CASE REPORT

Serratia marcescens osteomyelitis in Cushing's disease

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SUMMARY

We report a case of a 46-year-old man with fever, hypotension and arthralgias of the ankles and knees after brain surgery for a pituitary tumour causing Cushing's disease. Blood and urine cultures isolated *Serratia marcescens*; antibiotic susceptibility testing showed sensitivity to piperacillin-tazobactam and ciprofloxacin. Articular MRI showed inflammation and necrosis of both knees and ankles, and left hip and right elbow (compatible with osteomyelitis). Culture of an ankle abscess on the ankle joint was positive for *Serratia marcescens*. Bone scintigraphy confirmed osteomyelitic lesions. Medical treatment included antibiotics and strong opioid therapy for 14 weeks. The patient was discharged clinically improved maintaining ciprofloxacin for 24 additional weeks based on clinical and analytic recovery.

BACKGROUND

Serratia spp (particularly *Serratia marcescens*) have been recognised as a cause of serious infection in man since the 1960s, and even today account for approximately 2% of nosocomial infections (1.4% of nosocomial bloodstream infections, from any origin including the urinary tract).^{1–3} Cases of *S. marcescens* osteomyelitis in adults have been reported in association with intravenous drug use or other exogenous exposure (such as directly on a surgical site, trauma or from intra-articular injections).^{4–12} To the best of our knowledge, and based on a comprehensive literature review, this report is of a rare case of *S. marcescens* osteomyelitis in an adult with no history of drug use or any other direct exposure.^{13–16}

CASE PRESENTATION

We report a case of a 46-year-old man, with a medical history of hypertension, treated with captopril and an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma diagnosed the previous year (following investigation of a progressive visual loss) and submitted to surgical resection. He was re-admitted to the hospital after identification of a tumour regrowth, with a hormonal evaluation revealing low thyroid-stimulating hormone (TSH) and thyroxine (T4) levels, as well as elevated ACTH and cortisol compatible with Cushing's disease. He was again submitted to a trans-sphenoidal resection, after which he was started on levothyroxin and hydrocortisone. Two days after surgery, he developed fever (39°C), refractory hypotension and arthralgias of both ankles and knees. Blood tests revealed leucocytosis (13 800/L) and an elevated C reactive protein (474 mg/dL). Blood and urine cultures were positive

for *S. marcescens*; antibiotic susceptibility tests revealed sensitivity to piperacillin-tazobactam and ciprofloxacin. The patient was then admitted to our medical intermediate care unit, with a diagnosis of *S. marcescens* sepsis.

The infection was initially controlled with parenteral antibiotic therapy (piperacillin-tazobactam). However, over a period of 5 days, fever relapsed (38–39°C, persistent, only transiently relieved by antipyretics), with worsening of arthralgia (analgesic control was only achieved with opioid therapy) and progressive association of ankles, knees and right elbow with articular/periarticular inflammatory signs and development of obvious soft tissue inflammatory signs on both legs, along with marked limitation of movement.

On examination, the patient was alert and oriented, with stable vital signs. Apart from the cutaneous and articular features described, his abdominal, cardiac, pulmonary and neurological evaluation was normal.

He completed 14 days of antibiotic therapy with piperacillin-tazobactam, after which it was discontinued, and new culture tests were cropped.

FURTHER INVESTIGATION

Blood cultures were negative. To identify other possible infectious source, a thoracoabdominal CT scan

Figure 1 Sagittal T2-weighted MRI of left tibiotarsal joint, showing an abscess (green arrow), oedema and inflammation of tibial epiphysis (red arrow), and area of osteonecrosis with typical serpentine pattern or pathognomonic double-line sign in the Achilles tendon insertion (blue arrow).

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Figure 2 Coronal T1-weighted MRI scan of the femoral upper epiphysis (A) and lower epiphysis (B), showing areas of oedema and inflammation (red arrows).

was performed, which revealed mild bilateral pleural and pericardial effusion. Transoesophageal echocardiogram showed no masses or vegetations. Widal and Huddleson reactions were negative. Brain CT and MRI showed remnants of the surgical procedure, without evidence of abscess or any other infectious lesion. A lumbar tap revealed clear cerebrospinal fluid, with sterile bacteriological examination.

To explore the osteoarticular symptoms described (especially involving the legs, and mainly the left ankle), other examinations were performed. Left tibiotarsal radiography revealed a pathological fracture of the calcaneus; no other bone lesions were identified on radiological examination. There were no skin lesions or disruption to suggest a traumatic injury.

A MRI scan of the lower limbs revealed high-intensity areas on T2-weighted sequences suggesting oedema and inflammation compatible with osteomyelitis of the epiphysis of the femur and tibia, as well as the calcaneus, in contiguity with which an evident soft tissue abscess was identified (figures 1–3). Areas of osteonecrosis with a typical high-intensity serpentine pattern were also found on the same T2-weighted MRI sequences (figure 1).

Bone scintigraphy was also performed and confirmed the osteomyelitic lesions described (figure 4).

The external inflammatory signs on the left ankle evolved to an obvious cutaneous abscess lesion (also identified on the MRI), which was submitted to surgical drainage with removal of a large amount of purulent fluid (figure 1). The culture test was positive for *S. marcescens*, with the same antibiotic sensitivity as previous cultures.

These results were consistent with a diagnosis of *S. marcescens* osteomyelitis.

DIFFERENTIAL DIAGNOSIS

Before MRI results were available, and after exclusion of other sources of infection, we focused on the differential diagnosis of a possible arthritis involving several joints, mainly on the lower limbs. We considered two main hypotheses in order to explain our findings: a reactive or a septic arthritis.

Some features of the classic reactive arthritis were present in this case, such as an inflammation of fewer than five joints in addition to the primarily affected, predominantly of the lower extremities. This autoimmune condition is a cross-reactivity that develops normally in response to a genitourinary or gastrointestinal infection. It strikes men more commonly than it does women, and those between the ages of 20 and 40 years. Symptoms generally appear within 1–3 weeks of the initial infection. The arthritis that follows usually affects the large joints, such as knees, causing pain and swelling with relative sparing of the small joints.

While reactive arthritis is a sterile inflammatory process that usually results from an immune consequence of an infection, septic arthritis represents a direct invasion of joint space by a microorganism. This diagnosis should be considered whenever a rapid onset of joint pain on one or more joints is in question. This case involved an infectious process, therefore a reactive arthritis hypothesis seemed to be less likely.

To distinguish a septic arthritis from an osteomyelitis, other complementary diagnostic tests would be required. Radiography of the joint is neither sensitive nor specific. In osteomyelitis, radiography only shows changes after 7–10 days, and it takes 2 or more weeks for periosteal and lytic lesions to be revealed. In septic arthritis, radiograms can show widening of the joint

Figure 3 Coronal T1-weighted (A) and T2-weighted (B) MRI scan of the tibia, showing high signal intensity of vastus intermedius and lateralis muscles suggesting myositis (green arrow), areas of oedema and inflammation of tibial epiphysis (red arrow) and areas of osteonecrosis (blue arrow).

Figure 4 Body scintigraphy (Tc-99m and Gallium-67). (A) Multiple areas of inflammation and infection on knees and ankles, left hip, right elbow and skull base. (B) Extensive and multifocal areas of osteonecrosis, osteomyelitis and myositis.

space, with joint dislocation, but these are difficult to detect by this examination.

MRI is better for bone and soft tissue diseases. Signal abnormalities in the bone marrow, such as high-intensity areas on T2-weighted MRI, can indicate oedema and inflammation typical of osteomyelitis (figures 1–3) that are different from synovial enhancement, perisynovial oedema and joint effusion (typical of septic arthritis and absent in this patient). It has been reported that sensitivity of MRI for the detection of septic arthritis is 67% and specificity 98%, hence this process was excluded as a diagnosis in this patient.

Gallium-67 and technetium-99m scans are nuclear medicine studies that use a radioactive tracer to obtain images of a specific type of tissue or disease with an inflammatory process. Therefore, uptake of radioactive tracer on specific bone areas suggests osteomyelitis (figure 4). Technetium-99m protocol has three phases: soft tissue tracer uptake occurs in the first two and bone uptake (revealing osteomyelitis) only in the later phase, with a 2 h interval. This difference, associated with the ability of gallium to be taken up by inflammation and both, acute and chronic infection, allows the discrimination between soft tissue infection and bone osteomyelitis lesions shown by this patient (figure 4).

Figure 5 Body scintigraphy (Tc-99m and Gallium-67) performed 1 year after discharge. (A and B) Uptake of radioactive tracer on right knees and left ankle suggesting inflammatory process in resolution.

TREATMENT

Assuming the diagnosis of *S. marcescens* osteomyelitis, antibiotic therapy was resumed, with piperacillin/tazobactam (4.5 g four times a day) and ciprofloxacin (500 mg two times a day) according to the known antibiotic susceptibility test. Potent analgesic therapy was also maintained and a physical therapy programme was gradually introduced. Medical treatment with double antibiotic therapy was maintained for 14 weeks, after which piperacillin/tazobactam was suspended and oral ciprofloxacin was prolonged for 6 additional months, considering the progressive but slow clinical recovery and regression of inflammatory parameters, since optimal duration of therapy in these cases is not clearly established.¹⁷

OUTCOME AND FOLLOW-UP

The patient was clinically stable 30 days after reinstatement of antibiotic therapy. However, he only started to show slow but progressive improvement after 60 days (with increased motion range and reduction of pain, allowing for better physical therapy tolerance and analgesic therapy step down). It is important to note that subfebrile temperatures persisted for several weeks and afebrile only occurred after 63 days of treatment. Laboratory tests revealed a gradual decrease of inflammatory parameters with normal leucocyte count (9400 u/L; 68%

Figure 6 Coronal T1-weighted MRI scan of the femoral upper epiphysis (A) and lower epiphysis (B), performed 1.5 years after discharge, showing imaging improvement, with complete resolution of all inflammation areas within right femur, without fistulae or myositis areas (red arrow).

neutrophils) and reduction of the C reactive protein level (although it was still elevated—120.2 mg/dL). Therefore, it was decided to prolong the antibiotic therapy until clinical and analytic osteomyelitis control was achieved, which happened 6 months after single antibiotic therapy was started.¹⁷

In regard to the patient's ACTH-secreting pituitary adenoma, brain MRI showed good recovery after surgery, and endocrine tests remained stable under medication with levothyroxine and hydrocortisone.

One year later, the patient showed clinically important improvement (even though he was still attending a physical therapy programme and was dependent on a technical aid for walking). He repeated bone scintigraphy and lower limb MRI scan; both revealed signs of an inflammatory process in resolution (figures 5 and 6).

DISCUSSION

Serratia spp are opportunistic Gram-negative bacteria classified in the tribe Klebsiellae and the large family Enterobacteriaceae.^{18–20} In the hospital, *Serratia* spp tend to colonise the respiratory and urinary tracts, and cause nosocomial infections of the bloodstream, lower respiratory tract, urinary tract, surgical wounds, and skin and soft tissue in adult patients.^{7 21} Ninety per cent of patients with *Serratia* urinary tract infection have a history of recent surgery or instrumentation of the urinary tract. Most episodes of *Serratia* bacteraemia occur in males (68%) and children.^{3 4 22–24} Cases of *S. marcescens* meningitis, wound infections and arthritis have occurred in paediatric wards. In adults, most *Serratia* infections are isolated, but occasional nosocomial outbreaks occur.^{5 24} *Serratia* endocarditis, osteomyelitis and arthritis may develop following haematogenous spread in persons who are addicted to intravenous drugs or may be caused exogenously by surgery, open trauma or intra-articular injection, but these are rare cases. Recently, *S. marcescens* spinal epidural abscess formation following acupuncture and multiple skin ulcers due to *S. marcescens* in an immunocompetent patient were reported.^{15 16} *Serratia* infection carries a 7-day mortality rate of 5% and 37% at 6 months.^{3 4} The treatment of *Serratia* osteomyelitis involves antibiotics such as an aminoglycoside plus a broad spectrum β -lactam (or otherwise therapy guided by an antibiotic susceptibility test).¹⁹ Treatment should be maintained for long periods (months) because these bacteria grow rapidly in the bone and create biofilms rendering it difficult to eradicate the infection.^{3 19}

Some bacterial species may take advantage of bone weakness and immunosuppression induced by hypercortisolism, thereby causing osteomyelitis or arthritis.^{25 26} Cushing's syndrome refers to all causes of excess cortisol: exogenous ACTH tumour, adrenal tumour, excessive glucocorticoid treatment or, as shown in this case, pituitary ACTH-secreting tumour.^{27–29} Catabolic

response induced by excess cortisol causes muscle weakness, fatigability and osteoporosis in peripheral supportive tissue, creating an excellent environment for growth of some bacteria, such as the *Serratia* spp.³⁰ It is also important to remember that bone metaphysis has straight and narrow capillaries associated with larger veins, which decrease blood flow, facilitating bacterial proliferation (figures 1–3) and abscess formation in susceptible bone, as in this case (figure 1).^{28–30}

Furthermore, various strategies to resist therapy have been developed by *S. marcescens*, such as biofilm production, withdrawal of variants into the bone intracellular environment and the production of small-colony variants.⁶

We are aware that the patient reported in this article had Cushing's disease, which weakened his bone density and contributed to the development of osteonecrosis lesions, further facilitating *S. marcescens* invasion and severe osteomyelitis.²⁸

Learning points

- ▶ Nosocomial infection is serious and potentially life-threatening—minimise the risks by reducing unnecessary manipulations and procedures.
- ▶ *Serratia marcescens* is the cause of 2% of nosocomial infections; it is important to be aware of the severity and pathogenicity of this agent.
- ▶ The treatment of *Serratia* infection (osteomyelitis, particularly of concern in this case) is prolonged, due to the rapid bacterial growth in bone and likely involvement of biofilms.

Contributors All the authors were involved in the initial assessment, management and follow-up of the patient; and authors revised subsequent drafts and agreed on the final version before submission. HFGM was also involved in further follow-up and wrote the first draft. IB supervised patient management and case report writing.

Competing interests None declared.

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