

# A Coronavirus Disease 2019 (COVID-19) Mystery: Persistent Fevers and Leukocytosis in a Patient With Severe COVID-19

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Short-course glucocorticosteroids are being used and tocilizumab (TCZ) had been used to treat patients with severe coronavirus disease 2019 (COVID-19) disease. These agents, when administered individually, have been associated with tuberculosis (TB) during chronic use. We report a case of TB in a 44-year-old male with diabetes and severe COVID-19 who received high-dose short-course glucocorticosteroids and a single dose of TCZ. The clinical presentation was atypical with unresolving fevers and leukocytosis, progressive lower lobe cavities, and hilar adenopathy. Delayed diagnosis led to prolonged hospitalization and extensive antibiotic use.

**Keywords.** cavitary TB, COVID-19, respiratory infections, SARS CoV-2, tuberculosis

The rationale of using immunomodulatory agents in severe coronavirus disease 2019 (COVID-19) disease is to dampen the associated systemic inflammation that might contribute to respiratory deterioration, mechanical ventilation, and death. Short-course glucocorticosteroid therapy has been reported to improve survival of patients with severe COVID-19 and its use has been incorporated in guidelines [1, 2].

Although chronic use is associated with an increased risk of tuberculosis (TB) reactivation [3, 4], TB is rarely reported in the context of short-course high-dose glucocorticosteroid therapy [5]. Tocilizumab (TCZ) is approved for use in juvenile idiopathic arthritis and rheumatoid arthritis with routine preadministration screening for latent TB infection and chemoprophylaxis as clinically indicated. Tuberculosis is uncommon

during chronic use for these indications [6, 7]. Almost all of the few reported cases were seen in countries where TB was endemic [8]. Coexisting TB [9, 10] and delayed TB diagnosis [11] have been reported in patients with COVID-19. We report a case of TB in a patient with severe COVID-19 and highlight factors that led to delayed TB diagnosis.

## CASE DESCRIPTION

A 44-year-old man was transferred to our hospital in March 2020 after being intubated for hypoxia due to COVID-19-related pneumonia at another hospital. At presentation at the first hospital, the patient reported a dry cough and fever for 5 days. He denied any gastrointestinal symptoms, myalgias, or dyspnea. Medical history included hypertension, type II diabetes mellitus, and a previous stroke secondary to a left atrial thrombus. Outpatient treatment for diabetes included 1000 mg of metformin twice daily and 25 mg of alogliptin daily. Serum glucose 222 mg/dL. Hemoglobin A1C was not tested. Chest radiograph (CXR) revealed patchy ground-glass opacities. Severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction (RT-PCR) test was positive. Human immunodeficiency virus antibody test was negative. White blood cell count (WBC) was 16.9 (normal, 4.5–11 K/ $\mu$ L). After 2 days of azithromycin, ceftriaxone, and hydroxychloroquine, he developed worsening hypoxemia and was intubated. He then received cefepime and vancomycin and he was transferred to the medical intensive care unit at our facility.

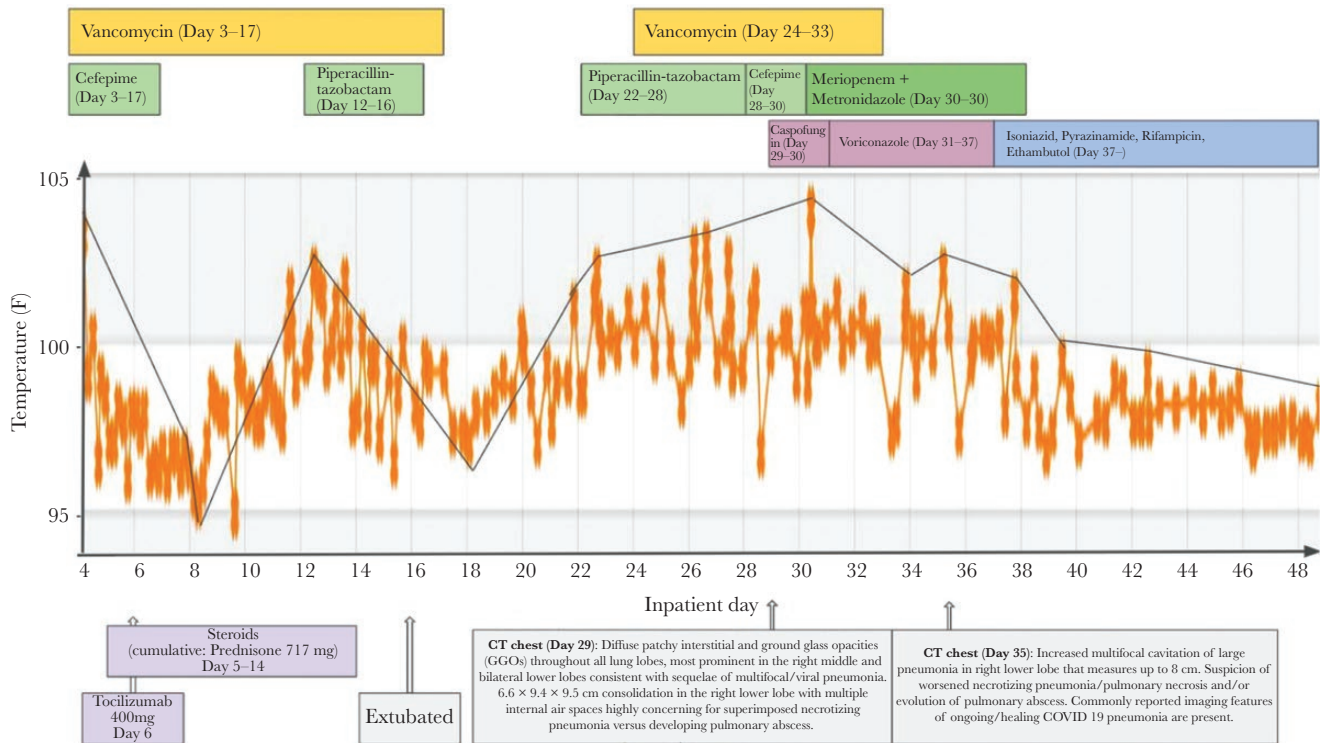
Upon transfer, he had a temperature of 102.8°F, blood pressure of 138/77 mm Hg, pulse of 114 beats per minute, respirations of 16, and an oxygen saturation of 95% while being mechanically ventilated. Weight was 91 kilograms. Laboratory studies revealed a WBC of 17.1, lactate dehydrogenase of 570 (normal, 100–220 U/L), C-reactive protein of 328 (normal, <5 mg/L), ferritin of 2043 (normal, 30–400 ng/dL), d-dimer of 0.74 (normal, <5  $\mu$ g/mL fibrinogen equivalent units), interleukin-6 of 21 (normal, 0–15.5 pg/mL), and procalcitonin of 5.59 (normal, 0.10–0.49 ng/mL). Interventions and fever course are shown in Figure 1. Vancomycin and cefepime were continued for 7 days. On day 5, dexamethasone (20 mg/day) was added intravenously for 2 days, followed by 10 mg of dexamethasone daily for 6 days and a single dose of methylprednisolone (40 mg). The cumulative dose was equivalent to 717 mg of prednisone. On the second day of dexamethasone, a QuantiFERON-TB Gold Plus (QFT-Plus) test was obtained before administration of 400 mg of TCZ intravenously. The QFT-Plus was negative. A repeat specimen was deemed insufficient for repeat verification. The patient became afebrile within 24 hours of the onset of dexamethasone. The WBC was 24.9 at completion of dexamethasone therapy.

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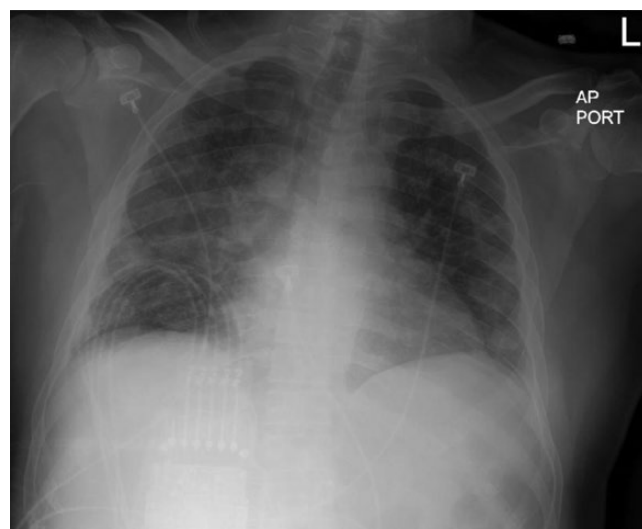
**Figure 1.** Timeline showing temperature trend and other clinical events. CT, computed tomography.

Two days after dexamethasone was discontinued, the patient's temperature rose to 102°F. He then received piperacillin/tazobactam (TZP) and vancomycin for 5 days for possible aspiration pneumonia after self-extubation with subsequent reintubation that same day. Tracheal aspirate and blood cultures were negative. Clinical status improved with fever resolution. He was extubated on day 16, placed on BiPAP (Bilevel Positive Airway Pressure), subsequently transitioned to a nasal cannula, and transferred to general medicine floor. Leukocytosis persisted at 16.7.

On day 22, the patient's temperature rose to 101.1°F along with a WBC of 14.7 with a left shift and a newly altered mental status. He was again treated with TZP the same day for another presumed hospital acquired pneumonia. Fever and leukocytosis persisted and vancomycin was added on day 24. Blood, urine, and fungal cultures, serum galactomannan, beta-D-glucan, and urinalysis were negative. The CXR revealed patchy infiltrates (Figure 2). Sputum Gram stain showed <10 polymorphonuclear cells/low-power field with moderate Gram-positive cocci in pairs and chains. Culture revealed moderate growth of *Klebsiella pneumoniae*. The isolate was resistant to TZP and susceptible to cefepime and carbapenems. Piperacillin/tazobactam was discontinued and cefepime was added. Fever and leukocytosis persisted. Blood and sputum cultures remain negative.

On day 29, computed tomography (CT) scan of the chest and abdomen revealed diffuse opacities, with a 6.6 × 9.4 × 9.5-cm consolidation in the right lower lobe with multiple internal

air spaces and right hilar lymphadenopathy with calcified subcarinal lymph nodes (Figures 3 and 4). The CXR 1 day before the CT scan showed patchy bilateral infiltrates. The patient was treated with meropenem, caspofungin, vancomycin, and metronidazole. Caspofungin was discontinued after 2 days and voriconazole was added. He continued to have leukocytosis with intermittent fever. Sputum cultures remained negative.

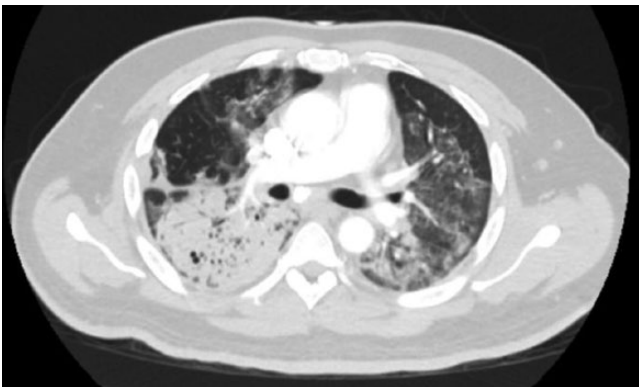


**Figure 2.** Chest radiograph on day 22 of admission showing patchy bilateral infiltrates.

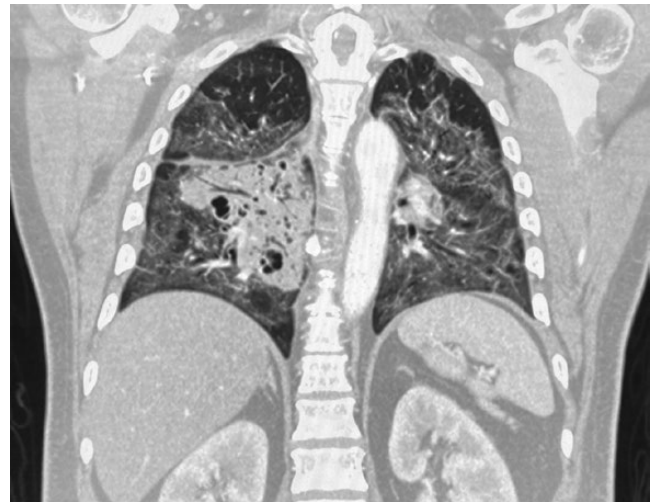


**Figure 3.** Computed tomography angiogram chest and abdomen with and without contrast on day 29 of admission showing the extent of disease. Diffuse patchy interstitial and ground-glass opacities can be visualized throughout all lung lobes. There is a 9.5-cm area of consolidation in the right lower lobe, with multiple internal spaces.

On day 35, chest CT scan revealed an 8-cm area of consolidation in the right lower lobe with increased multifocal cavitation (Figure 5). Blood cultures, urine *Legionella* antigen, serum galactomannan, beta-D-glucan, urine *Histoplasma* antigen, *Coccidioides* immunoglobulin G antibody, and repeat COVID-19 RT-PCR nasal and sputum swabs were negative. Three sputum smears were positive for acid-fast bacilli. *Mycobacterium tuberculosis* (MTB) complex was identified by



**Figure 4.** Computed tomography angiogram chest and abdomen with and without contrast on day 29 of admission showing the extent of disease. Diffuse patchy interstitial and ground-glass opacities can be visualized throughout all lung lobes. There is a 9.5-cm area of consolidation in the right lower lobe, with multiple internal spaces.



**Figure 5.** Computed tomography chest with intravenous contrast on day 35 of admission revealing increased multifocal cavitation within large right lower lobe consolidation that measures up to 8 cm. Multifocal bronchiectasis and bronchiolectasis are seen in (1) right upper and middle and (2) bilateral lower lobes. In addition, commonly reported imaging features of ongoing/healing coronavirus disease 2019 pneumonia are present.

AccuProbe. No rifampin resistance was detected by PCR. Upon further questioning, the patient reported having had a positive purified protein derivative (PPD) test and receiving 3 months of treatment at least 10 years prior for positive PPD. He was born in Haiti and travels there regularly. Antibiotics and antifungal agents were discontinued. The patient was treated with isoniazid, rifampin, ethambutol, and pyrazinamide with vitamin B6. Oxygen saturation improved to the high 90s, whereas breathing ambient air and fever and leukocytosis promptly resolved within 5 days. He was discharged after 3 negative sputum acid-fast smears with appropriate outpatient follow-ups to complete a full course of treatment for pulmonary cavitary TB. During hospitalization, diabetes was treated with with long-acting insulin and rapid-acting insulin as needed. Serum glucose levels ranged from 50 to 450 mg/dL, and 45% (79 of 174) of serum glucose values were greater than 180.

#### Patient Consent Statement

The patient's written consent was obtained. According to the Institutional Review Board (IRB), faculty who prepare a case report as an article for submission to a journal do not require IRB approval before preparation.

#### DISCUSSION

A preliminary report suggests that MTB coinfection is associated with severe COVID-19 disease [12]. We report a case of severe COVID-19 pneumonia with pulmonary TB in a diabetic patient who received a short-course of high-dose glucocorticosteroid therapy and TCZ. The patient was born in a country with high prevalence of TB and had a prior history

of incomplete TB chemoprophylaxis. Knowledge of country of origin and prior TB status could have led to more prompt evaluation of TB, decreased broad-spectrum antibiotic use, and reduced length of hospital stay.

It is likely that the patient presented with unrecognized pulmonary TB. Several factors led to delayed recognition. The patient was born in and had traveled to a TB-endemic area several times in the past. Concomitant presentation of COVID-19 and pulmonary TB have been recently reported in Haiti [9]. Furthermore, he has had 3 months of TB chemoprophylaxis. However, at the time of transfer to our hospital, our patient was intubated and information on country of origin and prior TB exposure or treatment was not obtained at baseline. His QFT-Plus test was negative on day 6 of hospitalization. The performance of interferon gamma release assays depends on the population and specific clinical situations [13]. A negative test did not exclude active TB [13]. However, although the negative QFT-Plus test was likely a false negative in our patient, this possibility was not confirmed because the test was not repeated after the diagnosis of active TB.

A 3-month course of TB chemoprophylaxis before the approval of isoniazid and rifampin would have been incomplete. A 3-month course of TB chemoprophylaxis with isoniazid does provide some TB risk reduction but not the same magnitude of risk reduction derived from 6- to 9-month courses [14]. Both glucocorticosteroids and TCZ can diminish TB host defenses [15, 16] and potentially lead to reactivation of latent TB. Patil et al [5] described a case of pulmonary TB of a patient who developed a febrile respiratory illness 2 weeks after a 3-day course of methylprednisolone with new findings of right middle collapse, pleural effusion, endobronchial narrowing, and had confirmation of TB by Gene Xpert/MTB. The patient in the Patil et al [5] report was also from a TB-endemic area. However, although chronic steroid therapy is a risk factor for TB [3, 4], the actual risk of reactivation of latent TB infection or TB progression, if any, of coadministration of short-course high-dose glucocorticosteroids and single dose TCZ is unknown.

In the absence of previous TB history, suspicion for active TB depends on risk factors and clinical findings. In a recent report of TB and COVID-19 disease, only 52% had radiographic features suggestive of TB [10]. In another case series, the diagnosis of TB was delayed until CT showed TB-consistent findings [11]. Serial CXRs in our patient over the entire hospital stay showed only findings consistent with the initial COVID-19 pulmonary disease until hospital day 29. These data suggest that radiographic features of TB can be obscured by COVID-19 infiltrates leading to delayed recognition. Earlier use of chest CT scan and sputum acid-fast specimens could have led to earlier diagnosis of TB and treatment.

Consideration of TB was also delayed by the effects of glucocorticosteroids on fever response and by the subsequent respiratory isolation of *K pneumoniae* and attribution of

persistent fever, leukocytosis, and CT findings of necrotizing pneumonia to hospital-acquired pathogens. Hypervirulent *K pneumoniae* is associated with tissue necrosis and pulmonary cavitation [17]. It is more common in community settings than in healthcare settings and is associated with high frequency of septicemia and metastatic infection, which were not present in our patient. Blood cultures were repeatedly negative in our patients, and there was no evidence of metastatic infection on CT scan on hospital day 29.

Diabetes, particularly in the setting of poor diabetes control, may depress TB host defenses via several mechanisms and is a risk factor for TB disease [18]. Although historical data on hemoglobin A1C were not available for our patient, he presented with a serum glucose of 222 mg/dL. Diabetes control was suboptimal during hospitalization. Lower lobe involvement of TB has also been reported in diabetes [18, 19] with more frequent lower lobe cavitation in diabetic patients compared with nondiabetic patients [19]. In our patient, lower lobe cavitory process initially led to an evaluation for hospital-acquired pathogens including COVID-19-associated pulmonary aspergillosis [20]. Although endobronchial specimens for galactomannan tests were not performed, serial sputum cultures and serum galactomannan tests were negative. Despite treatment for hospital-acquired pathogens, the cavitory lung process progressed within 1 week. Multiple factors could have contributed to the progression of cavitory disease including delayed diagnosis of TB, suboptimal diabetes control, and initial ineffective therapy of *K pneumoniae*.

## CONCLUSIONS

Clinical deterioration in severe COVID-19 disease may be associated with the presence of coexisting pulmonary infections, including TB, as our case demonstrates. The clinical presentation of these coinfections can be atypical and confounded by COVID-19 lung disease. Thus, vigilance and consideration of locally prevalent infections are needed to reduce the risk of adverse outcomes. Our case highlights the importance, even during the COVID-19 surge, of obtaining complete histories together with maintaining a high index of suspicion for both hospital-acquired infections and coinfection with TB when epidemiology, individual-level history, and relevant clinical findings are identified. With the expectations that glucocorticosteroids and other immunosuppressive therapies will be increasingly used, timely use of CT when clinical response is slow or atypical for isolated COVID-19 disease together with appropriate microbiological evaluation could lead to prompt identification of coinfections and improved outcomes.

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**Author contributions.** A. S. and A. A. were involved in the entire process including background research, initial draft, editing of the manuscript, and providing of imaging. S. C. and N. S. provided thorough guidance and editing of the entire manuscript. All authors reviewed the final manuscript and approved its contents.

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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