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Case report

Non-typhoidal Salmonella bacteremia in COVID-19 with recrudescence of fever after corticosteroid discontinuation: A case report

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ABSTRACT

It is challenging for clinicians to determine the cause of occurrence of fever in COVID-19 patients after corticosteroid discontinuation. Blood cultures help us distinguish between secondary infections and rebound phenomena. We report a case of non-typhoidal *Salmonella* bacteremia in a 34-year-old male COVID-19 patient who developed fever after discontinuing corticosteroids.

Introduction

The efficacy of corticosteroids for the treatment of COVID-19 has been established in clinical practice via several clinical studies [1]. Recent studies have shown that 8.5% of hospitalized COVID-19 patients have secondary bacterial infections, which result in a higher mortality [2,3].

Fever is one of the most common symptoms of COVID-19 [4]. A recent study revealed it is important to determine whether the occurrence of fever in COVID-19 patients after steroid discontinuation was caused by the rebound phenomenon or bacterial infections [5]. Bacterial infections have been reported in COVID-19 patients treated with corticosteroids, but the recrudescence of fever post-corticosteroid discontinuation has not been investigated [6,7]. Here, we report the case of an immunocompetent Japanese male patient with moderate COVID-19, who developed non-typhoidal *Salmonella* (NTS) bacteremia after methylprednisolone discontinuation.

Case report

A 34-year-old male patient described a five-day history of fever with dyspnea on exertion at a neighborhood hospital and was determined to be positive for COVID-19 using antigen-detecting rapid diagnostic tests for SARS-CoV-2. The patient was transported to our hospital for admission. On day five following the onset of symptoms, the patient's temperature was 38.4 ℃, and oxygen saturation was 95% on 3 L per minute of supplemental oxygen via nasal cannula. Blood test results demonstrated a leukocyte count of 4370 cells/μL (reference range, 3500–8500) and a C-reactive protein (CRP) value of 1.42 mg/dL (reference range, 0–0.30). Computed tomography (CT) scan of the chest showed multiple bilateral patchy ground-glass opacities (GGOs) (Fig. 1, panel A). Treatment with remdesivir and methylprednisolone (80 mg/day for three days followed by 40 mg/day for four days) was initiated. Oxygen therapy was not needed by day seven of hospitalization, and the patient was afebrile by day 10 of hospitalization.

On day 12 of hospitalization, the patient developed a fever of 39.0 ℃; chills and blood-tinged sputum were observed. The blood culture was positive for *Salmonella spp.* Colonies on sheep's blood agar were confirmed via matrix-associated laser desorption ionization–time of flight (MALDI-TOF; Bruker, Billerica, MA, USA) mass spectrometry. The isolates on Mueller–Hinton Agar (Becton Dickinson Japan, Fukushima, Japan) were tested with polyvalent O and O1 antigens as well as the Vi antigen (Denka, Osaka, Japan). Serological identification revealed that polyvalent O was positive (O9), polyvalent O1 was negative, and Vi was negative; these were categorized as *S. enteritidis* or *S. sendai.* The patient had no recent history of consumption of common foods of animal origin. During the hospital stay, the patient ate only cooked hospital meals. The sputum, urine, and feces cultures were negative for *Salmonella*. A follow-up chest CT on day 13 of hospitalization showed bilateral

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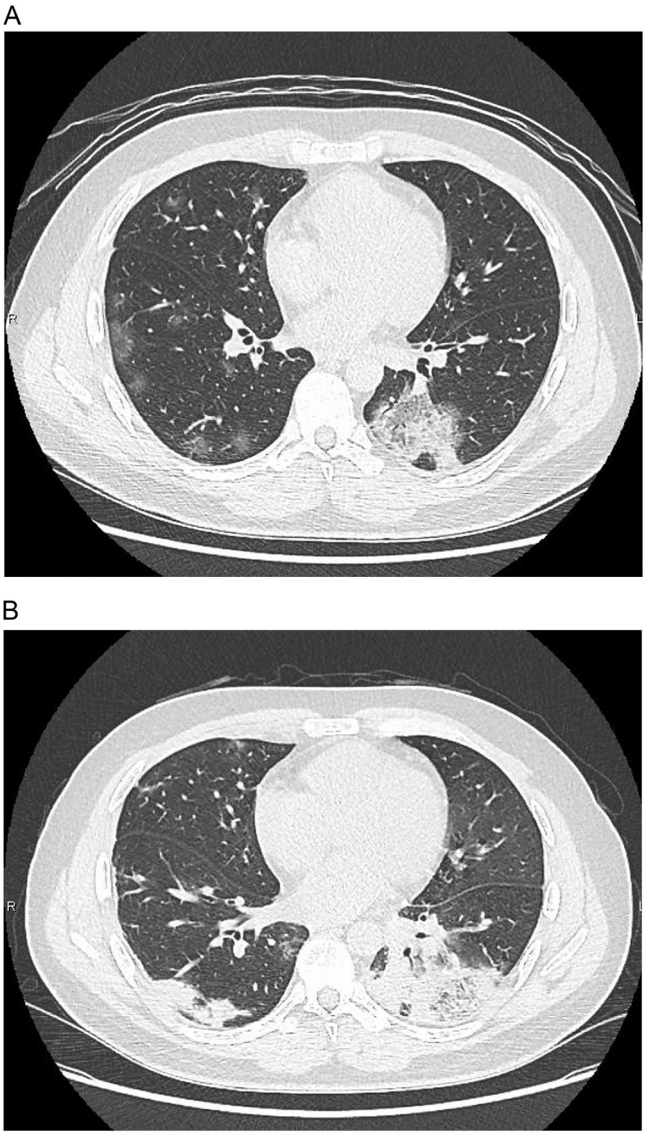

Fig. 1. Chest computed tomography (CT) scan of a patient diagnosed with positive antigen-detecting rapid diagnostic tests for SARS-CoV-2, Japan. A) Chest CT on day 1 of hospitalization showing multiple bilateral patchy ground-glass opacities (GGOs). B) Chest CT on day 13 of hospitalization showing bilateral consolidation and no worsening of multiple bilateral patchy GGOs.

consolidation and no worsening of multiple bilateral patchy GGOs (Fig. 1, panel B). No gallstones nor aortic abnormalities were observed on abdominal ultrasound and non-enhanced CT. The patient was HIV antigen/antibody-negative.

Ceftriaxone 1 g intravenously was initiated on day 14 of hospitalization, but the patient's fever remained unresolved. Two days later, the susceptibility to NTS was assessed according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The patient showed intermediate resistance to ceftriaxone and susceptibility to levofloxacin. Therefore, we initiated treatment with 500 mg of oral levofloxacin daily. The patient's fever and non-bloody sputum gradually disappeared. The patient was discharged on day 16 to complete a 14 day course of levofloxacin.

Discussion

NTS disease typically results in self-limited, acute gastrointestinal infections as well as bacteremia with or without extraintestinal focal infections [8]. The occurrence of NTS in hospitalized patients is uncommon, and bacteremia is more likely to occur in patients under clinical immunosuppressive conditions, such as those receiving corticosteroid treatment [9]. NTS can rarely cause pulmonary infections, especially in immunocompromised hosts [10]. Although the sputum culture after ceftriaxone administration was negative, the lung lesions could also have been caused by NTS. Our patient exhibited NTS bacteremia with the recrudescence of fever after initial defervescence, post-corticosteroid discontinuation. Blood cultures helped us to identify NTS bacteremia as the source of fever.

To our knowledge, we found no report differentiating between rebound phenomenon involving corticosteroids and secondary bacterial infection in patients with COVID-19. However, there are potential clues to differentiate the two. First, the time of the recrudescence of fever could be useful for differentiation. The rebound phenomenon can be observed after the reduction or cessation of steroid treatment for COVID-19, and it has been described within a median of 12 days (maximal median, 19 days) after symptom onset, which tends to occur in patients who receive corticosteroids for a shorter time. There has been no case of rebound phenomenon after 20 days [5]. On the other hand, the median time from admission to the diagnosis of secondary infection in is 19 days (range, 11–29.75 days), especially among COVID-19 patients in the intensive care unit [11]. Second, the risk of secondary infections and the causative pathogens in COVID-19 patients are similar to those in hospitalized patients without COVID-19 [12]. It is reasonable to focus more on changes in a patient's symptoms, except for the recrudescence of fever, and obtain microbiological cultures, including blood cultures, to identify the focus from secondary bacterial infections. We initially found no sign suggestive of bacterial infection, other than fever, in our patient on day 16 from symptom onset and thought the patient could have developed rebound phenomenon. However, subsequently, blood cultures showed that he had NTS bacteremia. A previous study showed that 80% of COVID-19 patients received antimicrobials at some point during hospitalization, with most patients receiving them despite having negative blood cultures [13]. From the antimicrobial stewardship perspective, it is essential to determine whether the fever in COVID-19 patients is associated with infection or with other factors, such as rebound phenomenon to corticosteroid, which will contribute to appropriate use of antimicrobials.

In conclusion, the recrudescence of fever in our COVID-19 patient after corticosteroid cessation was attributable to NTS bacteremia, and not the steroid rebound phenomenon. Blood cultures helped us to differentiate between the rebound phenomenon and secondary infection.

CRediT authorship contribution statement

Aoi Yogo was responsible for the coordination and writing of the clinical case. All authors contributed to the writing of the final manuscript, and agree to be accountable for all aspects of the work.

Ethical approval

The patient provided written informed consent for publication of this case report in print form in English.

Consent

The patient provided written informed consent for publication of this case report in print form in English

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Conflicts of interest

The authors have no competing interests to declare.

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