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Case report

Everolimus induced organizing pneumonia in a patient with tuberous sclerosis complex

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ABSTRACT

Organizing pneumonia is characterized by a distinct histologic pattern in the lung interstitium and presents clinically as hypoxemia, fever, cough, and dyspnea that is not attributable to concurrent infection. Typical etiologies of this condition include inflammatory disease, malignancy, toxic inhalation, and an array of medications including the mTOR inhibitor everolimus. In this report, we describe the case of a female with tuberous sclerosis complex on everolimus therapy for renal angiomyolipomas who presented to the hospital with persistent cough, dyspnea, and fevers and bilateral lower lobe opacities on chest X-ray despite multiple courses of antibiotic therapy. Bronchoscopy was performed with transbronchial biopsies, and results demonstrated a lymphocytic predominance and pathologic findings of intraluminal plugs composed of fibroblasts and myofibroblasts consistent with organizing pneumonia. Everolimus therapy was discontinued and patient completed a steroid course with resolution of symptoms. To our knowledge, this is the first published case of organizing pneumonia secondary to everolimus in a patient with tuberous sclerosis complex.

1. Introduction

Everolimus is a an orally available mammalian target of rapamycin (mTOR) inhibitor that belongs to the group of proliferation signal inhibitors, which also includes sirolimus and temsirolimus. These compounds have antiproliferative and antifibrotic properties [9]. Because of these properties they are typically used in the treatment of various malignancies and in patients with solid organ transplantation [8]. Both everolimus and sirolimus are known to induce pulmonary toxicity, such as interstitial pneumonia and organizing pneumonia [5].

Organizing pneumonia due to everolimus is an uncommon presentation of drug-induced interstitial lung disease that compromises the distal bronchioles, respiratory bronchioles and alveoli, specifically the alveolar wall. This condition is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue [11]. High resolution computed tomography often reveals patchy air-space consolidation, ground-glass opacities, small nodular opacities, and bronchial wall thickening with dilation [12].

In this case, we present a case of a female with tuberous sclerosis complex with symptomatic renal angiomyolipomas that developed organizing pneumonia secondary to everolimus.

2. Case report

46-year-old female with history of tuberous sclerosis complex with renal angiomyolipomas (Fig. 1) and stage II CKD that presented with one month of cough, dyspnea, and intermittent fevers. She was admitted one week prior for community-acquired pneumonia having already received a 10-day course of amoxicillin/clavulanate without improvement. During the second admission, the patient was treated with doxycycline and Azithromycin, transitioned to cefdinir at discharge.

Everolimus was started ten years prior to admission due to enlarging renal angiomyolipomas and patient had previously been stable on this therapy. On presentation, the patient was afebrile, tachypneic, and hypoxemic requiring 4 L nasal cannula to maintain oxygen saturation above 90%. Physical exam was notable for diminished bilateral lower breath sounds without wheezes. Laboratory studies included a white blood cell count of 10,300, platelets 608,000, C-reactive protein of 13.1 mg/dL, and procalcitonin of 0.53 mg/dL. Urinary streptococcal and

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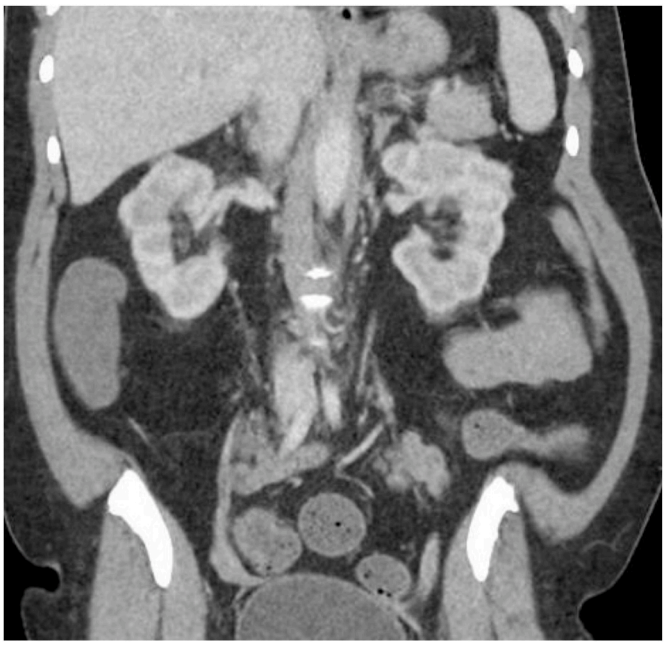

Fig. 1. Tomography of the abdomen.
Bilateral lobular kidneys with multiple fat-containing lesions consistent with renal angiomyolipomas commonly seen in tuberous sclerosis complex.

legionella antigens were negative. Chest X-ray (Fig. 2) showed bilateral lower lobe airspace disease. CT Chest (Fig. 3a, 3b) showed bilateral multifocal pulmonary infiltrates and ground-glass opacities (GGO) predominantly perihilar and lower lobe in location on the right, with extensive involvement of the left upper and lower lung zones. She received fluid resuscitation along with IV vancomycin and cefepime. Her hypoxemia failed to improve with appropriate antibiotics and bronchoscopy was performed. Bronchoalveolar lavage of the right middle lobe, endobronchial biopsies of the right upper lobe, and transbronchial biopsies of the right lower lobe were performed. Bronchoalveolar lavage

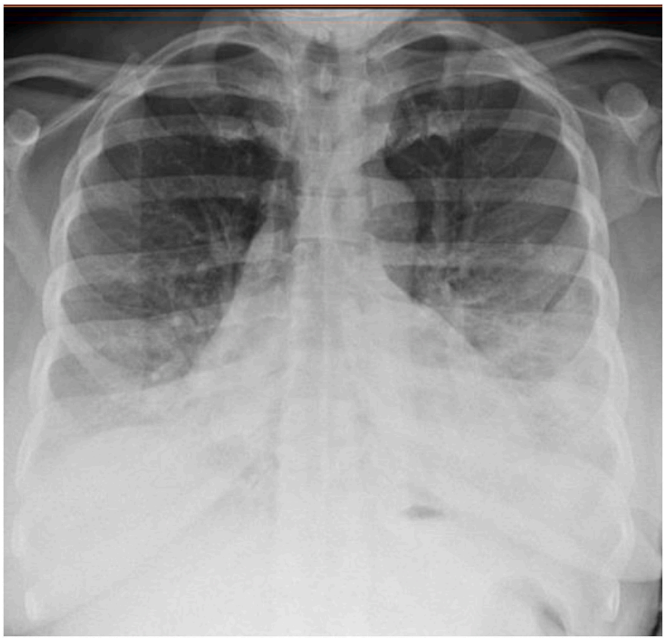

Fig. 2. Initial chest X-ray.
AP View chest x-ray showing bibasilar centrally located infiltrates, more prominent on the left.

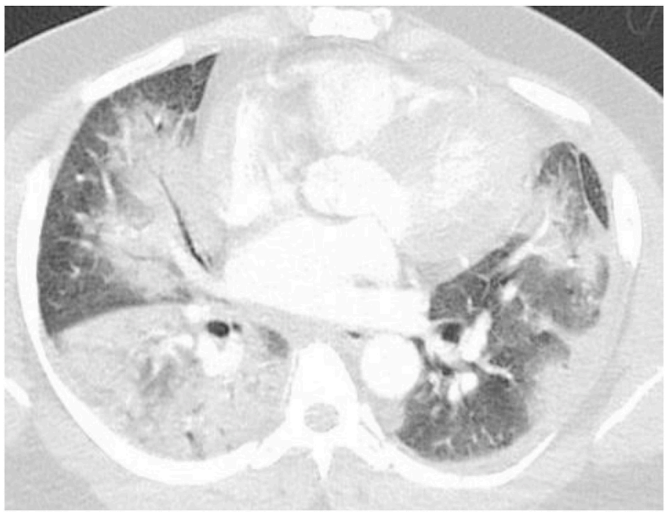

Fig. 3a. Initial chest tomography.
CT Chest demonstrating bilateral airspace disease with varying distributions. The consolidations are more bronchocentric in the right middle lobe with diffuse consolidation with some intervening ground glass in the right lower lobe. Infiltrates in the left lower lobe are more peripheral and subpleural in distribution.

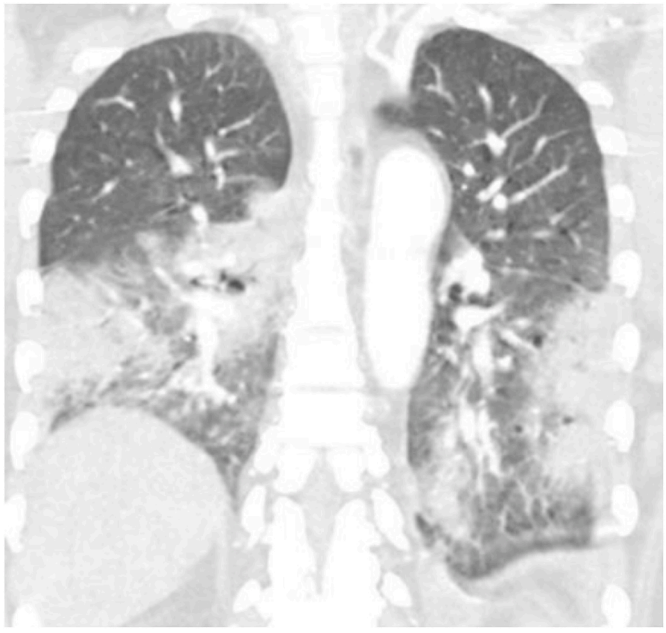

Fig. 3b. Initial chest tomography.
Coronal image of CT Chest showing both central and peripheral consolidations with surrounding ground glass infiltrates.

showed 678,000 WBC with 26% lymphocytes, 12% neutrophils, and 60% macrophages. Cultures from all the different specimens did not show any organisms. Transbronchial biopsies (Fig. 4a, 4b) demonstrated "patchy intraluminal plugs composed of fibroblasts and myofibroblasts embedded in loose connective tissue with mild chronic interstitial pneumonia" consistent with organizing pneumonia. Given these findings on transbronchial biopsies, a combined decision between pulmonary and urology was made to stop everolimus. She was started on oral prednisone at 0.75 mg/kg of ideal body weight and antibiotics were discontinued. The patient was discharged home on 2 L of oxygen and steroids. She was seen in Pulmonary clinic one month later and her hypoxemia has resolved. The patient was symptomatically back to

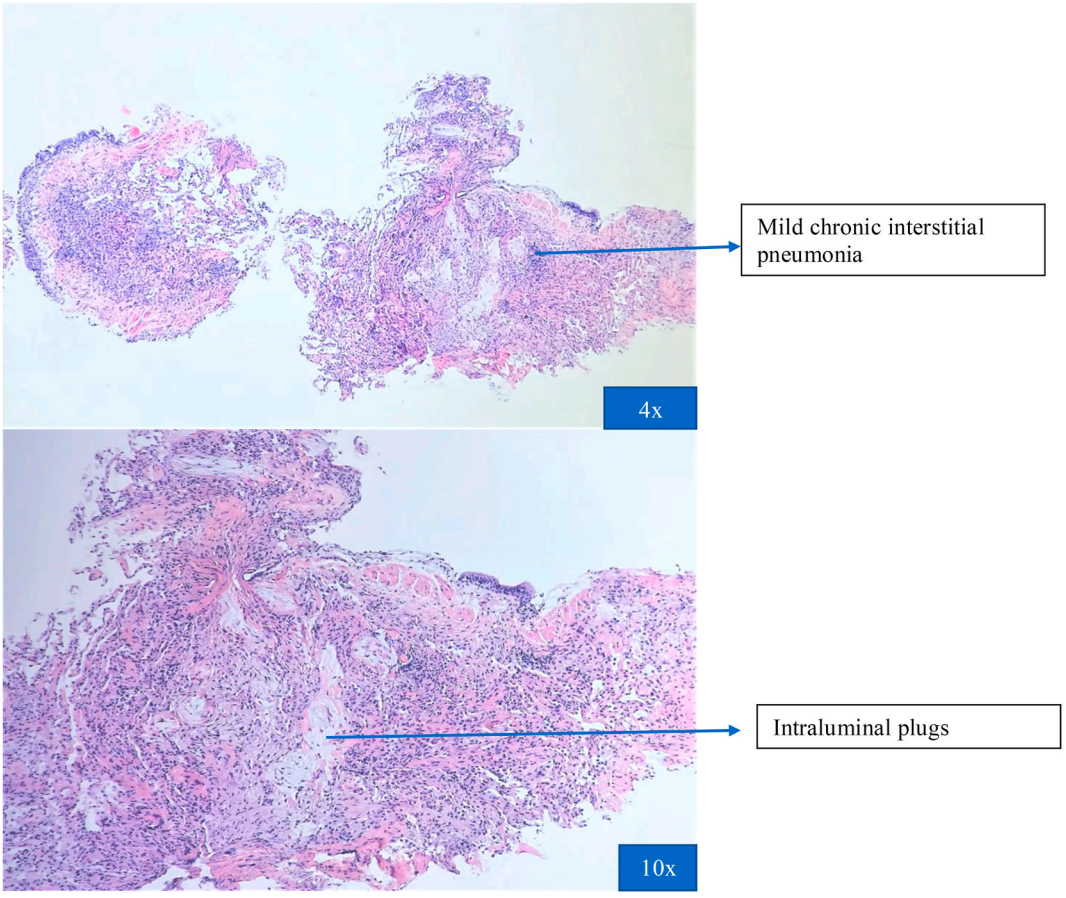

Fig. 4a. Pathology.

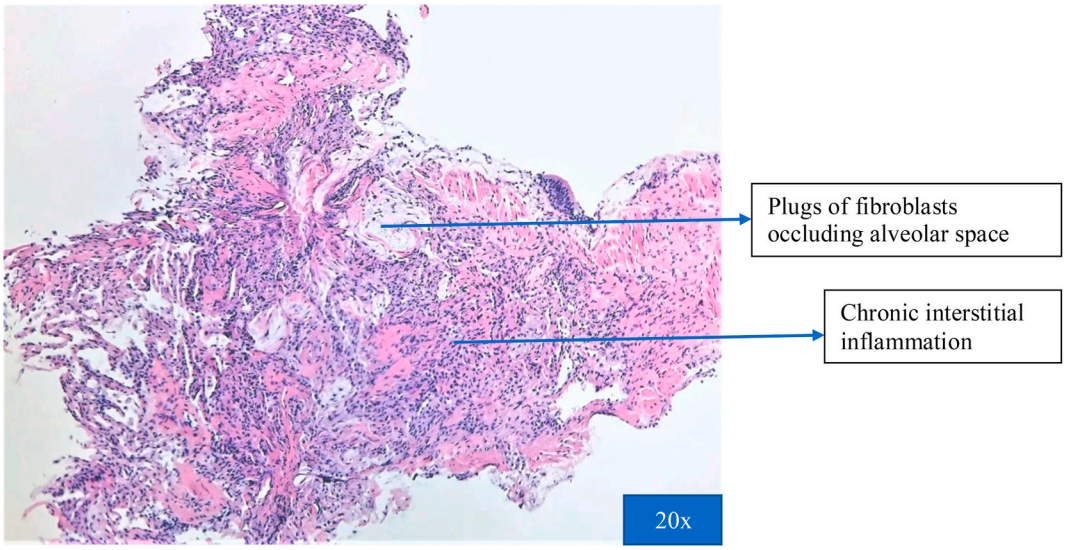

Fig. 4b. Pathology.
Pathology description
Microscopically, the biopsy demonstrates patchy intraluminal plugs composed of fibroblasts and myofibrobalsts embedded in loose connective tissue with mild chronic interstitial pneumonia.
Special stains were performed for microorganisms; which were negative.

baseline. Follow-up CT chest (Fig. 5) one month later showed improvement of the bilateral infiltrates. Chest x-ray Chest tomography one month later.CT Chest on month later shows interval improvement in the right lower lobe consolidations but more extensive ground glass in the left lower lobe with occasional subpleural cysts.(Fig. 6) two month after initiation of therapy showed resolution of the infiltrates. Steroids were weaned over the course of several months and the patient returned to her baseline functional status.

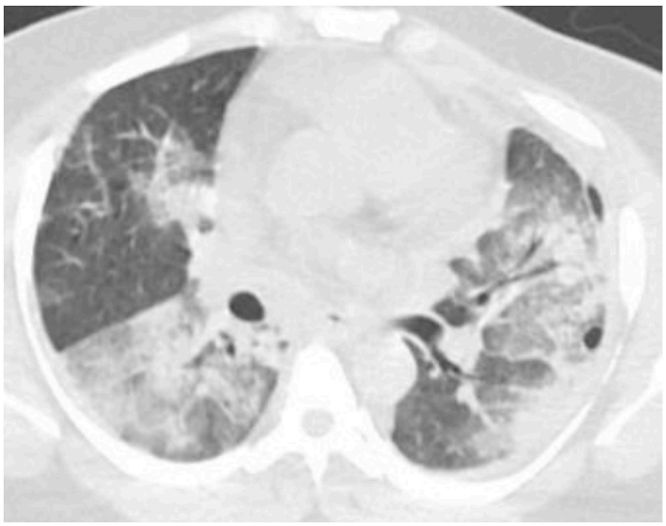

Fig. 5. Chest tomography one month later.
CT Chest on month later shows interval improvement in the right lower lobe consolidations but more extensive ground glass in the left lower lobe with occasional subpleural cysts.

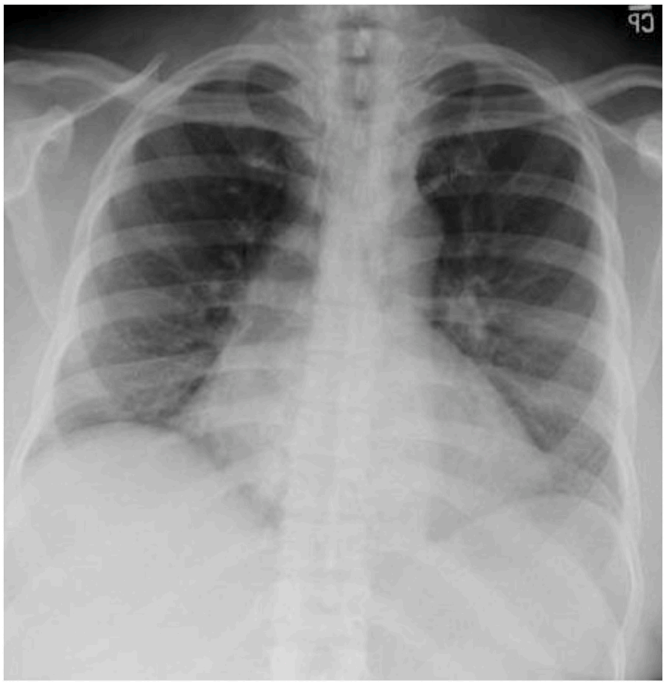

Fig. 6. Chest X-Ray two months after initiation of treatment with steroids.
Chest x-ray 2 months after treatment with corticosteroids. Bilateral lower zone infiltrates have nearly completely resolved.

3. Discussion

Organizing pneumonia is an uncommon subtype of interstitial lung disease. Organizing pneumonia can be classified as secondary due to medications or connective tissue disease or cryptogenic without an obvious etiology. Patients usually present with several weeks of constitutional symptoms and can mimic community-acquired pneumonia with fleeting pulmonary infiltrates. Not uncommonly, patients receive multiple rounds of antibiotics for bacterial pneumonias. Oral corticosteroids are the backbone treatment for organizing pneumonia, but other immunosuppressive medications have been used along with macrolides [13,14]. Here, we present a case of biopsy-proved everolimus-induced organizing pneumonia in a patient with tuberous sclerosis.

The benefit of use of Everolimus in tuberous sclerosis patients for the treatment of renal cell angiomyolipomas was first widely recognized with the publication of the EXIST-2 trial in 2013 [1], the first randomized, placebo-controlled, phase 3 study to assess everolimus efficacy and safety in patients with TS-associated renal angiomyolipoma. There have been numerous case reports and clinical trials documenting noninfectious pneumonitis and organizing pneumonia as a side effect of everolimus in use for treatment of a variety of conditions including renal cell carcinoma [2,5], Waldenstrom Macroglobulinemia [3], renal transplant [4,6], and insulinoma [10]. However, our study is one of few to document biopsy-proven organizing pneumonia as a side effect of everolimus in a tuberous sclerosis patient. One case report published in 2015 documented similar findings in a patient with concurrent pulmonary lymphangioleiomyomatosis and stage 3 CKD, proposing these comorbidities as a potential increased risk for everolimus-induced pulmonary toxicity [8]. Our patient similarly demonstrated stage 2 CKD at time if onset but had no underlying pulmonary disease. Additionally, a unique feature of our patient's presentation was the fact that everolimus had been initiated 10 years prior. In the aforementioned case study, patient symptoms occurred 6 months after initiation of the medications. Clinical trials have documented median time of onset as 108 days [2], 5.7 months [3], 162 days [6], and case reports range from 4 weeks [7] to 15 months [5]. However, we were unable to determine another potential trigger of patient's presentation with an extensive negative infectious workup and no improvement on antimicrobial therapy. Our patient did demonstrate marked improvement however with discontinuation of everolimus and initiation of steroids. We therefore recommend that, when developing a differential diagnosis for organizing pneumonia, providers seriously consider the administration of everolimus as a potential cause, regardless of treatment timeline.

4. Conclusion

Everolimus is a mTOR inhibitor used in the treatment of both renal cell carcinoma and tuberous sclerosis. Rarely, it can cause organizing pneumonia which can be treated with discontinuation of the medication and oral corticosteroids.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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