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Case Report

COVID-19 revealing pulmonary tuberculosis with 3 cases in the internal medicine department of the National Teaching Hospital Center (NTHC)-Hubert Koudougou Maga (HKM) of Cotonou: review of the literature

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Abstract

SARS-cov-2 is the pathogen responsible for COVID-19 disease. COVID-19 primarily causes respiratory manifestations ranging from moderate to severe with risk of death. It may be indicative of latent tuberculosis, although people with COVID-19 and tuberculosis have similar symptoms. Pulmonary tuberculosis should be considered a potential risk factor for severity in COVID-19 co-infection. We report three cases of COVID-19 pulmonary tuberculosis co-infection diagnosed in the internal medicine department of the CNHU-HKM of Cotonou. The patients were all initially infected with SARS-cov-2; then declared cured after 2 negative PCR tests (on nasopharyngeal swab). A few days later, they got fever, cough, and respiratory difficulties. The diagnosis of pulmonary tuberculosis was made on the basis of the presence of mycobacterium tuberculosis DNA by the GenXpert technique in the gastric tube fluid. The three patients were put on antituberculosis treatment, Ethambutol Rifampicin Isoniazid Pyrazinamide (ERHZ) protocol. The evolution was favorable with complete disappearance of respiratory signs and fever after two weeks.

Keywords: Pulmonary tuberculosis, COVID-19, CNHU-HKM Cotonou.

INTRODUCTION

Since December 2019, the world has faced the COVID-19 pandemic and its causative agent is SARS-cov-2. The first case was detected in Wuhan, China. On January 30, 2020, the World Health Organization (WHO) declared the emerging pandemic as an emergency of international concern (WHO, 2005). It was officially declared a global pandemic by the WHO on March 11, 2020. COVID-19 mainly causes acute respiratory manifestations, ranging from moderate to severe with risk of death (Chen et al., 2020). Since the beginning of the pandemic, nearly 130 million people have been infected with just under 3 million deaths (Wordlometer, 2021). COVID-19 poses a serious threat especially to poor communities. In the United States, studies have highlighted the extreme vulnerability of the underprivileged black populations of the South to this pandemic (Price-Haywood et al., 2020). Tuberculosis, which has a preferential pulmonary tropism, already affects a quarter of the world's population and represents one of the 10 leading causes of death in the world (1.5 million deaths in 2018) (Mirzayev et al., 2021). Many studies have

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shown in the past that this infection due to a mycobacterium of the tuberculosis group, is aggravated by certain viruses, probably due to a depression of the immune system (Griffin et al., 1995 ; Kempe et al., 1965). The co-infection of tuberculosis endemic in sub-Saharan Africa and South-East Asia with this new virus is still poorly studied, especially in African countries that have been hard hit by tuberculosis and still have to deal with this new public health issue. In the daily management of COVID-19 cases in the department of CNHU-HKM, 3 clinical cases caught our attention. Actually, we got co-infection of tuberculosis and COVID-19 diagnosed in the department in three patients all vaccinated with BCG that we will clarify with a literature review.

Clinical case n° 1

A 41-year-old man with no previous history of infection got SARS-CoV-2 and was treated and declared cured. The man, vaccinated with BCG, has no comorbidity. He was admitted to the department for investigation of a cough with fever two days after his discharge from the COVID-19 Management Center. The onset would date back to 3 weeks before his admission with the appearance of a cough, arthromyalgia in a non-febrile context. In view of this clinical picture and the current pandemic, a COVID-19 test was performed and came back negative; a chloroquine phosphate prophylaxis (1 tablet of 250mg morning and evening) was started but stopped on the 2nd day of treatment due to side effects. Ten days later, a fever was associated with the clinical table. A second COVID-19 test was done and came back positive. He was treated with chloroquine phosphate 250 mg, 1 tablet morning and evening for 10 days, Azythromicime 250mg 1 tablet morning and evening the first day, then 1cp/dr from the second day to the fifth day. The evolution was marked 3 days later by the appearance of acute dyspnea associated with laryngeal edema and hiccups requiring the association of oxygen therapy, dexamethasone, and chlorpromazine before stabilization of the patient's condition. With two negative COVID PCR controls, he was declared cured and discharged from the COVID-19 management center. Two days after his discharge, the reappearance of cough and fever, treated with a well-conducted antibiotic therapy consisting of Amoxicillin + Clavulanic Acid and Spiramycin without improvement of the symptoms, led to a consultation in the internal medicine department for better care. He had no diarrhea or other digestive manifestations. The general condition at entry according to the WHO performance index was 3, there was a systemic inflammatory response syndrome with (fever 39.5°C, blood pressure 140/90mmHg, he was tachycardic with a pulse of 110 beats per minute). On physical examination, there was a right pulmonary condensation syndrome. Faced with this picture of pulmonary condensation syndrome in a febrile context evolving after a SARS-CoV-2 infection, we thought of a complication of the clinical picture by evoking the oozing diagnoses:

- Superinfected embolism
- Pulmonary fibrosis
- Pulmonary TBC on COVID-19

The first two diagnoses were quickly eliminated by angioscan. Biologically, the GeneXpert test on gastric tubing found the DNA of Mycobacterium Tuberculosis, sensitive to Rifampicin; this allowed the diagnosis of a COVID-19 - pulmonary tuberculosis co-infection. We did not find any extra-pulmonary localizations of tuberculosis.
On the radiological level, the lesion is illustrated by the figure n°1.
Chest CT showed multiple foci of diffuse parenchymal condensation of the right upper and right middle lobes, bilateral frosted glass area, multiple right upper lobar cavities, with one left upper lobar (Figure 2-3).
The treatment was the one retained by the National Tuberculosis Program (NTP) and was Ethambutol (E) Rifampicin (R) Isoniazid (H), Pyrazinamide (Z). The evolution was favorable.

Clinical case n° 2

A Young woman, 33 years old, vaccinated with BCG, with no specific comorbidity but recently unemployed, was infected by SARS-CoV-2 three months before admission for exploration of hypoxemic dyspnea. The onset of symptoms was about 6 months ago with a dry cough becoming productive and bringing back whitish sputum, a dyspnea at NYHA stage II. The patient would have taken an unspecified treatment. When the symptoms persisted, she consulted a local hospital 2 months later where a COVID-19 test was positive. The patient was put on a chloroquine phosphate and macrolide protocol for 10 days. The evolution after treatment was marked by persistent cough and worsening of dyspnea at NYHA stage 4 without orthopnea, fever, and significant weight loss without figures; she was put on several antibiotics (among others ceftriaxone, a combination of amoxicillin + clavulanic acid) without clinical improvement. The onset of physical asthenia becoming more and more intense, associated with the symptomatology, motivated her transfer to the department for better management. In addition, the patient reported secondary amenorrhea evolving for 3 months. No digestive symptoms were reported by the patient.
On admission, she had an altered general condition with a WHO performance index of 3. A systemic inflammatory response syndrome (fever 39°C, heart rate 112 beats per minute), a hypoxemic syndrome (spontaneous desaturation 89%), a pulmonary condensation syndrome (exaggerated vocal vibrations, submatiety, and crepitus rales). Faced with this picture of a hypoxemic pneumopathy evolving in a febrile context; in a patient

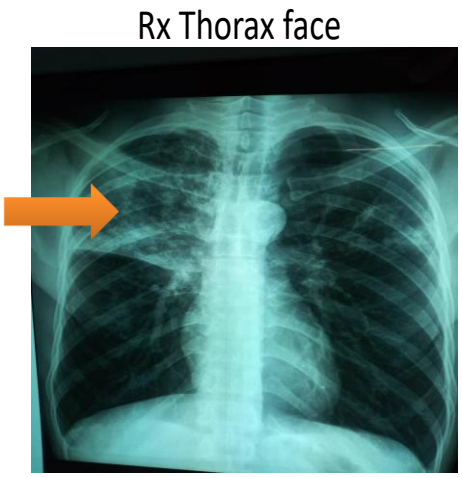


Figure n°1 :

Chest radiography shows sheet-like opacities in the right upper lobe (Figure 1)

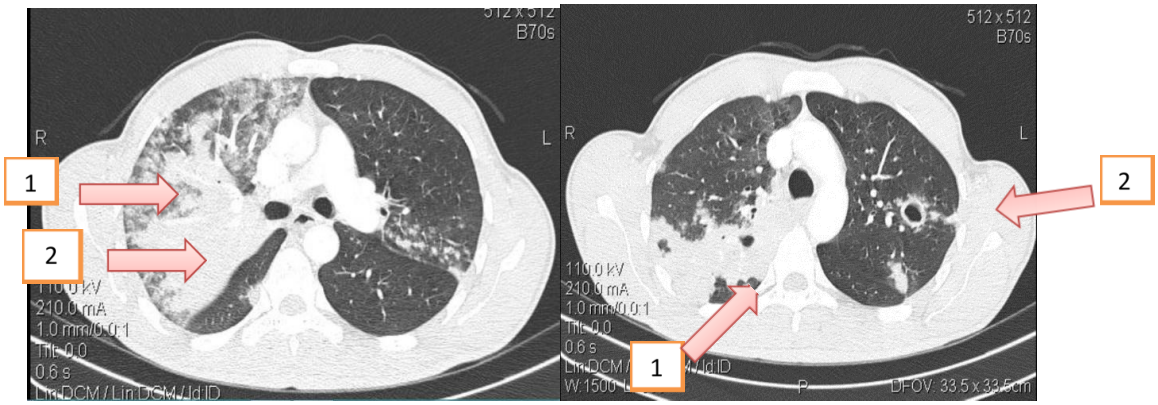


Figure n°2 : Thoracic angioscan

1- Pulmonary condensation
2- Frosted glass image

Figure n°3 : Thoracic angioscan

1- Pulmonary condensation
2- Cavity image

followed for SARS-cov-2 infection. We evoked the following hypotheses:

- a pulmonary superinfection
- superinfected embolism
- pulmonary tuberculosis

Chest X-ray showed a bilateral alveolar-interstitial syndrome

(Figure 4)

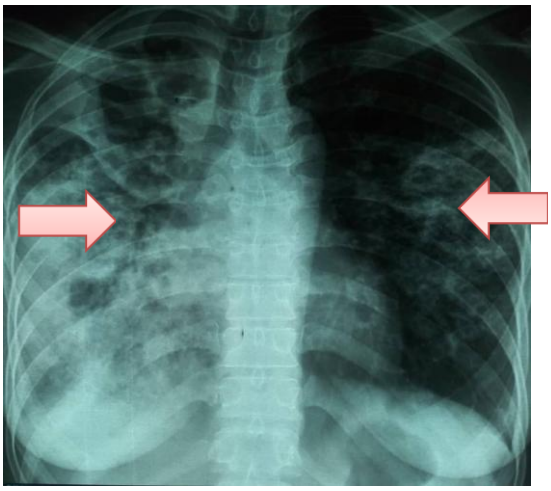
The test for Mycobacterium Tuberculosis DNA in the gastric tubing fluid by the GenXpert technique was positive. No other location of tuberculosis was found.

Given the picture of hypoxemic pneumonia, pulmonary condensation syndrome, positive DNA of Mycobacterium Tuberculosis, SARS-cov-2 infection, the diagnosis of a Tuberculosis-COVID-19 Co-infection was retained. The patient was put on anti-tuberculosis treatment (ERHZ), oxygen therapy at 8 liters/min, which was gradually lowered. The evolution was favorable.

Clinical case n° 3

A 16-year-old overweight student who had been a smoker for 1 year with no comorbidities was infected with SARS-CoV-2 one month before admission. He was vaccinated with BCG at birth. The onset of symptoms was three months

Figure n°4 : Chest X-ray shows a bilateral, predominantly right-sided alveolar-interstitial syndrome



ago and was marked by intermittent fever associated with profuse night sweats and a weight loss of about 20% of body weight in three months. The association, 2 months later, of a dry cough, exertional dyspnea, and neurosensory signs such as agueusia and anosmia motivated the realization of the PCR COVID-19 which confirmed the infection with SARS-CoV-2. The patient was treated according to the national protocol for the treatment of SARS-CoV-2 infection in Benin, and the evolution was initially marked by a regression of the symptoms. Then, one week after his return home, a sudden onset of hypoxemic dyspnea associated with a resumption of fever was noted. No other symptoms were reported by the patient. In view of this picture, pulmonary embolism was considered. A thoracic angioscanner performed for this purpose did not reveal any pulmonary embolism. The COVID-19 PCR test came back negative. He was then referred to Internal Medicine for further management. On admission, the patient was found to be in an altered general condition (WHO Performance Index 2). There was a systemic inflammatory response syndrome with a fever of 38.9°C, a left pulmonary condensation syndrome, and a hypoxemic syndrome (90% desaturation on room air). The patient was borderline overweight (BMI 25.03 kg/m2), despite having lost 20 kg in three months. A new PCR COVID-19 was performed and came back negative. Because of the fear of a bacterial superinfection, an infectious workup was carried out, which showed a biological inflammatory syndrome (Table II). But the different blood cultures (4) and ECBU (2) were negative. A chest X-ray showed an alveolar-interstitial syndrome with destruction of a large part of the pulmonary parenchyma (figure 5).

GenXpert of the gastric tube fluid identified the DNA of Mycobacterium Tuberculosis. A pulmonary tuberculosis without other localization was retained. The patient was then put on antituberculosis treatment. The evolution was favorable with progressive oxygen weaning obtained on the seventh day of treatment and thermal defervescence.

DISCUSSION

To our knowledge, few publications are available on Covid 19 and tuberculosis. Our study is among the first in sub-Saharan Africa. A series of 3 cases was reported by Aazri et al. in Morocco in North Africa(Aazri et al., 2021).These three clinical cases highlight several important points: the clinical history of the patients' symptomatology, how SARS-CoV-2 infection can reveal or unmask tuberculosis, and tuberculosis and COVID-19 co-infection in our tuberculosis endemic setting. All three patients had got cough, fever and dyspnea. These symptoms are very common during SARS-CoV-2 infection. The series of Chen and Huang estimated the frequency of fever at 83% and 98% respectively and that of cough at 81% and 76% (Chen et al., 2020 ; Huang et al., 2020). This respiratory symptomatology is not specific to SARS-CoV-2 pneumonia but is present in mainly infectious pneumonia. These signs are also found in pulmonary tuberculosis (Campbell et al., 2006). However, whereas the COVID-19 pandemic is by definition responsible for an acute disease, tuberculosis readily takes a chronic course with, in most cases, a latent form with the possibility of transition to the patent forms which are symptomatic (Loddenkemper et al. 2016). For patient n°1 who developed arthromyalgia and hiccups, these symptoms, although non-specific, are also found in the literature among those of patients with SARS-CoV-2 pneumonia (Prince G, et al., 2020 ; Hong et al., 2021).All of our patients were vaccinated with BCG. Recent reviews showed a strong correlation between the BCG and cross

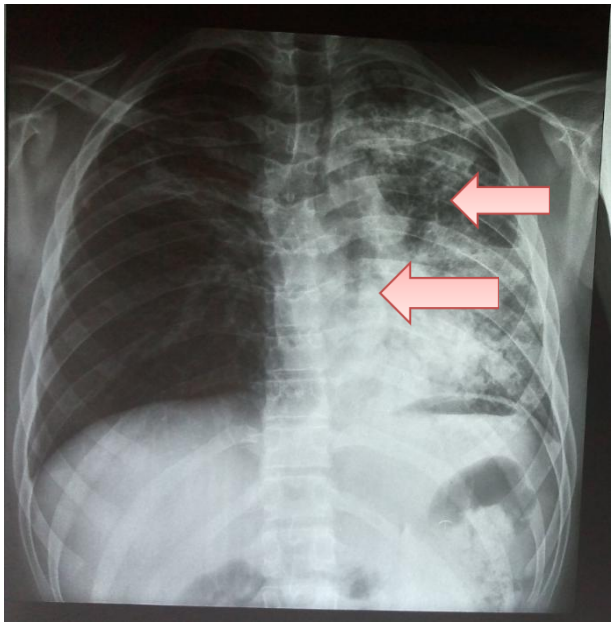


Figure n°5 : Chest X-ray shows a left alveolar-interstitial syndrome

protection from COVID -19, with every 10% increase in BCG administration resulting in 10.4% reduction in COVID -19 mortality (Mishra et al., 2021 ; Escobar et al., 2020 ; Miyasaka et al., 2020).In addition, apart from the 16-year-old adolescent who is overweight and a smoker, our patients are without comorbidities. They also do not have extrapulmonary tuberculosis as found in the Tadolini cohort (Tadolini et al., 2020). This probably contributed to the favorable evolution of their clinical condition.Biologically, all 3 patients had hyperleukocytosis with neutrophilic predominance, in contrast to leukopenia, classically described in the rare series available. Only the patient of clinical case n°2 had lymphopenia, classical in SARS-CoV-2 infection (Debuc et al., 2020) ; including in the rare series described of coinfection with tuberculosis (Stochino et al., 2020). Other biochemical abnormalities were found in our patients such as the increase in transaminases found by Stochino et al; and the more frequent hypokalemia, described with no relation to the severity of the SARS-CoV-2 infection (Alfano et al., 2021).

How does SARS-CoV-2 infection make Koch's bacillus infection obvious? Koch's bacillus infection affects about one third of the world's population. In the vast majority of cases, the infection is latent and therefore does not cause clinical pathological manifestations. In 2019, approximately 10 million people were ill with tuberculosis worldwide, with six Asian countries (India, Indonesia, China, Philippines, Pakistan, Bangladesh) and two African countries (Nigeria and South Africa) accounting for two-thirds of cases. These data confirm the very high endemicity of the disease in South East Asia and Africa (WHO, 2020). Several factors have been recognized as favoring the passage from a latent to an active form of the disease such as arterial hypertension, diabetes, immunodepression in general and HIV infection in particular, and low socioeconomic status (Cobelens et al., 2017). None of our three patients had these risk factors. This probably explains the absence of a probable primary tuberculosis infection prior to the symptomatology that led to the diagnosis of SARS-CoV-2 infection. Regarding the activation of a Koch's bacillus infection by COVID-19, several hypotheses have been put forward such as reactivations of dormant tuberculosis lesions due to the pulmonary inflammation caused by the virus, and the outbreak of TB lesions due to co-infection with viruses such as influenza A, triggering the type 1 interferon signaling pathway that is also important for mycobacterial growth and activation of defense mechanisms mediated by mesenchymal stem cells (CD271+BM-MSCs) (Pathak et al., 2020 ; Thomas et al., 2020). Other pathogenic mechanisms have been suggested. Thus, SARS-CoV-2 infection could predispose to tuberculosis by triggering aggressive inflammation through increased secretion of cytokines such as interleukin-1β (IL-1β), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), interleukin-4 (IL-4) and interleukin-10 (IL-10), causing an increase in their plasma levels and leading to a cytokine storm responsible for the severity of the infection (Zhang et al., 2019). These different pathogenic mechanisms mentioned above will result in a temporary immunosuppression which will "reawaken" bacterial infections including tuberculosis. In our patients, it is this temporary immunodepression that

was undoubtedly at the origin of the transition from a latent form to an active form of tuberculosis, despite the fact that our patients have no known comorbidities apart from the overweight of the 16 year old.

What then are the consequences of COVID-19 and pulmonary tuberculosis co-infection in our tuberculosis endemic context? About one third of the world's population is infected with the Koch's bacillus. But less than 10% will develop clinical manifestations. The eruption of this pandemic, which has already affected several tens of millions of people worldwide, and with the activating potential of latent tuberculosis forms as seen above, is likely to cause the number of tuberculosis cases in the world population to soar. The first studies on the subject around the world show that clinical pictures of COVID-19-pulmonary tuberculosis co-infection are more rapidly evolving and more severe (Chen et al., 2020 ; 20 Singh et al., 2020). Our southern countries represent large reservoirs of latent tuberculosis cases. It is therefore to be feared that there will be a sharp increase in symptomatic tuberculosis cases if the COVID-19 pandemic should become more widespread. In light of this, the search for pulmonary tuberculosis could be integrated into the overall management strategy of COVID-19 positive patients. This co-infection could have serious consequences for the health systems of African countries, which will then have to face a potential outbreak of the current pandemic and soon after an epidemic of TB cases.

CONCLUSION

Tuberculosis is endemic in our countries of the South but the majority of infected subjects have a latent form. Several factors can be at the origin of the passage from a latent to a patent form. The emergence of the COVID-19 pandemic would probably be a factor because of the temporary immunosuppression that it would induce, thus facilitating the transition to the patent form in subjects with COVID-19. In our tuberculosis endemic contexts, in COVID positive patients, it is therefore imperative to look for co-infection with pulmonary tuberculosis, especially if respiratory symptoms persist.

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