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Case Report
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Dasatinib Related Cardiac Tamponade

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Abstract

Dasatinib is one of the second generation BCR-ABL Tyrosine Kinase Inhibitors (TKI) used for the treatment of Chronic Myeloid Leukemia (CML). We present a case of CML on dasatinib who presented with Cardiac Tamponade (CT). A 61 year old female with imatinib intolerant CML and on 100 mg dasatinib presented with shortness of breath along with weight gain. Chest X-ray showed pulmonary edema and Echocardiogram (Echo) showed tamponade. She underwent pericardiocentesis and dasatinib was stopped. She was treated with diuretics and a short course of steroids. Follow up Echo showed resolution and dasatinib was resumed after one month at lower dose of 80 mg. Dasatinib is well known to have pleural and pericardial effusion as side effects, but cardiac tamponade is rare. Expedited evaluation and management are key to prevent severe complications.

Background

Dasatinib is one of the second-generation BCR-ABL Tyrosine Kinase Inhibitors (TKI) used for the treatment of Chronic Myeloid Leukemia (CML). It is used for both induction treatment as well as maintenance therapy. Labeled indications for use include Ph+ acute lymphoblastic lymphoma and CML [1]. As seen in the DASISION trial, except for a higher rate of Pleural/Pericardial Effusion (PE) in Dasatinib, the non-hematologic adverse effects with Dasatinib are either lesser or the same as with Imatinib [2,3]. It can cause fluid retention including pleural and pericardial effusions, cytopenias, and bleeding. The pericardial/pleural effusion can occur anytime during the treatment course and are dose dependent [4]. Dose adjustments and closer monitoring are essential. High clinical suspicion and prompt treatment are critical components in avoiding deplorable consequences.

Case Presentation

A female in her 60's with medical history of Chronic Myeloid Leukemia (CML) on Dasatinib 100 mg daily for imatinib intolerant chronic phase CML presented to the oncology clinic with one-month history of shortness of breath, chest heaviness, and was unable to sleep supine. She gained 20 lbs in 2 months. She was in complete remission for 2 years on the Dasatinib. She developed upper respiratory infections one week prior to presentation. Chest X-ray showed cardiomegaly and moderate pulmonary edema along with small right pleural effusion (Figure 1). EKG showed sinus rhythm with first degree A-V block (PR 210 milliseconds) and rightward axis (Figure 2). Echo showed an ejection fraction of 55% to 60%, moderate to large pericardial effusion, dilated Inferior Vena Cava (IVC) 3 cm and diastolic Right Ventricle (RV) collapse on subcostal images, suspicious for CT (Figure 3). Pulses paradoxus was 15 mmHg to 20 mmHg.

Treatment

Emergent pericardiocentesis was done with drain placement, 350 cc serous fluid removed, and opening pressure was 15 mmHg to 20 mmHg. Fluid sent for flow cytometry-showed no evidence of monoclonal B cell population. Pericardial fluid analysis showed yellow cloudy fluid with amylase 16 U/L, lactate dehydrogenase 230 U/L, white cell count of 1,155 with predominant lymphocytes/monocytes. Culture of the fluid was positive for *Corynebacterium* species but was thought to be a contaminant. TKI was believed to be the cause hence Dasatinib was held. She was treated with diuretics and a short course of steroids.

Outcome and follow-up

Follow up echo 2 days later showed small pericardial effusion and subsequent echo 10 days later showed trace fluid. Her symptoms completely resolved. She remained off Dasatinib for one month and was restarted on lower dose of 80 mg daily.

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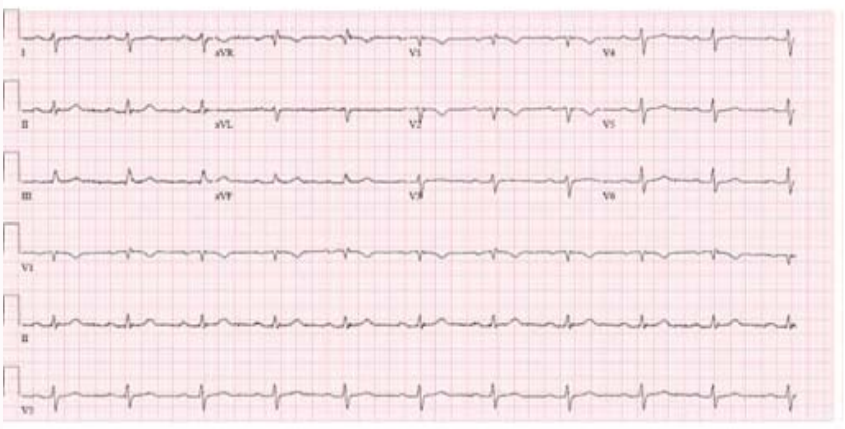

Figure 1: EKG-normal sinus rhythm with first degree AV blocks (210 milliseconds).

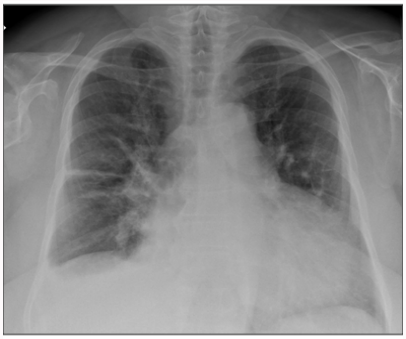

Figure 2: Chest X ray-cardiomegaly, moderate pulmonary edema and small right pleural effusion.

Discussion

Dasatinib is one of the second-generation TKI that is indicated for treatment of Philadelphia (Ph) chromosome positive CML. FDA labeled indications include all phases (chronic, accelerated, myeloid and lymphoid phases) of CML either as first line or second line in case of Imatinib failure/intolerance. Of note, even though Dasatinib is approved for frontline use as mentioned above and has a better efficacy profile, Imatinib is still the most used first line TKI due to low cost, better safety profile and 20+ years of experience. However, as seen in the DASISION trial, except for a higher rate of Pleural/ Pericardial Effusion (PE) in Dasatinib, the non-hematologic adverse effects with Dasatinib are either lesser or the same as with Imatinib [2,3]. This case report is based on an infrequently reported side effect of Dasatinib – pericardial effusion leading to CT.

In our case, the patient was switched from Imatinib to Dasatinib due to a generalized rash which is most common adverse effect of Imatinib leading to intolerance [5]. Approximately 2 years after starting the drug, patient presented with pulmonary edema and pericardial effusion. The timing of development of PE is variable but is generally seen to be in the long term (2 to 4) years. The onset of symptoms is usually insidious, and progression is subacute to chronic in nature. PE is generally seen along with pleural effusion as noted in our patient. The mechanism for development of pleural/pericardial effusion is unclear but various theories have been proposed based on *in-vitro* studies. Commonly accepted ones are serosal inflammation and off-target action of TKIs on the Platelet Derived Growth Factor Receptors (PDGFR) beta kinases present in the pericytes which line the serosa (pericardial, pleural, peritoneal spaces). Another theory is based on another off-target action of TKIs on Bruton Tyrosine Kinase which leads to a clonal expansion of Large Granular Lymphocytes [6,7]. This may explain the lymphocyte predominance seen in this case. However, flow cytometry analysis of the PE did not demonstrate any clonality of the B/T cells. Because, no other cause of PE was found, it was presumed as Dasatinib induced PE as a diagnosis of exclusion. The drug was therefore withheld. Resolution of the effusion after stopping the drug further supported the diagnosis of Dasatinib induced PE.

Higher doses of Dasatinib are associated with higher incidence and severity of pleural and PE. This dose response relationship can be explained by off target binding of Dasatinib on PDGFR beta kinase. The observation that the incidence of effusion is much higher with Dasatinib than Imatinib is likely because the potency of the former is ~325 times that of Imatinib [8]. The severity of effusions also depends on patient and disease related factors and not only on the dose of Dasatinib. Treatment of advanced stages of CML with the drug is also associated with higher incidence, severity (grades 3 to 4 pleural effusions) and higher recurrences of the effusion. Some experts use the Charlson Comorbidities Index (CCI) to predict the severity [9]. Much more data is needed to corroborate these findings. Expert opinion on management of pleural/PE is interruption of therapy until symptoms resolve and restarting the drug at a lower dose. The interim period should be managed with high dose steroids and diuretics, as seen in our patient.

In summary, Dasatinib is associated with higher rates of PE and should be kept in mind when treating a patient with the drug. Indeed, it is the most prevalent non-hematologic side effect. Fortunately, however, in most cases, the effusions are grade 1 to 2 and hardly ever require therapeutic tapping, and patients respond to dose de-escalation. But one should have a low threshold for suspicion of life-threatening CT and timely management is the key to saving life.

Conclusion

Drug induced tamponade is rare. 1% of patients experience severe PE due to dasatinib. This side effect should be kept in mind while using TKI. Drug should be withheld whenever there is suspicion of effusions. Treatment includes stopping the drug and using diuretics for volume management. A short course of steroids can also be

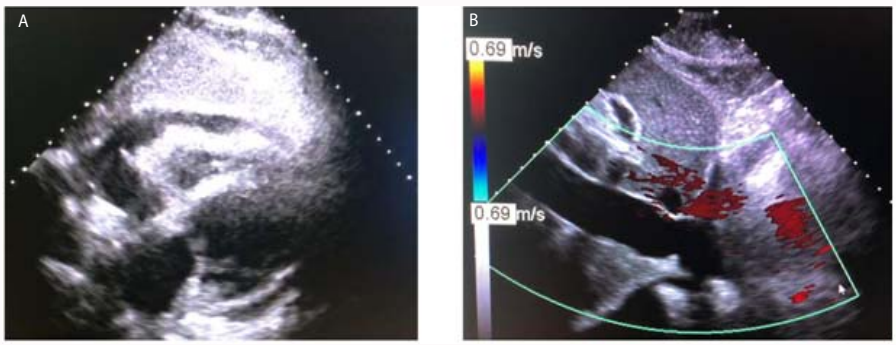

Figure 3: Large pericardial effusion, IVC 3 cm and diastolic RV collapse on subcostal images, confirming CT (A and B).

used. The patient can be managed by serious echocardiogram in the outpatient settings to evaluate the PE. TKI can be restarted at a lower dose. This case highlights expedited work up and management of patients on TKI therapy with cardiopulmonary symptoms.

Learning Points/Take Home Messages 3-5 Bullet Points

- Drug induced PE are rare but should be kept in mind when using TKI.
- Expedited evaluation and management are key to prevent the catastrophe.
- Drug should be withheld whenever there is a suspicion of the PE.
- In the interim, patients should be treated with diuretics and steroids.
- Patient should be monitored with serial echo based on the clinical condition.
- The TKI should be restarted at a lower dose.

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