Indolent presentation of cardiac toxicity in metastatic GIST treated with Sunitinib: A Case Report

Hannah Choi MD and Jason Ngo MD

Kaiser Permanente Research

INTRODUCTION

Sunitinib is a multi-receptor tyrosine kinase inhibitor that is used to treat metastatic renal cell carcinoma, chronic myeloid leukemia, and unresectable gastrointestinal stromal tumors (GIST), which in rare cases can cause a life threatening side effect of cardiotoxicity which is reported in approximately 10% of patients [1].

CASE STUDY

- A 74 year old male with a history of metastatic gastrointestinal stromal tumor initially was treated with imatinib starting December 2019.
- Due to disease progression, treatment was changed to sunitinib in October 2021.
- On January 20, 2022, patient contacted outpatient palliative physician for left knee and hip pain for one day and patient was started on prednisone. X-ray ordered which did not show new lytic lesions.
- Patient went to the emergency room on February 2 for ongoing abdominal pain. Focused abdominal, heart, and lung exam, lab work, and CT of abdomen were unremarkable with incidental improved trace residual pleural effusions. Patient discharged home.
- MRI hip/lumbar spine ordered on February 10 due to new left groin and neuropathic pain. MRI resulted without central cord abnormality or metastatic burden but noted edematous tissues; suspicion for myositis, workup started and referral to Neurology placed given ongoing lower extremity weakness.
- On March 3 - March 4, patient had telephone visit with both nurse and physician for worsening anxiety and functional status. No mention of shortness of breath or increased edema in legs.
- Patient went to the emergency room on March 11 because of recurrent falls. Physical exam showed bilateral lower extremity edema, numbness, and decreased strength of the left lower extremity. Labs were significant for BNP of 1,911 and troponins of 203. ECHO showed EF of 10-15%. CT showed bilateral large pleural effusions. Patient was started on Lasix and Dobutamine.
- Patient had prolonged hospitalization from March 11 – April 14, with PRN thoracenteses. Patient gradually weaned off Lasix drip and dobutamine and discharged on April 14.

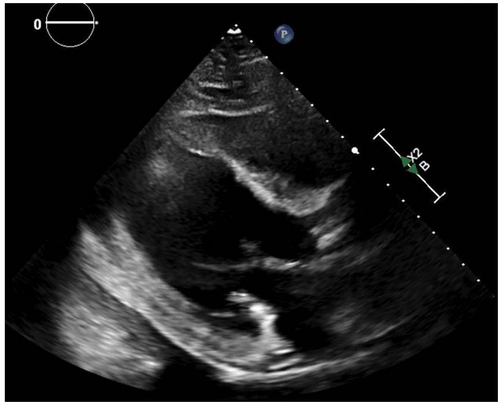

FIGURE 1: ECHO with Moderately increased left ventricular size and severely reduced systolic function with an estimated ejection fraction of <10-15 %.

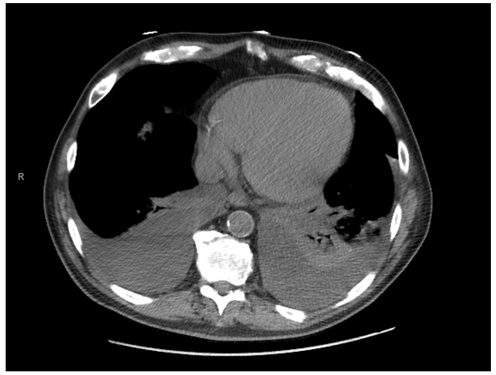

FIGURE 2: CT demonstrating large bilateral pleural effusion

DISCUSSION

Sunitinib is a multi-receptor tyrosine kinase inhibitor and this widespread inhibition of kinase activity in non-malignant cells leads to many side effects including diarrhea, hypertension, fatigue, nausea, and vomiting [2]. In rare cases, it can cause cardiotoxicity. Although the pathogenesis of the cardiac toxicity caused by sunitinib is not completely understood, it has been thought that it induces change in the myocardial metabolism of glucose which causes cardiac fibrosis, thus leading to reduced systolic ejection fraction; inhibition of angiogenesis may also reduce coronary blood supply to cardiomyocytes [3]. In GIST patients, one study documented 11% of patients on sunitinib to have lower left ventricular ejection fraction. Grade 3 LVEF reductions to <40% occurred in 1% of patients [4].

This case demonstrates that there can be cardiotoxicity with tyrosine kinase inhibitors (TKIs) which can be difficult to recognize. Many symptoms can mimic normal side effects of the chemotherapy (i.e. fatigue) or symptoms of cancer (i.e. shortness of breath or bone pain). Although not common, TKIs can cause cardiotoxicity and cardiac damage is largely underestimated. This case demonstrates the limitations of telemedicine and the importance of an in person physical exam to be able to correlate symptoms to imaging, labs, and diagnoses. It was not until March 11 where a physical exam was performed which showed lower extremity swelling consistent with heart failure.

Currently, there is no standardized monitoring for cardiac toxicity. Although the reversibility is unknown, cardiac damage can potentially be managed or prevented with cardiovascular monitoring and treatment. Such suggested monitoring includes assessing symptoms, EKG's, ECHOs (monitoring LV function), and labs (such as troponin and kinase) [1]. One study monitored potential cardiac damage with echocardiograms, cardiac biomarkers (high-sensitivity troponin I and BNP), and questionnaires with symptoms. However, it was shown to have limited utility given poor correlation between true LV dysfunction and changes in biomarkers [5] and the utility is still being studied. Although using these methods to monitor potential toxicity effects may have limited use, having a baseline of the ECHO and cardiac markers has been recommended by other studies [6]. With the understanding that the cardiac side effects of tyrosine kinase inhibitors are not as uncommon as once thought, our hope is that there will be more routine monitoring for cardiac function to reduce the chances of the cardiotoxicity.

This case also highlights limitations of telemedicine when initial clinical decision making does not fit into the postulated differential diagnoses. Given underlying malignancy history and report of unilateral muscle weakness, workup was started for metastatic burden to the spinal cord, or less likely for myositis induced injury from sunitinib. However, it is important to highlight that patients undergoing acute heart failure may have atypical symptoms, such as generalized weakness, prior to onset of acute shortness of breath or orthopnea. The increased use of telemedicine may result in improved access to care, though a physical exam by bringing patients to clinic should always be considered when atypical presentations occur despite initial workup [7-8].

REFERENCES

1. Schmidinger, M., Zielinski, C., Vogl, U., Bojic, A., Bojic, M., Ruhsam, C., Henja, M., & Schmidinger, H. (2016, September 22). Article tools. Journal of Clinical Oncology. Retrieved May 9, 2022, from https://ascopubs.org/doi/10.1200/JCO.2007.15.6331
2. Mehren, M. V., & Joensuu, H. (2018, January 10). Gastrointestinal stromal tumors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Retrieved May 9, 2022, from https://pubmed.ncbi.nlm.nih.gov/29220298/
3. Mellor, HR. Cardiotoxicity associated with targeting kinase pathways in cancer. Toxicol. Sci (2011)
4. Mulet-Margalef N, Garcia-Del-Muro X. Sunitinib in the treatment of gastrointestinal stromal tumor: patient selection and perspectives. Onco Targets Ther. 2016;9:7573-7582. Published 2016 Dec 15. doi:10.2147/OTT.S101385
5. Prospective Evaluation of Sunitinib-Induced Cardiotoxicity in Patients with Metastatic Renal Cell Carcinoma
6. Cardiac Toxicity of Sunitinib and Sorafenib in Patients With Metastatic Renal Cell Carcinoma | Journal of Clinical Oncology (ascopubs.org)
7. Calton B et al. Patient and Caregiver Experience with Outpatient Palliative Care Telemedicine Visits. Palliative Medicine Reports.Dec 2020.339-346.
8. Adepoju OE et al. Transition to telemedicine and its impact on missed appointments in community-based clinics. Ann Med. 2022

KAISER PERMANENTE®