

Case Report

Bacteremia with the Triad Osteomyelitis, Deep Vein Thrombosis, and Pulmonary Septic Emboli in Pediatric Age: A Case Report

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Abstract

Acute osteomyelitis (AOM) is defined as an inflammation of the bone secondary to infection. Among the most common complications of AOM is the development of a periosteal abscess and the extension of the focus locally to muscle (pyomyositis) and/or joint (osteoarthritis). However, complications with much lower incidence have been described, including deep vein thrombosis (DVT) and septic pulmonary embolisms (SPE), mainly associated with *S. aureus* infections. The AOM + DVT + ESP triad is a fairly uncommon entity in the pediatric population; however, if it is not diagnosed and treated in time, it implies a high morbidity and mortality. Treatment, which must be early and aggressive, includes targeted antibiotic therapy, anticoagulation, and focused control surgery. In this article, we describe the case of a 14-year-old boy with disseminated staphylococcal infection associated with the triad AOM+ DVT + SPE.

More Information

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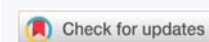
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Introduction

Acute osteomyelitis (AOM) is a relatively common pathology in children, which is defined as inflammation of the bone secondary to an infection, usually bacterial [1]. Based on its pathogenesis and evolution, it is classified as:

1. Acute hematogenous osteomyelitis. It is more common in children.
2. Osteomyelitis secondary to a contiguous source of infection (open trauma, penetrating wound, infected post-surgical wound, prosthesis, etc.). It is the second form of presentation in childhood.
3. Osteomyelitis secondary to vascular insufficiency is a very rare process in the pediatric population.

Complications of acute osteomyelitis include:

1. Extension of the focus locally to muscle (pyomyositis),

joint (osteoarthritis), or development of a periosteal abscess.

2. Deep vein thrombosis (DVT).
3. Septic pulmonary embolisms (SPS).

These last two complications have been described, mainly associated with *S. aureus* infections, especially methicillin-resistant strains or Panton-Valentine leucocidin-producing strains [2].

Osteoarticular infections are difficult to identify in the early stages of the disease and generally pose problems in both diagnosis and medical and surgical management [3].

In the literature, the presence of the triad AOM + DVT + SPE has been described as a form of presentation associated with disseminated staphylococcal infection. However, such a triad is clearly rare, and there are hardly any published cases of it. The first paper in which the OMA + DVT + SPE triad was

reported as a form of disseminated staphylococcal infection was published by Gorenstein, who suggests that the presence of this triad should prompt aggressive treatment with the appropriate antibiotics, anticoagulation, surgical drainage, and other specific treatment when indicated [4].

Case presentation

A 14-year-old adolescent presented to the Emergency Department with fever (max. temperature 39 °C) for 4 days, associated with general malaise and chest discomfort with deep inspiration, with no other associated infectious symptoms. In addition, 48 hours before admission, and being in a feverish peak, he suffered a fall with impact in the proximal area of the left tibia, with a radiological image suggestive of a probable fracture line in the tibial tuberosity, by which the limb was immobilized with a plaster cast. The patient comments, on the other hand, that about a month ago he presented 2 bites with the appearance of superinfection on both knees and nose, receiving treatment with topical mupirocin and oral amoxicillin-clavulanic [5].

No other medical history of interest. Age-appropriate weight and height.

On arrival at the emergency department, the patient was febrile and tachycardic. He complained of discomfort in the left lower limb, for which he was reassessed by traumatology, which removed the cast and remobilized him with bandages and knee orthosis. Remainder of nondescript physical examination. Normal ECG. Laboratory tests showed an increase in Ultrasensitive Troponin I (44 ng/l -cut-off point: 40 ng/l), elevation of acute phase reactants (APR) (CRP 32.1 mg/dl, Procalcitonin 49.8 ng/ml) and MDW (monocytes distribution width) (34.0), and coagulation alteration (Derived Fibrinogen 899 mg/dL, NT-proBNP 765 pg/ml, D-Dimer 17542 ng/mL, Prothrombin activity 51%, INR 1.58). On echocardiogram, pericardial effusion at the lateral ventricular level of up to 8 mm, without hemodynamic involvement, with normal cavities and mild ventricular dysfunction. With all this, microbiological screening (blood cultures) is performed, and it is decided to admit to the Pediatric ICU for management.

On admission to the Unit, and in view of the clinical suspicion of bacteremia, empiric broad-spectrum antibiotic treatment with meropenem and linezolid was initiated.

Torpid evolution in the first 48 hours with persistence of fever peaks and rebound of RPA. In the event of increased pain in the left lower extremity (LLE), the immobilization splint was removed, revealing a swollen and erythematous extremity. Venous Doppler ultrasound was performed, and extensive deep vein thrombosis was diagnosed in the territory of the left femoral and popliteal veins; therefore, anticoagulation with enoxaparin at therapeutic doses was initiated (which was maintained in range throughout admission, with serial AntiXa controls according to hematology guidelines) [6].

In the following 24 hours (day 3 of admission), pain persists, and the perimeter of LLE increases. A new ultrasound was repeated to rule out an infectious complication associated with this level, and myositis and a possible bone focus were observed. At the same time, bacteremia due to Methicillin-Susceptible *Staphylococcus Aureus* (MSSA) with negative Pantan-Valentine leucocidin was confirmed in blood cultures.

In the event of bacteremia complicated by MSSA, meropenem and linezolid were discontinued, and targeted bi-therapy with cloxacillin and daptomycin was initiated [7]. Likewise, an MRI was performed with findings suggestive of tibial osteomyelitis (also ruling out a fracture at that level) (Figure 1).

Given the extensive DVT and the possibility of surgery to clean up osteomyelitis, which would involve withdrawal of anticoagulation for at least 24 hours, with the potential risk of embolisms that this entails, on the 6th day of admission, and after joint assessment with cardiovascular surgery, it was decided to place a vena cava filter, which is withdrawn after 20 days, without incident (Figure 2).

In addition, from the 5th day of admission, the patient presented respiratory deterioration with poor mechanics and FiO₂ needs of 28% - 30% to maintain saturations, with



Figure 1: MRI of the knee joint. In the proximal metaphysis and diaphysis of the left tibia, there is a marked alteration in signal intensity, which appears hyperintense at T2 and hypointense at T1, with multiple well-defined focal lesions of serpiginous and irregular morphology suggestive of multiple bone infarctions in the context of osteomyelitis.

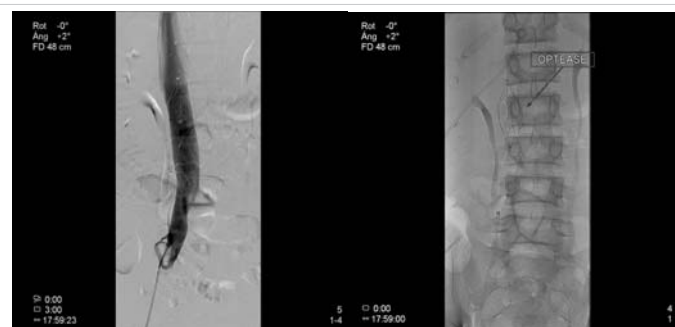


Figure 2: Image showing placement and location of the vena cava filter in an infrarenal location.

an image of condensation/left retrocardiac atelectasis on chest X-ray. Given the previous diagnosis of DVT, and with the suspicion of bacteremia complicated by the AOM triad + DVT + septic embolisms, a thoracic CT scan was performed in which pulmonary septic emboli were confirmed. In view of these findings, coverage with clindamycin is extended to cover the pulmonary focus more specifically (Figure 3).

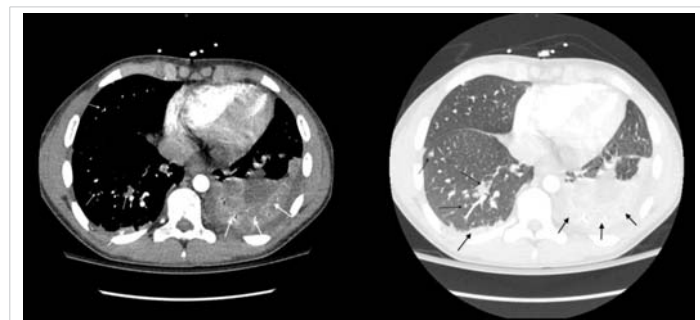


Figure 3: CT scan showing a small bilateral pleural effusion slightly larger on the left side with passive atelectasis of both pulmonary bases (thick arrows). Multiple bilateral nodular lesions, some of them cavitated, in relation to septic embolisms with an associated pulmonary infarction (thin arrows).

Poor evolution over the next two days despite targeted antibiotic coverage, with sustained fever, moderate-severe pain in LLE, and persistent bacteremia. On the 8th day of admission, it was finally decided to clean it in the operating room (perforations of the left tibia + surgical cleaning + bone graft substitute with vancomycin and gentamicin), with abundant purulent content (also isolated MSSA in surgical samples) [8].

As an adjuvant treatment, hyperbaric oxygen therapy is initiated, which is suspended after the first session due to the patient's claustrophobia, which makes it impossible for him to enter the chamber.

In the days following surgery, the patient had a slow but favorable clinical evolution, with improvement in pain, progressive decrease in fever, negative blood cultures, and decrease in RFA.

Repeated chest ultrasound due to persistent need for oxygen (oxygen through nasal prongs 2 lpm) despite improvement in general condition, the presence of left pleural effusion with minimal associated atelectasis was confirmed, and conservative management was decided with respiratory physiotherapy with an incentive, without placing a drain.

On day 11 of admission, after re-evaluating days of treatment and clinical evolution, with a very torpid onset and persistence of sustained fever, it was decided to maintain cloxacillin (treatment aimed at MSSA, with good bone penetrance) and daptomycin and clindamycin were changed for ceftaroline (after an exhaustive assessment of the case, due to its torpid evolution, despite not being a MRSA) which ensures good coverage at all levels with the idea of complying with the antibiotic therapy regimen for 6 weeks from the first negative blood cultures [9].

Given the persistent bacteremia caused by *S. aureus*, successive echocardiograms were performed during admission, in which the resolution of the pericardial effusion was verified, and the absence of infectious complications at that level was verified. Likewise, in a Doppler ultrasound of pre-discharge control, deep femoral and partially permeable left popliteal artery were observed.

The rest of the levels (hemodynamic, neurological, digestive, metabolic, and renal) have remained stable at all times.

Laboratory tests at discharge from ICU with practically normalized RFA, corrected coagulopathy, reactive thrombocytosis in clear decrease, and slight anemia after surgery (8.5 g/dL) that has been slowly corrected without requiring transfusion.

The patient was discharged from the hospital after 6 weeks of intravenous antibiotic treatment, maintaining home anticoagulation for three months [6].

Discussion

Disseminated staphylococcal disease can cause a wide spectrum of disease in children. It occurs mainly in previously healthy people, between 5 and 15 years of age, and carries high morbidity and mortality rates. Diagnostic criteria include infection in 2 or more areas and isolation of coagulase-positive *Staphylococcus* from the blood or a source of infection [1].

S. aureus is the most common cause of osteomyelitis in children. Complications and/or sequelae after an osteoarticular infection, diagnosed early and with appropriate treatment, range between 5 and 10%, being more frequent in MRSA infections and/or with the presence of virulence factors (Panton-Valentine leucocidin) [10].

Among the most frequent complications is the extension of the focus locally to muscle (pyomyositis), joint (osteoarthritis), or the development of a periosteal abscess.

A less common, though more serious complication, is DVT. This complication is more common in men, adolescents, and with osteomyelitis of the tibia or femur caused by *S. aureus*, mainly by methicillin-resistant strains.

In the pathophysiology of DVT associated with osteomyelitis, there are, beyond the causative germ, which plays a fundamental role in the disease, associated risk factors such as AT III deficiency [3].

As for the causative germ, *S. aureus* can release various exotoxins that act on cell membranes, producing smooth muscle spasm and platelet aggregation. In addition, they release a large number of enzymes (e.g., coagulase) that interact with fibrinogen, causing plasma coagulation.

On the other hand, and regardless of the causative agent, in sepsis there may be an acquired deficiency of multifactorial



AT III, secondary to a decrease in synthesis, an increase in its consumption, and an increase in capillary permeability due to the state of inflammation itself [11].

In 2014, Cilla LA, et al. and Vargas-Gutiérrez M, et al. published several cases of DVT with staphylococcal osteomyelitis in children, and in both studies, the presence of DVT associated with *S aureus infection* without prothrombotic factors coincided [12,13].

In the case we present, no immunological study or hematological tests were performed at the acute moment to demonstrate or rule out a prothrombotic state; However, the patient presented an important risk factor, such as immobilization of the left limb with an orthosis.

Another complication, even less frequent, although highly serious, is SPE, which can cause necrotizing pneumonia, emphysema, or bronchopleural fistula, among others. Different articles suggest that the association of DVT + SPE plays a fundamental role in the morbidity and mortality of disseminated staphylococcal disease in childhood [4,14].

Treatment of DVT and SPE is based on anticoagulation in addition to targeted antibiotic therapy.

Despite the lack of conclusive data, recent reviews argue for anticoagulation with low molecular weight heparin (LMWH) over unfractionated heparin (UFH) and vitamin K antagonists, as the response of the latter in children tends to be unpredictable and requires close monitoring and dose adjustment. As for direct-acting oral anticoagulants (DOAC), as they are a relatively new group of agents, there is insufficient evidence on their use in children [15].

Regarding the placement of a vena cava filter, the indications are also unclear. In a prospective study of 175 patients, it was concluded that in hemodynamically unstable septic patients who cannot tolerate respiratory compromise secondary to pulmonary embolisms, the placement of an endovascular filter would be justified, and the decision should be individualized in the rest of the patients [16].

In our case, anticoagulation with enoxaparin at therapeutic doses was initiated, with serial Anti-Xa controls according to the Hematology regimen for dose adjustment. In addition, given the extensive DVT and the need for withdrawal of anticoagulation for osteomyelitis cleansing surgery, with the potential risk of embolisms that this entails, it was decided by consensus with CCV to place a vena cava filter.

Regarding the causal treatment, it is recommended that the association of targeted antibiotic therapy + control of the surgical focus + anticoagulation, being this association the one that has shown a more satisfactory clinical evolution.

The most commonly used antibiotics with which there is the most experience in children are cefazolin, cloxacillin,

and clindamycin. In our case, in sepsis of uncertain origin, empirical antibiotic therapy with a broad spectrum of initiation (linezolid + meropenem) was used, and it was sequenced throughout the admission to achieve specific coverage of the causative germ (MSSA) and the focus. Thus, upon the diagnosis of bacteremia complicated by MSSA, linezolid + meropenem was discontinued and bi-therapy with cloxacillin + daptomycin was initiated. Subsequently, in view of the finding of septic pulmonary embolisms, coverage with clindamycin was extended to cover the pulmonary focus. And, finally, after re-evaluating the days of treatment and the clinical evolution, very torpid despite targeted antibiotic therapy, it was decided to maintain cloxacillin as a treatment aimed at MSSA, with good bone penetrance, and daptomycin and clindamycin were replaced by ceftaroline, which ensured good coverage at all levels (despite not being the first choice in MSSA osteomyelitis with negative Panton Valentine leukocidin) [9,17].

In addition to medical treatment, surgical cleaning of the lesion is recommended when a collection is observed, or in case there is no clinical improvement after 48-72 h of antibiotic therapy. However, subperiosteal abscesses, even larger than 3 mm, could evolve favorably without surgical drainage, only with targeted antibiotic therapy instituted early [1,18].

In our case, surgical cleaning was performed on the 8th day of admission, due to evidence of a partial response to antibiotic treatment.

Hyperbaric oxygen treatment has clear indications in anaerobic or mixed soft tissue infections, always as an adjunct treatment to antibiotic treatment and surgical cleaning. Myositis and osteomyelitis due to *S. aureus* is not a clear indication for the hyperbaric chamber but given the great experience of our center in hyperbaric therapy as an adjuvant for the treatment of infectious lesions with tissue devitalization, this therapy was tested, although it had to be discontinued due to lack of tolerance on the part of the patient [19].

Conclusion

The presence of osteomyelitis, sepsis and bacteremia associated with clinical deterioration should alert us to the possibility of presenting DVT and SPE, which require a high level of suspicion, specific imaging studies and early, multidisciplinary, and specialized targeted treatment, based on antibiotic therapy, surgical control of the focus and anticipation and high degree of suspicion to diagnose complications that considerably increase the morbidity and mortality.

Author's contribution

All authors have contributed to the conception, drafting, and revision of the manuscript, and approve its final version for submission.



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