Ibrutinib-induced cardiomyopathy
Htay Htay Kyi¹, Yazan Zayed ² and Samer Al Hadidi ³

¹Internal Medicine Department, Hurley Medical Center/Michigan State University, Flint, USA; ²Hematology/Oncology Department, Baylor College of Medicine, Houston, TX, USA

ABSTRACT
The use of ibrutinib for the treatment of chronic lymphocytic leukemia (CLL) and other hematologic malignancies is blooming. Atrial fibrillation is a known side effect of ibrutinib but cardiomyopathy was not reported previously. We present an 88-year-old man with CLL who was admitted to the hospital with new-onset atrial fibrillation and symptomatic systolic congestive heart failure one month after ibrutinib initiation. Although ibrutinib was discontinued, the patient continues to have a low ejection fraction four months after discontinuation. Ischemic heart disease was ruled out with normal cardiac catheterization. This case highlights a possible new side effect of ibrutinib that needs to be monitored while patients receive this medication.

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1. Introduction
Treatment of cancer has changed to a targeted approach, especially via inhibition of tyrosine kinases. Ibrutinib is one tyrosine kinase inhibitor. However, ibrutinib has multiple side effects. The most frequently (≥20%) reported adverse reactions include neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia, and hemorrhage [1]. Atrial fibrillation (AF) is one of the uncommon adverse cardiac events associated with ibrutinib use (1% to 10%). In a randomized controlled trial comparing ibrutinib and chlorambucil, 6% of ibrutinib patients developed atrial fibrillation [2]. This was supported by a recently published meta-analysis that involved 4 randomized clinical trials which showed that the pooled relative risk of AF associated with ibrutinib as compared with the comparator was 3.9 (2.0–7.5, P<0.001) [3].

Cardiomyopathy is not a well known adverse reaction to this new medication. We will present a case of systolic heart failure induced by ibrutinib that persisted despite discontinuation of ibrutinib.

3. Investigations
His investigations showed white blood cell count of 216 K/UL (Reference: 4.0–10.8 K/UL), hemoglobin of 9.9 (Reference: 12–16 g/dL) and platelet of 161 (Reference: 130–430 K/UL). Thyroid stimulation hormone was normal. Two sets of troponin were 0.03 (Ref: 0.00–0.04 NG/ML). Urine drug screen was negative. Antinuclear antibodies were negative.

Electrocardiogram (ECG) showed atrial fibrillation with a heart rate of 125 but no significant ST-T changes (Figure 1). His Chest X-ray showed mild pulmonary congestion (Figure 2).

Echocardiogram showed an ejection fraction of 30–35%, mild concentric left ventricular hypertrophy and no evidence of valvular disease or stress induced cardiomyopathy.

4. Treatment
Ibrutinib was discontinued. He was managed for pulmonary edema with diuretics. Heart rate was controlled with diltiazem. The patient received apixaban as anticoagulation.
5. Outcome and follow-up

Patient symptoms started to improve gradually and he was discharged from the hospital for outpatient follow up. Repeat echocardiogram one month later showed EF of 40–45 %. Unfortunately, the patient had persistent symptoms of decompensated heart failure even though his heart rate was controlled with diltiazem, so cardiac catheterization was done to rule out ischemic heart disease and showed normal coronaries. Two repeats of the echocardiogram 4 months after initial presentation to our hospital showed persistently reduced ejection fraction of 40–45%. The cardiac evaluation he had was ten years prior to starting ibrutinib with a nuclear scan that revealed normal ventricular systolic function and normal coronaries, as well as a normal EKG and the patient denied any symptoms consistent with congestive heart failure before starting ibrutinib.

6. Discussion

Ibrutinib selectively and irreversibly inhibits Bruton tyrosine kinase (BTK) within B lymphocytes to block constitutively activated intracellular signaling pathways that are critical to cell migration and survival [4].

One of the pathways regulated by BTK is the phosphoinositide 3-kinase (PI3K)-Akt pathway. This pathway is an essential regulator of cardiac protection...
in stressful situations. Surgical specimens from patients with AF showed significantly lower cardiac PI3K-Akt activity than those from patients in sinus rhythm [5].

Ibrutinib is frequently used in CLL and small lymphocytic lymphoma (SLL) after it was found to improve overall survival in clinical trials and observations [6]. It was also approved for all patients with Waldenstrom macroglobulinemia [7].

Diagnosis of dilated cardiomyopathy is a diagnosis of exclusion in our case. He developed atrial fibrillation and cardiomyopathy one month after starting ibrutinib.

Cardiomyopathy and ventricular tachycardia associated with ibrutinib use were described in one case report, Systolic dysfunction resolved after ibrutinib was discontinued and ventricular tachycardia was managed by antiarrhythmic medications [8].

Another case highlighted reversible heart failure caused by concomitant use of amiodarone and ibrutinib which resolved after amiodarone was discontinued [8].

Median time to onset of atrial fibrillation after starting ibrutinib was 7.6 months [9]. Our patient took only one month to develop atrial fibrillation. Arrhythmia-induced cardiomyopathy is a relatively rare cause of a dilated cardiomyopathy resulting from prolonged periods of rapid ventricular heart rates. Arrhythmia-induced cardiomyopathy often improves or resolves following treatment and is associated with a good prognosis in most patients. However, our patient had persistently low EF even after stopping ibrutinib.

Given this new association of ibrutinib and cardiomyopathy in our case, clinicians may need to monitor patients who receive ibrutinib for this possible side effect. Follow-up after ibrutinib initiation is essential even for asymptomatic patients to check for possible side effects including serious cardiac events.

Disclosure statement
No potential conflict of interest was reported by the authors.

ORCID
Yazan Zayed http://orcid.org/0000-0002-0179-512X
Samer Al Hadidi http://orcid.org/0000-0003-4297-8042

References
[1] Raedler LA Imbruvica (Ibrutinib) now FDA approved as first-line treatment for chronic lymphocytic leuke-mia and small lymphocytic lymphoma. 2017 Oncology Pharmacy Guide to New FDA Approvals.
[2] Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373(25):2425–2437.
[3] Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood. 2016;128(1):138-140.
[4] Vrontikis A, Carey J, Gilreath JA, et al. Proposed algorithm for managing ibrutinib-related atrial fibrillation. Oncology (Williston Park). 2016;30(11):970-4, 980-1, C3.
[5] Pretorius L, Du XJ, Woodcock EA, et al. Reduced phosphoinositide 3-kinase (p110alpha) activation increases the susceptibility to atrial fibrillation. Am J Pathol. 2009;175(3):998–1009.
[6] Byrd JC, Furman RR, Coulter SE, et al. Three-year follow-up of treatment-na†ve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015 Apr 16;125(16):2497–2506.
[7] Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom’s macroglobulinemia. N Engl J Med. 2015;372:1430–1440.
[8] Wallace N, Wong E, Cooper D, et al. A case of new-onset cardiomyopathy and ventricular tachycardia in a patient receiving ibrutinib for relapsed mantle cell lymphoma. Clin Case Rep. 2016;4(12):1120–1121.
[9] Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibril-lation in patients receiving ibrutinib. Blood Adv. 2017;1 (20):1739–1748.