Case Report

Atypical clinical presentation of inflammatory marker negative septic arthritis, osteomyelitis, and bacteremia following a single dose of tocilizumab in the treatment of COVID-19: a case report

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Background: Tocilizumab is an immunomodulating agent that inhibits the inflammatory cascade via interleukin-6 (IL-6) signaling. A recent meta-analysis written by the World Health Organization, and other large, randomized trials, have found that the medication results in reduced all-cause mortality in the treatment of severe coronavirus disease 2019 (COVID-19) illness, likely by targeting aberrant inflammatory pathways. With the medication now recommended by infectious diseases societies in the treatment of COVID-19, many providers will begin using this medication in critically ill patients, and for some it will be their first exposure to the medication and its side effects. Although atypical secondary infections have been observed following multiple administrations of tocilizumab, our case is significant as it displays an atypical presentation of invasive bacterial illness and sepsis following a single dose.

Case Description: Our case consists of a 52-year-old man with severe COVID-19 pneumonitis who was given tocilizumab due to worsening respiratory status and elevating inflammatory markers, who later developed severe, invasive bacterial disease with minimal objective findings suggesting severe illness. Six days following tocilizumab administration, the patient was diagnosed with *Staphylococcus aureus* (*S. aureus*) bacteremia, septic arthritis, and osteomyelitis, at which time inflammatory markers were within normal limits, he was no longer febrile or tachycardic, and his only objective findings suggesting illness were a tender shoulder with an isolated, neutrophilic predominant leukocytosis. This complication resulted in a washout of a septic joint, a 6-week course of intravenous antibiotics, and a 59-day hospitalization. The patient was discharged without new chronic medical issues, including a lack of new end-organ dysfunction or chronic pain of the joint affected by septic arthritis.

Conclusions: This case demonstrates an atypical presentation of gram-positive systemic infection, displaying the complications which may develop with the use of immunomodulators. Because of the potential for severe infection with atypical, insidious presentation, a high index of suspicion should be maintained in all patients receiving these agents.

Keywords: Tocilizumab; coronavirus disease 2019 (COVID-19); bacteremia; delayed diagnosis; case report

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Introduction

Two years into the global pandemic caused by coronavirus disease 2019 (COVID-19), our treatments for this disease have improved beyond our initial interventions, however, the need for more therapeutic options could not be greater. Promising interventions to date have targeted severe disease, which is typically characterized by elevated acute phase reactants and inflammatory markers suggesting a pathogenic host response similar to cytokine storm syndrome (1). Therefore, reducing the severity of this inflammatory process is a key target in interventions being investigated, supported by the mortality benefit observed with steroids (2). Interleukin-6 (IL-6) elevation has been noted to be prognostic of respiratory failure requiring mechanical ventilation and in-hospital mortality (3,4), making IL-6 inhibition a potential target for disease modification.

Tocilizumab is a humanized anti-IL-6 receptor antibody which inhibits receptor binding, commonly used in severe and refractory rheumatologic ailments, which results in inhibition of pro-inflammatory downstream processes and prevention of activation of T-cells (5). A meta-analysis (1) of data from randomized control trials has recently shown a decrease in 28-day all-cause mortality (6), with data of the RECOVERY (7) and REMAP-CAP (8) trials showing reduced mortality, leading to an increase in the use of the medication. With its strong immunomodulatory and immunosuppressive effects comes increased risk for bacterial, viral, and fungal infections (9), particularly when co-administered with other immunosuppressive agents (10). Compared to other immunomodulating agents, tocilizumab results in significantly increased risk of serious bacterial infections (11). In one case report, a patient receiving tocilizumab weekly was observed to have inflammatory marker negative septic arthritis without leukocytosis (12). This suggests that there is not only an increased risk for infections, but that these infections may have subtle or atypical presentations which can result in delayed diagnosis. With this, we will describe a case of inflammatory marker negative septic arthritis, osteomyelitis, and bacteremia in a patient treated with a single dose of tocilizumab. We present the following case in accordance with the CARE reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-121/rc).

Case presentation

A 52-year-old man with a history of diabetes, hypertension, and recent myocardial infarction was admitted from the emergency department with increasing dyspnea on exertion 4 days after a diagnosis of COVID-19 infection established after evaluation for flu-like symptoms. The patient was tachycardic and required supplemental oxygen with a PaO_2 to FiO_2 ratio of 228. Chest imaging revealed diffuse pulmonary infiltrates with a small right sided-pleural effusion. Laboratory data included elevated C-reactive protein (CRP), D-Dimer, and Ferritin with a normal white blood cell (WBC) count with neutrophilia, as shown in *Table 1* (along with trends and significant in-hospital events).

On admission, the patient started a 5-day course of intravenous remdesivir (200 mg once followed by 100 mg) and a 10-day course of intravenous dexamethasone (6 mg daily). His outpatient medications, metoprolol 100 mg and aspirin 81 mg daily were continued in addition to insulin for glycemic control. On the next day, the patient's oxygen requirement increased (PaO_2 to FiO_2 ratio of 72), requiring transfer to the medical intensive care unit at which point convalescent plasma (2 units) was administered. On day 4, the patient became tachycardic and febrile, radiographic opacities progressed, and inflammatory markers increased significantly. He was felt to have "cytokine-storm" and tocilizumab (approximately 6 mg/kg) was administered per the hospital wide protocol. On day 7, the patient required noninvasive positive pressure ventilation at a continuous pressure of 10 mmHg. The patient's SOFA score would increase from 2 to 4 due to the use positive pressure ventilation, and his PaO_2 to FiO_2 ratio would reach its lowest value of 70. Positive pressure ventilation was discontinued the following day. He did not require invasive mechanical ventilation.

On day 9, the patient developed right shoulder pain associated with limited range of motion, new hypotension, and leukocytosis without fever or inflammatory marker elevation. Blood, sputum, and urine cultures were obtained. On day 10, the patient's leukocytosis worsened, he remained tachycardic, but he looked well and remained afebrile, though he did receive a single dose of 650 mg acetaminophen for shoulder pain. The following day, both blood cultures grew gram positive cocci, and his urine culture grew *Staphylococcus aureus* (*S. aureus*). Vancomycin was started and the dose was adjusted to a level of 10–15 µg/mL,

Table 1 Course of laboratory tests and other objective data with significant in-hospital events over time

Trended data	Hospital intake	ICU admission		Tocilizumab given		NIV begun	Blood cultures collected	Antibiotics started			MRI positive for septic arthritis	Surgical I&D and washout		Discharge
	Day 0	Day 1	Day 2	Day 4	Day 5	Day 7	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 59
PaO_2/FiO_2	228	72	85	80	73	70	140	136	165	182	204	203	200	428
Max. T, ℃	37.7	36.7	37.1	39.2	37.2	36.7	37.0	37.1	36.7	37.0	37.4	36.8	36.8	36.6
Max. HR, beats/min	110	95	85	123	88	–	100	119	118	112	114	121	95	89
Min. BP, mmHg	96/59	108/71	117/65	102/53	109/59	93/56	86/60	94/64	112/54	104/68	109/64	107/51	112/68	101/59
WBC count, k/μL	8.1	5.2	10.5	10.5	12.0	9.3	15.8	21.4	21.2	13.6	9.4	11.5	12.5	8.0
Neutrophil, %	79.4	73.3	82.3	87.2	87.2	85.8	86.6	92.7	92.5	82.4	79.4	83.7	83.0	52.2
Lymphocyte, %	12.6	16.5	9.0	7.4	7.0	6.4	6.7	4.2	3.2	10.4	10.8	7.8	8.8	24.3
Eosinophil, %	0.0	0.0	0.0	0.2	0.2	0.4	0.8	0.2	0.1	1.8	1.9	2.6	2.8	14.2
CRP, mg/dL	10.02	–	3.53	16.48	–	–	0.61	–	–	0.15	–	0.27	–	0.40
D-Dimer, μg/L	123	103	75	157	–	–	162	–	–	–	–	–	–	230
Ferritin, ng/mL	1,497	2,346	2,025	–	–	–	907	–	–	–	–	1,089	–	417
ESR, mm/h	–	–	–	–	–	–	4	–	–	13	–	–	–	–

NIV, non-invasive ventilation; I&D, incision and drainage; Max., maximum; T, temperature; HR, heart rate; Min., minimum; BP, blood pressure; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

then switched to cefazolin at 2 g every 8 hours when antibiotic susceptibility became available. The following day, his blood pressure stabilized, but his shoulder was more painful with severe limitation in range of motion refractory to opioids.

On day 13, MRI revealed septic arthritis of the acromioclavicular joint with osteomyelitis. The patient remained afebrile. A source for the patient's staphylococcal bacteremia with septic arthritis and osteomyelitis was not obvious as the patient had no central venous, arterial, or foley catheters, and he had no areas of skin breakdown. The patient did have a peripheral intravenous catheter in place for greater than the recommended 4-day use, and though there was no gross evidence for phlebitis at the IV site, it was felt that the source for infection was a subclinical peripheral phlebitis from the peripheral intravenous line.

On day 15, surgical incision, drainage, and washout of the right acromioclavicular joint and subacromial space was performed. Exudate obtained during the operation grew *S. aureus* with identical resistance patterns to previous positive urine and blood cultures. Inflammatory markers, excluding ferritin, remained within normal limits throughout this time. From the time of acquisition of positive blood cultures to the patient's surgical washout resulting in definitive source control, the patient's SOFA score remained 2 with no end organ dysfunction. On Day 59, the patient was discharged to complete a 6-week course of intravenous cefazolin for septic arthritis and osteomyelitis. At the time of discharge, the patient had no residual pain or organ dysfunction. Although his stay was prolonged, he was able to go home without pain, without the need for supplemental oxygen and was pleased to have avoided intubation.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Although studies estimate a low incidence of bacteremia due to a peripheral catheters causing peripheral phlebitis (13,14), the use of significant immunosuppressive agents may have added to the patient's risk of bacteremia from this source. In addition to increasing the risk of developing serious systemic infections, the use of tocilizumab may have contributed to an atypical presentation of bacterial sepsis—the absence of fever and tachycardia on the day blood cultures were collected. Multiple comorbidities plus the use of immunosuppressive agent in patients critically ill with COVID-19, or in patients with severe rheumatologic ailments, may cause atypical presentations of invasive bacterial disease. In our patient, the presence of high-dose steroids, antipyretics, beta-blockers, and a history of diabetes are factors that also might prevent the typical response to infection. Although the patient was undergoing dexamethasone therapy (6 mg daily), a recent case series described 9 cases of inflammatory marker negative invasive disease in patients receiving multiples doses of tocilizumab with or without steroids (15), suggesting tocilizumab, independent of coadministration with other immunosuppressants, is a significant cause for atypical presentation of infection.

Our case is notable in its developing following a single dose of the medication. Regarding single-dose administrations of tocilizumab in the treatment of COVID-19, studies have shown an increase in late-onset secondary infections and a mean decrease in CRP by 80% 5 days following tocilizumab administration at doses of 4 mg/kg or higher (16), similar to the observation in the described case. Although the degree of the effect of tocilizumab in this presentation of sepsis is not clear because of the patient's history of non-insulin dependent diabetes mellitus, the appreciable suppression of inflammatory markers 5 days following the drug's administration was consistent with the effect noted by Pettit *et al.* (16). Because the patient did not have typical signs of sepsis, empiric antibiotic therapy was delayed until cultures were reported as positive. Despite being septic, the patient had few sequelae of sepsis given his SOFA score remained low and did not at any point significantly increase. Although the antibiotic therapy was initially delayed, further delay would be possible if not for a high index of suspicious resulting in early culturing for a potential secondary bacterial infection. Altogether, our case suggests that the use of tocilizumab may increase the risk of developing serious infection, including from less common etiologies such prolonged peripheral intravenous catheter placement, and may result in an atypical presentation with the potential to delay diagnosis and treatment conferring additional risk.

A recent meta-analysis conducted by the World Health Organization (6) and other large, randomized control trials (7,8) studying the efficacy of tocilizumab in COVID-19

have shown a decrease in all-cause mortality compared to early in the COVID-19 pandemic. This will lead to a significant increase in the use of the medication, possibly for the first time for some. Although the presence of adverse events was rare in all mentioned studies, multiple instances of secondary bacterial infection have been noted, including with *S. aureus*. This is consistent with previous data associating tocilizumab with increased risk of infection (10,11), which is of concern in COVID disease because this appears to occur even following a single dose of the agent.

With the recent addition of tocilizumab to recommendation guidelines for those affected with severe disease of increasingly infectious COVID-19 variants, the use of the tocilizumab will continue to increase. For many, this will be one of the first contexts in which providers will have experience with this immunomodulator. Therefore, when patients are treated with tocilizumab and/or other immunosuppressive agents in the context of COVID-19 or rheumatologic diseases, this case report serves as an example of potential secondary effects and the high index of suspicion required when secondary infections are being investigated, regardless of lab results or vital signs which may be otherwise reassuring.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-121/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-121/coif). WDC is an unpaid member of the Board of Directors of a local Christian Health Center and teaches a course on spirometry at University of Illinois Great Lakes Center. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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