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CASE REPORT

DRESS syndrome due to antibiotic therapy of osteoarticular infections in children: Two case reports[☆]



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Abstract Osteoarticular infection in children frequently occurs before 10 years of age. Surgical drainage is sometimes required, whereas acute osteomyelitis can be treated with antibiotic therapy alone. The duration of antibiotic therapy varies, 2 weeks is sufficient for septic arthritis, whereas 6 weeks is often required for complicated cases. Some of these antibiotic drugs present direct complications with low clinical impact in certain individuals.

Hypersensitivity to these drugs causes different reactions in children. DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) is a severe and potentially life-threatening drug reaction. It is characterised by high fever, malaise, lymphadenopathy and skin rash. From a clinical perspective, these symptoms can lead to an exacerbation of the initial infectious process for which treatment was commenced.

The liver is the organ most often affected in DRESS syndrome associated with haematological changes, potentially similar to sepsis.

We present two cases of children with osteoarticular infections who developed DRESS syndrome after antibiotic therapy. Both patients made a complete recovery after cessation of the antibiotic drugs used.

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Síndrome de DRESS como complicación de la antibioterapia en niños tratados por infecciones ortopédicas. A propósito de 2 casos

Resumen La infección osteoarticular en el niño es frecuente por debajo de los 10 años. El tratamiento consiste en la administración de antibióticos y en algunos casos tratamiento quirúrgico. El tiempo de antibioterapia varía, desde 2 semanas para las artritis, hasta 6 semanas en

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casos de osteomielitis más abigarradas. Algunos de estos medicamentos poseen complicaciones individuales directas con baja repercusión clínica.

Existen diferentes cuadros de hipersensibilidad a drogas descritos en la población infantil. El síndrome de DRESS consiste en una toxicodermia grave, que en ocasiones incluso puede comprometer la vida. Se caracteriza por fiebre elevada, mal estado general, adenopatías, y exantema. Desde el punto de vista clínico son síntomas superponibles a una exacerbación del proceso infeccioso previo por el que el paciente inició el tratamiento. Generalmente aparece afectación de órganos internos (sobre todo el hígado) y alteraciones hematológicas, que pueden hacer pensar en un cuadro séptico general.

Presentamos dos casos de infección osteoarticular bacteriana en niños que fueron tratados con antibióticos y que presentaron este cuadro. Ambos regresaron tras la retirada de la medicación antibiótica.

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Introduction

Osteoarticular infection in children usually causes local pain, reddening, functional failure and often high fever in cases with septic arthritis and a lower fever in cases of acute or chronic osteomyelitis. Depending on the germ involved, patients may also present a skin rash and local lymphadenopathies.

The most common origin of osteoarticular infection in children is haematological. Generally, a respiratory or gastrointestinal germ crosses into the bloodstream and may colonise a distant joint or bone region. The initial treatment is based on administration of wide-spectrum antibiotics and surgical drainage in cases, which require it. The duration of antibiotic therapy varies depending on the specific infectious process, and may last for a long period. Some of these drugs entail specific direct complications with low clinical repercussion. These complications normally remit once the drug treatment is removed.¹

Different cases of hypersensitivity to drugs have been described in children.¹⁻⁴ There is a severe type of toxicoderma, known as DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms),²⁻⁴ which consists in the belated appearance of fever and malaise in patients treated previously for an infectious process. The first thought of the surgeon is usually a worsening of the initial symptoms and failure of the medical or surgical treatment. This syndrome is characterised by high fever, lymphadenopathies, exanthema, involvement of internal organs (particularly the liver) and haematological alterations, which occasionally may even compromise the life of the patient.

DRESS syndrome was first proposed by Bouquet et al.⁵ in 1996. Even today, its diagnostic criteria and aetiopathogenesis are not well defined. It is clearly a case of family-related hypersensitivity to drugs. The compounds involved most frequently are anticonvulsants, antiretrovirals and antibiotics, which are the most relevant to orthopaedic surgeons (penicillin and derivatives, cephalosporins, sulphonamides, minocyclines).^{6,7}

Symptoms usually appear between the 2nd and 4th week after the start of the osteoarticular infection treatment, with high fever (39–41 °C) being the initial symptom, and skin lesions appearing afterwards. Systemic involvement usually takes place 1 or 2 weeks after the onset of fever, with hepatic function being significantly compromised.⁷

The treatment consists in immediate suspension of the responsible drug. In cases of systemic involvement, the administration of systemic corticosteroids normally improves the symptoms and prognosis of the process.⁷

We present 2 cases of children who suffered bacterial osteoarticular infection treated with antibiotics and who presented these symptoms. The superposition of symptoms between a reactivation of infection and DRESS syndrome should make us pay very close attention to children who receive antibiotic therapy and present renewed fever, malaise, skin rash and lymphadenopathies. The different treatment of both cases should encourage us to learn about this syndrome.

First case

We present the case of a 7-year-old boy with no relevant history. He had been treated at another centre due to septic arthritis in his right knee through repeated arthrocenteses and intravenous antibiotic therapy (cloxacillin and cefotaxime for 14 days). The results of the analysis conducted at the time of admission included: leucocytes: $19.5 \times 1000/\mu\text{L}$ (neutrophils 75%, eosinophils 1.8%); haemoglobin Hb: 12.3 g/dL; haematocrit Hct: 36.3% and platelets: $469 \times 1000/\mu\text{L}$. The general biochemical analysis with normal hepatic enzymes was normal. C-reactive protein (CRP): 3.4 mg/dL.

Following an initial clinical improvement, after 7 days of admission he began to suffer fever with peaks of 40 °C. The analysis obtained after 11 days of admission showed a deterioration of hepatic function (GOT: 501 U/L, GPT: 555 U/L) and the haemogram (leucocytes $3200 \times 1000/\mu\text{L}$, Hb: 10.1 g/dL, platelets: $163 \times 1000/\mu\text{L}$).

He was transferred to our centre following a diagnosis of prolonged fever syndrome and bicytopenia. The patient presented malaise, fever of 39°C and reduced exanthema in the thoracoabdominal region. The analysis obtained upon admission reported: leucocytes $2.91 \times 1000/\mu\text{L}$ (neutrophils $1.69 \times 1000/\mu\text{L}$, with atypical lymphocytes); Hb: 9.9 g/dL; Hct: 28.7%; GOT: 597 U/L; GPT: 496 U/L; GGT: 109 U/L; LDH: 1,140 U/L; CRP: 7.8 mg/dL; erythrocyte sedimentation rate (ESR): 78 mm. The coagulation study was normal.

At the time of admission, the knee presented an unremarkable clinical exploration, with pain in the entry points of the punctures. We decided to interrupt antibiotic therapy until the study was completed. On the following day, the patient remained afebrile and his condition improved.

The markers for hepatitis, serology for cytomegalovirus and Epstein-Barr were all negative. Serum ferritin was 11,894 ng/mL and transferrin 193 mg/dL. Rheumatoid factor and antinuclear antibody (ANA) analyses were negative. A hepatic ultrasound showed limited hepatomegaly. The bone marrow study was negative.

Two days after removing the antibiotic, the haemogram improved and showed leucocytes $5.54 \times 1000/\mu\text{L}$ (neutrophils $2.62 \times 1000/\mu\text{L}$); Hb: 10.5 g/dL; Hct: 30.2%; platelets $311 \times 1000/\mu\text{L}$, as well as hepatic enzymes (GOT: 68 U/L; GPT: 298 U/L; GGT: 100 U/L; LDH: 594 U/L; CRP: 2.9 mg/dL; ferritin: 5,317 ng/mL).

The patient was discharged 6 days after admission, following excellent clinical and analytical progression. The haemogram and hepatic enzyme results obtained 20 days after removing antibiotic treatment were normal.

Second case

The second case was a boy aged 8 years and 7 months, with no history of interest. He began to suffer pain in the forefoot and 4 days later presented fever and intense redness over the first metatarsal and cuneiform. The analysis revealed leucocytosis and increased acute phase reactants. A simple radiography study and magnetic resonance imaging (MRI) scan led to a high suspicion of osteomyelitis, so the patient was started on an intravenous cloxacillin treatment, 150 mg/kg/day and cefotaxime 200 mg/kg/day. The symptoms improved and 2 weeks later the patient was asymptomatic.

However, on day 16 he began to suffer high fever, around 39–40°C, and general malaise. Subsequently, a maculopapulous rash with pruritus appeared in the thorax and limbs, along with lymphadenopathies in the cervical, left submaxillary and inguinal regions, pain upon palpation in the right hypochondrium and hepatomegaly of 2 cm. The patient did not present pain or tumefaction in the region of the affected metatarsal. The analysis revealed leukopenia ($1.88 \times 1000/\mu\text{L}$, neutrophils 2.4%, eosinophils 1.1%, and activated lymphocytes), and thrombocytopenia ($43 \times 1000/\mu\text{L}$), without anaemia. In addition, he also presented hepatic involvement (GOT: 548 U/L, GPT: 281 U/L; GGT: 294 U/L, LDH: 2528 U/L) and ESR: 32 mm with CRP: 9.8 mg/dL. The coagulation study was normal.

The antibiotic treatment was interrupted due to suspicion of an adverse reaction to the drugs and the patient remained afebrile throughout admission. The next day, the

maculopapulous lesions extended to the face and upper limbs and a gastrointestinal reaction with abdominal pain and gastroenteritis appeared, which was resolved in 3 days. The skin lesions started to disappear on the 4th day of admission.

Markers for hepatitis, cytomegalovirus serology, Epstein-Barr and Paul Bunnell reaction were negative. Serum ferritin was measured at 26,820 ng/mL. The immunology and autoimmune studies were normal and herpes virus 6 and 7 were negative.

Echocardiography and abdominal ultrasound were normal. A bone marrow study was not performed. A clear improvement of the analytical parameters was observed on the day after admission and removal of antibiotic treatment. On day 3, the patient presented leucocytes $4.33 \times 1000/\mu\text{L}$ (neutrophils 13%); Hb: 12.8 g/dL; platelets $81 \times 1000/\mu\text{L}$; GOT: 218 U/L; GPT: 196 U/L; GGT: 238 U/L; LDH: 1481 U/L; CRP: 4.9 mg/dL and ferritin: 5456 ng/mL.

The patient was discharged after 9 days of afebrile admission with no skin lesions. After 22 days of removal of the antibiotic treatment, the patient presented a normal haemogram and hepatic enzymes.

Discussion

Infectious osteoarticular processes are frequent among children. Morbidity and mortality have decreased in recent decades thanks to antibiotic treatment and to improvements in diagnosis and surgical treatment. Nevertheless, antibiotic treatment is not without complications and orthopaedic surgeons must be aware of them in order to allow early management.

Cases of severe toxicoderma secondary to antibiotic treatment in children are rare, but the possibility should be taken into account due to its severe general effects. In 1996, Bouquet et al.⁵ proposed the term DRESS syndrome in an attempt to describe this clinical entity. It consists in a severe idiosyncratic hypersensitivity reaction to a drug. Diagnosing this condition may be difficult, as there are no established diagnostic criteria. The following are accepted as main diagnostic criteria for DRESS syndrome⁵: fever, generalised skin rash, occasionally pruriginous, haematological alterations: eosinophilia ($>1500/\text{mm}^3$) and/or atypical lymphocytes; systemic involvement: lymphadenopathies and/or hepatitis (increase in transaminases over twice the normal value) and/or interstitial nephritis and/or interstitial pneumonitis and/or carditis.

The pathogenesis of this process is not yet clear.^{8,9} It has been related to an excess of toxic metabolic products secondary to an alteration of drug detoxifying enzymes. These toxic products trigger an immune response by acting as haptens or by causing oxidative damage in cells. On the other hand, there have been reports of mutations in the genes encoding these enzymes, which could explain the previous history in some families and the predisposition among individuals of black race. Immunosuppression could also be an individual predisposing factor, particularly when associated to a prior infection or reactivation of infection by herpes virus 6 and 7, cytomegalovirus and Epstein-Barr virus. No predisposing factors associated to the process were identified in the 2 cases presented.

The incidence differs according to the drug responsible, varying between 1/1000 and 1/10,000 patients.⁶ There are several possible drugs involved, with anticonvulsants (carbamazepine, phenobarbital, phenytoin) being the most common. There have also been reports of cases secondary to the use of antibiotics (vancomycin, sulphonamides, beta-lactams) and ibuprofen.⁶ Our hospital, like other centres, has a protocol for the use of cloxacillin associated to cefotaxime in the treatment of osteoarticular infections in children. Currently, these are the only 2 cases registered in the Traumatology Service due to severe reaction during treatment for osteoarticular infection.

In general, the condition starts with high fever (39°–41°), which is inexplicable due to the prior improvement of infection symptoms. Next, a skin rash appears, generally erythematous and morbilliform, which can affect the face, thorax and limbs. There have also been reports of generalised erythrodermia, pustulous eruption, bullseye-shaped lesions, mucositis and facial oedema.⁶ The diagnostic problem faced by the surgeon is discriminating the superimposable symptoms of this entity from those of the initial infection. As described herein, both include fever, erythrodermia and lymphadenopathies. In the case of DRESS syndrome, if the symptoms continue, the condition becomes systemic and includes lymphatic, haematic and hepatic involvement, as well as renal (nephritis), pulmonary (pneumonitis), cardiac (myocarditis) and gastrointestinal (gastroenteritis, dehydration) in some cases, as in the second of our patients.

Generalised lymphadenopathies appear in up to 75% of cases. Similarly to some osteoarticular infections, the appearance of leucopenia or lymphopenia is frequent and usually precedes typical leucocytosis by weeks. Up to 30% of cases present eosinophilia, usually appearing 2 weeks after the onset of the symptoms. There may also be associated thrombocytopenia and/or anaemia.

The liver is the most frequently affected organ, with variable degrees of hepatitis, as well as possible hepatosplenomegaly. Hepatic enzymes are elevated in up to 70% of cases and take weeks to normalise after removing the drug responsible. In general, there is anicteric hepatitis without cholangitis. The causative viruses of hepatitis are negative. Hepatic involvement can cause fulminant hepatic failure, requiring hepatic transplant and being the most frequent cause of death in this process. Hepatic involvement in children is more severe but also rarer. Nevertheless, it is important to bear in mind, as it is the main cause of death. However, this hepatopathy does not normally appear in cases of osteoarticular infection and can lead to diagnostic suspicion of DRESS syndrome. Upon clinical suspicion of this toxicoderma, patients should undergo, at least, a haemogram and biochemical analysis with hepatic and renal profiles. In most cases, patients should be cared for in intensive care units.

The differential diagnosis should consider rashes with a viral origin, infectious mononucleosis, other toxicodermas, Kawasaki disease and other vasculitis, systemic lupus erythematosus, Still disease, sepsis, lymphomas and leukaemias. A differential diagnosis to rule out reactivation of the initial infection with sepsis should be carried out, particularly in children treated for an infectious process.

The treatment consists in removal of the responsible drug; therefore it requires a high level of suspicion, since this measure will prevent organic damage. Once the drug has been removed, the evolution is usually favourable. Occasionally, hepatic involvement may persist for some weeks. In cases of severe involvement, mortality may reach up to 10% of patients.¹⁰ Systemic oral glucocorticoids (0.5–1 mg/kg/day) are currently the treatment of choice for cases with significant organ involvement. The two cases described recovered rapidly after the initial removal of the antibiotic.

The problem to be solved by surgeons is the decision to remove the antibiotic, at the risk of reactivating the osteoarticular infection. DRESS syndrome appears between 2 and 3 weeks after starting treatment with the antibiotic responsible. In general, this period of time is enough to see the clinical condition and the analytical parameters of an osteoarticular infection improve.

Most patients suffering DRESS syndrome present a full recovery once the responsible drug is removed. Children present a better prognosis than adults, do not normally develop sequelae, and have a faster recovery.

Conclusions

Osteoarticular infection is frequent among children and is generally resolved with the correct treatment. Reactions to the antibiotics used normally in children are rare and easily resolved. However, there are some reports of severe toxicodermas, like DRESS syndrome, which must be taken into account, given their significant repercussions. The initial symptoms of this condition may confuse orthopaedic surgeons by leading them to consider a reactivation of the initial infectious process. Maintaining the antibiotic responsible can cause severe organ damage, which may even compromise the life of the patient.

Level of evidence

Level of evidence III.

Ethical responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict of interests

The authors have no conflict of interests to declare.

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