CLINICAL VIGNETTE

Non-Fatal Severe Pneumonitis and Ventricular Tachycardia in a Patient Treated with Crizotinib for EML-Alk-Positive Non-Small Cell Lung Cancer

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Case Study

This is a 70-year-old female non-smoker who was diagnosed with adenocarcinoma of the lung with liver and bone metastasis in May 2015. She was found to have an anaplastic lymphoma kinase (ALK) gene rearrangement and was started on crizotinib therapy on 7/15/2015 as first-line chemotherapy. She developed nausea and was treated with ondansetron and oral dexamethasone. About four weeks into her chemotherapy treatment, she developed shortness of breath, nonproductive coughing, and fevers. She also had some visual floaters. The crizotinib and dexamethasone were stopped; she was started on empirical ciprofloxacin. Her shortness of breath worsened, and she presented to the emergency room.

Upon being evaluated in the emergency department, she was noted to be in moderate respiratory distress with oxygen saturations of 70% on room air. Initial arterial blood gas (ABG) showed a PaO2 of 47 mmHg on a 15L non-rebreather face mask. Her chest x-ray (Figure 1) and noncontrast CT scan of the chest (Figure 2) showed extensive moderately-severe patchy bilateral airspace disease with small to moderate bilateral pleural effusions, all new when compared to a CT chest performed 3 months prior to admission. Of note, there was a reduction in the size of the liver metastases. She was afebrile on admission with a normal WBC and differential. Her EKG, BNP, and troponin were within normal limits. She was started on BiPAP, IV levofloxacin, and methylprednisolone 40 mg q12 hours and admitted to the intensive care unit. Overnight on hospital day number 1, she went into ventricular tachycardia and with cardiac arrest. She was successfully resuscitated with chest compressions and defibrillation and was completely lucid immediately thereafter. There was some concern for ST segment elevations in the anterior precordial leads on EKG, and she was taken immediately to the cardiac catheterization lab where she underwent coronary angiography, which was negative for significant atherosclerotic disease. Transthoracic echocardiogram was within normal limits. Electrolytes were within normal limits and at no time did any rhythm strip or EKG show evidence of QT prolongation. An ABG 8 hours after admission showed a PaO2 of 197 mmHg on BiPAP (I:E of 16/12 cm H20) with an FiO2 of 1.0. Infectious Disease consultation was obtained, and piperacillin-tazobactam and vancomycin were added to her medication regimen. The following day fiberoptic bronchoscopy was recommended, but the patient refused, stating that she was beginning to feel better. Over the course of the ensuing hospital days, the patient remained afebrile with a mild increase in WBC to 12.6 x 10,[3] felt to most likely be secondary to the systemic steroids she was receiving. Her dyspnea and chest x-ray abnormalities improved dramatically over several days (Figure 3), and she was easily weaned off of BiPAP and eventually to room air. She was discharged on hospital day number 6. The steroids were tapered off over the next 2 weeks, and she remained without pulmonary symptoms at follow-up 3 weeks later.

Discussion

Molecularly targeted therapy is becoming more common in cancer treatment as new oncogenes are identified along with drugs targeting them. Crizotinib is an orally-administered echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) tyrosine kinase inhibitor that was approved in 2012 as a first-line treatment for ALK positive locally advanced or metastatic non-small cell lung cancer. This fusion oncogene is present in approximately 5% of non-small cell lung cancers.[1] When compared to EML4-ALK negative patients, EML4-ALK positive patients tend to be younger in age at time of diagnosis, are never smokers, and have adenocarcinoma histopathology.[2] Common side effects include visual changes, nausea, diarrhea, vomiting, constipation, peripheral edema, and transaminitis.[2] Potentially life-threatening side effects include QT interval prolongation (2.7%)[3] and pneumonitis. In clinical trials reported to the FDA, of 1225 patients receiving crizotinib about 31 patients (2.5%) developed interstitial lung disease (ILD). Of these, 17 patients (1.5%) had severe life-threatening or fatal ILD.[4]

Although this patient did not have any evidence of QT prolongation either prior to or after her ventricular tachycardia arrest, it is possible a transient QT prolongation was the precipitating factor. She was also receiving a fluoroquinolone, which is a known potential cause of QT prolongation, and the combination of the two medications together may have potentiated this effect. Fortunately, this patient was resuscitated quickly and was totally lucid immediately thereafter.

There have been case reports of both fatal and non-fatal pneumonitis secondary to crizotinib.[5-8] In our patient, crizotinib-induced pneumonitis appears to have been the cause

of her respiratory failure. Although she did report fevers at home, she was afebrile on presentation and throughout her hospitalization. Her WBC was essentially normal throughout and culture was negative, thus making an infectious process less likely. Cardiogenic pulmonary edema also appeared less likely as her BNP and echocardiogram were within normal limits. Her rapid response to systemic steroids is consistent with other described cases of nonfatal crizotinib-induced acute lung disease.[5,8] It is possible that the dexamethasone she was taking prior to admission for her nausea attenuated the pulmonary toxic effects of the crizotinib, which may be why her symptoms worsened significantly when her dexamethasone was discontinued.

The incidence of severe lung disease with tyrosine kinase inhibitors has been reported to be higher in patients with a history of smoking, prior interstitial lung disease, Asians, and males. Our patient did not fit into any of those categories. Her clinical presentation, though, did fit the commonly reported scenario of acute dyspnea, low grade fever, and nonproductive cough occurring within 2 months of starting therapy. Since there are no clearly defined criteria for drug-induced lung disease, a high index of suspicion must be maintained. No specific treatment has proven effective besides discontinuation of the agent. Glucocorticoids have been recommended in the more severe cases based on case reports.[9]

Physicians treating patients with crizotinib need to be aware of the potentially life-threatening cardiac and pulmonary side effects of this medication. They should also be aware of any medications which may potentiate its side effect profile.

Figures

Figure 1. Her chest x-ray showed extensive moderately-severe patchy bilateral airspace disease with small to moderate bilateral pleural effusions, all new when compared to a CT chest performed 3 months prior to admission.

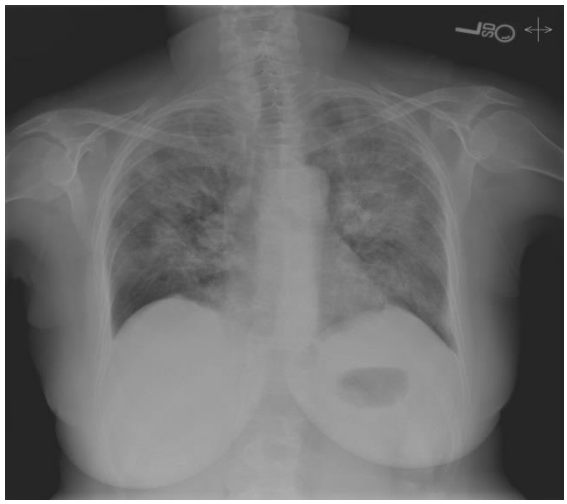


Figure 2. Her noncontrast CT scan of the chestshowed extensive moderately-severe patchy bilateral airspace disease with small to moderate bilateral pleural effusions, all new when compared to a CT chest performed 3 months prior to admission.

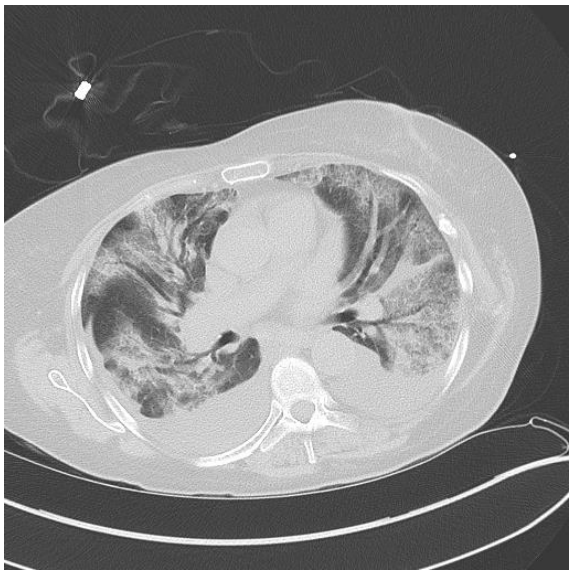
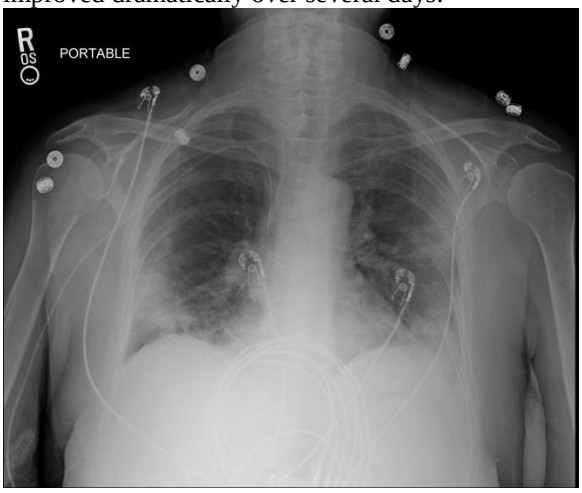


Figure 3. Her dyspnea and chest x-ray abnormalities improved dramatically over several days.



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