Concurrent cavitary pulmonary tuberculosisand COVID-19 pneumonia with in vitro immune cell anergy:a case report.

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Case Report

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Abstract

Tuberculosis (TB) is top infectious disease killer caused by a single organismresponsible for 1.5 million deaths in 2018. Both COVID 19 and the pandemic responseare risking to affect control measures for TB and continuity of essential services forpeople affected by this infection in western countries and even more in developingcountries. Knowledges about concomitant pulmonary TB and COVID-19 are extremelylimited. The double burden of these two diseases can have devastating effects. Herewe describe from both the clinical and the immunological point of view a case of apatient with in vitro immune cell anergy affected by bilateral cavitary pulmonary TB andsubsequent COVID-19-associated pneumonia with a worst outcome. COVID-19 can bea precipitating factor in TB respiratory failure and, during ongoing SARS COV 2 pandemic, clinicians must be aware of this possible coinfection in differential diagnosisof patients with active TB and new or worsening chest imaging

Background

Experience with concomitant TB and COVID-19 is extremely limited. Both *M. tuberculosis* and SARS-CoV-2 affect primarily the lungs and interfere with host immunity [1]. Here we describe a case of a patient with in vitro immune cell anergy affected by bilateral cavitary pulmonary TB and subsequent COVID-19-associated pneumonia with a worst outcome. The patient was also included in a cohort of 69 patients [2]; here we present a deeper focus on clinical and moreover immunological features.

Case Presentation

During the COVID-19 outbreak in Italy a 45-year-old man of Moldovan origin presented himself to an Emergency Department of another hospital referring TB-like symptoms as cough, fatigue and weight loss since 3 months before.

He has been always in good health, to note only an ethilism addiction in the clinical history.

During hospitalization in the Emergency Department, a thorax CT scan showed multiple cavitary lesions on the right lung and an idropneumothorax with complete atelectasis of left lung (Fig. 1, a).

Acid-fast bacilli were present in the sputum and standard therapy with rifampicin, isoniazid, ethambutol and pyrazinamide was started.

Qualitative real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) for SARS-CoV-2 (Altona Diagnostics GmbH, Germany) on two nasopharyngeal swabs were negative.

Arterial blood gas analysis showed mild impairment with arterial oxygen tension (PaO_2) 102 mmHg; fraction of inspired oxygen (FiO_2) was 31% with a PaO2/FiO_2 ratio of 329 mmHg.

Therefore, a chest tube drainage was positioned and after seven days he was referred to L. Spallanzani Institute in Rome with a diagnosis of pulmonary TB and idropneumothorax.

Physical examination at admission in our Institute showed cachexia (Body Mass Index: 19). Respiratory rate was normal (RR 12/min) but he presented respiratory failure. Arterial blood gas analysis revealed moderate impairment with PaO_2 67 mmHg (FiO_2 was 35%) and $PaO2/FiO_2$ ratio of 191 mmHg.

Tachycardia was present at 116 beats per minute with a blood pressure at 120/60 mmHg; body temperature was 36 °C. No vesicular murmur was present at left lung auscultation. A significant subcutaneous emphysema involved the left chest.

A high-resolution computed tomography (HRCT) of the chest was repeated and showed an incomplete re-expansion of the lung despite a well-positioned drainage and a new appearance of multiple patchy ground grass opacities with pattern “crazy paving” in the right lung (Fig. 1, b).

Blood routine tests revealed liver function impairment with aspartate aminotransferase/alanine aminotransferase 87/130 U/L, albumin 2 mg/dl, increased C-reactive protein (7.55 mg/dl) and lymphophenia (735 lymphocytes/mmc with a percentage of 11.1%). HIV test was negative.

Numerous acid-fast bacilli were present in the sputum; *M. tuberculosis* (Real-time PCR Anyplex, Seegene Inc. Republic of Korea) indicated sensitivity to rifampin, isoniazid, fluorochinolones and aminoglycosides. Antitubercular regimen was modified for liver function impairment according to the institutional protocol, including rifampicin, ethambutol, amikacin and moxifloxacin.

At admission, he underwent again naso-pharingeal swab with detection of SARS-CoV-2 (Altona Diagnostics GmbH, Germany). Hidroxicloroquine and corticosteroids were prescribed according to local protocol.

QuantiFERON TB Plus test (QFT-Plus; QuantiFERON®-TB Gold Plus, Qiagen, Germany) was undertermined (TB1: 0.08 IU/ml; TB2 0.26 IU/ml; Mitogen: 0.02 IU/ml).

Despite treatment, respiratory failure worsened: at day 4 from the admission arterial blood gas analysis performed with FiO_2 50% reported a $PaO2/FiO_2$ ratio of 101. Due to this severe impairment of respiratory function oxygen with a non-rebreather mask at 15 Lt/min was delivered.

A chest HRCT at day 6 from the admission showed an increase in the number and extent of ground grass opacities with pattern “crazy paving” of the right lung (Fig. 1, c).

After a rapid clinical deterioration patient died at day 7 from referral to our Institute.

Discussion

Here we describe a case of a patient with in vitro immune cell anergy affected by bilateral cavitary pulmonary TB and subsequent COVID-19-associated pneumonia with a worst outcome.

The clinical spectrum of SARS-CoV-2 infection encompasses asymptomatic infection, mild upper respiratory tract illness and severe viral pneumonia with respiratory failure and even death.

Initial signs and symptoms of this highly infectious disease are similar to other respiratory infections such as TB [3], but clinical course and treatment differ among them with a higher mortality rate of COVID-19.

The pathogenicity of COVID-19 still remains unknown and experience with concomitant TB is extremely limited.

It is well documented that certain viral infections, such as measles, have been known to exacerbate pulmonary TB, presumably as a result of depressed cellular immunity [4].

Influenza coinfection in TB cases is associated with a pro-inflammatory response, an increased mycobacterial load [5], and mortality rate in both animal models and patients [6-7].

Descriptive studies have reported a high prevalence of TB in cases of severe pandemic influenza, but available data about pandemic influenza and TB co-infection are low [7].

A recent study from China reported that persons with active or latent TB have increased susceptibility for SARS-CoV-2 infection associated with rapid progression and severe involvement while a case of co-infection always from China reported with a good SARS-CoV-2 outcome [8]. Unfortunately, in our case the patient died of COVID-19 after 13 days from TB diagnosis.

TB typically requires cellular immunity, in particular CD4-mediated immunity but not only as CD8 T cells play an important role [9-10]. TB disease may be transiently immunosuppressive. The combined effect of TB and SARS-COV-2 infection likely caused a pronounced lymphocytopenia [11] and consequently a CD4+ cell decrease as described in COVID-19 [12] and TB and SARS coinfection [13].

Lymphopenia is a reliable indicator of the severity and hospitalization of COVID-19 patients [11]. Various mechanisms of lymphopenia have been speculated, including lymphocyte death due to direct infection trough receptor ACE 2, direct damage of SARS COV 2 to lymphatic organs and lymphocytes deficiency induced by pro-inflammatory cytokines such as tumour necrosis factor (TNF)α and interleukin (IL)-6 [11, 14].

In our case, regarding TB-specific tests, the laboratory findings showed an indeterminate result of IGRA test. This result is important in light of the fact that in 2016 Auld et al. showed in large study that a negative or indeterminate score to IGRA in TB patients is associated with an increased risk of disseminated disease and death after initiating antitubercular treatment [15]. Our patient was immune-suppressed, as shown by the low lymphocyte number and by the lack of response to an immune-based assay likely by both disease, TB and COVID-19, and this may have contributed to the deterioration of the patient and death.

IFN-γ levels in QuantiFERON-tests correlate with lymphocyte count, and CD4+ cells play an important role against *M. tuberculosis* [16]. The response is mediated by CD4 or CD8 effector memory T cells. In COVID-19, the SARS-CoV-2-specific CD4+ T-cells in blood were typically central memory, CD8+ T-cells typically had a more effector phenotype [17]. The high *M. tuberculosis* and SARS-CoV-2 loads may have paralized the immune system, as previously seen in patients with severe TB which may be the result of a compartmentalization of T-specific cells at the pathogen site [17].

In the pathogenesis of other infectious diseases, the elimination of effector T cells may occur when T cells encounter high concentrations of antigens [18-19]. Moreover, in severe forms of TB, the high load of *M. tuberculosis* may generate inefficient dendritic cells functions by infecting newly recruited monocytes with the functional consequence of reducing the pool of specific IFNg–producing T cells [20].

From a clinical management prospective, in presence of a clinical suspect of COVID-19 in a patient with concurrent pulmonary TB, it is important repeating the naso-pharingeal swab to provide an early diagnosis, promptly isolation precautions and specific treatment.

Despite a rapid diagnosis of co-infection, our patient had a bad prognosis.

We confirm that in a patient with active TB, a negative or indeterminate IGRA score is a prognostic marker of an immunodepressive status and a worst outcome in patients coinfected with COVID-19.

Spreading of pandemic SARS-CoV-2 will involve patients affected by both latent and active TB.

Our study describes the clinical report of concurrent pulmonary TB and COVID-19-associated pneumonia.

This coinfection will give us the opportunity to understand biological mechanisms of *M. tuberculosis* and SARS-CoV-2 coinfection.

Efforts in understanding pathogenesis of this coinfection will help managing both of them.

COVID-19 must be considered a death risk factor in a frail population as TB patients with a considerable impact on the healthcare system.

In our case COVID-19 was the precipitating factor of TB respiratory failure. The pathogenic hypothesis of this deterioration is unclear, a possible cause is the immunodepression of the patient with advanced TB.

TB and COVID share many similarities both in symptoms, as coughing, fever and dyspnea and in their radiological aspects, which can confound each others.

During ongoing pandemic clinicians must be aware of the possibility of COVID-19-associated pneumonia in differential diagnosis of patients with active TB and new or worsening chest imaging.

Declarations

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Consent for publication: patient gave informed consent for publication.

Availability of data and materials: not applicable.

Competing interests: patient was also included in a cohort of 69 patients described by Motta et al. [2]. The authors declare that they have no other competing interests.

Code availability: not applicable.

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Figures

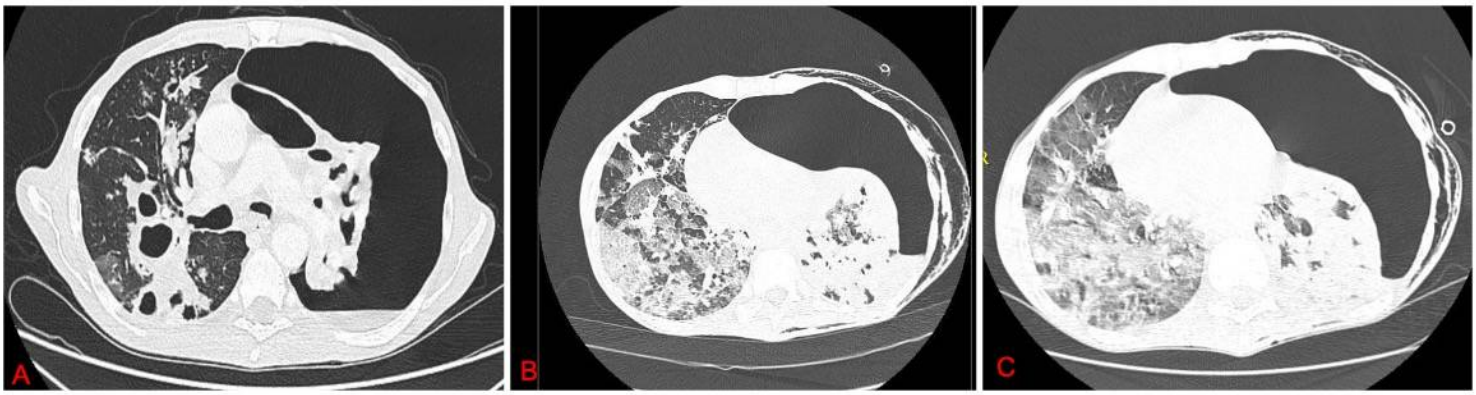

Figure 1

Patient’s chest CT at admission in the emergency department (a), at the admission to “L. Spallanzani”Institute (b)and seven days after admissionto “L. Spallanzani”Institute(c).