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LATE TUBERCULOSIS REACTIVATION AFTER SEVERE COVID-19

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ABSTRACT

Background: Although there is no specific therapy for COVID-19, it is recommended that patients with severe SARS-CoV-2 infection are treated with corticosteroids and anti-IL-6 receptor monoclonal antibodies. Both COVID-19 itself and the treatment modalities mentioned above have suppressive effects on the immune system which may lead to an increased susceptibility to other infections. In patients with latent tuberculosis (TB) reactivation of TB infection after recovery from severe COVID-19 has been described. Most of these cases have occurred in parts of the world where tuberculosis is endemic.

Case description: The patient is a female in her 70s who was born and raised in Southeast Asia and has lived in the Netherlands for more than 30 years. She was treated for a severe COVID-19 requiring mechanical ventilation for several weeks and pharmaceutical treatment with corticosteroids and anti-IL-6 receptor monoclonal antibodies (Sarilumab). She recovered well. Two years later she was readmitted with symptoms of a serious pulmonary infection and meningitis. Her condition deteriorated in a short time. An active TB infection was diagnosed. Despite adequate antibiotic treatment and supportive therapy her condition worsened and four days after admission to the ICU she deceased.

Discussion: Reactivation of latent TB after recovery from a severe COVID-19 has been described several times and may occur several months after the SARS-CoV-2 infection. In this case the reactivation presented two years after COVID-19. This case illustrates that long-term follow-up of patients with latent TB that recover from a severe COVID-19 may be indicated.

KEYWORDS

Tuberculosis reactivation, COVID-19, treatment modality given to COVID-19

LEARNING POINTS

- Reactivation of latent tuberculosis infection in patients treated for a severe COVID-19 may occur even two years after recovery from SARS-CoV-2 infection.
- Most cases of reactivation of tuberculosis after COVID-19 are described in regions where tuberculosis is endemic. However, it may also occur in countries with a relatively low prevalence of tuberculosis infection. The exact incidence of tuberculosis reactivation after COVID-19 is unknown and probably underestimated.
- A long-term follow-up of patients after severe COVID-19 treated with corticosteroids and/or anti-IL-6 receptor monoclonal antibodies with a history of tuberculosis or patients migrated from countries where tuberculosis is endemic seems to be important.

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INTRODUCTION

Although tuberculosis (TB) rates in Europe and the United Kingdom in the recent decades have been emerging, the incidence in this part of the world remains still low. In 2021 the number of patients diagnosed with TB in the Netherlands was 622[1]. During the COVID-19 pandemic in 2020 we saw a substantial decrease in the number of TB cases, probably due to a decrease in migration from refugees to the Netherlands and the precautions taken to avoid the spreading of COVID-19. On the other hand, COVID-19 may induce a dysregulation of the immune response that may lead to reactivation of TB. Moreover, pharmacological interventions for critically ill COVID-19 patients (including among others corticosteroids and anti-IL-6 receptor monoclonal antibodies tocilizumab and sarilumab) may favour TB reactivation[2].

Several cases of TB in individuals who suffered from a severe COVID-19 are described[3]. The vast majority of these cases occurred in countries where TB is endemic. Symptoms of TB usually occur weeks to months after recovery of SARS-CoV-2 infection. We report an endogenous reactivation of TB in a woman two years after treatment and recovery of a severe COVID 19 in the Netherlands.

CASE DESCRIPTION

A woman in her 70s, born and raised in Southeast Asia, living in the Netherlands for more than 30 years, presented at the emergency department with fever, coughing and complaints of abdominal pain, headache, and progressive confusion for five days. She had a medical history of hypertension, atrial fibrillation, and a severe SARS-CoV-2 infection two years before requiring ICU treatment including (among others) mechanical ventilation and treatment with corticosteroids, and anti-IL-6 inhibition by sarilumab. She recovered well from COVID-19. A few days before admission she was diagnosed with polymyalgia rheumatica (based on an elevated erythrocyte sedimentation rate (ESR) and symmetrical pain in both shoulders and hips) and prednisolone 20 mg once daily was started. She lived independently with her husband and received limited help from her family in daily care. Physical examination revealed a temperature of 38.9 °C without any other abnormalities. A chest X-ray revealed bilateral consolidations. Blood tests were within normal limits; C-reactive protein (CRP) and leucocytes were not elevated. Blood cultures were taken. Treatment with a broad-spectrum antibiotic (ceftriaxone) was started. However, in the following days her condition worsened, and a blood culture was positive for *Staphylococcus aureus*. A whole-body F18-fluorodeoxyglucose PET/CT, obtained four days after admission, showed serious accumulation in both lungs without any accumulation in the brain. Two days later her condition deteriorated: a decrease in level of consciousness and stiffness of the neck developed. Amoxicillin and acyclovir were added. Further evaluation included serum cryptococcal antigen, HIV antigen and aspergillus antigen, and was negative. A QuantiFERON-TB assay was performed; a brain scan showed a communicating hydrocephalus. Because of a strong suspicion of pulmonary and meningeal located TB infection, a bronchoalveolar lavage and a lumbar puncture were performed. During the next day the patient's neurologic condition further deteriorated. The fluorochrome procedure (auramine-rhodamine dye) of both the liquor fluid and the bronchoalveolar fluid appeared to be positive. TB infection was shown by PCR specific for *Mycobacterium tuberculosis* being positive for bronchoalveolar lavage (Ct value 29.5) and for cerebral spinal fluid (Ct value 27.5). Treatment with isoniazid, rifampicin, pyrazinamide, ethambutol, moxifloxacin, and dexamethasone was started. Because of her worsening neurological condition, a CT scan was repeated and showed an increased dilatation of the ventricles and periventricular hypodensity, compatible with a communicating hydrocephalus. An external ventricular drain was placed. However, the patient's condition did not improve and two days later, she died. Her relatives and other people close to her were screened for TB infection; none of them appeared to be positive.

DISCUSSION

In the past two years several cases of endogenous TB reactivation and new TB infection have been reported in individuals who recovered from severe COVID-19[2]. Although most of the cases described occurred in regions of the world with a high prevalence of latent TB infection, the presented case illustrates that reactivation of latent TB due to severe COVID-19 and treatment of the latter may also be seen in countries with a very low incidence of TB. The exact incidence of TB reactivation after COVID-19 recovery is unclear. However, it is likely that the incidence of reactivation of TB after COVID-19 in high TB burden regions is underestimated. SARS-CoV-2 infection as a possible risk factor for reactivation of latent TB is more difficult to recognise under the given circumstances (high prevalence of both COVID-19 and TB infection).

The patient migrated more than 30 years ago from a country with a high incidence of TB to the Netherlands, which has a very low incidence of TB. None of the individuals close and occasional to her appeared to test positive for TB, suggesting that in her case TB was reactivated many years after she was infected it. Rates of reactivation of latent TB decline over time[4,5]; after five years approximately 200 cases per 100,000 person-years occur, probably declining further in time[4].

Severe COVID-19 induces a supraphysiologic immune response known as a cytokine storm, associated with substantially increased systemic levels of inflammatory cytokines. Corticosteroids and anti-IL-6 receptor monoclonal antibodies are therefore recommended as treatment for patients with a severe SARS-CoV-2 infection. Besides their anti-inflammatory effects, both treatment modalities have immunosuppressive properties, potentially inducing an increased susceptibility for reactivation of latent TB[2]. Whether there is a causal relationship between,

on the one hand, COVID-19 itself and/or its treatment (including corticosteroids and anti-IL-6 receptor monoclonal antibodies), and on the other hand reactivation of TB infection in the case described, remains unsure. However, in an earlier evaluation of TB in patients that recovered from COVID-19, the time window between SARS-CoV-2 infection and the development of TB extended up to 7 months[2]. Our observation emphasises the importance of long-term follow-up after a severe COVID-19 in patients treated with corticosteroids and/or anti-IL-6 receptor monoclonal antibodies with a history of TB, or patients who have migrated from countries where TB is endemic. Other risk factors (not present in the case above) such as comorbidities (diabetes mellitus) may possibly also attribute to the development of TB.

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