

Unusual, spontaneous aneurysm formation in a patient being treated with ibrutinib for chronic lymphocytic leukemia

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Ibrutinib has been shown to be beneficial for B-cell malignancies with overall response rates of 71% in initial clinical trials for chronic lymphocytic leukemia (CLL), irrespective of high-risk characteristics [Byrd *et al.* 2013; Parmar *et al.* 2014]. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor approved for the treatment of selected leukemias and lymphomas, has been associated with bleeding events [Byrd *et al.* 2013, 2014; Wang *et al.* 2013]. Kamel and colleagues illustrated that BTK inhibitors, such as ibrutinib, cause an interruption in collagen-mediated platelet aggregation, and thus increase bleeding risk [Kamel *et al.* 2015]. Levade and colleagues demonstrated ibrutinib's effects on adhesion of platelets to von Willebrand factor by the disruption of collagen receptors. It was also shown that removal of the drug, and the generation of new, unaffected platelets provided a decrease in the risk of bleeding [Levade *et al.* 2014]. While as many as 50% (or half) of patients may experience grade 1 or 2 bleeding on ibrutinib, other studies have revealed more serious bleeding events [Jones *et al.* 2014]. Wang and colleagues evaluated patients with mantle cell lymphoma being treated with ibrutinib. Approximately 5% of patients were shown to have grade 3 or higher bleeding events; however, the majority of these patients had sustained some sort of trauma [Wang *et al.* 2013]. Burger and colleagues compared ibrutinib with chlorambucil as initial therapy for patients with CLL. The median treatment duration with ibrutinib was 17.4 months, and major hemorrhage was reported in 4% of these patients [Burger *et al.* 2015]. Despite a noted disruption in platelet function, ibrutinib has been shown to improve overall platelet counts with the control of the underlying CLL [Farooqui *et al.* 2012]. Jones and colleagues evaluated the concomitant use of antiplatelet agents and anticoagulants in patients treated with ibrutinib, and the majority of the patients having major bleeding were treated with one of these agents, in addition to the BTK inhibitor [Jones *et al.* 2014].

Though major bleeding events have been present in patients treated with ibrutinib, the role of vascular remodeling has not previously been described. We present the case of a patient with an unusual bleeding event secondary to a vascular anomaly on ibrutinib for the treatment of CLL. The patient is a 46-year-old man treated for CLL with ibrutinib with no other medical history. He had no prior lines of therapy for his disease. At presentation he had diffuse lymphadenopathy, lymphocytosis with a white blood count of 35,000 mm³, splenomegaly and platelet count of 65,000 mm³. The patient had Rai stage IV CLL at diagnosis which was his indication for treatment. Three months after starting therapy, he experienced a dramatic positive response both in lymph node size and peripheral blood counts. WBC did increase to 55,700 mm³ within a month of treatment but had normalized to 5600 mm³ within 3 months. However, he was admitted to the hospital 3 months after initiating therapy with a severe headache and found to have a subarachnoid hemorrhage on CT and magnetic resonance imaging. Ibrutinib was discontinued upon hospitalization. He was not on any home medications including antiplatelet agents or anticoagulants at the time of this event, nor was any trauma experienced prior to admission. He had no prior history of bleeding diathesis. His prothrombin time (PT), partial thromboplastin time (PTT) and fibrinogen were within normal limits and his platelet count was 99,000 mm³, which was a significant improvement from his pretreatment platelet count of 65,000 mm³. His pretreatment hemoglobin (Hb) was 12.6 g/dl and had normalized to 15.3 g/dl within 3 months of treatment. Hb was stable throughout hospitalization averaging 15 g/dl, as well as platelet count, with no evidence of autoimmune hemolysis. Initial angiography was normal, but 5 days later repeat angiography demonstrated slow filling of an unusual aneurysm arising from the basilar artery demonstrated by the blue arrow in panels A and B of Figure 1. Three days later, a third angiogram was performed which

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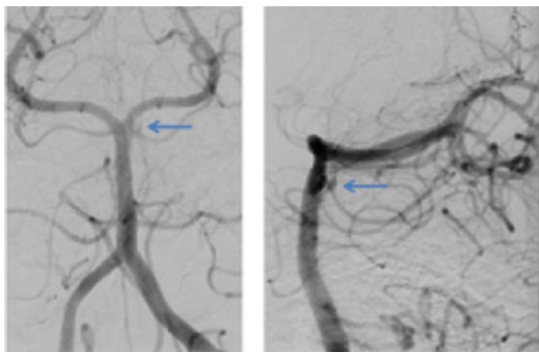


Figure 1. Angiogram performed on day 8 of hospitalization demonstrating unusual aneurysm. The blue arrow in panels A and B indicates location of this abnormal aneurysm from different views. This aneurysm was not present on initial angiography and was absent during angiography 3 days later for a planned intervention.

showed spontaneous resolution of the aneurysm. Ibrutinib was held during the patient's hospitalization and he ultimately recovered. He had no further bleeding episodes. We hypothesize that ibrutinib may interact with the collagen component of vasculature, leading to abnormal remodeling which may be associated with the increased risk of bleeding described with this agent.

Some researchers have used this known disruption in collagen structure and function as a beneficial side effect of ibrutinib. Dubovsky and colleagues described using the drug to deliberately interrupt collagen's role in forming the fibrotic tissue changes that contribute to chronic graft-versus-host disease [Dubovsky *et al.* 2014]. The aforementioned patient likely did not have bleeding that was secondary to disrupted platelet aggregation, but rather, we hypothesize that ibrutinib may have caused some intermittent disruption or remodeling of the collagen fibers comprising his vasculature. This intermittent nature of disruption could explain his lack of initial aneurysm at presentation, spontaneous aneurysm formation, and its subsequent resolution with removal of the drug. The package insert for ibrutinib quotes a 6% grade 3 or higher bleeding risk in patients treated with ibrutinib, with this risk increased in patients on other anticoagulants or antiplatelet therapy (ibrutinib package insert, Pharmacyclics, Sunnyvale, CA, 2013). As the mechanism for bleeding events secondary to ibrutinib is not completely understood, this case illustrates that abnormal vascular remodeling leading to aberrations in normal vasculature could be a component of these hemorrhagic events in addition to disruption in platelet aggregation.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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