Case Report

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Citrobacter freundii-associated osteomyelitis and thromboembolic events following Moderna COVID-19 vaccination: a rare case report from Nepal

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Introduction: Vaccination against coronavirus disease 2019 (COVID-19) is essential for controlling the ongoing cases of this disease. Citrobacter infections of the bones and joints are extremely uncommon. Thromboembolism and deep vein thrombosis (DVT) are very rare complications.

Case presentation: The authors present a rare case of osteomyelitis, septic arthritis, deep venous thrombosis, and pulmonary embolism in a 15-year-old previously healthy boy occurring shortly after receiving the second dose of the Moderna COVID-19 vaccine. He experienced pain, swelling in the right leg, shortness of breath, and fever, followed by chest pain and leg edema. Treatment included anticoagulation, ketorolac for pain management, antipyretics, and intravenous antibiotics (Tazobactam/Piperacillin, Linezolid, Clindamycin) for osteomyelitis.

Discussion: The risk of COVID-19 vaccine-related thrombotic events is minimal. Thrombotic events reported among mRNA is very rare. *Citrobacter freundii* bone and joint infections are very rare, accounting for a small percentage of cases. Some documented cases include cefotaxime-resistant strains causing necrotizing fascitis and osteomyelitis, including postarthroplasty infections. Due to the diverse range of susceptibility patterns and the widespread occurrence of drug resistance, personalized treatment based on culture and sensitivity testing is recommended. However, in rare cases, severe complications like DVT and joint infections associated with Citrobacter infection may occur and should be reported to the vaccine adverse events reporting system.

Conclusion: Administering the COVID-19 vaccine to enhance natural antibodies is crucial, despite the low risk of infection, thromboembolism, and DVT. Healthcare providers should stay vigilant about adverse effects postvaccination and promptly report those cases.

Keywords: *Citrobacter freundii*, deep venous thrombosis septic arthritis, moderna COVID-19 vaccination, osteomyelitis, pulmonary embolism

Introduction

Vaccination against coronavirus disease 2019 (COVID-19) is the cornerstone of controlling and mitigating the ongoing pandemic[1]. In December 2020, the United States Food and Drug Administration issued an Emergency Use Authorization (EUA) for the Moderna COVID-19 vaccine (mRNA-1273 SARS-CoV-2)[2]. Initial trials have shown the 2-dose vaccine efficacy to be 94.1% in preventing COVID-19 illness including severe disease[3]. The risk of COVID-19 vaccine-related thrombotic events is minimal and likely manageable with available treatments. *Citrobacter freundii* infection and thrombotic adverse events reported among mRNA-vaccine remain extremely rare[4].

HIGHLIGHTS

- Vaccination against coronavirus disease 2019 is essential for controlling the disease.
- Side effects of the Moderna COVID-19 vaccine includes mild to moderate pain at the site of injection, swelling, itching, fever, and shortness of breath within a few days of vaccination.
- Pulmonary embolism and deep venous thrombosis are rare complications of vaccination.

The Citrobacter genus is part of the Enterobacteriaceae family and comprises 13 officially acknowledged species. C. *freundii* and C. *koseri* are the two species most commonly linked to human infections. These bacteria are present in the digestive tracts of both humans and various animals, as well as in various environmental settings. C. *freundii* primarily exerts its impact on human health as an opportunistic pathogen. As such, it is associated with a broad spectrum of infections, including but not limited to urinary tract infections, respiratory tract infections, wound infections, and septicemia[5]. C. *freundii* infections of the bones and joints are uncommon. We report the rare adverse event

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of *C. fruendii*-associated acute osteomyelitis, septic arthritis, acute deep venous thrombosis, and pulmonary embolism following the Moderna COVID-19 vaccination. We present the following article in accordance with the CARE reporting checklist[6].

Case presentation

A 15-year-old Asian boy without a history of trauma, insect bite, or any pre-existing chronic disease presented with complaints of pain and swelling of the right leg for 7 days, shortness of breath for 4 days and fever for 2 days, symptoms starting just 3 days after receiving the second dose of Moderna COVID vaccination on his right arm. When he was given the first dose of this vaccine it was tolerated well with only mild soreness at the site of injection. He developed pain in the right leg that was sudden in onset, progressive, and continuous cramping in nature, severe enough to restrict his daily activities. The pain worsened at night and on standing. The swelling initially involved the right foot then rapidly progressing up to the thigh, and became severe enough to restrict his walking. A few days later, he developed gray-blackish discoloration of the affected leg. Following these symptoms, he developed pricking chest pain on the right side, which was on and off in nature. It was associated with shortness of breath at rest. The fever was relieved by antipyretics. His past medical history and family history are unremarkable without any previous COVID-19 infection or prior thromboembolism. He does not smoke or consume alcohol. He was not under any medication and was never tested for thrombophilia. On physical examination he was ill-looking without any pallor, icterus, cyanosis. Tenderness, a local rise in temperature, and pitting edema over the right leg extending upto the right thigh was noticed without any abnormal examination findings of the contralateral leg. All the peripheral pulses were palpable. His respiratory rate was 44 breaths per minute, blood pressure was 118/60 millimeters of mercury, temperature was 102° Fahrenheit. The pulse was regular with a rate of 120 beats per minute and Jugular Venous Pressure (JVP) was normal. The respiratory system examination showed bilateral crepitation and bilateral equal air entry on auscultation. On cardiac examination, heart sounds were normal without any murmur. The abdominal examination showed normal findings. His mini-mental state examination score was found to be normal. One and a half months after the admission, a single sinus draining purulent discharge with bony pieces was observed in the right proximal leg. Microbiological tests showed negative for *Mycobacterium tuberculosis* on pus specimens from the wound of the affected leg. A blood culture did not reveal any pathogen. But the culture of the wound swab showed *C. freundii* sensitive to Ciprofloxacin, Cotrimoxazole, Gentamicin, and Piperacillin/Tazobactam. Biochemical evaluations showed normal blood glucose and urea with raised creatinine and normal electrolytes levels. C reactive protein (CRP) latex test was positive (3 +). Laboratory parameters of the patient are shown in Table 1.

Computed tomography pulmonary angiogram showed a hypodense nonenhancing filling defect in the segmental branch of the ascending and descending branch of the right pulmonary artery. On ultrasonography of the affected leg, a smooth, soft intraluminal mass was observed in the popliteal vein and the vein was noncompressible, suggesting the features of the popliteal vein. Based on history, examination, and investigations he was diagnosed of Deep Venous Thrombosis (DVT) and pulmonary embolism with acute respiratory distress syndrome (ARDS) and pneumothorax along with the osteomyelitis of right tibia progressing to chronic form with sinus tract formation, complicating to septic arthritis of the right knee and ankle joint. Emergency debridement, decompression and arthrotomy, proximal tibial corticectomy, long leg slabbing and external-fixation were performed. Time to time dressing was done for the discharging sinus tract. He was started on Rivaroxaban for anticoagulation and ketorolac for pain management, antipyretics, intravenous antibiotics for osteomyelitis (Tazobactam/Piperacillin, Linezolid, Clindamycin). Regular monitoring was done by imaging and Prothrombin time (PT) or international normalized ratio (INR). Figure 1 showing proximal tibial corticectomy. Figure 2 showing external fixators applies in the patient legs. The patient is currently in good health and he is on his usual activities with no any comorbidities.

Table 1

Laboratory parameters of the patient.

Parameter	Finding	Unit	Reference range
Erythrocyte segmentation rate(ESR)	65	mm/hour	0.9
Hemoglobin (Hb)	7.8	gm%	12–18
Packed cell volume(PCV)	24	%	36–54
Red blood cell (RBC) count	2.5	Million/mm^3	4.5–5.5
Platelets count	414 000	/mm^3	150 000–400 000
Mean corpuscular volume (MCV)	96	fl	82–92
Mean corpuscular hemoglobin concentration (MCHC)	32	%	32–36
Total leukocyte count (TLC)	11 300	/mm^3	4000–11 000
Differential leukocyte count (DLC)			
Neutrophils	85	%	45–75
Lymphocytes	10	%	25–45
Prothrombin time (PT)	13	s	

Discussion

After the administration of 13.8 million doses of Pfizer-BioNTech and Moderna COVID-19 vaccines to the US population during the first month of the vaccination program, the postauthorization safety profiles for both vaccines were reassuring[7]. When considered in the context of morbidity and mortality from COVID-19, the benefits of vaccination far outweigh the risk of anaphylaxis, which is treatable[8]. A recent article highlights vaccine hesitancy as a major issue in South Asian countries like India, driven by misinformation and distrust, particularly in rural areas where 65.5% of the population resides[9]. For instance, in Jamsoti village, Uttar Pradesh, there is a common belief that SARS-CoV-2 does not exist in rural areas[9]. Compared to other vaccine platforms, mRNA vaccines possess unique advantages including versatility, efficient delivery, use of the protein translational machinery of the host, and short developmental time[10]. mRNA vaccines work by introducing a small piece of genetic code (mRNA) that carries instructions for producing a particular viral protein, typically a segment of an outer membrane protein[11]. When this mRNA enters cells, they use it to manufacture the viral protein. When the immune system detects this foreign protein, known as an antigen, it typically triggers

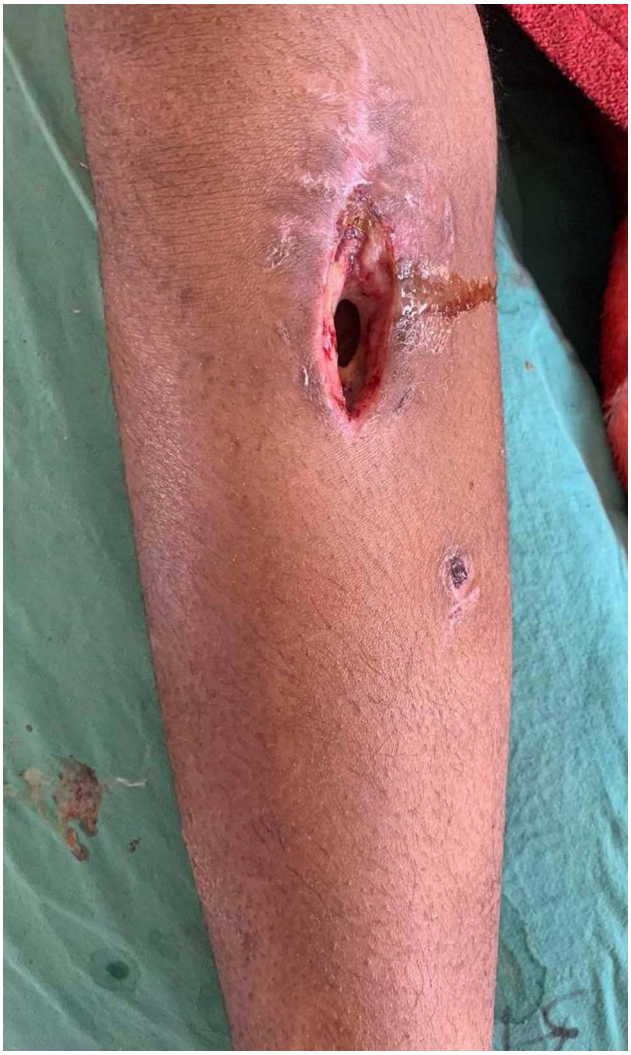

Figure 1. Showing proximal tibial corticectomy.

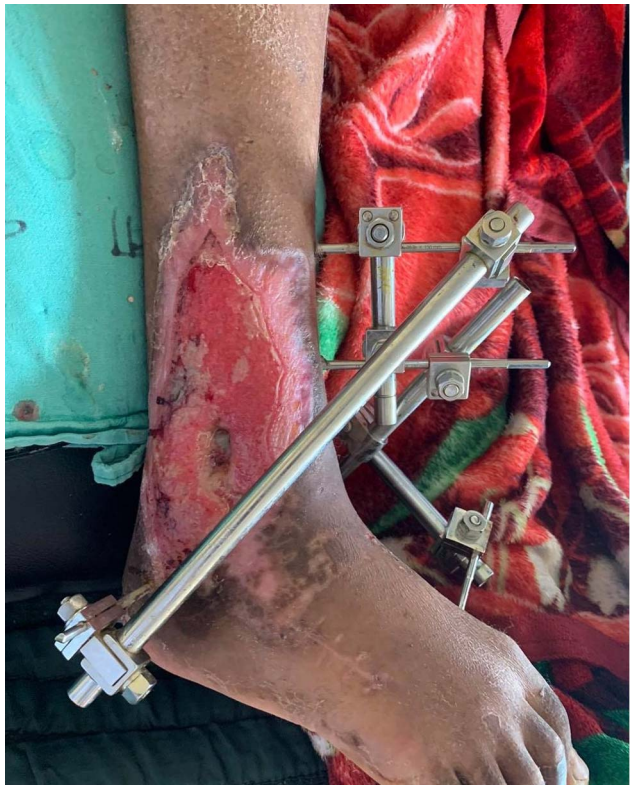

Figure 2. Showing external fixators applies in the right leg of patient.

the production of antibodies[11]. Side effects like pain at the injection site, swelling, itching, fever, and shortness of breath mostly occur within 1–2 days of vaccination and are usually of mild to moderate intensity. Systemic effects are more commonly observed in younger age groups, owing to more robust immunities as compared to the elder age groups. Adverse effects usually last for 24–48 h before resolving on their own[12]. Some studies suggest convalescent plasma therapy play a crucial role in treating individual with severe COVID-19 cases as it has the potential to act as an antiviral, reduce inflammation, modulate the immune system, and prevent blood clot formation[13]. In an article published it has been mentioned that emergency use of inactivated virus vaccines (Sinovac and Sinopharm) can prevent COVID-19 cases to some extent[14]. The Nepal government procured the Moderna vaccine for the vaccination of children aged 12–17 years[15]. Our patient developed pain and swelling in the right leg 3 days after taking the Moderna vaccine, which was diagnosed as deep vein thrombosis (DVT) of the lower limbs with osteomyelitis of the right tibia with septic arthritis of the right tibia and ankle joint associated with *C. freundii*. Adverse events that occur in a recipient after receipt of the COVID-19 vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS)[16].

C. freundii infections of the bones and joints are extremely uncommon. Lipsky *et al.*[17] conducted a comprehensive case series in which only 3.7% of the isolates were obtained from patients suffering from osteomyelitis, with many of these cases involving *C. freundii* as part of a mixed microbial population. Furthermore, Chuang *et al.*[18] reported a case of necrotizing fasciitis and osteomyelitis caused by a strain of *C. freundii* that was cefotaxime-resistant. Bruehl and Listernick[19] reported a case of septic arthritis in an 8-month-old infant, with *C. freundii* as the causative agent affecting the elbow. Stricker *et al.*[20] documented another case where a previously healthy 5-year-old boy developed septic arthritis and osteomyelitis of the elbow due to a dual infection involving both *C. freundii* and *Haemophilus influenzae* type b. In a 50-year-old diabetic woman, Nemade *et al.*[21]reported emphysematous septic arthritis of the knee caused by *C. freundii*. Pant *et al.*[22]documented a 46-year-old diabetic patient who developed septic arthritis of the knee joint after a recent arthroplasty due to a dual infection with *Serratia marcescens* and *C. freundii*. As per our knowledge, this is the first postvaccination infection with *C. freundii* to cause a bone infection.

The occurrence of DVT concurrent with osteomyelitis is relatively uncommon, and it has typically been reported as a complication of Staphylococcal infections owing to bacterial virulence[23]. In our literature search, we did not find any documented association between DVT and *C. freundii* osteomyelitis[23]. Nevertheless,

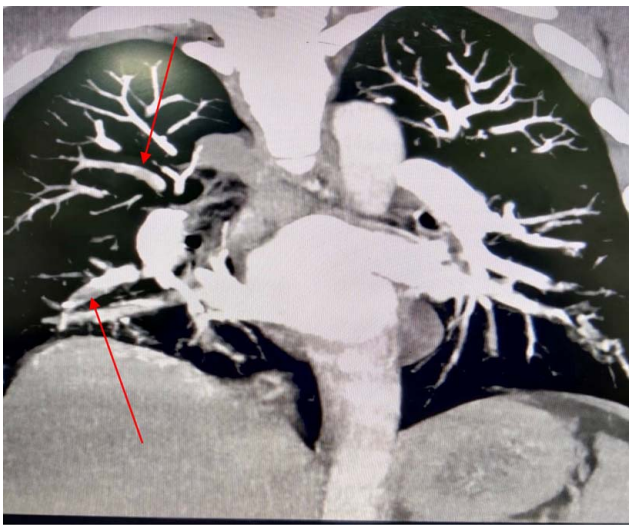

Figure 3. CT scan showing hypodense nonenhancing filling defect in right pulmonary artery. (red arrow).

possibility remains open. The most common cause of pulmonary embolism (PE) is DVT. PE occurs when a blood clot obstructs a lung artery, causing blood flow to be disrupted[20].

The risk of COVID-19 vaccine-related thrombotic events is minimal and likely manageable with available treatments. Thrombotic adverse events reported for the three vaccines (Oxford-AstraZeneca, Pfizer, Moderna vaccine) remain extremely rare[4]. In the systematic review and meta-analysis of eight RCTs conducted by Uaprasert *et al.*[24] involving nearly 200 000 participants showed that the risks of overall thromboembolism, arterial thromboembolism, venous thromboembolism, hemorrhage, and death related to thromboembolism and hemorrhage were not significantly increased with vaccination against SARS-CoV-2. Some research has suggested a transient increase in proinflammatory cytokine production after influenza vaccination[25,26] which could theoretically indicate towards association with thromboembolism. Some study has also suggested that the mRNA COVID-19 vaccine may bind to pattern recognition receptors (PRR) in the endosomes and cytosol leading to a proinflammatory cascade and coagulopathy[27]. In our case, the patient was diagnosed to have pulmonary embolism whose symptoms started to appear only a few days after the vaccination, which was diagnosed based on the computed tomography of the chest. Moreover, bilateral pleural effusion and pneumothorax with collapse consolidation of basal segments of both lungs was also seen. The pleural effusion and pneumothorax were comparatively more in left and right lung, respectively. The thrombotic event could be due to osteomyelitis or a direct adverse effect of the vaccine. Owing to history of our patient with no co-morbidity and any risk factors, we highly suspect vaccination as a provoking factor for the infection and thromboembolic event.

C. freundii is a formidable pathogen, and research has shown that a significant number of isolates frequently exhibit drug resistance[28,29]. Because of the variety of susceptibility patterns and the high prevalence of drug resistance, tailored treatment for each patient based on culture and sensitivity testing is advised[21]. Our patient was treated accordingly Figures 3, 4.

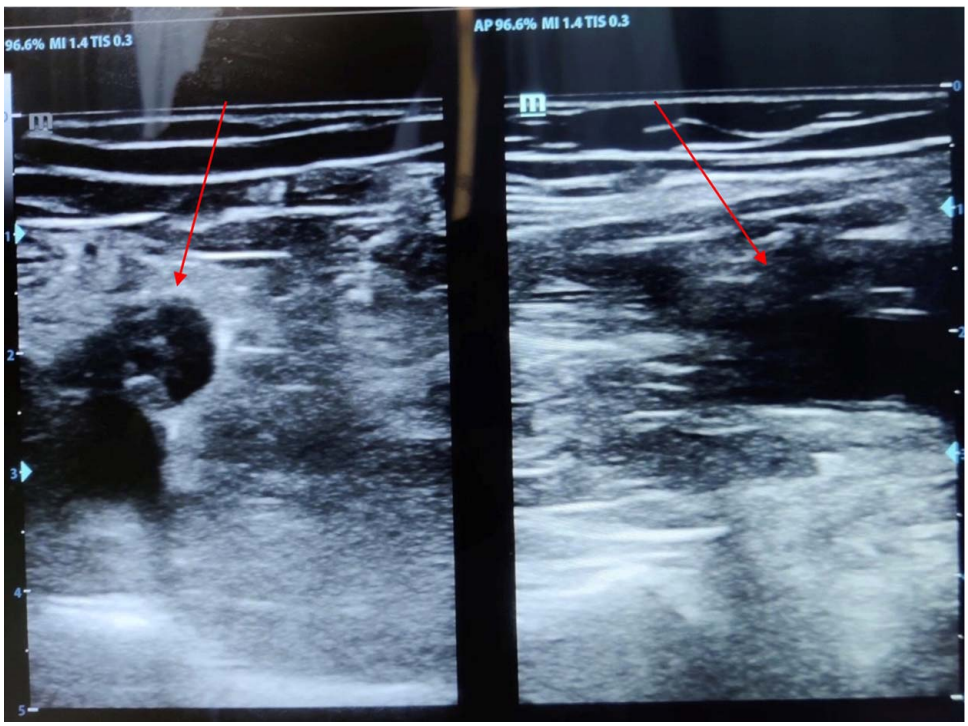

Figure 4. Ultrasonography showing echogenic content within noncompressible popliteal vein. (red arrow).

Conclusion

In summary, we have presented a very rare case of our region of *C. freundii*-associated osteomyelitis, DVT, and thromboembolism due to the Moderna vaccine with a slightly elevated platelets level. Vaccination against COVID-19 with a booster dose to increase endogenous antibodies is essential even though there is a very low risk for infection and subsequent thromboembolism and DVT as in this case. We encourage clinicians to remain alert about adverse effects after SARS-CoV-2 immunization and report these cases to the Vaccine Adverse Events Reporting System (VAERS) or an equivalent system of other countries.

Ethical approval

The ethical committee of our institute 'IOM-IRC' does not require approval for case reports.

Consent

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 Editor-in-Chief of this journal on request.

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No funding was received for the study.

Author contribution

S.A., P.P., S.K.C., S.B., Y.R.A.: wrote the original manuscript, reviewed, and edited the original manuscript; S.D., B.P. and M.B. P.: reviewed and edited the original manuscript.

Conflicts of interest disclosure

Authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

None.

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

All available data are within the manuscript itself.

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