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Case Report

Multidrug-resistant tuberculosis in COVID-19: Double trouble

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ABSTRACT

COVID-19 pandemic has changed the lives of many especially those living with chronic diseases. India has the highest burden of multidrug resistant tuberculosis (MDR TB) in the world. The pandemic and the lockdown created multiple bottlenecks in the provision of healthcare as well as the distribution of medications.

The stigma of tuberculosis leads to mental trauma, suffering, delay in diagnosis, and non-compliance to therapy. Lockdown imposed due to COVID-19, aggravated the fears of each patient and had made medical care access difficult. Here we describe a patient with MDR TB and chronic hepatitis B and how the course of the disease and its management was affected by COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) has taken the world by storm and has disrupted many lives especially of those with other comorbidities. India despite being the hub of tuberculosis (TB) was on course to eliminate TB by 2025. This plan has been side-lined due to the lockdown and shift of health care focus towards saving the lives of those afflicted with COVID-19. Around 4,36,000 deaths were reported in our country due to TB as per the global TB report 2020. These numbers are only expected to increase given the prolonged lockdown which has hampered the programmes for the detection and management of TB in India.[1,2] Analysis has estimated that the total number of cases per annum could rise to those seen back in 2015.[3,4] Lockdown has led to a decrease in the number of patients reporting for TB evaluation, and there has been a concurrent decline in the rate of diagnosis. There have been

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reports of patients not able to procure medicines due to acute shortage arising out of disruption in the drug delivery chain.[5] All these factors are likely to cause an increase in the number of TB cases as well as an increase in patients with multidrug-resistant tuberculosis (MDR TB). Two previous reports have mentioned possible association among the disease which might also lead to the development of severe COVID pneumonia in patients with TB.[6,7] Here we report a case of MDR TB who acquired COVID-19 while he was being transferred to a higher centre for management and how it complicated the course of his disease. This is the first report of COVID-19 co-infection with multidrug-resistant pulmonary TB.

Case report

A 34-year-old male patient, who was previously diagnosed with chronic hepatitis B, presented to a peripheral hospital with complaints of cough with yellowish expectoration and dyspnoea of more than one-month duration. It was associated with a history of 10-kg involuntary weight loss in the past 3 months. His chest radiograph showed a cavity involving the right upper and middle zone, and he was labelled as a case of presumptive TB. His sputum evaluation revealed acid-fast bacilli on Ziehl-Neelson staining, and he was started on antituberculous therapy (isoniazid, rifampicin, ethambutol and pyrazinamide). Gene Xpert MTB/Rif assay (CBNAAT; Cartridge based nucleic acid amplification system) performed on sputum elucidated high level of *Mycobacterium tuberculosis* which was resistant to rifampicin. As there were no facilities for evaluation of second-line drug resistance, he was planned for transfer to a higher centre, which however could not be carried out due to the strict lockdown. He was continued on first-line therapy and he managed to reach our centre after 2 weeks. On arrival, he was severely cachexic with a body mass index of 16 kg/m^2 and had fever, tachypnoea and tachycardia. Unfortunately, while being planned for bedaquiline (BDQ), the mandatory throat swab reverse-transcriptase polymerase chain reaction for SARS-CoV-2 turned out to be positive at the time of hospitalisation at our centre. Further evaluation for his chronic hepatitis B infection revealed the presence of Hepatitis B e antibody and elevated HBV DNA viral count of 54,628 IU/ml. The patient had persisting tachypnoea, tachycardia, along with fever and developed type 1 respiratory failure secondary to COVID-19 pneumonia. He was started on oxygen along with steroids (injection dexamethasone 6 mg twice daily) for the management of COVID-19 pneumonia while being continued on first-line ATT. Line probe assay of sputum revealed resistance to rifampicin, isoniazid and fluoroquinolone, and his diagnoses was revised to pre-XDR (extensively drug resistant) TB. His serological evaluation revealed a deranged liver function test likely secondary to COVID-19 and chronic hepatitis B and the introduction of BDQ was deferred. As the patient had persisting symptoms and had difficulty in weaning from oxygen, computed tomography pulmonary angiography (Fig. 1) was performed which showed destruction of the right upper lobe, multiple cavitary lesions in the right lower lobe and left upper lobe and scattered areas of

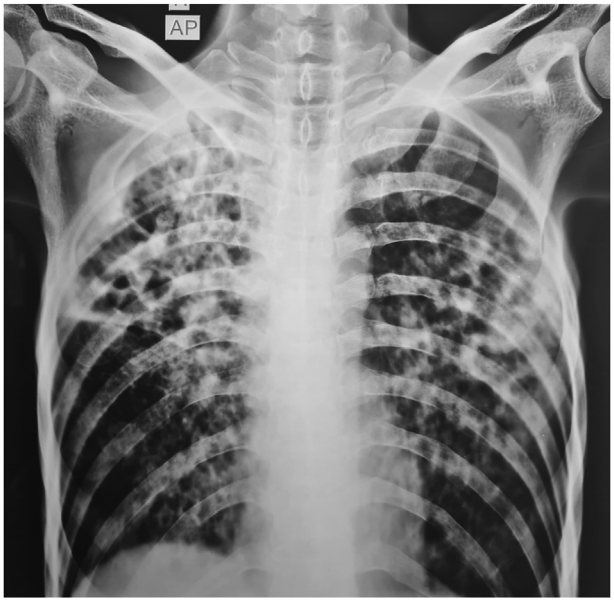

Fig. 2 – Chest radiograph taken after 1 month of starting bedaquiline.

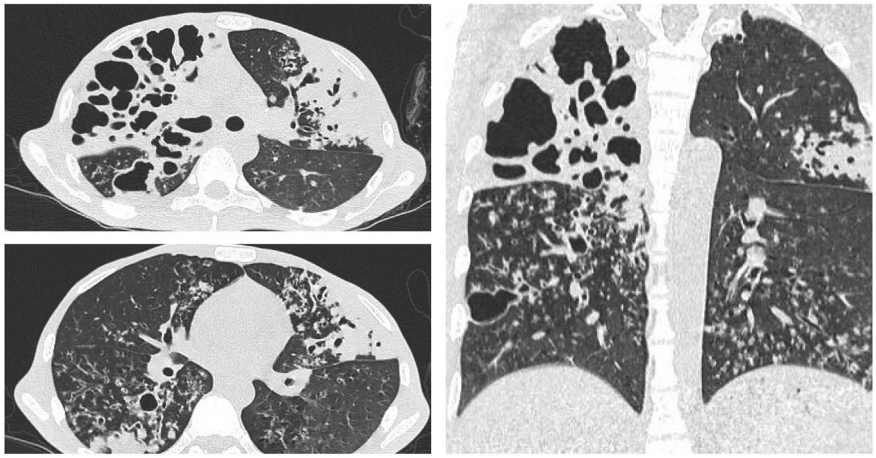

Fig. 1 – CT chest showing multiple extensive cavitary disease involving both the lungs.

centrilobular nodules with tree in bud appearance in all lung fields, and there was no evidence of pulmonary embolism. After five days of steroids, his inflammatory parameters had settled but the oxygen requirement did not decrease. The liver function test had normalised, and BDQ containing regimen was started as per the latest WHO guidelines.[8] The patient showed significant improvement and was weaned off oxygen within the first week of initiation of BDQ. The patient is presently tolerating his medications well and is in the continuation phase of MDR regimen and has shown good clinical and significant radiologic improvement (Fig. 2).

Discussion

COVID-19 has disrupted the lives of everyone in our country but has brought misery to those afflicted with TB. The social stigma associated with TB and COVID-19 and the worry of being ostracised by society has spread fear in the minds of all.[9] They avoid visiting a doctor, with the hope that the symptoms will resolve on their own in due course of time. As the number of COVID-19 cases rapidly increased, many hospitals were converted into 'COVID-19 only' facilities and the routine functioning of many departments came to a standstill. Numerous reports have confirmed that the lockdown enforced has worsened the financial stability of the country and has led to poor accessibility to doctors and diagnostics in addition to the various medications.[10] The stringent lockdown kept patients away from the hospitals as was seen in our patient, who presented late, after nearly three months from the onset of symptoms. He was aggressively worked up and an early diagnosis of rifampicin-resistant TB was made. As per the latest guidelines, any individual with rifampicin resistance detected on CBNAAT assay should be evaluated for resistance to isoniazid, fluoroquinolones and second-line injectables.[8] These tests are not available in most centres and patients must be transferred to tertiary care hospitals. In our patient, treatment initiation was further delayed due to the lockdown which prevented his transfer to a higher centre. When he was finally transferred, he acquired COVID-19 pneumonia which complicated his disease. Treatment of MDR TB as per the latest WHO guidelines consist of an all-oral regimen comprising 4–5 drugs which have been made possible with the introduction of the new drug BDQ.[8] The patient was at high risk for liver injury because he had chronic hepatitis B. The study by Wong et al[11] has shown that hepatic dysfunction is higher in TB patients with chronic hepatitis B.[11] Despite an overall increased risk of liver injury in chronic hepatitis, BDQ and delamanid have a good safety profile.[12]

BDQ was started, almost a month after presentation to the hospital and nearly 3 months after the onset of the illness which resulted in progression of the disease. This delay was due to the late presentation to the hospital and also because of the hepatic dysfunction.

The dilemma of when to initiate antituberculous therapy can be difficult in COVID 19 and MDR TB co-infection, as the treatment consists of drugs that have poor tolerability and multiple drug interactions exist with BDQ. COVID-19 can also cause gastrointestinal side effects in addition to the direct effects of the disease on the liver. This causes a delay in initiating appropriate therapy in our patient, but the introduction should be attempted as early as possible failing which clinical deterioration is inevitable.

In a meta-analysis of six studies consisting of 2765 patients by Gao et al,[13] there was a 2.10-fold increased chance of severe COVID-19 in TB, but this was not statistically significant. They concluded that patients with TB are not at increased risk of acquiring COVID-19, but when they present with co-infection, it can lead to serious complication. This case shows that, while managing COVID-19 and MDR TB, management of the former takes precedence over the latter. COVID-19 has caused a shift in healthcare focus from diseases such as TB over the past few months with all resources being utilised for the same. Patients with TB, who are already discriminated against by many parts of our ill-informed society, are unlikely to visit hospitals due to COVID-19 as well as the lack of social support, thereby delaying their treatment. The mode of spread of both COVID-19 and TB is predominantly through aerosols. The use of masks, social distancing and cough etiquette would have reduced the spread of TB and COVID-19. But with more patients with TB staying indoors for longer periods, especially in overcrowded and poorly ventilated spaces, the risk of aerosol transmission can profoundly increase.[9] We need to be prepared to tackle the increased number of TB cases as well as the complications arising out of delayed diagnosis, treatment and drug defaulting. Lockdown might have been able to control the spread SARS-CoV-2, but can we justify the detrimental effects it has had on patients with TB and other diseases, the debate will continue!

Disclosure of competing interest

The authors have none to declare.

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