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Diabetic Foot Osteomyelitis Caused by Francisella Tularensis

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ABSTRACT

Purpose: A rare patient case of a diabetic foot osteomyelitis caused by Francisella tularensis is presented.

Summary: A 69-year-old Caucasian female was admitted for the treatment of diabetic foot osteomyelitis. Her past medical history included type II diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, hypothyroidism, hyperuricemia and thyroidectomy. Empiric antimicrobial therapy consisting of clindamycin 600mg i.v. every 8hrs and impanel/cilastatin 200 mg i.v. every 6hrs hours was initiated immediately after admission. During her hospitalization, a pus sample from the infection site was taken for culture which showed a gram negative microorganism: Francisella tularensis. The strain was resistant to all the antibiotics tested with the exception of ciprofloxacin, ofloxacin, gentamicin, ceftazidime, cefepime, piperacillin/tazobactam and colistin. After culture results, the treatment regimen was changed to piperacillin/tazobactam 4.5g i.v. every 12hrs and ciprofloxacin 400mg i.v. every 12hrs. The patient continued to receive both antibiotics during hospitalization for 9 days with noted clinical improvement. The patient was discharged on piperacillin/tazobactam 4.5g i.v. every 12hrs and oral ciprofloxacin 500mg every 12hrs to complete a total duration of 6 weeks.

Conclusion: This is the first reported case of a diabetic foot osteomyelitis caused by Francisella tularensis.

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Introduction

In 2020, 34.2 million people in the United States (10.5% of the population) are living with diabetes [1]. One of the most debilitating complications that can arise from uncontrolled diabetes is diabetic foot ulcers (DFUs). Approximately 60% of diabetic foot ulcers progress to become diabetic foot infections (DFIs), and 20% of those infections lead to some form of amputation [2]. Diabetic foot osteomyelitis (DFO) is mostly a complication of a preexisting infected foot ulcer, arising via contiguous spread that can be with or without vascular insufficiency. Overall, about 20% of patients with a diabetic foot infection (and over 60% of those with severe infections) have underlying osteomyelitis, which dramatically increases the risk of lower-extremity amputation [3].

Indeed, osteomyelitis is one of the most difficult aspects of the management of DFIs due to decreased antibiotic penetration to the less vascularized bone tissue. Furthermore, the treatment is complicated by the presence of diabetic neuropathy and peripheral vascular disease. Staphylococcus aureus is the most common isolated pathogen, followed by Staphylococcus epidermidis. Methicillin-resistant Staphylococcus aureus is more likely to occur in patients with carbuncles or abscesses who have failed initial antibiotic treatment, in patients who are markedly immunosuppressed, in patients with systemic inflammatory response syndrome and hypotension, and in patients with previous history of MRSA infection or colonization [4]. Among the gram-negative bacilli, Escherichia coli, Klebsiella pneumoniae, and Proteus species are the most common pathogens. Pseudomonas aeruginosa is isolated mainly in areas of high local prevalence, warm climate, and frequent exposure of foot to water. An increasing prevalence of multi-drug resistant bacteria, already established for soft tissue infections of the diabetic foot, has also been reported for DFO [4].

Francisella tularensis is a highly infectious, fastidious, aerobic, gram-negative coccobacillus. It causes a rare but potentially serious bacterial zoonosis, called tularemia. F. tularensis can be transmitted by handling infected animals, tick bites, animal bites especially cats, and ingestion of contaminated food or water. Infection can also occur by inhalation of contaminated dust. It is endemic in large areas of the northern hemisphere and incidence was positively correlated with the presence of lakes and rivers. During 2001–2010, a total of 1,208 cases were reported (median: 126.5 cases per year) [5]. After an incubation period of 3–10 days,

the patient typically develops a skin lesion (ulcer eschar) at the entry site of the organism along with tender adenopathy in regional lymph nodes. The illness is often associated with substantial fever, chills, headache, and malaise [6].

Very few case reports of human infection by F. tularensis are reported in the literature; only one of which described a hand osteomyelitis infection in a non-diabetic patient [7].

Here, we present the case of a 69-year-old female admitted to our hospital for a diabetic foot osteomyelitis with vascular insufficiency caused by F. tularensis. To our knowledge, this is the first reported case of DFO caused by F. tularensis.

Case report

A 69-year-old Caucasian female (height: 166cm; weight: 82 kg, no known food or drug allergies) presented with a right diabetic Charcot foot ulcer, with necrosis of the left big toe and right ankle wound. The patient's history goes back to 4 days before hospital admission when she presented for outpatient laboratory tests and cultures (white blood cell (WBC) count: 16.04 x10^3/µL, serum creatinine (SrCr): 2.57 mg/dL). The patient has a past medical history of hypertension, type II diabetes mellitus of more than 10 years ago, coronary artery disease (CAD) around 9 years ago, chronic kidney disease (CKD) stage IV with a baseline SrCr = 2.8-3.0 mg/dL, hypothyroidism, hyperuricemia and thyroidectomy. Upon admission, the patient was afebrile 98.6°F (37°C) with a normal heart rate of 76 beats per minute (bpm) and a normal respiratory rate of 20 breaths per minutes. The findings of cardiovascular examination were normal. Blood pressure and fasting blood glucose concentration were uncontrolled with 147/77 mmHg and 166-214 mg/dL respectively. The calculated creatinine clearance upon admission using the Cock-croft Gault equation was 17.4 ml/minute. Initial laboratory test results are shown in table 1.

Table 1: Baseline laboratory test results

Laboratory test results	Patient's results	Normal range
White Blood Cells (x10^3/mm^3)	10.98	4-10
Hemoglobin (g/dL)	7.4	13-17
Platelet count	413,000	140,000-400,000
Neutrophils (%)	81.8	54-62
Blood urea nitrogen (mg/dL)	73	8-18
Serum creatinine (mg/dL)	3.82	0.8-1.2
C-reactive protein (mg/dL)	7.3	<0.5
Polymerase Chain Reaction COVID-19	Negative	Negative

On physical examination, there was evidence of lower extremity edema, ulcer oozing, and blackish discoloration of the toes. Magnetic resonance imaging (MRI) was done to confirm the suspected osteomyelitis. Consequently, the patient was diagnosed with a DFO with vascular insufficiency. Appropriate wound debridement and drainage was performed. The empiric antimicrobial treatment consisted of linezolid (Zyvox®,Pfizer) 600 mg i.v. every 12 hours and imipenem/cilastatin (Tienam®, Merck, Sharp & Dohme) 200 mg i.v. every 6hrs hours. Due to medication shortages, the patient took only 2 doses of linezolid then it was switched to clindamycin (Clindamycin Vianex®, Vianex SA) 600mg i.v. every 8hrs. During hospitalization, the patient experienced an acute kidney injury with a SrCr: 3.82 mg/dL, CKD anemia, uncontrolled type II diabetes mellitus, uncontrolled hypertension.

Concomitant medications during hospitalization included: amlodipine, bisoprolol, acetyl salicylic acid, atorvastatin, levothyroxine, allopurinol, esomeprazole, metoclopramide, insulin sliding scale, hydration and acetaminophen as needed. After 5 days, blood and deep wound culture results were positive showing F. tularensis. The strain's susceptibility results are summarized in table 2. Accordingly, the empirical treatment was discontinue and piperacillin/tazobactam (Tazocin®, Pfizer) 4.5g i.v. every 12hrs and ciprofloxacin (Ladinin®, Pharmathen) 400mg i.v. every 12hrs were initiated. The isolated F. tularensis strain was relatively a resistant microorganism, showing sensitivity only to ciprofloxacin, ofloxacin, piperacillin/tazobactam, ceftazidime, cefepime, gentamicin, and colistin. During the hospitalization in the internal medicine ward, the patient showed clinical and laboratory improvement. Therefore, the patient was discharged on piperacillin/tazobactam (Tazocin®, Pfizer) 4.5g i.v. every 12hrs and ciprofloxacin 500mg p.o every 12hrs to complete a total duration of 6 weeks of antimicrobial therapy.

Table 2: Susceptibility results of the Francisella Tularensis strain

Antibiotic	Susceptibility
Ampicillin	R
Amoxicillin/clavulanic acid	R
Piperacillin	R
Cefazolin	R
Ceftriaxone	R
Ertapenem	R
Nalidixic acid	R
Tigecycline	R
Trimethoprim / Sulfamethoxazole	R
Piperacillin/tazobactam	S
Fosfomycin	S
Ceftazidime	S
Cefepime	S
Ofloxacin	S
Ciprofloxacin	S
Colistin	S
Gentamicin	S

Discussion

Osteomyelitis is widely considered the most difficult and controversial aspect of treating a diabetic foot infection4. Our patient also had a Charcot foot, a neuro-osteoarthropathy that is sometimes difficult to distinguish from DFO. These two conditions can coexist, which may render osteomyelitis diagnosis more difficult and may also mask progressive bone destruction [4].

The identified organism was F. tularensis, which is an aerobic gram-negative coccobacillus bacterium and the causative agent of tularemia. Serious complications potentially associated with tularemia can include sepsis and disseminated infections [2].

Streptomycin and gentamicin are the preferred antibiotics for the treatment of severe tularemia. For mild to moderate tularemia, tetracycline and doxycycline are appropriate. Oral levofloxacin or ciprofloxacin may be reasonable options [6]. B-lactams show variable unreliable activity against F. tularensis as many strains can be inherently resistant. Because F. tularensis is a facultative intracellular bacterium, only antibiotics with appropriate intracellular pharmacokinetic and pharmacodynamic properties are active [6].

The isolated strain in this patient case was a relatively resistant organism. The patient received piperacillin/tazobactam and ciprofloxacin after the results of the culture were available. Our patient, having an acute kidney injury on top of CKD, wasn't prescribed aminoglycosides due to potential drug accumulation and the risk of nephrotoxicity, ototoxicity, and neurotoxicity.

Tetracyclines were not an option as well because the strain was resistant to tigecycline. The strain was sensitive to ciprofloxacin and ofloxacin but was resistant to nalidixic acid. Due to the cross resistance between fluoroquinolones, we ideally need a minimum inhibitory concentration (MIC) to confirm the efficacy of ciprofloxacin on the specific strain. Our patient was prescribed dual antimicrobial therapy with piperacillin/tazobactam and ciprofloxacin. The choice of double antibiotic treatment may be due to the fact that the organism is an unfamiliar cause of osteomyelitis. The patient clinically improved and thus was discharged on intravenous piperacillin/tazobactam and oral ciprofloxacin.

The only other case report of F. tularensis causing osteomyelitis described a 10-year-old girl who developed a persistent hand osteomyelitis following a cat bite [7]. The patient presented with a recurring fever of 103°F (39.4°C) that was persistent and the onset was around 2 weeks after the animal bite. The patient was treated with gentamicin and was able to maintain full dexterity of her hand after a 2-month follow-up and had complete resolution of the infection after 6 months [7]. The culture results and susceptibilities were not provided in the published case report.

Conclusion

This is the first case report in the literature describing the isolation of F. tularensis from a diabetic foot osteomyelitis. The patient was treated with surgical wound debridement and dual antibiotic therapy for a total duration of 6 weeks.

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