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Case Report

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Ibrutinib induced atrial fibrillation complicated with massive hemoptysis

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Abstract

Background: *The oncologic patient faces multiple adverse effects with cytotoxic medications, from tissue damage and intoxications that could be evident from muscle damage, neurologic to cardiac toxicity.*

Case: *This is a case of a 79-year-old female who presented to our ED with the complaint of hemoptysis for one day, denied any associated cough, fever, chills, chest pain, SOB, nausea, vomiting, or abdominal pain. No history of trauma. Her medical history includes hypertension, uterine cancer status post-resection. The patient denied prior similar episodes, family history of similar complaints.*

Chest X-ray showed extensive bilateral infiltrates and cardiomegaly. CT chest ruled out pulmonary em-bolism but showed extensive multifocal pneumonia vs. ARDS, lymphoproliferative changes. While in the ED, the patient started having bloody nasal secretions noted, requiring nasogastric lavage revealing dark blood secretions, and then started having massive hemoptysis and rapidly decompensated requir-ing endotracheal intubation hypoxic respiratory failure. An emergent bronchoscopy was performed, which showed suspected alveolar hemorrhage (Figure 1). The CBC showed severe anemia requiring multiple transfusions due to active bleeding (Table 1). The patient was admitted to ICU.

The patient's PCP was contacted to obtain further information that reported a new history of atrial fi-brillation on rivaroxaban recently started, CLL on ibrutinib, and Coombs Hemolytic Anemia.

The hospital course was complicated by distributive shock and ARDS. She was covered with broad-spectrum antibiotics and required fresh frozen plasma due to persistent bleeding. The patient improved after anticoagulation and ibrutinib were held. The patient was eventually extubated, required physical therapy for deconditioning, and then was discharged.

Conclusion: *This case represents clear evidence of how an appropriate assessment on time and the collateral gath-ering of medical history could impact the outcome of our patients. The literature review has shown new-onset atrial fibrillation and bleeding events related to ibrutinib. Given the risk for bleeding with rivaroxaban, their combination could present with massive alveolar hemorrhage that could become fa-tal if not recognized early.*

Keywords: Ibrutinib, Atrial Fibrillation, Alveolar Hemorrhage, Bleeding, Arrhythmia.

Introduction

Medical pharmaceutics has faced important advances, challenging our capacity to the new side effects and interaction between medications [1], including oncologic and anticoagulation therapy [2]. It is well known that the oncologic patient faces multiple adverse effects with cytotoxic medications, from tissue damage and intoxications that could be evident from muscle damage, neurologic to cardiac toxicity [3,4]. One of the most challenging conditions is atrial fibrillation in a patient with cancer history and the need for anticoagulation to increase the risk of bleeding due to active chemotherapy.

Cardiac arrhythmias could represent life threatening condition especially in critically ill patients [5,6]. Mul-tiple conditions and medications are known to cause arrhythmias including atrial fibrillation [7-9], reason why an appropriate approach in a time matter could represent an importance piece in the patient out-come [10].

Here we present an interesting case of a patient on Ibrutinib and

concomitant anticoagulation due to atrial fibrillation and her consequently unfortunate events including respiratory failure and shock, who was finally discharged home.

Case

This is a case of a 79-year-old female who presented to our ED with the complaint of hemoptysis for one day, denied any associated cough, fever, chills, chest pain, SOB, nausea, vomiting, or abdominal pain. No history of trauma. Her medical history includes hypertension, uterine cancer status post-resection. The patient denied prior similar episodes, family history of similar complaints.

Chest X-ray showed extensive bilateral infiltrates and cardiomegaly. CT chest ruled out pulmonary em-bolism but showed extensive multifocal pneumonia vs. ARDS, lymphoproliferative changes. While in the ED, the patient started having bloody nasal secretions noted, requiring nasogastric lavage revealing dark blood secretions, and then started having massive hemoptysis and rapidly decompensated requir-ing endotracheal intubation hypoxic respiratory failure. An emergent bronchoscopy was performed, which showed suspected alveolar hemorrhage (Figure 1). The CBC showed severe anemia requiring multiple transfusions due to active bleeding (Table 1). The patient was admitted to ICU.

Figure 1: Bronchoalveolar Lavage.

Table 1: Initial Labs.

Laboratory	Value	Normal Range
Platelet	188	150-400 k/ul
Hemoglobin	7.5	12-16 g/dl
Hematocrit	23.2	42-51 %
MCV	103.7	80-96 fL
RDW	15.4	10.5-14.5 %
LDH	791	110-210 unit/L
Cardiolipin Ab IgA	<11	<=11 ZZ
Cardiolipin Ab IgG	<14	<=11 ZZ
Cardiolipin Ab IgM	16	<=11 ZZ
PT	28.3	9.9-13.3 sec
PTT	43.1	27.2-39.6 sec
INR	2.40	0.85-1.14

The patient's PCP was contacted to obtain further information that reported a new history of atrial fi-brillation on rivaroxaban recently started, CLL on ibrutinib, and Coombs Hemolytic Anemia.

The hospital course was complicated by distributive shock and ARDS. She was covered with broad-spectrum antibiotics and required fresh frozen plasma due to persistent bleeding. The patient improved after anticoagulation and ibrutinib were held. The patient was eventually extubated, required physical therapy for deconditioning, and then was discharged.

Discussion

Oncologic medications could present with multiple side effects, including bleeding events, Ibrutinib is a capsule form medication used for chronic lymphocytic leukemia, mantle cell lymphoma, chronic graft versus host disease, Wandstorm's macroglobulinemia, and marginal zone lymphoma; its mechanism is based on the inhibition of Bruton's tyrosine kinase pathway affecting the CD40 sig-naling and the B cell adhesion & migration.The side effects related to his therapy has been infec-tions, neutropenia, thrombocytopenia, GI distress, headache, musculoskeletal pain edema, fever and significant bleeding in some instances [11,12]. Other less common side effects are skin cancer (basal and squamous), interstitial lung disease, uric acid elevation, leukopenia, bruises, hematoma, dizzi-ness, allergic reactions, high blood pressure, and atrial fibrillation [13].

The bleeding mechanism is unclear, but Bruton Tyrosine Kinase affects the GP1b and GPVI signal, possibly affecting the platelet aggregation and adhesion through von Willebrand factor and collagen, respectively [14].

Multiple authors have exposed ibrutinib-associated atrial fibrillation between 3.6-16% of cases; the hypothesis of the mechanism is based on the reduction of phosphoinositide 3-kinase-protein kinase B reduction caused by ibrutinib, the cardiac protective effect of this pathway in stressful conditions would be lost [15,16].

Extensive literature has established the anticoagulation therapy in atrial fibrillation based on the risk for thromboembolic events, and the new direct-acting oral anticoagulation therapies have been emerging as an option in these patients [17-19].

The rivaroxaban and ibrutinib undergo CYP3A4-mediated, it is not known how the presence of both substrates, Ibrutinib and a CYP3A4-metabolized DOAC, affects their respective metabolism, mainly as DOAC levels are not routinely monitored, we need to be aware of the impact in CYP3A4 pathway in patients taking ibrutinib, knowing that concurrent administration of additional CYP3A4 inhibitors (e.g. fluconazole) will likely increase plasma concentrations of both drugs, potentially leading to a significantly increased risk of bleeding [20].

The controversy could be present when these patients require anticoagulation therapy due to a high risk for thrombotic events in atrial fibrillation with an increased risk of bleeding while the patient is on Ibrutinib [21,22]. Different papers published in the American College of Cardiology suggest the therapy with anticoagulation in patients with ibrutinib-associated atrial fibrillation, but the decision for the treatment should be based on CHADVASC/HASBLED scores. Based on empiric data exposing the emerging incidence of bleeding while on ibrutinib, the appropriate individual approach in a timely matter is needed to re-start this oncologic therapy on this population of patients [23].

Conclusion

This case represents clear evidence of how an appropriate assessment on time and the collateral gath-ering of medical history could impact the outcome of our patients. The literature review has shown new-onset atrial fibrillation and bleeding events related to ibrutinib. Given the risk for bleeding with rivaroxaban, their combination could present with massive alveolar hemorrhage that could become fa-tal if not recognized early.

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