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Tuberculosis and COVID 19 Coinfection

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Abstract **Case Report**

The ongoing pandemic of novel corona-virus disease 2019 (COVID-19) has received worldwide attention by becoming a major global health threat. The tuberculosis and SARS-COV2 co-infection has not been frequently reported. The purpose of this work is to establish a focus on Tuberculosis and SARS-COV2 co-infection, to study the impact of HIV infection on the occurrence of COVID-19, and evaluate the place of BCG vaccination in reducing the morbidity and mortality linked to Covid-19. We reported three cases of co-infection tuberculosis and covid 19, in one case an HIV infection was noticed. The tuberculosis was pleural in the first case, multifocal in the second case and a miliary in the third case. The treatment consisted of antibacillaries, azithromycin and hydroxychloroquine with a favorable evolution. through published studies, we noticed that persons with active or latent TB have increased susceptibility for SARS-CoV–2 infection associated with rapid progression and severe involvement. Patients with severe immune-deficiencies, may be at risk for a severe course of COVID-19 disease. Regarding efficiency of BCG vaccination, limited data are available and does not confirm the existence of a protective effect of BCG against COVID-19.

Keywords: Tuberculosis, SARS-COV2, HIV, treatment, BCG vaccination.

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INTRODUCTION

The 2019 novel coronavirus (2019-nCoV) or recently renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2), has been rapidly spreading with emergence from Wuhan City of Hubei Province of China in December 2019 to the rest of the world [1, 2].

Disease associated with SARS-CoV–2 also termed as Coronavirus disease 2019 (COVID–19), has now become a major threat to global health; who has declared this disease as a pandemic on 11th March 2020. Since then, 243 896 973 confirmed cases and 4 956 267 deaths have been reported worldwide (23 October 2021) [2].

Tuberculosis (TB) is already existing as unprecedented pandemic worldwide with 10 million people affected and 1.5 million deaths in 2018 [3], but the coinfection of SARS-CoV–2 and TB has been rarely reported. Here, we present three cases of coinfection of SARS-CoV–2 and TB.

In the light of these observations, we will propose to:

- Establish a focus on co-infection Tuberculosis and SARS-COV2.
- Study the impact of HIV infection on the occurrence of COVID-19.
- Study the place of BCG vaccination in reducing the morbidity and mortality linked to Covid-19.

PATIENTS AND METHODS

First Observation

A 19-year-old patient, BCG vaccinated, never treated for tuberculosis and without recent tuberculosis contagion or toxic habits or any comorbidities. He presented a dry cough, a dyspnea stage 2 of sadoul evolving for a month, associated with myalgia, fever and deterioration of general condition.

Pleuro-pulmonary examination founded a right fluid effusion syndrome confirmed by chest x-ray, The pleural puncture objectified a yellow citrine fluid with higher protein levels and a larger percentage of

lymphocytes, and without bacillus of 1174och on direct examination.

The pleural biopsy demonstrated the presence of an epithelioid granuloma with Langhans giant cells and central caseation necrosis. A respiratory PCR was carried out objectifying an associated SARS-COV2 respiratory infection.

The biological investigation showed a lymphopenia (840/µL), an inflammatory anemia (10g/dl), a hyperferritinemia (704), a correct liver function, and elevated LDH (600) and D-Dimers (9830).

The CT angiography did not objectify a pulmonary embolism, on the other hand it showed bilateral, peripheral, posterior and basal ground-glass opacities. Right pleural and scissural effusion and mediastinal lymphadenopathies.

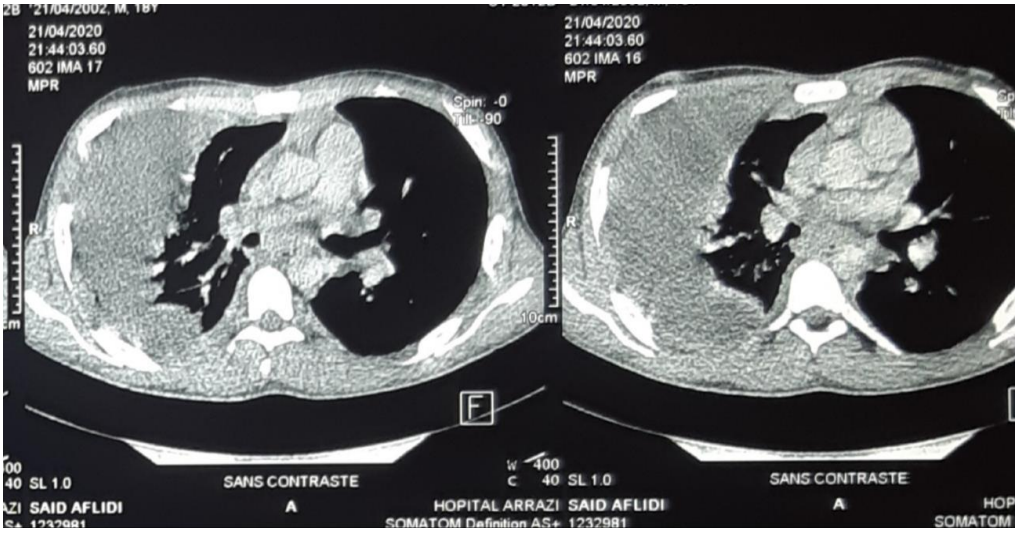

Figure 1: Right pleural effusion and mediastinal lymphadenopathies

The diagnosis of pleural tuberculosis associated with COVID19 infection was retained after collecting clinical, biological, radiological and histological arguments. An anti bacillary treatment based on 2RHZE / 4RH combined with a treatment with hydroxychloroquine and azithromycin for 10 days has been established, with good clinical and biological progress.

Second Observation

A 38-year-old woman, BCG vaccinated, never treated for tuberculosis and without recent tuberculosis contagion or toxic habits or any comorbidities, who have a husband and 3 children affected by Coronavirus disease 2019 (covid 19).

The patient was admitted in the medical unit of our hospital with a history of fever, night sweats persistent dry cough and right basi-thoracic pain 6 month ago. Otherwise, she has anorexia, asthenia and weight loss of 20 kg in 2 months.

Pleuro-pulmonary examination founded a right fluid effusion syndrome confirmed by chest x-ray. Also, we have noticed the presence of a right para-hilar opacity evoking a lymphadenopathy.

The CT scan showed bilateral, peripheral and basal nodular ground-glass opacities, multiple pulmonary nodules and micronodules associated with mediastinal lymphadenopathies, and a right pleural and pericardial effusion.

The pleural puncture objectified a yellow citrine fluid with higher protein levels and a larger percentage of lymphocytes, and without bacillus of koch on direct examination. Two pleural biopsies demonstrated a non-specific inflammation. A second CT scan showed a regression of pleural and pericardial effusion.

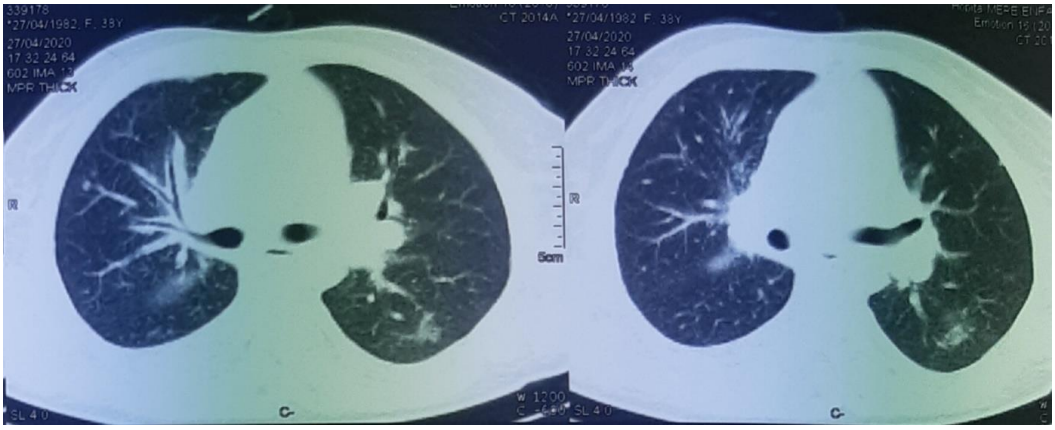

Figure 2: Nodular ground-glass opacity

A respiratory PCR was carried out objectifying an associated SARS-COV2 respiratory infection. The biological investigation showed a neutropenia (1300 / µL), a lymphopenia (600/ µL), an inflammatory anemia (10g/dl), a correct liver function, and LDH. The tumor markers CEA, AFP, CA125 and CA15-3 returned negative.

A multifocal tuberculosis (pleura-pulmonary, pericardial, lymph node) associated with coronavirus disease was retained.

An anti bacillary treatment based on 2RHZE/7RH combined with a treatment with hydroxychloroquine and azithromycin for 10 days has been established with good clinical and biological progress.

Third Observation

39-year-old woman, with no particular pathological history, BCG vaccinated, admitted in the medical unit of our hospital with a history of fever, night sweats persistent productive cough and dyspnea stage III of sadoul 20 days ago. Otherwise, she has anorexia, asthenia and weight loss.

The biological investigation showed a lymphopenia (160/ µL), an inflammatory anemia, an hyponatremia, and an elevated LDH.

Thoracic CT scan was carried out objectifying the aspect of miliary tuberculosis, associated with peripheral and basal ground-glass opacities evoking an associated corona-virus disease 2019.

A respiratory PCR was carried out objectifying an associated SARS-COV2 respiratory infection. Otherwise, the direct examination of sputum for mycobacterium tuberculosis was positive. An HIV serology was performed objectifying an associated retroviral infection.

DISCUSSION

1/ SARS-COV2 and pulmonary tuberculosis co-infection: explications

There are studies that have reported coinfection of SARS-CoV–2 with other respiratory pathogens particularly influenza virus. While the tuberculosis and SARS-COV2 co-infection is rarely reported.

Few studies have reported coinfection of TB with SARS-CoV–1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) during outbreaks in 2003 and 2012 respectively [4-7]. Most of cases were having pulmonary TB initially followed by viral superinfection [8, 9, 11] while few contracted TB after recovery from viral infection.

A study from China recently reported that persons with active or latent TB have increased susceptibility for SARS-CoV–2 infection associated with rapid progression and severe involvement [10].

In studies that have evaluated the tuberculosis and SARS-COV1 coinfection, it has been postulated that there is augmentation of dual infection as both cause a transient suppression of cellular immunity predisposing to new infection or exaggerated reactivation of latent infection. Induction of Type 1 interferons during infections with viruses like influenza and SARS-CoV–1 inhibit immune responses mediated by interferon-gamma leading to flare up of TB infection [12]. However, a recent study observed that SARS-CoV–2 did not significantly induce any types of interferons and only upregulated few pro-inflammatory cytokines or chemokines unlike SARS-CoV–1 [13]. Therefore, this coinfection is it a mere coincidence or it could be a temporal relationship?

2/Tuberculosis and Covid 19: similar symptoms

Differentiation between TB and SARS-CoV–2 is quite difficult as both can manifest with similar respiratory symptoms like fever, cough, breathlessness and weakness but there is gradual or chronic progression of symptoms in TB as compared to acute or

rapid progression in case of COVID 19 [14]. On the other hand, both share common risk factors such as old age, diabetes, malnutrition, HIV and other chronic diseases. This is a major concern, as the diagnosis of tuberculosis may be missed or delayed due to the ongoing COVID-19 pandemic, which could lead to significant transmission of the infection in the community. Therefore, clinicians should be careful when assessing patients admitted for covid 19 [14].

3/Impact of HIV infection on Covid 19

The immune status that makes people living with HIV vulnerable to tuberculosis could also make them susceptible to coronavirus infection.

Antiretroviral therapy (ART) in people living with HIV (PLWH) increases their life expectancy, but many physical complications related to long-term use of ART and aging can occur [15, 16].

Older PLWH, in particular, have a higher risk of comorbidities [17-20]. Putative mechanisms for these comorbidities include aging itself and chronic inflammation caused by HIV and/or ART [21].

Epidemiologic evidence suggests that both older age and a number of comorbidities, including hypertension, diabetes, and chronic obstructive lung disease, are risk factors for severe COVID-19 disease [22]. While limited data are available on COVID-19 and HIV-coinfection [23–25], and on the potential protective effects of HIV antivirals [1, 25], the interaction between these comorbidities nonetheless lends itself to an understanding through a syndemic framework [26]. Expression of the angiotensin-converting enzyme 2 (ACE2), identified as a crucial factor that facilitates SARS-CoV-2 virus to bind and enter host cells, is substantially increased in patients with diabetes and hypertension, who are often treated with ACE inhibitors and angiotensin II type-I receptor blockers [27]. Further, there is a concern that individuals with severe immunodeficiencies, such as HIV, may be at risk for a severe course of COVID-19 disease.

Older PLWH may not be the only members of the HIV seropositive population at risk for the negative health sequelae of COVID-19. younger PLWH may also be at heightened risk for mortality due to COVID-19 complications. Such risk is predicated on the fact that PLWH under age 50 are both less likely to be diagnosed (and in effect more likely to be immunocompromised) and also less likely to access and be retained in care, yielding viral suppression of a mere 37% on those age 25–34 [28].

This is in line with our study, which reports a single case of a 38-year-old woman with HIV, which makes her vulnerable to tuberculosis infection and COVID19.

4/BCG vaccination and Covid19:

BCG (Bacillus Calmette- Guerin) is a live attenuated vaccine against tuberculosis (TB) administered intradermally to infants shortly after birth.

Ordinarily, a vaccine provides protection from a particular pathogen, by inducing effector mechanisms directed to that pathogen. However, certain live attenuated vaccines like the Bacillus Calmette–Guerin (BCG), an attenuated strain of Mycobacterium bovis, provide protection not only to a specific pathogen, but also against unrelated pathogens, some of which cause acute respiratory tract infections. The underlying mechanism for the BCG vaccination-induced non-specific protection is thought to be mediated via the induction of innate immune memory, or "trained immunity''[29-35] .

Based on these observations, we hypothesized that countries who continue BCG immunization programs would contain the spread of this new coronavirus better than those that did not have or have ceased their national BCG vaccination programs [36]. To check the validity of this hypothesis, a recent study in turkey compared the number of cases and deaths per million people from 40 countries according to BCG vaccination status.

Results showed that COVID-19 associated deaths relative to the size of the population were statistically significantly lower in countries with a national BCG vaccination programme than those that did not have or have ceased their national BCG vaccination programs. The most affected country with the highest death toll was Italy, which historically never had a national BCG vaccination policy for all [36].

If BCG vaccination has a general non-specific protective effect against spread of SARS-CoV-2 or COVID-19-associated morbidity and mortality, then would BCG re-vaccination of populations offer a viable alternative of partial protection until a specific vaccine is available? If this strategy is worthwhile, then there is the question of which BCG vaccine strain to chose.

BCG vaccine was first introduced in 1921 and the initial seeds were distributed to various countries. During their serial passage, BCG strains accumulated genomic alterations, including deletions, single-nucleotide polymorphisms and duplications of genomic regions, leading to the emergence of several substrains [37]. So, BCG vaccine is divided into early vaccine strain (BCG Japan, BCG Russia and BCG Moreau/Brazil), and late vaccine strain (like Pasteur, Denmark, Connaught strains)

Early strains seem to be more efficient than late strains because their genome is almost similar to the bacillus Calmette Guerin. To confirm this hypothesis, two studies evaluated BCG Japan and BCG

Denmark. One of them, conducted in Africa, showed that BCG Japan induces a stronger proliferation of CD4 +, CD8 +, and a higher secretion of TNFα, IL-2, and interferon-γ, compared to BCG Denmark. These results suggest that BCG Japan is more efficient than BCG Denmark in inducing the production of several types of inflammatory cytokines and therefore more efficient against various pathogens including SARS-COV2 [38].

In our study, our 3 patients are vaccinated against BCG and actually have a non-serious form of SARS-COV2 infection. However, data from both Finland and Australia seemingly contradict the hypothesis that early BCG strains confer resistance to COVID-19 morbidity. These countries ceased their universal BCG vaccination programs some years ago (2006 in Finland and mid-1980s in Australia), yet they show a low mortality of COVID-19, compared with countries with current mandatory BCG vaccination. Thus, BCG vaccination—if it does contribute to lower COVID-19 mortality—is clearly not the only factor. Two relevant traits shared by Finland and Australia are their excellent medical care systems and low population densities [39].

CONCLUSION

The tuberculosis and SARS-COV2 co-infection is rarely reported. Few studies noticed that persons with active or latent TB have increased susceptibility for SARS-CoV–2 infection associated with rapid progression and severe involvement.

Patients with severe immunodeficiencies, such as HIV, old age and other comorbidities, may be at risk for a severe course of COVID-19 disease.

Regarding efficiency of BCG vaccination, all the studies mentioned above are observational and does not confirm the existence of a protective effect of BCG against COVID-19. The only observation to remember is that none of these studies has shown an increased risk of infection associated with the use of BCG.

Conflicts of interest: There are no conflicts of interest.

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