

Acute Tuberculosis pneumonia and COVID-19 in a patient vaccinated with Bacille Calmette-Guérin (BCG)

Michelangelo Luciani (✉ michelangelo.luciani@uniroma1.it)

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Ho

Enrico Bentivegna

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Ho

Valerio Spuntarelli

Sapienza University, Faculty of Medicine and Psychology, Emergency Medicine CoViD-19 Unit, Sant'Andrea University Hospital,

Ludovica Guerritore

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Hospital

Dario Chiappino

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Hospital

Gabriele Nalli

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Hospital

Maria Proietta

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Hospital

Flavia Del Porto

¹Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Hospital

Paolo Martelletti

Sapienza University, Faculty of Medicine and Psychology, Emergency Medicine CoViD-19 Unit, Sant'Andrea University Hospital, Sapienza University

Giorgio Sesti

Sapienza University, Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, Internal Medicine Unit, Sant'Andrea University Hospital

Case Report

Keywords: Covid-19, SARS-CoV-2, Tuberculosis, pneumonia, immunity, BCG

Posted Date: August 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-59744/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at SN Comprehensive Clinical Medicine on August 18th, 2020. See the published version at <https://doi.org/10.1007/s42399-020-00601-9>.

Abstract

COVID-19 is a respiratory tract infection caused by the new coronavirus SARS-COV2, that can be complicated by acute distress respiratory syndrome and multiorgan failure. In light of the high rate of mortality associated with COVID-19, pharmacological and non-pharmacological strategies to prevent the infection are currently being tested. Among non-pharmacological preventive measures, vaccines represent one of the main resources for public health. It has been suggested that Bacille Calmette-Guérin (BCG) vaccine may protect individuals against infection from COVID-19 virus, and two clinical trials addressing this question are underway. Here, we report the case of a 32-year old woman, vaccinated with BCG when she was 1 year old, who was diagnosed with apical tuberculous pneumonia of the right lung along with COVID 19 pneumonia.

Introduction

COVID-19 is a respiratory tract infection caused by the coronavirus SARS-COV2. This virus was first reported in Wuhan (China) with rapid spread worldwide causing a pandemic¹ with over 300,000 deaths to date². Non-pharmacological strategies have been adopted to prevent infection diffusion, including quarantine, social distancing, and personal protective equipment. COVID-19 clinical features include a spectrum of manifestations, ranging from absence of symptoms, gastro-intestinal disorders, and flu-like symptoms including fever, cough, and astenia³. In older patients with comorbidities, SARS-COV 2 leads to interstitial pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and, eventually, death. COVID-19 can be complicated by bacterial superinfections. Antibiotics, immunosuppressants, low weight heparin, and antiviral drugs were used to treat patients^{3,4}. Among preventive measures, vaccine represent a major resource for public health. It was suggested that Bacille Calmette-Guérin (BCG) vaccine may protect individuals against COVID-19 infection, and two clinical trials addressing this hypothesis are underway⁵.

Here, we report the case of a 32-year old woman simultaneously affected by COVID-19 and tuberculous pneumonia although she was vaccinated with BCG.

Case Presentation

A 32-year old woman with history of BCG vaccination at one year of age was hospitalized on 29th March 2020 for high fever, and muscle pain. The patient had a positive epidemiological link for travel to Milan, an area in Italy severely hit by COVID-19, and was treated with amoxicillin/clavulanic acid 1000 mg/BID and paracetamol 1000 mg/day.

The first nasopharyngeal swab RNA test for SARS-CoV2 genes resulted undetermined, while two subsequent tests were negative. High resolution chest computer tomography (HRCT) revealed parenchymal consolidation of 54 x 25mm, with air bronchogram in context, at the apical segment of the right upper lobe (RUL). Other consolidation areas with the same feature were located in the posterior

segment of the same lobe in the parascissural site, in the middle lobe in the paramediastinal site, and contralaterally to the anterior segment of the left upper lobe (LUL) in the subpleural area. Large right pleural effusion leading to atelectasis of the right lower lobe (RLL) was also detected.

Blood tests revealed lymphopenia, increase in high sensitive C-reactive protein (hsCRP 18.08 mg/dL) and procalcitonin (PCT 0.43 ng/mL), fibrinogen (882 mg/dL) and d-dimer (622 ng/mL). Antibiotic therapy was started with Clarithromycin 500 mg/BID together with Piperacillin/Tazobactam 4.5 g/TID.

Three days later a new nasopharyngeal swab RNA test for SARS-CoV2 genes resulted positive, despite the fact that both IgG and IgM antibodies assays were negative. The patient was transferred to a dedicated COVID-19 unit, where hydroxychloroquine and antiviral therapy with lopinavir/ritonavir were initiated. A first measurement of the QuantiFERON gave an indeterminate result with the indication to repeat the exam because of insufficient production of gamma interferon upon stimulation with the mitogen. HIV test was negative. Seven days later, Linezolid 500 mg/BID was introduced by replacing the previous antibiotic therapies due to the lack of clinical improvement. Thoracentesis was performed with removal of one liter of citrine yellow liquid. The chemical-physical and cytological analyses of the pleural fluid were consistent with exudative effusion, while culture tests for common germs and real-time polymerase chain reaction assay (RT-PCR) of KB were both negative. Due to rapid relapse of large pleural effusion, pleural drainage with pigtail catheter was inserted. A second assay for the QuantiFERON gave an indeterminate result. Due to the uncertain interpretation of chest CT images despite the reduction of pleural effusion, a lung CT biopsy procedure was performed with histological examination showing multiple areas of caseous necrosis delimited by a fibrous wall, and giant multinucleated cells suggestive for tuberculosis infection. RT-PCR performed on histological samples resulted positive for KB.

The patient repeated three nasopharyngeal swab RNA tests for SARS-CoV2 genes which were negative, while clinical conditions improved. The antiviral therapy was first stopped followed by the hydroxychloroquine treatment. After discharge, the patient observed a 14-day quarantine period, and due to positive tests for tuberculosis, a combined therapy with isoniazid and rifampicin was introduced.

Discussion

To our knowledge, this is the first report of acute tuberculosis infection superimposed on COVID-19 pneumonia. The association of these two infections has been previously described in 3 patients, but none of them developed an acute tuberculous disease, even because two of them were under treatment with quadruple anti-tuberculosis therapy, which was able to prevent the reactivation of the disease⁶.

Interestingly, our patient had a history of BCG vaccination, a life attenuated vaccine for tuberculosis that contains a weakened strain of *Mycobacterium bovis*. It is given to children in their first year of life in several countries, conferring protection against active tuberculosis in about 60% of treated individuals⁷. BCG increases immune response also to other pathogens, conferring a nonspecific protection against a wide range of bacterial, protozoa and viral infections, throughout the activation of the innate immune

system⁸. Also induces the innate immune system to develop a "memory", which is called "trained immunity", through epigenetic reprogramming of monocytes, macrophages and natural killer cells^{9,10}. Trained immunity induced by BCG may affect different microorganisms other than Mycobacterium tuberculosis. In a recent study carried out in healthy volunteers, vaccination with BCG was shown to reduce viremia in response to the yellow fever vaccine (live attenuated vaccine). This response was associated with epigenetic changes in monocytes which were related to a better antiviral response¹¹. The broad immunomodulatory capacity of BCG on respiratory tract pathogens was supported by a study in Guinea-Bissau showing that BCG reduced the incidence of respiratory syncytial virus infection¹², while a similar protective effect of BCG on infections respiratory tract has been reported in elderly subjects in Indonesia¹³.

It has been hypothesized that trained immunity can exert protective actions also against COVID-19. In countries that do not have a universal vaccination policy against the BCG, such as Italy and the United States, a higher mortality associated with COVID-19 has been reported as compared with nations with long-standing universal vaccination policies with BCG, such as South Korea and Japan¹⁴.

BCG confers immunity against mycobacterium tuberculosis for about 10 years although some reports describe a duration of immunity up to 20 years¹⁵.

This case suggests that in some individuals the immune response to BCG vaccination may be defective as supported by the findings that results of QuantiFERON assay were indeterminate indicating a condition of non-responsiveness of T lymphocytes to the antigenic stimuli. Moreover, the effect of the BCG vaccination on trained immunity seems to be limited to one year in most cases. Thus, it is conceivable that in our patient, BCG vaccination did not induce a trained immunity capable to provide protection against either tuberculosis infection or COVID-19 infections. Indeed, the patient's immune system was unable to react to mycobacterium tuberculosis infection by generating a latent infection that subsequently was flared up under a stressful condition induced by viral superinfection with coronavirus-19¹⁶.

Clinical trials are underway to investigate the effect of BCG vaccination to protect the elderly individuals from infections, and to explore the possibility to prevent serious COVID-19 infection in healthcare professionals. The current case report argues against the possibility that vaccine with BCG exerts long-lasting protection from Coronavirus-19 infection, and highlights the importance of further research aimed to explore the role of trained immunity induced by BCG vaccination in COVID-19 management¹⁷.

Declarations

Conflicts of interest

None of the authors have any conflict of interest.

Funding

None.

Ethical approval

Prot. n. 52 SA_2020 del Registro Pareri Rif. CE 5773_2020

Consent

Written informed consent was obtained by patient for publication of this case report and accompanying images.

Author contribution

Dr Luciani participated in article preparation.

All authors materially participated in the research.

All authors participated in data collection.

All authors have approved the final article.

Registration of research studies

Guarantors

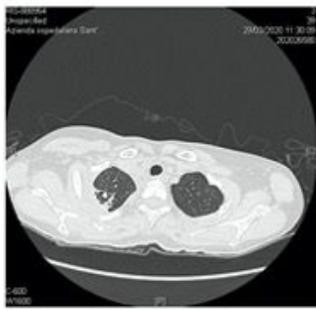
Prof Martelletti Paolo, MD and Prof. Sesti Giorgio, MD.

References

1. Zhu N, Zhang D, Wang W et al A novel coronavirus from patients with pneumonia in China. *N Engl J Med* 2020;382(8):727-33
2. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at John Hopkins University (JHU)". ArcGIS. Johns Hopkins University. Retrieved 15 May 2020.
3. Strumia A, Scarlata S. COVID-19 diagnosis and managment: a comprehensive review. *J Intern Med.* 2020 May 13 : 10.1111/joim.13091. doi: 10.1111/joim.13091 [Epub ahead of print]
4. Bentivegna, E., Luciani, M., Spuntarelli, V. *et al.* Extremely Severe Case of COVID-19 Pneumonia Recovered Despite Bad Prognostic Indicators: a Didactic Report. *SN Compr. Clin. Med.* (2020). <https://doi.org/10.1007/s42399-020-00383-0>
5. O'Neill LA, Netea MG BCG Induced trained immunity: can it offer protection against COVID-19? *Nat Rev Immunol* 2020;11: 1–3
6. Jing Cai, et al. COVID-19 in Tuberculosis patients: a report of three cases *J Med Virol.* 2020 Apr 28;10.1002/jmv.25943.

7. Roy A, Eisenhut M, Harris RJ, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic re- view and meta-analysis. *BMJ* 2014;349:g4643.
8. Shann F. The non-specific effects of vaccines. *Arch Dis Child* 2010; 95:662-7 .
9. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A* 2012;109:17537–42.
10. Kleinnijenhuis J, Quintin J, Preijers F, et al. BCG-induced trained immunity in NK cells: role for non-specific protection to infection. *Clin Immunol* 2014;155:213–9.
11. Covian C, Retamal-Diaz A, Bueno SM, Kalergis AM. Could BCG vaccination induce protective trained immunity for SARS-Cov-2?. *Front Immunol* 2020; 11: 970. Published online 2020 May 8
12. Stensballe, L. G. et al. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls community based case-control study. *Vaccine* 23, 1251–1257 (2005).
13. Wardhana, et al. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. *Acta Med. Indones.* 43, 185–190 (2011)
14. Miller A, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv.
15. Martin C, et al. Vacunación frente a tuberculosis. *Enferm Infecc Microbiol Clin*. 2017. <https://doi.org/10.1016/j.eimc.2018.02.006>
16. Bentivegna, E., Sentimentale, A., Luciani, M., Speranza, M.L., Guerritore, L. and Martelletti, P. (2020), New IgM seroconversion and positive RT-PCR test after exposure to the virus in recovered COVID-19 patient. *J Med Virol*. doi:10.1002/jmv.26160
17. Hegarty PK, et al. COVID-19 and Bacillus Calmette-Guérin: What is the Link? *Eur Urol Oncol* (2020), <https://doi.org/10.1016/j.euo.2020.04.001>

Figures



1A



1B



1C



1D



2A



2B



2C



2D

Figure 1

First HRCT showing parenchymal consolidation with air bronchogram at the right apical segment (1A). Other consolidation areas were located in the posterior segment of the RUL and contralaterally (1B and 1C). Large right pleural effusion leading to atelectasis of RLL was also detected (1D). Second HRCT performed after two weeks showing reduction of parenchymal consolidation (2A, B and C) and resolution of pleural effusion (2D).