

Invasive Pulmonary Aspergillosis with Spontaneous Pneumothorax and Systemic Dissemination (Thyroid and Spleen) after Receiving Tocilizumab: A Case Report

AlHarbi AR*, Paramasivam BAMP and Nadma AR

King Saud University, Kingdom of Saudi Arabia

*Corresponding author:

Abdullah Rashed AlHarbi,
King Saud University, Kingdom of Saudi Arabia

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1. Abstract

Invasive pulmonary aspergillosis in critical ill patients with viral pneumonia has been reported in the past and as well with Covid-19 pneumonia. Such presentation was rarely reported in Covid-19 patients who received Tocilizumab (IL-6, inhibitor) [1]. We are reporting an invasive pulmonary aspergillosis and spontaneous pneumothorax in a patient with severe covid pneumonia after receiving a single dose of Tocilizumab and who do not require mechanical ventilation.

2. Background

Severe Acute Respiratory Coronavirus-2(SARS-Cov-2) which is commonly known as COVID-19, has emerged as a global pandemic that has affected millions of population with overall fatality rate of 3.9% [2]. It's well established that Covid-19 causes ARDS secondary to cytokine storm even in immunocompetent persons and high mortality [3]. Interleukin-6 (IL-6) plays a central role in the cytokine storm [4]. The IL-6 receptor antagonist, tocilizumab, has been widely used in select cases of COVID-19 to suppress the suspected inflammatory damage [3]. Covid-19 management guidelines from different health authorities authorized the use of Tocilizumab in critically ill patients with extensive lung involvement and requiring either high flow oxygen requirement, NIV or mechanical ventilation and with evidence of cytokine Storm [5].

Tocilizumab decreases inflammation in COVID patients, as meas-

ured with both fever and serum inflammatory markers such as C-reactive protein [6]. A Chinese study showed the patients who received Tocilizumab had no reports of development of secondary infection or clinical deterioration [3].

There are evidence in the literature that immune modulating therapies are having high risk of developing opportunistic infections including invasive pulmonary aspergillosis (IPA) [7]. In the current Covid-19 pandemic also several case series have been reported with incidence of IPA in critically ill patients, almost all are requiring mechanical ventilation [8]. This case report presents a patient with severe COVID-19 pneumonia who developed invasive pulmonary aspergillosis (IPA) and spontaneous pneumothorax after treatment with tocilizumab.

3. Case Report

A 41 years old male known to have Diabetes mellitus only on diet control with HbA1C 6.1, was admitted with 4 days history of fever, sore throat, non-productive cough and severe myalgia. He was tested positive for RT-PCR Covid-19 test. On admission he also had breathing difficulty of mMRC class 2 dyspnoea with chest tightness. He was febrile with temperature 39.5 degree Celsius, tachycardic with HR 114. He was tachypnoeic with RR 36 and saturated 74% on room air. He was hemodynamically stable with BP 140/69 mmHg. Blood gases revealed hypoxic respiratory failure with PaO₂ 57.2, PH 7.533, PCO₂ 28.1, HCO₃ 26.3. Chest x-ray

done which showed bilateral peripheral airspace opacities consistent with Covid-19 pneumonia (Figure 1). He was started on HFNC with FiO₂ 60% and flow rate 90L and his saturation improved to 91%. He was then shifted to the ICU for close observation and management.

He was treated with empirical antibiotics to cover CAP (Azithromycin, Ceftriaxone), Dexamethasone 6mg, paracetamol and prophylactic enoxaparin for DVT. He had lymphopenia, high LDH 840U/L, Ferritin 1500 mcg/L and CRP 210mg/L. All cultures were negative. He was later switched to Methylprednisolone 80 mg IV thrice daily.

His Oxygen requirement remains high with FiO₂ 90% in spite on prone positioning and the high inflammatory markers were consistent with cytokine storm. He received a single dose of Tocilizumab 8mg/Kg on day 4 of hospital admission. He showed clinical improvement from day 5 onwards with decreasing requirement of Oxygen progressively to 5LPM on simple face mask when he was transferred to the ward on day 11.

On day 12 his Oxygen requirement suddenly increased to 12 LPM on NRBM and had a spike of temperature and leucocytosis. Chest X-ray showed new opacity (Figure 2). He was started on Piperacillin /Tazobactam considering as hospital acquired infection. CT chest was done on day 18 which revealed bilateral consolidation with cavity (Figure 3). Subsequently his Covid swab RT-PCR was negative twice. Considering the clinical deterioration and new onset cavitory lung lesion decided to rule out opportunistic infections such as fungal pneumonia, he underwent Bronchoscopy on day 20 and BAL obtained from Left Upper Lobe and Right Lower Lobe.

The BAL was negative for bacteria culture, PCR-TB and AFB smear. The BAL fungal culture grown mould on Day 23 and later confirmed as *Aspergillus fumigatus*. His BAL Galactomannan Optical Density Index (ODI) was 4.65 and serum Galactomannan ODI was 1.34. He was diagnosed as Invasive Pulmonary Aspergillosis and started on Liposomal Amphotericin B on day 23. On day 25 he developed spontaneous pneumothorax on right side and was managed with chest drain and underwater seal. The lung expanded well and was no further air leak and the drain was removed on day 27. His steroid dose was tapered slowly and then stopped. He was treated with Liposomal Amphotericin B and showed clinical improvement. He able to ambulate and his oxygen requirement has improved to 1 LPM. The follow up CT chest after 2 weeks of Amphotericin showed improvement in the consolidation, ground glass opacity but there is increase in the size of the cavity. Also noted new cystic lesions of thyroid lobe and hypodense splenic lesion which could represent disseminated fungal infection (Figure 4). We didn't proceed any further work up for his thyroid and splenic lesions as he had no symptoms and clinically improving. He received Liposomal Amphotericin B for 3 weeks and then switched to oral Voriconazole 200 mg oral twice daily for six weeks. He was discharged with a follow up in the outpatient clinic.

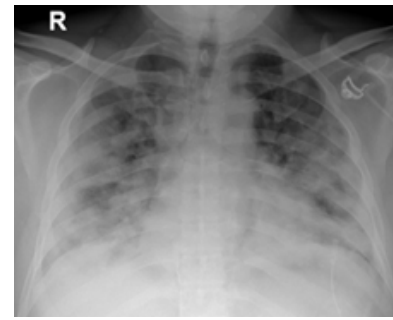


Figure 1: Chest Xray PA view on admission shows bilateral multiple peripheral predominant airspace opacities involving all zones.

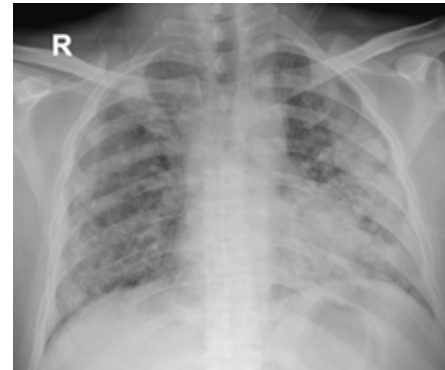


Figure 2: Chest Xray PA view on day 12 shows new increase in opacity over left MZ and lower zone

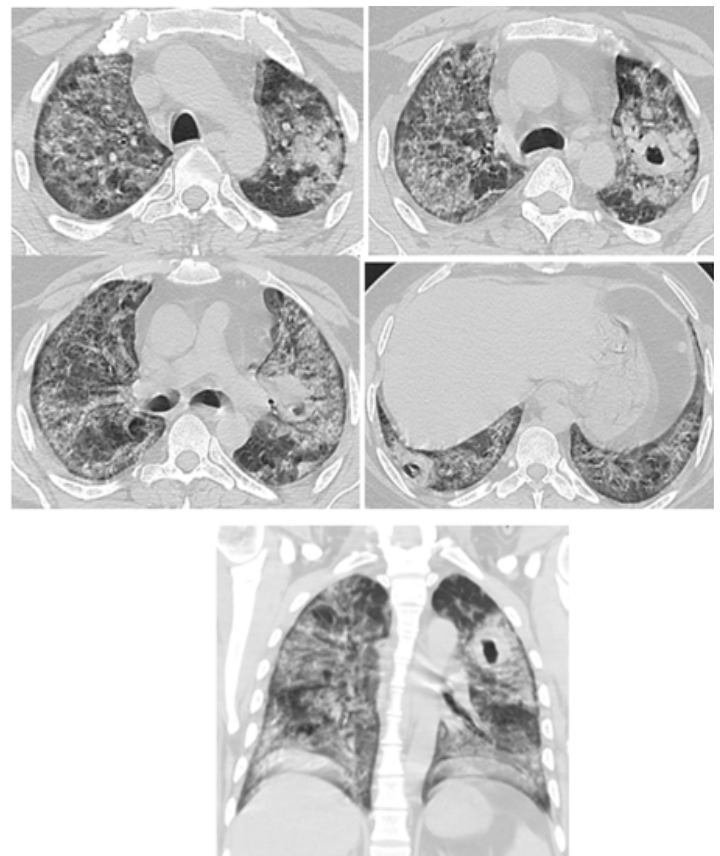


Figure 3: CT chest Axial cuts shows bilateral diffuse airspace and ground glass opacities with nodular area of consolidation with cavitation in left upper lobe as well as posterior segment right lower lobe

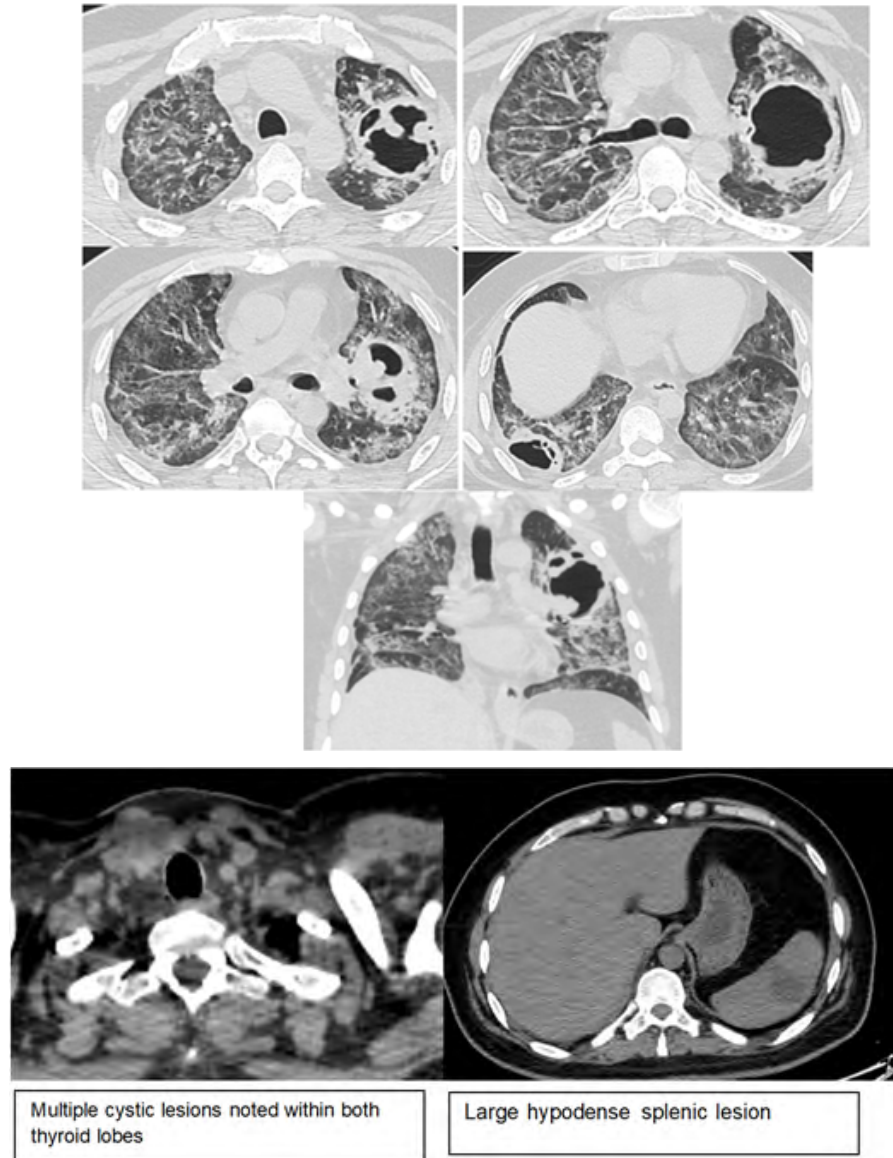


Figure 4: Follow up HRCT shows improvement of ground glass opacities and increase in size of know left upper lobe and right lower lobe posterior segment cavitary lesions with thinning of the wall and surrounding consolidation

4. Discussion

We described a novel case of Invasive Pulmonary Aspergillosis, post Tocilizumab and Spontaneous right pneumothorax in a patient with severe Covid-19 pneumonia who was managed with only high flow nasal cannula.

Invasive Pulmonary Aspergillosis is a well-known complication in critically ill patients. It was first reported in 1950's and its association with severe viral pneumonia was reported in greater number during H1N1 influenza pandemic from 2009-2011 [9].

Invasive pulmonary aspergillosis in Covid -19 pneumonia is also not uncommon. Most of the study population had severe disease, need mechanical ventilation and long stay in MICU and all were managed with IV steroids and broad spectrum antibiotics. In a prospective Aspcovid-19 study by Tobias Lahmer et al (10), Covid-19 Associated Invasive Pulmonary Aspergillosis (CAPA) was reported in 34% of the study population and a high mortality of 36%

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versus 9.5% without CAPA. From different studies and reviews in the literature the incidence of IPA in Covid-19 patients are ranging from 8% to 34% [10]. The cumulative incidence of IPA in the ICU patients ranged from 1.0% to 39.1% [10-12].

Yet, the prevalence of IPA among non-ventilated Covid -19 patients and as well post Tocilizumab remains unknown.

The radiographic patterns in Covid-19 with IPA patients were generally described as mixture of findings of ground glass opacities and crazy-paving (findings consistent with airway inflammation), bronchiectasis, airway wall thickening and irregularity, bronchiectasis (mucus plugging), and consolidations, tree-in-bud nodules (findings consistent with airway-invasive disease) [12]. In some cases, larger nodules with necrosis and cavitation were noted [12].

The diagnosis of IPA in Covid-19 was challenging due to the infection control protocols and many depends on non-invasive techniques like CT-scan and serum markers (Aspergillus Galac-

tomannan) and tracheal aspirate culture. Bronchoscopy was rare [12]. The criteria used to diagnose CAPA by White et al, [13] are cultural growth of BAL, Galactomannan-Enzyme Immune Assay (GM-EIA) of ≥ 0.5 in serum and ≥ 1 in BAL, clinical signs and radiological features.

Our case report was unique as the patient doesn't have any co-morbid items other than labelled diabetes mellitus not on any medication with HbA1C 6.1. He was managed on high flow nasal cannula and did not require mechanical ventilation. He also not received any broad spectrum antibiotics in the beginning of Covid management. He received a single dose of Tocilizumab (800 mg). So for only one case report of Post Tocilizumab IPA in Covid-19 patient was available on PubMed search and that patient received broad spectrum antibiotics, high dose of steroids and mechanical ventilation before the development of invasive aspergillosis. Also our patient developed spontaneous right pneumothorax and cystic thyroid lesions and hypodense splenic lesion could represent fungal dissemination. The diagnosis also fits the criteria clinically, radiological, cultural growth of *Aspergillus fumigatus* and high GM ODI of 1 in serum and 5 in BAL.

The review of the literature shows the high incidence of IPA in critically ill patients, it must to screen the patient with serum GM-EIA and/or respiratory secretions culture for fungus before the administration of immunomodulatory medications. Invasive aspergillosis still remains a big clinical challenge and diagnosis relies largely on histopathological evidence of mycelial growth in tissue, or positive culture from body fluid or BAL in high risk patients. Unfortunately, for many such cases where histology is most needed, this diagnosis becomes available only at autopsy. We recommend to closely observe the patients of Covid-19 or any critically ill patients who are receiving Tocilizumab for any change in the clinical parameters like spike of temperature, leucocytosis and new opacity in chest x-ray as what happened in our patient and need to be investigated for invasive Pulmonary aspergillosis.

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