Triple infection with disseminated tuberculosis, invasive aspergillosis and COVID-19 in an organ transplant recipient with iatrogenic immunosuppression

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SUMMARY

A 39-year-old man with diabetes mellitus and hypertension presented two years following renal transplantation with evening pyrexia, night sweats and loss of weight. He was diagnosed with disseminated tuberculosis and invasive aspergillosis and commenced on antituberculous and antifungal therapy. Immunosuppressants except for the maintenance dose of steroids were discontinued. Two weeks later, he acquired severe COVID-19 pneumonia complicated with type 1 respiratory failure and haemodynamic instability. He was treated with non-invasive ventilation and inotropic support with a vasopressor-augmenting dose of steroids. Management challenges were diagnosing the respiratory pathologies with limited investigations, deciding on continuation of steroids in an organ transplant recipient with disseminated infection and deciding the ceiling of care in a low-resource setting given the background of multiple pulmonary insults. A multidisciplinary team decided to continue high-dose steroids and escalate to a full ceiling of care. He recovered from COVID-19 pneumonia 15 days following diagnosis and was discharged home. The potential adverse effects of steroids on tuberculosis and aspergillosis are to be monitored during follow-up.

BACKGROUND

Immunocompromised individuals are at high risk of opportunistic pulmonary infections. The concomitant impairment of multiple immune-mediated pathways by the use of immunosuppressive medications leads to a variety of bacterial, fungal and viral infections and, on rare occasions, coinfections.

Here, we report the case of a patient with iatrogenic immunosuppression following a renal transplant who was simultaneously infected with disseminated tuberculosis, invasive aspergillosis and COVID-19 pneumonia.

This is the first reported case of this unusual triple infection, and the article discusses possible disease mechanisms and pharmacological and non-pharmacological challenges in management, specifically with regard to the use of steroids and the determination of ceiling of care in a resource-limited setting.

CASE PRESENTATION

This patient was a 39-year-old man with well-controlled type 2 diabetes mellitus, hypertension and iatrogenic immunosuppression due to a renal transplant in 2019. His immunosuppressive therapy included prednisolone, tacrolimus and mycophenolate mofetil (MMF), and his renal function was within normal range. He was positive for cytomegalovirus (CMV) IgG and had not received the COVID-19 vaccination. In late March 2021, he presented to a general medical ward with a month-long history of evening fever, dry cough, loss of appetite and significant loss of weight.

On examination, he had shotty right upper deep cervical lymphadenopathy and stony dullness with reduced breath sounds over the right lower lung zone with overlying coarse crackles. His vital signs were within normal range, and oxygen saturation (SpO2) on air was 98%. The rest of the systems examination revealed nothing of note.

INVESTIGATIONS

Inflammatory markers were unremarkable inclusive of ESR, which was 25 mm in the first hour. Ultrasound scan of the neck region done to visualise the enlarged cervical lymph node revealed evidence of right-sided parotitis with abscess formation (1.4×0.9 cm) in the deep lobe and multiple small cervical lymph nodes. Tuberculous PCR (GeneXpert) in aspirated material from the parotid abscess was positive. Sputum for TB GeneXpert was positive, but TB GeneXpert in bronchoalveolar lavage was negative. Pleural fluid for acid fast bacilli was positive.

High Resolution Contrast Tomography of the chest at this time showed diffuse pleural thickening of the right hemithorax, with an associated pleural effusion, right lower lobe collapse, multiple parenchymal nodules and pleural nodule (8 mm). The largest parenchymal nodules were seen in the left (9×7 mm) and right upper lobes (8×9 mm). These radiological findings were highly suggestive of pulmonary and pleural tuberculosis and invasive aspergillosis. Pleural fluid was found to be exudative with an adenosine deaminase level of 37.5 U/L (<30 U/L). Both serum and lavage were positive for *Aspergillus* galactomannan antigen, with titres of 0.56 and 2.18 respectively (cut-off <0.5). Blood and pleural fluid cultures yielded no growth, and at

this time, his reverse transcription–PCR test for COVID-19 was negative. Microbiological tests for CMV, *Pneumocystis jirovecii* pneumonia (PJP) and fungal cultures were not available at the current setting.

In light of the above investigations, a diagnosis of disseminated tuberculosis involving the lung, pleura and parotid glands superimposed on invasive pulmonary aspergillosis was made. As histopathological evidence could not be arranged due to resource limitations, the diagnosis relied strongly on microbiological and radiological findings and clinical likelihood.

He was started on the standard regime of antituberculous therapy (ATT) and voriconazole (200 mg twice daily). Tacrolimus and MMF were withdrawn, but prednisolone was continued to prevent transplant rejection and, also, avert the consequences of steroid withdrawal during disseminated infection.

Two weeks following initiation of ATT, the patient became dyspnoeic and was found to be hypoxic on room air (SpO_2: 85%). Testing for COVID-19 using STANDARD Q rapid antigen testing (RAT) at this time yielded a positive result, and he was, thereafter, managed for severe COVID-19 pneumonia with type 1 respiratory failure at a high-dependency unit. COVID-19 pneumonia was considered to be severe in this patient due to a saturation of 85% on room air, increased respiratory rate around 40 breaths per minute and ratio of partial pressure of oxygen to fraction of inspired oxygen at 196 mm Hg.

Blood investigations at this time revealed lymphopenia (0.57/mcL), elevated C reactive protein (221 mg/L), high serum lactate dehydrogenase (730 U/L) and high D-dimer levels (1410 Ng/mL). CT pulmonary angiogram did not reveal any evidence of pulmonary embolism. Repeat HRCT during the period of desaturation showed changes consistent with COVID-19 pneumonia with superimposed secondary bacterial infection (ground glass changes, septal thickening, crazy paving appearance and right lower zone consolidation) in addition to previously noted right-sided pleural effusion. Sputum culture and blood culture were negative, and procalcitonin level was not freely available. Additionally, his renal functions remained within normal range throughout the period of hospitalisation.

TREATMENT

This patient was treated with non-invasive respiratory support in the mode of continuous positive airway pressure (CPAP) for 5 days following this; he was gradually weaned off of oxygen therapy over 2 weeks using decreasing percentages of Venturi masks. Chest physiotherapy and awake proning were used.

Intravenous dexamethasone 6 mg daily was given for 2 days. Following this, the patient became haemodynamically unstable with normal anion gap metabolic acidosis with normal lactate levels. Inotropic support was provided with norepinephrine, and a vasopressor-augmenting dose of steroids (intravenous hydrocortisone 50 mg six hourly) was prescribed alongside. A prophylactic dose of anticoagulation was given. Antibacterial cover was provided with fourteen days of imipenem and three doses of teicoplanin. ATT and voriconazole were continued. Other drugs of note were cotrimoxazole and valganciclovir both of which were part of the patient's routine medications for prophylaxis of CMV and PJP. Tocilizumab was not considered in him due to underlying immunosuppression and the presence of disseminated infections.

An additional event that developed during his period of COVID-19 pneumonia was ATT-induced liver injury, due to which a bridging regime of ATT was resorted to. However, as the patient was on thromboprophylaxis, instead of the usual intramuscular streptomycin therapy given as part of the bridging regime, intravenous amikacin was given to avoid intramuscular haematoma formation. Renal functions were rigorously monitored and remained within normal range.

OUTCOME AND FOLLOW-UP

The patient recovered after 15 days from RAT positivity with the above management regime, and steroids were gradually tailed off to a maintenance dose for prevention of transplant rejection. He is planned to be followed up by the respiratory unit with regard to tuberculosis, aspergillosis and possible long-term effects of COVID-19 pneumonia.

Three weeks following discharge, he experiences mild shortness of breath on exertion with no exertional desaturation. ATT and voriconazole are being continued.

DISCUSSION

Iatrogenic immunosuppression renders organ transplant recipients susceptible to opportunistic pulmonary infections.[1] Impairment of neutrophil action and T-cell-mediated and B-cell-mediated immune responses lead to a variety of viral, fungal and fastidious bacterial infections. Infections of note are pulmonary or disseminated tuberculosis, aspergillosis, PJP and CMV. Impairment of the T-cell response increases the risk of tuberculosis.[2] Impairment of neutrophilic action and structural lung defects including granulomas caused by tuberculosis thereby increase the risk of aspergillosis.[3] Due to this correlation, coinfections with tuberculosis and aspergillosis have been described before.[3]

Interestingly, coinfections of tuberculosis and COVID-19 19 have also been described,[4–6] and in fact, an observational study has concluded that tuberculosis increases the susceptibility to COVID-19.[7] A meta-analysis however showed no increase in susceptibility but concluded that patients with pre-existing tuberculosis are more likely to develop serious complications from COVID-19.[8] Since this patient developed COVID-19 approximately 2 weeks after diagnosis of the two other infections, it is likely that the COVID-19 infection was acquired from the hospital. And in keeping with the findings from the above studies, underlying tuberculosis may have played a role in the development of COVID-19 pneumonia and progression to oxygen dependency in this patient.

To our knowledge, triple infection with tuberculosis, aspergillosis and COVID-19 has not been described before, and we believe the complex immunodeficiency in this patient due to the use of three differently acting immunosuppressive medications may have rendered him susceptible to this one-of a-kind coinfection.

The first challenge that came up during the management of this patient was establishing his respiratory pathologies with limited available investigations. Histopathology of cervical lymph nodes and bronchial tissue and fungal cultures could not be readily arranged due to resource constraints. The lack of these in the establishment of the diagnosis is a major limitation in this case study. The diagnoses, therefore, were supported by the available microbiology, the suggestive radiological findings, the high local prevalence of these illnesses and the predilection of said patient to these opportunistic infections.

The second challenge was determining the appropriateness of using high-dose steroids for COVID-19 pneumonia on a background of disseminated tuberculosis and aspergillosis. Treating COVID-19 pneumonia with steroids in patients with pulmonary tuberculosis has been described before with variable outcomes.[9] In this patient, withholding all forms of immunosuppression may

have inevitably led to unfavourable outcomes with respect to his renal function, but the disseminated nature of the tuberculosis and the superimposition of a fungal infection raised questions regarding the appropriateness of this decision.

This patient, however, developed haemodynamic instability requiring inotropic support, and therefore, the use of a vasopressor-augmenting dose of steroids was deemed beneficial for survival. However, since the maximum respiratory support required in this patient was only NIV despite three pulmonary insults and his oxygen requirement gradually decreased, we believe high-dose steroids may have played a favourable role in preventing the progression of the cytokine storm and development of acute respiratory distress syndrome (ARDS). On the other hand, it is entirely possible that the use of steroids may have had unfavourable effects on the two underlying pulmonary infections, which will only be evident during the follow-up process.

The third challenge in this case was deciding the ceiling of care in a resource-limited setting in the midst of a global pandemic. A multidisciplinary team comprising respiratory physicians, intensivists and nephrologists was involved in the care of this patient, and a full ceiling of care with intubation and ventilation was settled on, given his age and premorbid status of independent functioning. The argument against escalation of care that came up during the decision-making process was the presence of multiple pathologies affecting his lung parenchyma and pleura, which would lead to a poor chance of recovery if ARDS was to develop and the adverse long-term effects on his respiratory function leading to poor quality of life.

Patient's perspective

Ever since my renal transplant, I have been cautious about contracting any kind of infection, and to have been affected by three rare and life-threatening infections all at once was truly a terrifying experience. I had many sleepless nights while I was hospitalised, not knowing what the outcome might be. I have an immense amount of respect and gratitude for the healthcare staff who took care of me, in the middle of this pandemic. I am cautious now even more than I ever was.

Learning points

- This is the first reported case of coinfection with disseminated tuberculosis, invasive aspergillosis and COVID-19 in an immunocompromised patient.
- Decisions regarding the use of steroids in COVID-19 pneumonia in organ transplant recipients with underlying disseminated infections need to be individualised.
- Multidisciplinary team input is needed for deciding the ceiling of care in patients with multiple medical comorbidities with several acute pulmonary insults.

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