A case report on disseminated tuberculosis in the setting of coronavirus disease 2019: cause or consequence?

Himsikhar Khataniar*, Diya Sunil, Lalitha AV

Abstract
Tuberculosis (TB) is a deadly infection that can lead to disseminated disease in children <15 years of age exhibiting risk factors such as low host immunity, concurrent infection(s), and/or malnutrition. A case involving a 14-year-old boy diagnosed with disseminated tuberculosis is reported. On investigation, the patient was positive for coronavirus disease 2019 (COVID-19) antibodies, GeneXpert (Cepheid, Sunnyvale, CA) positive for TB with multisystem involvement, lymphopenia, and highly elevated inflammatory markers, indicating multisystem inflammatory syndrome in children (MIS-C) and disseminated TB. The patient was started on antitubercular treatment (ATT), steroids, and supportive treatment. His condition improved over the ensuing few days, and he was discharged with ATT and antiepileptics. Although a few studies involving adults have established a connection between the progression of TB and COVID-19, this case report establishes a similar clinical picture in a child, which has not yet been reported.

Keywords: Case report, COVID-19, Disseminated tuberculosis, Steroids, Tuberculosis

Introduction
Mycobacterium tuberculosis (MTB) is an infectious agent that causes tuberculosis (TB), accounting for approximately 1.5 million deaths worldwide in 2020,[1] making it the 9th most common cause of death worldwide.[2,3] Currently, approximately 23% of the world’s population is infected with MTB. TB spreads via inhalation of aerosol droplets that contain bacteria.[4] Disseminated TB is defined as the presence of TB infection in ≥2 noncontiguous sites of the body (lungs, brain, abdomen) resulting from haematogenous spread of MTB.[5]

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused the ongoing pandemic.[6] Globally, however, fewer COVID-19 cases have been reported in children than in adults. Most cases occurring in children are mild, and treatment consists of supportive care. However, recent reports suggest a new COVID-19-related clinical syndrome, known as multisystem inflammatory syndrome in children (MIS-C), presenting with significant inflammation and similarities to Kawasaki disease (KD).[7]

Many studies have associated TB reactivation with viral infection.[8] An increased probability of latent TB infection evolving into active TB has also been observed in previous outbreaks of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the H1N1 epidemics.[9-13]

Case report
A case involving a 14-year-old male, who presented with a history of weight loss, decreased appetite for 2 months, fever for the past 2 weeks, and abnormal movements for 1 week, is reported. The child was admitted to a peripheral hospital and treated with meropenem, vancomycin, levetiracetam, and valproate for 2 weeks. The child was referred to the authors’ center due to persistent fever and poor sensoria. In the emergency department, the child was irritable, febrile, tachypnoeic, and tachycardic, with poor peripheral perfusion and respiratory distress and reduced breath sounds on the left side.

The primary suspicion in this case was respiratory distress secondary to lung parenchymal involvement, compensated shock, and primary brain dysfunction. He was started on oxygen via face mask, fluid bolus, and intravenous antibiotics, and was transferred to the pediatric intensive care unit (PICU) for further management. In the PICU, he was irritable, but hemodynamically stable, with minimal respiratory distress and reduced breath sounds on the left side, and a respiratory distress score (RDS) of 1/10 and minimal astylosis. On central nervous system examination, he had a Glasgow Coma Score (GCS) of 13/15, left-sided hemiplegia, and no cranial nerve involvement. The patient had a history of tubercular meningitis with post-meningitis sequelae, hydrocephalus-ventriculo-peritoneal (VP) shunt placement, for which he was treated with antiepileptics until 5 years of age. There was a family history of TB in his father previously, for which he was adequately treated. He also had a history of COVID-19 contact. Laboratory investigations revealed a white blood cell count of 3290 cells/mm³ (80% neutrophils, 14.6% lymphocytes, 4.9% monocytes, 0.3% eosinophils), a procalcitonin level of 15.11 μg/mL, a ferritin level of 1129 ng/L, and a C-reactive protein (CRP) level of 28 mg/L. Renal and liver function parameters were...
within the normal ranges. Human immunodeficiency virus test results were negative. COVID rapid antigen test and reverse transcription polymerase chain reaction tests were negative. Chest radiography revealed bilateral infiltrates with left pleural effusion.

A provisional diagnosis of subacute to chronic TB meningitis/MIS-C/ventriculitis due to VP shunt infection was made, as the child experienced a spiking fever despite 9 days of antibiotic treatment (meropenem and vancomycin). The patient was continued on maintenance intravenous (IV) fluids, IV ceftriaxone, vancomycin, levetiracetam, and valproate. Continuous hemodynamic, GCS, and RDS monitoring was performed. An opinion from neurosurgery was sought regarding shunt infection/shunt block, following which ventricular tapping and chamber tapping were performed and free flow was noted, which confirmed VP shunt patency. Cerebrospinal fluid analysis suggested TB meningitis with low glucose (40g/L), high protein (400g/L), low chloride (108mg/dL) levels, and lymphocytic predominance (65%) with GeneXpert (Cepheid, Sunnyvale, CA) positivity for MDR-TB. Pleural fluid aspirate sent for analysis exhibited exudative characteristics (lactate dehydrogenase [LDH] 580 U/L, protein 4.47 g/dL, amylase 21 U/L, and glucose 53 mg/dL), acid-fast bacilli (AFB) positivity (Fig. 1), and GeneXpert negativity. Ultrasonography (USG) of the abdomen suggested moderate ascites with thick internal septations (Fig. 2), minimal bilateral pleural effusion, and splenomegaly. Peritoneal tapping was avoided due to minimal abdominal distension. Given the COVID-19 pandemic and significantly increased levels of inflammatory markers, a COVID antibody test was performed and was positive (47.8). Additionally, markers of acute inflammation were elevated: D-dimer (3.35 mg/mL), LDH (387 U/L), ferritin (1129 ng/L), and procalcitonin (15.11 µg/mL) (Table 1). Accordingly, a diagnosis of dissemination TB (TB meningitis, TB peritonitis, pulmonary Kochs) was made, supported by the result of a rarely encountered phenomenon of “MIS-C due to COVID-19 exposure in children.” In view of disseminated TB, an ophthalmological evaluation was performed, which was suggestive of bilateral partial optic atrophy. Magnetic resonance imaging (MRI) of the brain was performed, which suggested communicating hydrocephalus, multiple calcified granulomas, a glotic area in the right gangliocapsular region, but no features of acute meningeal inflammation (Fig. 3). He was started on second-line antitubercular therapy (Inj. Amikacin, T. ethambutol [E], T. levofloxacin, and IV steroids, as per guidelines). Because the child was hemodynamically stable, IV immunoglobulin was not administered. Enoxaparin differed because of deranged coagulation parameters. Subsequently, the child improved, experienced no fever spikes, was hemodynamically stable, exhibited improved sensorium, and was placed on oral feeds. Inflammatory markers on day 6 of PICU admission were D-dimer (1.15 µg/mL), LDH (210 U/L), ferritin (540 ng/L), and procalcitonin (5.8 µg/mL), following which he was transferred to the ward for further management. In the ward, the child continued to improve and was discharged after 5 days of monitoring for T. rifampicin (R) 450 mg/T. isoniazid (H) 225 mg/T. pyrazinamide (P)1g for 1 week, followed by a plan to restart 2 months of HRZE plus 10 months of HRE and anti-seizure drugs.

Discussion

COVID-19 is associated with other respiratory system diseases.[8] One such infection is the probable flare-up of TB, leading to disseminated TB as a result of SARS-CoV-2 exposure. Antibody-positive COVID-19 with apparent symptoms pertaining to widespread TB infection raises the question of what leads to TB dissemination. Concurrent TB and COVID-19 has been previously reported. A study by Tadolini et al. reported on 9 patients with simultaneous COVID-19 and active TB.[14] Stochino et al. reported 20 patients with TB and COVID-19 coinfection, of which 3 patients were diagnosed with extrapulmonary TB.[15] Mustafa et al. identified the development of miliary TB in a patient with peritoneal TB after COVID-19 infection,[16] and Yao et al. described 2 cases of active pulmonary TB infection from latent pulmonary TB infection.[17] However, to the best of our knowledge, all cases reported have been adults, and reports describing a flare-up of TB infection following COVID-19 exposure, in the paediatric age group, have not been reported. Based on a meta-analysis by Song et al., patients with concurrent COVID-19 and TB were two to three times more likely to die or develop severe COVID-19.[18]
patients with COVID-19 and TB coinfection were administered antitubercular drugs; however, only 11.2% received steroids. A few other drugs reported to be used among individuals with concurrent COVID-19 and TB include hydroxychloroquine, azithromycin, lopinavir/ritonavir, darunavir/cobicistat combination, and anticoagulants (enoxaparin and parnaparin). Although it has been widely reported that the use of steroids in those with COVID-19 leads to a reduction in short-term mortality, the use of immunosuppressive drugs requires further investigation. In the case of MIS-C in children, IV immunoglobulin—either as a monotherapy or in combination with steroids—has been reported to yield favorable results. In the present case, the child recovered with antitubercular drugs, corticosteroids, and supportive care, with no requirement for IV immunoglobulin or intensive care after a few days, and experienced almost complete recovery. Therefore, although disseminated TB in the setting of MIS-C due to COVID-19 in the pediatric age group may be regarded as a severe illness, early identification, prompt treatment, and adequate titration of drugs can improve prognosis. This is an important point to be considered when using exploratory therapy.

**Limitations**

This novel case provides insight into a new observation in the pediatric population and serves as a major educational tool for future cases. However, a case report describing a single case in the pediatric population is insufficient evidence to support a causal association between COVID-19 and TB. Therefore, our findings are not generalizable to the entire pediatric population. Furthermore, given the ever-evolving nature of COVID-19, its interactions with TB and other respiratory pathogens may change over time. Hence,

---

**Table 1**

| Parameters                          | Result          | Normal Value |
|-------------------------------------|-----------------|--------------|
| CSF analysis                         |                 |              |
| Color                               | Turbid yellow   | Colorless    |
| Lymphocyte (%)                      | 65              | 30           |
| Chloride (mEq/L)                    | 108             | 115–130      |
| Glucose (mg/dL)                     | 40              | 40–70        |
| Protein (mg/dL)                     | 400             | 15–40        |
| CSF ADA (U/L)                       | 2.7             | 0–5          |
| CSF GeneXpert for mycobacterium tuberculosis | Positive | Negative     |
| Pleural fluid analysis               |                 |              |
| Appearance                          | Cloudy          | Clear        |
| Color                               | Yellow          | Straw colored|
| Lymphocyte (%)                      | 93              | 30           |
| LDH (U/L)                           | 580             | 124          |
| Amylase (U/L)                       | 21              | 200          |
| Glucose (mg/dL)                     | 53              | 95–100       |
| Protein (g/dL)                      | 4.47            | 1–2          |
| Pleural fluid GeneXpert for mycobacterium tuberculosis | Negative | Negative     |
| Pleural fluid acid fast bacilli     | Present         | Absent       |
| Gastric aspirate analysis           |                 |              |
| Gastric aspirate GeneXpert for mycobacterium tuberculosis | Negative | Negative     |
| Gastric aspirate acid fast bacilli  | Absent          | Absent       |
| Blood/serum investigations          |                 |              |
| Leucocyte count, cells per mm³      | 3290            | 4000–11,000  |
| LDH (U/L)                           | 387             | 230–460      |
| CRP (mg/L)                          | 28              | 0–5          |
| D-dimer (µg/mL)                     | 3.35            | <0.25        |
| Ferritin (ng/L)                     | 1129            | 10–291       |
| Procalcitonin (µg/L)                | 15.11           | 0.5          |
| COVID-19 antibody test              | Positive        | Negative     |

ADA, adenosine deaminase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase.

The link between TB and COVID-19 is, in large part, bidirectional. Temporary immunosuppression caused by TB may increase the predisposition to COVID-19 infection compared to other chronic lung diseases such as chronic obstructive pulmonary disease and asthma. In contrast, COVID-19 may also increase susceptibility to TB. According to a study from Wuhan, China, 76% of the 522 COVID-19 infected patients, both paediatric and adult, exhibited substantial depletion in T-cell lymphocyte counts. While both CD4 and CD8 counts were severely decreased, the surviving T cells also appeared to demonstrate “functional exhaustion.” T-cell depletion and dysfunction may promote the development of active TB in patients with latent TB bacilli infection (LTBI).

Clinical symptoms, such as fever, cough, dyspnea, weight loss, fatigue, and expectoration, occur along with markedly elevated levels of inflammatory markers, including CRP, procalcitonin, ferritin, LDH, and D-dimer. A decrease in lymphocyte count and hemoglobin has been reported among patients with concurrent COVID-19 and TB. COVID-19 in children can occur in the form of MIS-C, with symptoms of fever, fatigue, multiple organ involvement, and elevated inflammatory enzymes. A study by Payne et al. estimated the incidence of MIS-C in be 5/million children with COVID-19. In the case described, the patient was treated with second-line antitubercular drugs in view of MDR-TB, along with injectables such as amikacin and IV steroids. According to a meta-analysis, 88% of
a prospective cohort study involving paediatric patients with COVID-19 can provide better insight and explanation of the observations of our case report.

Conclusion

Clinical features reminiscent of MIS-C in COVID-19 should alert primary care, emergency units, and pediatricians during the expected surge of COVID-19 infections worldwide. Routine screening for MTB among patients with COVID-19 in countries with a high TB burden (eg, India) should be considered given the poor prognosis of concurrent COVID and TB and their overlapping clinical presentations. In conclusion, further studies are required to better understand the pathogenic mechanism of COVID-19, which may in turn help to identify appropriate interventions for individuals with concurrent COVID-19 and TB.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

AV L was involved in the diagnosis and management of the patient. She was also involved in data collection, drafting the initial manuscript, and critically reviewing the original manuscript for important intellectual content. Khataniar H and Sunil D conceptualized and designed the case report, analysis, and interpretation of the data, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding

None.

Ethical approval of studies and informed consent

This study was approved by the Institutional Ethics Committee of St. John Medical College and Hospital, and written informed consent of the patient for the use of his data and for the publication of the data that appear in the article.

Acknowledgements

None.

References

[1] World Health Organization. Tuberculosis. Accessed May 16, 2021. https://www.who.int/news-room/fact-sheets/detail/tuberculosis

[2] Karthika M, Philip S, Prathibha MT, Varghese A, Rakesh PS. Why are people dying due to tuberculosis? A study from Alappuzha District, Kerala, India. Indian J Tuberc. 2019;66(4):443–447. doi:10.1016/j.ijtbh.2018.05.001

[3] Jain VK, Iyengar KP, Samy DA, Vaithya R. Tuberculosis in the era of COVID-19 in India. Diabetes Metab Syndr. 2020;14(5):1439–1443. doi:10.1016/j.dsx.2020.07.034

[4] Centers for Disease Control and Prevention. Global health- Tuberculosis (2021). Accessed May 10, 2021. https://www.cdc.gov/globalhealth/newsroom/topics/tb/index.html

[5] Khan FY. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. J Family Community Med. 2019;26(2):83–91. doi:10.4103/fcm.JFCM_106_18

[6] Centers for Disease Control and Prevention. Basics of COVID-19. Accessed May 15, 2021. https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19/basics-covid-19.html

[7] Centers for Disease Control and Prevention. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. Accessed December 6, 2021. https://www.cdc.gov/covid-data-tracker/#demographics

[8] Von Pirquet C. Das Verhalten der kutanen tuberkulin-reaktion während der masern. Dtsch Med Wochenschr. 1908;54:1297–1300. doi:10.1055/s-0028-1135624

[9] Liu W, Fontanet A, Zhang PH, et al. Pulmonary tuberculosis and SARS, China. Emerg Infect Dis. 2006;12(4):707–709. doi:10.3201/eid1204.050264

[10] Low JG, Lee CC, Lee YS, Low JG, Lee CC, Leo YS. Severe acute respiratory syndrome and pulmonary tuberculosis. Clin Infect Dis. 2004;38(12):e123–e125. doi:10.1086/421396

[11] Walaza S, Tempia S, Dawood H, et al. Influenza virus infection is associated with increased risk of death amongst patients hospitalized with confirmed pulmonary tuberculosis in South Africa, 2010-2011. BMC Infect Dis. 2015;15:26. doi:10.1186/s12879-015-0746-x

[12] Mendy J, Jarju S, Bosanj AL, Kampmann B, Sutherland JS. Changes in mycobacterium tuberculosis-specific immunity with influenza co-infection at time of TB diagnosis. Front Immunol. 2019;9:3093. doi:10.3389/fimmu.2019.03093

[13] Noh JY, Lee J, Choi WS, et al. Concurrent tuberculosis and influenza, South Korea. Emerg Infect Dis. 2013;19(1):165–167. doi:10.3201/2019.111613

[14] Tadolini M, Codecasa LR, Garcia-Garcia JM, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. Eur Respir J. 2020;56(1):2001398. doi:10.1183/13993003.01398-2020

[15] Stochino C, Villa S, Zucchi P, Parravicini P, Gori A, Raviglione MC. Clinical characteristics of COVID-19 and active tuberculosis coinfection in an Italian reference hospital. Eur Respir J. 2020;56(1):2001708. doi:10.1183/13993003.01708-2020

[16] Elziny MM, Ghazi A, Ellett KA, Aboukamem M. Case report: development of miliary pulmonary tuberculosis in a patient with peritoneal tuberculosis after COVID-19 upper respiratory tract infection. Am J Trop Med Hyg. 2021;104(5):1792–1795. doi:10.4269/ajtmh.20-1156

[17] Yao Z, Chen J, Wang Q, et al. Three patients with COVID-19 and pulmonary tuberculosis, Wuhan, China, January-February 2020. Emerg Infect Dis. 2020;26(11):2735–2738. doi:10.3201/eid2611.201536

[18] Song WM, Zhao JY, Zhang Q, et al. COVID-19 and tuberculosis coinfection: an overview of case reports/case series and metaanalysis. Front Med (Lausanne). 2021;8:657006. doi:10.3389/fmed.2021.657006

[19] Liu C, Yu Y, Fleming J, et al. Severe COVID-19 cases with history of active or latent tuberculosis. Int J Tuberc Lung Dis. 2020;24(7):747–749. doi:10.3588/ijtld.20.00163

[20] Dao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827. doi:10.3389/fimmu.2020.00827

[21] Yue H, Bai X, Wang J, et al. Clinical characteristics of coronavirus disease 2019 in Gansu province, China. Ann Palliat Med. 2020;9(4):1404–1412. doi:10.21037/apm-20-887

[22] Centers for Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). Accessed May 2021. https://www.cdc.gov/mis-c/hcp/index.html

[23] Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open. 2021;4(6):e2116420. doi:10.1001/jamanetworkopen.2021.16420

[24] Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children—inital therapy and outcomes. N Engl J Med. 2021;385(1):23–34. doi:10.1056/NEJMoa2102605

How to cite this article: Khataniar H, Sunil D, AV L. A case report on disseminated tuberculosis in the setting of coronavirus disease 2019: cause or consequence? Emerg Crit Care Med. 2022;2(3):175–178. doi: 10.1097/ECC.0000000000000039