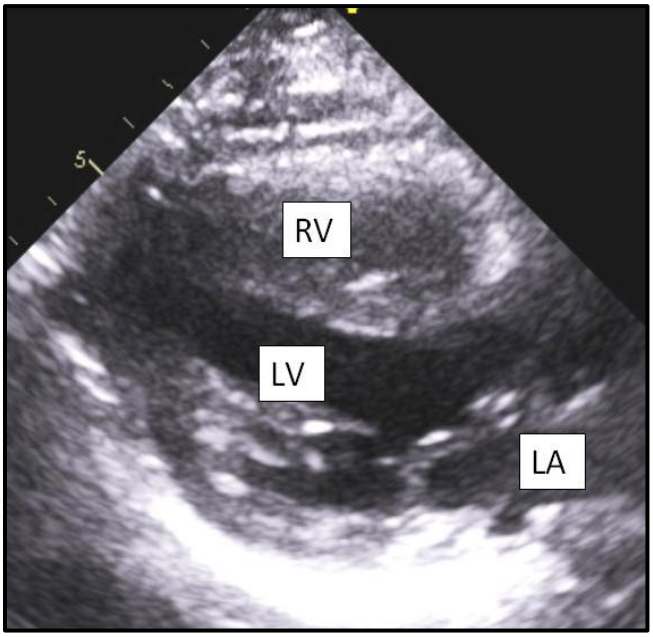

Figure 4: Echocardiogram, LVEF= 35-40%. (Abbreviations as in Figure 2).

4. Discussion

TKI are anti-humoral chemotherapeutic agents approved for therapy of advanced soft tissue sarcomas and renal cell carcinomas. Most of the patients on TKI have had prior exposure to anthracyclines prior to the initiation of TKI. In the case of Anthracyclines, it has been known for years now that the cardiotoxic effects of the medication results from the production of reactive oxygen derived free radicals which cause direct damage to proteins, and lipids resulting in cardiomyocyte apoptosis ergo LV dysfunction. Cardiotoxicity is related to cumulative dosing **[1]**. The pathophysiology for the development of congestive heart failure (CHF) as a result of TKI is believed to be associated to hypertension **[2]**. In addition, patients with prior history of hypertension and coronary artery disease may be at a higher risk of a cardiovascular event **[2]**. CHF has been reported to occur in 8% of patients on Sunitinib **[2]**. It is thought that there may be some hypoxic signaling that takes place during VEGF inhibition that results in cardiac hibernation and transient LV dysfunction which is reversible with drug cessation **[5]**. In the case of Pazopanib, 13/239 patients developed decrease LV function, of which 3 had symptomatic heart failure **[6]**. Only one case has been reported of a patient with acute cardiogenic shock from Pazopanib who also had prior exposure to Adriamycin, unfortunately the patient died despite suspension of Pazopanib therapy and use of inotropic agents **[7]**. In our case, the patient developed rapid and progressive acute heart failure culminating in cardiogenic shock that was reversed with the use of Impella device. It is possible that the rapid unloading of the LV, improvement in hemodynamic and cardiac output, decrease oxygen demand, and suspension of Pazopanib allowed for acute myocardial recovery with resultant improvement in LV function.

5. Conclusions

This case reports the potential use of a temporary percutaneous ventricular assist device such as the Impella in the setting of acute cardiogenic shock from chemotherapy with success. In addition, it also increases awareness of the impending increased cardiovascular risk of subsequent use of TKI after prior exposure to Anthracyclines.

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