CASE REPORTS

Case report: Infected foot ulcer and methicillin-resistant staphylococcus aureus bacteremia in a diabetic patient

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ABSTRACT

Diabetic foot ulcer is one of the most frequent complications affecting the diabetic patient. While there has been considerable progress regarding the diagnostic tools and the range of antibiotic choices, the outcome is often unsatisfactory, the presence of peripheral arterial occlusive disease being among the main factors influencing the evolution. This paper describes the management of a patient presenting with an infected foot ulcer and persistent methicillin-resistant Staphylococcus aureus bacteremia, further complicated by spondylodiskitis and infectious endocarditis: the case gives an opportunity to review the literature in search of the optimal care and the right treatment choices.

Key Words: Diabetic foot ulcer, Bacteremia, MRSA, Spondylodiskitis

1. INTRODUCTION

The infected foot ulcer is a frequent and serious complication associated with diabetes. The majority of cases present a poor outcome; furthermore, the health care costs cannot be overlooked.[1] It is estimated than 15%-25% of all diabetic patients are at risk of suffering from an infected foot ulcer during their lifetime.[2]

What is the mechanism implicated in the diabetic foot infection? Knowing that diabetics present foot ulcers far more often than the general population, one could easily speculate that two factors play a major role: diabetic polyneuropathy and macrovascular or microvascular ischemia (due to pe-

ripheral arterial occlusive disease of the lower extremities - PAOD). With no sufficient arterial blood flow, the access of the macrophages in the site of the infection is restrained, therefore considerably limiting the concentration of the antimicrobial agent, augmenting thus the risk of infection. The infection induces micro-thrombosis, responsible for more tissue ischemia and necrosis, leading to gangrene – ultimate stage before amputation. Diabetic foot is a chronic inflammatory disease, demanding constant and specialized care, as well as recurrent hospitalizations. It must be also underlined that perpetual use of antimicrobial therapy in these patients enhances the risk of developing multidrug-resistant bacteria strains. Foot ulcers are commonly colonized with

more than one microorganism, and a foot ulcer infection can accelerate dramatically with devastating consequences if appropriate treatment is not given promptly. The choice of antibiotic therapy should be based on culture isolation and antibiogram.

2. CASE PRESENTATIONS

A 71-year-old man was admitted to the hospital for fever persisting for > 24 hours; he also presented redness and swelling of his frontal right foot and an ulceration on the left 5th toe. His medical history included:

- diabetes known for at least 20 years
- coronary heart disease (3 bypass)
- peripheral arterial occlusive disease (endovascular stent placement in the left common iliac artery and left external iliac artery)
- amputation of his left 4th toe a year earlier (due to an infected foot ulcer)

In admission, the patient had a temperature of 39.8°C with chills. Cardiac auscultation revealed a heart murmur of 4/6 (known); lung and abdominal exam unremarkable. The right frontal foot was erythematous and cold. There was also an erythematous, exudative ulcer on the external side of the left foot.

The patient was evaluated in the Emergency Department of our hospital: CRP was 80 mg/L and WBC $8,530 \times 10^3$ mm^3 with 90% neutrophils; X-rays of both feet did not reveal anything in particular (nevertheless, taking into consideration the patient's medical history, an osteomyelitis could not be excluded based on X-rays alone). Blood cultures were also performed and revealed the presence of methicillin-resistant Staphylococcus aureus (MRSA), sensitive to vancomucin (MIC between 0.5 and 1 μg/ml). The patient was put under treatment by vancomycin IV, with plasma concentrations followed at 48-hour intervals. A transoesophageal echocardiography (TEE) was performed (due to his MRSA-bacteremia and his preexisting valvular disease) and found negative for endocarditis. A SPECT/CT of the lower extremities showed an extensive cellulitis of the right foot, but no signs of osteitis. Fundoscopy did not reveal septic emboli. A doppler ultrasonography confirmed the presence of severe ischemia of the right leg, with occlusion of the right femoral artery; an angiography was scheduled, considering the possibility of revascularization by femorotibial artery bypass.

The patient's fever resolved in the course of a few days under antimicrobial treatment with vancomycin, with plasma concentrations being optimal (never below 20.5 mg/L) at all times; nevertheless, CPR reached a peak of 269 mg/L, later

declining only to 86 mg/L, while blood cultures (realized regularly at 48-hour intervals) remained positive for MRSA - always with a MIC < 1 μg/ml. In the presence of persistent MRSA-bacteremia, despite antimicrobial therapy, an abdominal scanner was performed, in search of an abscess – and turned out negative. Once more a SPECT/CT (whole body this time) confirmed the cellulitis of the right foot with no signs of osteitis; nevertheless, an increased uptake was also discovered at L2/L3 (it was that same day that the patient started to complain of lumbar pain, that kept worsening every day). An MRI confirmed the presence of a spondylodiskitis L2/L3 as well as a paravertebral abscess. Vancomycin was maintained but tigecycline was added to his treatment, due to the presence of abscess. At the same time, necrotic lesions appeared at the 4th and 5th right toes, turning to dry gangrene in the course of only a few days. The patient was transferred to the Department of Cardiovascular Surgery, for a scheduled femorotibial artery bypass; nevertheless, due to the rapid expansion of the necrosis on the right foot, a transfemoral amputation was performed. Tigecycline was discontinued, while vancomycin went on for 5 weeks altogether. Cultures realized on the site of amputation one week after surgery did not reveal any presence of MRSA – no blood cultures were performed, as the patient remained apyretic. On terms of biology, however, an inflammatory syndrome was always present, with a CRP remaining at 86.5 mg/L.

The patient was once again admitted to our Department 20 days after his amputation, presenting a fever at 38.3°C and disabling lumbar pains (making convalescence impossible). The same old MRSA (with a MIC at 2-3 μg/ml this time) was isolated in blood cultures, with no glycopeptide- or exotoxine-resistant sub-population. A new MRI of the spine confirmed once more the pre-existing spondylodiskitis at L2/L3, as well as necrotic erosion of the L2 vertebral body. The patient was immediately placed under linezolid 600 mg 3x daily. Transthoracic echocardiography (TTE) revealed an endocarditis of the mitral valve (with vegetations > 2.5 cm). Considering the critical condition of the patient, surgery was not an option; pursuing antimicrobial treatment with linezolide for 6 weeks seemed the only possibility (the risk of myelosuppression taken into account). Under this treatment, an improvement of his clinical (no fever) and biological status (CRP declining from 90.7 mg/L to 8.8 mg/L at day 22) was witnessed, with the blood cultures remaining nevertheless persistently positive for MRSA. It was after 4 weeks of linezolide treatment that a blood culture turned negative for MRSA for the first time; it was also at that same day that a pancytopenia was observed (WBC: 3,700/mm^3, 1,900 neutrophils, Hb: 8.0 g/dl, PLT: 105,000/mm^3) – not extraordinary, considering a daily dose of 1,800mg linezolide for

more than 20 days. With pancytopenia worsening the following days (WBC: 3,700/mm^3, 1,700 neutrophils, Hb: 7.1 g/dl, PLT: 94,000/mm^3), antibiotic therapy had to be discontinued; the patient's condition deteriorated within days, and he died 2 weeks later.

3. DISCUSSION

Staphylococcus aureus is a leading cause of both community-acquired and hospital-acquired bacteremia. Patients with Staphylococcus aureus bacteremia (SAB) can develop a broad array of metastatic infections, that may be difficult to recognize initially and can increase morbidity and mortality; SAB often causes infectious endocarditis, septic arthritis, osteitis or spondylodiskitis; it can also lead to sepsis and septic shock.[3] These issues make the treatment of SAB particularly challenging. Despite of the use of new antimicrobial agents and support treatments, mortality remains high, from 20% to 32%; predictive factors include:[4–10]

- age (the most prominent factor)
- multiple comorbidities (cirrhosis, chronic renal failure, cardiac congestion, immunosuppression)
- site of primary infection (bacteremia following pneumonia and endocarditis present the highest mortality rates)
- persistent bacteremia
- presence of septic shock
- intensive care unit stay
- duration of antimicrobial therapy before SAB is identified / antimicrobial therapy chosen empirically
- delay in source control of foci of infection
- evaluation by infectious disease specialist

Glycopeptides like vancomycin constitute a first-choice antibiotic therapy to treat MRSA-bacteremia,[11, 12] inasmuch as sensibility is confirmed by antibiogram. In fact, vancomycin MIC is considered an independent predictive factor of MRSA-bacteremia associated mortality: Van Hal et al.[13] note that a vancomycin MIC > 1.5 μg/ml is associated with higher mortality rates in MRSA-bacteremia; the MIC being $\geq$ 2 μg/ml, the authors' advice is choosing a different antibiotic. IDSA (Infectious Diseases Society of America) suggests linezolide in persistent MRSA bacteremia and vancomycin treatment failure;[14] Holmes et al also found an association between vancomycin MIC $\geq$ 1.5 μg/ml and mortality rate in patients with SA bacteremia, independent of the antibiotic chosen (suggesting that the use of vancomycin was not per se the crucial factor in case of poor outcome).[15] However, other studies failed to confirm those findings: Adani et al.[16] did not find any apparent association between the vancomycin MIC and clinical outcomes;

Baxi et al.[17] failed to show any significant increase in mortality, readmission or recurrence of the disease in a cohort of individuals with SAB attributable to vancomycin MIC.

Vancomycin remains the antimicrobial therapy of reference in most cases of MRSA-bacteremia,[3] and obviously the initial antibiotic of choice for the treatment of MRSA-bacteremia due to isolates with vancomycin MIC $\leq$ 2 μg/ml, with daptomycin and ceftarolin being promising alternatives.[18] Van Hal et al.[11] also suggest the use of teicoplanine or tigecycline as alternative options, even if their efficacy in terms of survival remains to be proven.

So, where can we attribute the failure of vancomycin treatment of a MRSA-bacteremia despite a MIC within the susceptible range? Although often attributed to antibiotic failure, persistent MRSA-bacteremia more often is due to poor control of foci of infection.[12] Literature data suggests various independent risk factors: endocarditis and pneumonia as the source of bacteremia present are predictors of vancomycin treatment failure;[18] infection is always more complicated in case of osteomyelitis,[19] when an infected foreign body is present (IV catheter or prosthesis), or in the case of endovascular infections.[20] Other risk factors are: poor APACHE-II score (Acute Physiology and Chronic Health Evaluation – describing the severity of the general status), MRSA rather than MSSA strains, older age, acute renal failure,[21] no response to antimicrobial treatment within 72 hours from introduction.[22]

In the case of diabetic foot infection, the presence of chronic arterial occlusive disease (peripheral arterial occlusive disease – PAOD) of the lower extremities is an important predictive factor. The healing of a diabetic foot ulcer has been shown to be considerably slower in patients with PAOD, whereas the presence of occlusive arterial disease also seems to be an important predictive factor of major amputation in patients presenting diabetic foot ulcers;[23] moreover, it has been shown that, in type 2 diabetic patients, the presence of micro and macrovascular complications was related with increased infection-related mortality.[24] At present, it is not entirely clear why a diabetic foot infection is more prevalent and so more difficult to treat in the presence of PAOD: peripheral vascular disease (and not the diabetes per se) could limit the delivery, and therefore penetration, of antibiotics to infected foot tissues.[25] We can only speculate whether aggressive revascularization could contribute to a better control of the infection, considering that even after revascularization of major arteries (bypass or stenting), microvascular artery disease would still be present. In the case of our patient, the peripheral artery disease was prominent: a fact that could explain the poor outcome, despite the early introduction,

optimal antimicrobial therapy choice and optimal plasma concentrations obtained.

It is also a subject of speculation whether the site of primary infection in the case of our patient was only his foot, or whether a metastatic infection was already present when he was admitted at the hospital. The cellulitis of the soft tissues in the right foot was confirmed twice (with two consecutive SPECT/CTs), but no osteitis was found. It was a third, whole body SPECT/CT that revealed an area of high tracer uptake at L2/L3, turning out to be an infectious spondylodiskitis (very probably, though not confirmed, by the same MRSA strain). It should be noted that the patient only described lumbar pains for the first time on the day he had his second SPECT/CT performed; this is why his spondylodiskitis was initially considered to be a metastatic infection. But was it so? It is practically impossible to know the exact moment of infection of an intervertebral disk by septic emboli in the case of hematogenous infectious spondylodiskitis; still, in the case of postoperative infectious spondylodiskitis (where the moment of infection obviously is known), the onset of symptoms occurs at an average of 27.7 days following surgery

(2-53 days),[26] or even longer,[27] with fever and chills appearing well before lumbar ache. In the case of our patient, lumbar pain emerged 20 days after his admission to hospital; so, the hypothesis of a preexisting MRSA-spondylodiskitis, even before hospital D1, certainly cannot be confirmed - but not excluded, either. In that case, the spondylodiskitis could have been the factor contributing to the persistent bacteremia and treatment failure by vancomycin, during the first crucial weeks.

4. Conclusion

We have presented the case of a diabetic patient with an infected foot ulcer associated with a persistent MRSA-bacteremia. The approach in such cases remains a major problem, with optimal (confirmed by blood cultures) antimicrobial therapy introduced promptly, as well as evaluation by an infectious disease specialist, playing a crucial role. Nevertheless, even when all evidence-based care processes are followed respectfully, the outcome remains a challenge.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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