Left Atrial Appendage Occlusion as an Alternative to Anticoagulants in Ibrutinib-Induced Hemorrhagic Pericardial Effusion

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ABSTRACT

Bleeding tendency increases with concomitant use of ibrutinib and anticoagulants. Our patient presented with shortness of breath and was found to have a nonmalignant hemorrhagic pericardial effusion. Ibrutinib was resumed, and percutaneous left atrial appendage occlusion was performed as a substitute for the chemical anticoagulation to decrease the drug-drug interaction. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2022;4:751–754) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 75-year-old man presented to the emergency department with shortness of breath on exertion and orthopnea. He also reported a weight gain of 10 lbs and decreased urination for the past week. The patient was afebrile (98.6 °F), had tachycardia with a heart rate of 105 beats/min, and had a respiratory rate of 22/min. His arterial oxygen saturation was 88% on 2 L of supplemental oxygen. Body mass index was 46.1 kg/m². Physical examination was significant for elevated jugular venous distension, muffled heart sounds, and +2 bilateral lower-extremity pitting edema.

LEARNING OBJECTIVES

• To be cognizant of the potential for atrial fibrillation and hemorrhage in patients treated with ibrutinib for hematologic malignancies.
• To understand the mechanism of hemorrhagic pericardial effusion associated with ibrutinib with concomitant use of anticoagulants.
• To explore alternative treatment options in patients with life-threatening hemorrhagic pericardial effusion, necessitating anticoagulation for stroke prevention.

PAST MEDICAL HISTORY

He had a history of chronic lymphocytic leukemia (CLL), atrial fibrillation with a CHA2DS2-VASc score of 4, diabetes mellitus, and hypertension. The patient’s home medications were ibrutinib, apixaban, metformin, and lisinopril.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included acute heart failure, valvular heart diseases, malignant pericardial effusion, and acute pericarditis.
INVESTIGATIONS

Laboratory investigation revealed a white blood cell count of 17.2 K/µL, hemoglobin of 12.8 g/dL, which was decreased from 14.2 g/dL 6 months earlier, and serum creatinine of 1.78 mg/dL. The rest of the laboratory data are summarized in Table 1. The electrocardiogram showed rate-controlled atrial fibrillation (Figure 1). Chest X-ray showed an enlarged cardiac silhouette and a left-side pleural effusion (Figure 2). An emergency transthoracic echocardiography (TTE) was done, which revealed a large pericardial effusion anteriorly (3.6 cm) and posteriorly (1.5 cm) along with a left lateral pleural effusion and right atrial and right ventricular collapse (Video 1). Of note, this patient’s left atrial diameter was unable to be accessed during this study; however, a previous study done 1 year earlier showed a normal left atrial diameter of 3.6 cm. The patient underwent pericardiocentesis, and a pericardial drain was placed with the removal of 1,250 cc of hemorrhagic fluid. His shortness of breath improved significantly after the procedure, and supplemental oxygen was weaned. The following day, repeated TTE showed decreased pericardial effusion anteriorly (1.0-1.5 cm) and posteriorly (0.5 cm) respectively (Video 2).

MANAGEMENT

The patient was started on a bumetanide infusion; apixaban and ibrutinib remained on hold over his hospital course. The pericardial fluid examination was negative for malignancy (lactate dehydrogenase level of 1,245 U/L), protein 5.7 g/dL, glucose 77 mg/dL, numerous red blood cells, and benign epithelial cells). His creatinine and liver function tests returned to baseline, and the pericardial drain was removed.

In further discussion with cardiology and hematology/oncology, the decision was made to continue apixaban, which would be discontinued after the placement of a left atrial appendage occlusion device. In addition, ibrutinib was held until an alternative mode of stroke prevention was achieved.

DISCUSSION

Although ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, has shown a high response rate and progression-free survival in patients with CLL, certain severe and life-threatening complications have limited its efficacy in such patients. Of all the adverse reactions reported, the bleeding risk is the highest, including 1% life-threatening bleeding events such as brain and gastrointestinal bleeding, especially with concurrent use of antiplatelet or anticoagulants.\(^1\) Recently, hemorrhagic pericardial effusions secondary to ibrutinib have been recognized as a rare side-effect. To the best of our knowledge, only a few cases have reported this rare complication.\(^2\)\(^3\) The present case not only reports this rare complication, but also illustrates the mechanism and alternative treatment options, particularly in high-risk patients, ie, those with a high CHA\(_2\)DS\(_2\)-VASc score, who are prone to this life-threatening complication. Of the proposed antiplatelet mechanisms by which ibrutinib increases the bleeding risk, the simultaneous inhibition of BTK and tyrosine kinase expressed in hepatocellular carcinoma is the primary mechanism, as illustrated in Figure 3. The inhibition of these receptors interferes with platelet function and enhances the risk of bleeding.\(^6\)\(^7\)

The other important side-effect of ibrutinib includes atrial fibrillation, which creates a unique challenge in balancing bleeding and thrombosis, especially with the concomitant use of vitamin K antagonists. The use of direct oral anticoagulants (DOACs) is recommended in such patients.\(^8\) However, interestingly, both ibrutinib and DOACs are metabolized by the cytochrome P450 (CYP) 3A4 system, and co-administration leads to further drug-drug interaction, resulting in enhanced ibrutinib toxicity and bleeding risk by decreasing its clearance.\(^9\) We think that the aforementioned mechanisms and CLL in itself being a strong risk factor for platelet dysfunctions resulted in spontaneous hemorrhagic pericardial effusion. There are no standard guidelines to manage such patients. However, once suspected,
pericardiocentesis and further testing of the pericardial fluid should be done immediately. In previous reports, discontinuing either one or both of the medications or dose reduction was done; however, no clinical trials support such an approach. Given the presence of atrial fibrillation and a high CHA2DS2-VASc score in our patient, we pursued percutaneous left atrial appendage occlusion as an alternative to DOACs and resumed the ibrutinib after 2 weeks.

**FOLLOW-UP**

After 2 weeks, the left atrial appendage occlusion device was placed, ibrutinib was resumed, and apixaban was discontinued. The patient remained symptom free at the 6-month follow-up.

**CONCLUSIONS**

Ibrutinib is generally well tolerated but can have life-threatening events such as hemorrhagic pericardial effusion, particularly with concomitant use of antiplatelets or anticoagulants. Physicians should be aware of this rare presentation. Nonpharmacologic strategies such as percutaneous left atrial appendage occlusion can be considered for stroke prevention in patients with atrial fibrillation and who are on ibrutinib. This management approach needs further studies, however. Physicians should also keep in mind and caution patients about the concurrent use of CYP3A4 inducers or inhibitors.

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APPENDIX For supplemental videos, please see the online version of this paper.