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Interstitial Lung Disease Induced by Pazopanib Treatment for Metastatic Renal Cell Carcinoma at the Time of COVID-19 Pandemic

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Abstract

Interstitial lung disease is a reported complication of therapy with tyrosine kinase inhibitors. Pazopanib, a vascular endothelial growth factor inhibitor approved for first line treatment in metastatic renal cell cancer and second line therapy for advanced sarcoma, is rarely associated with lung complications. However, interstitial lung damage is the major problem associated with coronavirus pandemic and the cause of severe respiratory syndrome. We describe the development of pneumonitis in a patient with metastatic renal cell carcinoma treated with pazopanib during the peak of coronavirus disease in Italy. This report notifies the possible onset of pazopanib induced pneumonitis and how to diagnose and manage drug induced interstitial lung disease during the pandemic of coronavirus.

Keywords: Interstitial lung disease; Pneumonitis; Coronavirus; Renal cell carcinoma; Pazopanib

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Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2; RT-PCR: Reverse Transcription-Polymerase Chain Reaction; CT: Computed Tomography; ILD: Lung Interstitial Disease; TKI: Tyrosine Kinase Inhibitor; VEGF: Vascular Endothelial Growth Factor; RCC: Renal Cell Cancer; EGFR: Epithelial Growth Factor Receptors

Introduction

Coronavirus Disease 2019 (COVID-19) is a highly infectious respiratory syndrome caused by a novel coronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) that was first identified in Wuhan (China) in December 2019. It rapidly spread worldwide causing thousands of deaths and a serious cluster of COVID-19 was reported in Italy, with a total of 9,136 confirmed deaths on March 2020 [1].

Common symptoms of COVID-19 are fever, cough, myalgia or fatigue; about 17% of patients positive for the infection complicated with lung damage [2]. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is considered the gold standard for disease diagnosis but also Computed Tomography (CT), thanks to its high sensitivity, plays a critical role. The major CT pattern of COVID-19 is bilateral ground glass opacities (50.2%), mixed ground glass opacities plus consolidation (44.4%), consolidations (24.2%), and reticular pattern (9.9%) [3].

Nevertheless cough, fever, dyspnea, and hypoxemia are also clinical manifestations of Interstitial Lung Disease (ILD), a reported complication of treatment with Tyrosine Kinase Inhibitor (TKI). ILD is usually diagnosed by exclusion of other causes of lung damage and, during TKI treatment, its incidence ranges between 0.35 to 1% with a mortality rate of 20% to 50% [4]. Computed tomography can help oncologists to ILD diagnosis but imaging findings are nonspecific; the major CT patterns of ILD are area with ground-glass attenuation, a multifocal area of airspace consolidations, patchy distribution of ground-glass attenuation accompanied by interlobar septal thickening, and extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis [5].

Among TKI, pazopanib targets Vascular Endothelial Growth Factor (VEGF) and platelet-derived growth factor; it has demonstrated efficacy as first line treatment in metastatic clear cell Renal Cell Cancer (RCC) [6] and after failure of standard chemotherapy in metastatic non-adipocytic soft-tissue sarcoma [7]. Unlike other TKI, the association of ILD and pazopanib is not well defined and no cases of pazopanib induced ILD are reported in patients with metastatic renal cell carcinoma.

Since COVID-19 pneumonia and TKI-induced ILD have similar clinical course and CT findings, we reported a clinical case of interstitial lung damage in a patient treated with pazopanib for metastatic RCC during the peak of COVID-19 in Italy.

Case and Methods

A 70-years old man, with a history of clear cell RCC, was transferred to our hospital for fever and dyspnea. He was a current smoker of 13 pack years, in good clinical conditions with an Eastern Cooperative Oncology Group performance status of 0. No significant comorbidities were present except for a history of paroxysmal atrial fibrillation treated with flecainide. In December 2014, he underwent a left nephrectomy for a clear cell renal cell carcinoma (Fuhrman grade 2) with infiltration of perirenal adipose tissue; the Tumor Node Metastasis stage was pT3N0. During his regular follow-up, in November 2019, an abdomen magnetic resonance revealed six nodular metastases of the right kidney and a chest CT showed a lung nodular metastasis of 12 mm above the left diaphragm. In December 2019, he started oral therapy with pazopanib 800 mg daily. In March 2020 after 12 weeks of treatment, a total body CT scan was performed and showed stable disease according to the Response Evaluation Criteria in Solid Tumors.

However, ten days after the CT scan, he complained of dyspnea, cough, and fever. On clinical examination, body temperature was 38.4°C, blood pressure 130/65 mmHg, heart rate 77 bpm, and oxygen saturation 95%. Blood and urine cultures were negative for bacterial and fungal infections. A chest radiograph was performed, demonstrating a bilateral lung reticular shadow (Figure 1).

Laboratory test on admission showed lactate dehydrogenase 263 U/L, procalcitonin 0.09 ng/mL, creatinine 1.03 mg/dL, C-reactive protein 174.7 mg/L, white blood cells $8.03 \times 10^3/\mu L$, hemoglobin 12.6 g/dL, platelets count $261 \times 10^3/\mu L$. An arterial blood gas showed a pH 7.452, pCO2 38.8, pO2 80.7 in VM60% P/F 135. Due to clinical worsening a high-resolution chest CT was performed and it showed bilateral ground-glass opacities with thickening of the interlobular septa consistent with interstitial pneumonia (Figure 2).

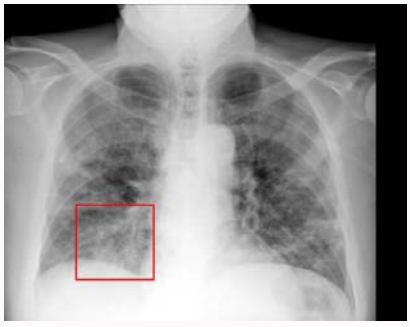

Figure 1: Chest X-ray at admission: diffuse bilateral areas of ill-defined lung opacities with a small parenchymal consolidation on the right base (red box).

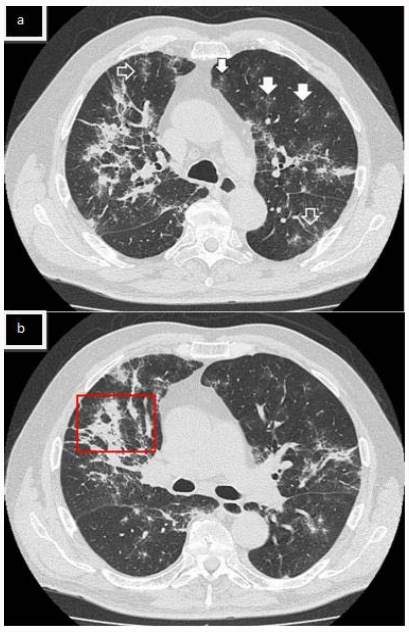

Figure 2: Chest CT: bilateral and multifocal interlobular septal thickening (empty arrows in a) together with small ground glass opacities (white arrows in a) and a discrete consolidative opacity (red box in b).
CT: Computed Tomography

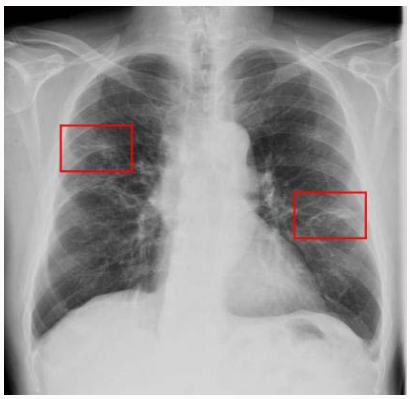

Figure 3: Chest X-ray after pazopanib stopping and steroid treatment: resolution of previous lung abnormalities with two residual area of septal thickening.

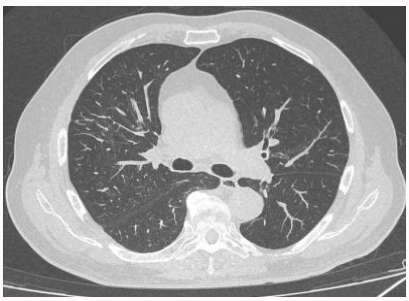

Figure 4: Chest CT after five months of pazopanib stopping: complete resolution of previous lung abnormalities.
CT: Computed Tomography

Considering clinical symptoms, radiological findings and epidemiological data that reported a high number of COVID-19 cases in Italy, a pharyngeal and nose swab was performed; it resulted

negative for SARS-CoV-2 infection. Bronchoalveolar lavage resulted negative for cancer cells as well as for common and opportunistic infections including *Mycobacterium* and *Aspergillus*. Moreover, the research of SARS-CoV-2 was performed on the bronchial fluid, resulting negative.

Patient started empirical antibiotic treatment with piperacillin-tazobactam 4.5 g IV every 6 h and methylprednisolone 1 mg/kg IV. In the following days there was a gradual improvement of clinical symptoms and hypoxia, and he was discharged on day 21 with steroid tapering at home.

On day 24 patient re-started treatment with pazopanib but after only 4 days, he was readmitted to hospital for fever and dyspnea. Laboratory test showed C-reactive protein 140.8 mg/L, procalcitonin 0.08 ng/mL, white blood cells 6.37 × 10^3/μL, platelets count 231 × 10^3/μL. Symptoms resolved with pazopanib stopping and retreatment with high dose steroid.

Immunoglobulin G for COVID-19 were performed on day 60, after symptoms resolution, and confirmed negative for the viral infection. The first follow up chest X-ray on day 60 showed a significant reduction of lung abnormalities (Figure 3), and the last chest CT after five months of pazopanib discontinuation showed the total disappearance of lung infiltrates (Figure 4).

Radiological findings, clinical course, and negative tests for common, opportunistic, and SARS-CoV-2 infection, led us to the diagnosis of interstitial lung disease caused by pazopanib treatment.

Discussion

We report a clinical case of interstitial disease induced by pazopanib at the time of the outbreak of COVID-19 in Italy, so generating diagnostic troubles.

Typical outset of drug induced ILD is with fever and respiratory symptoms; CT scan shows nonspecific signs of interstitial pneumonia, but an exclusive diagnostic test is missing, and so diagnosis is usually made by exclusion of other causes of lung damage.

Pulmonary events are more frequently reported with Epithelial Growth Factor Receptors (EGFR) inhibitors and ILD incidence in trials with erlotinib, gefitinib or afatinib ranged from 0.5% to 5.3% [8].

For VEGF TKI used in the treatment of metastatic RCC, lung complications are reported with sunitinib and sorafenib [9]. In a retrospective series of targeted therapies in metastatic RCC, 65.4% of patients after the resolution of drug-induced ILD switched to subsequent targeted therapies without any ILD-reoccurrence [9]. Despite its biological mechanism similar to other TKI that caused ILD, it is a rare complication during treatment with pazopanib. A previous case of interstitial pneumonia correlated to pazopanib was reported in a man with leiomyosarcoma suffering from chronic lung disease. He was treated with high-dose methylprednisolone and immunosuppressant tacrolimus [5]. More recently, another case of organizing pneumonia in a patient treated with pazopanib for a leiomyosarcoma was published. The histological specimen from the bronchoscopy revealed intraluminal fibrosis alveolar spaces and confirmed the diagnosis of pazopanib-related organizing pneumonia. A gradual improvement was obtained after treatment with oral prednisolone [10]. Similarly to our case, time to onset of symptoms in these reports was respectively two and four months after the start of pazopanib treatment. No previous data exist about pulmonary complications induced by pazopanib in patients with renal cell carcinoma.

COVID-19 breaks out after an incubation of 2 to 7 days with fever and dry cough. In 10% to 20% of cases after 3 to 7 days, there is a respiratory worsening with dyspnea and hypoxemia. Around 3% develop SARS-CoV-2 [11]. Chest CT has high sensitivity but a quite poor specificity, revealing nonspecific abnormalities like focal and unilateral ground-glass opacities that quickly interest both lungs, [3] and so final diagnosis is made by nucleic acid analysis of virus specimen from nasopharyngeal swab [12]. More recently virus antigen or serological antibody test are under evaluation to help in diagnostic accuracy [13]. Seroconversion occurs after 7 days of symptomatic infection in 50% of patients, and in all patients after 14 days [14].

Differences between COVID-19 and EGFR associated ILD were recently reported. Distinguishing features were in the time to onset of symptoms (median of 5 days for COVID-19; while months are needed after start of TKI to develop a pulmonary distress) and in treatment (TKI-induced ILD is treated with steroid and drug discontinuation but no standard treatment is approved for COVID-19). However, a rapid test such as RT-PCR, isothermal amplification assays, or serology tests could be helpful to diagnose COVID-19 and to exclude drug induced lung toxicity [15].

Conclusion

Lung damage requires a correct and timely diagnosis to start the right treatment and improve symptoms. Pulmonary events during pazopanib treatment should not be neglected because of the reported risk of developing ILD.

Despite ILD and COVID-19 have similar clinical and radiological pattern, the rapid execution of SARS-Cov-2 test and the focus on some clinical differential aspects, could help for achieving the right diagnosis and for the disease management.

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