Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 09/29/2022
Approved on: 02/27/2023

ORIGINAL ARTICLE

Osteomyelitis in patients with sickle cell disease

Andréia Regina Augusto dos Santos[1], Maria Aparecida Gadiani Ferrarini[1], Josefina Aparecida Pellegrini Braga[1]

Keywords:
Hemoglobin SC Disease, Anemia Sickle Cell, Infant, Osteomyelitis, Hemoglobinopathies.

Abstract

Objective: identify clinical and laboratory characteristics of osteomyelitis (OM) in 3 patients with sickle cell disease (SCD). **Method:** Retrospective evaluation of medical records of a tertiary University Hospital in São Paulo. **Discussion:** The cases described were comparable to Weisman, 2020, regarding age and the higher frequency of involvement of long bones, and 2 of the 3 patients are homozygous for SCD. The three patients had leukocytosis similar to those found in the literature (Fontalis et al, 2019), and all showed an increase in CRP as the OM progressed, showing reduction in values ?? when treatment started. Pain and local edema were present in the reported cases, and two of them presented pain in different sites, being diagnosed in these cases. In this study, no agent was isolated in blood cultures, as reported by Fontalis 2019. In case 1, the imaging exam showed expected changes, while in cases 2 and 3, the patients had involvement of long bones, the most common sites of previous bone infarction , acute and chronic alterations were found. (Al Farii et al , 2020) **Conclusion:** SCD patients are at increased risk for osteomyelitis. The differential diagnosis between bone infarction related to vaso-occlusive crisis is a challenge, as the initial clinical presentation is similar. Osteomyelitis should be suspected in patients with SCD who present a vaso-occlusive crisis in only one site, with prolonged fever and an increase in inflammatory evidence. Early antibiotic therapy directed at the most frequent agents can avoid complications and allow for better prognosis.

[1] Universidade Federal de São Paulo, Departamento de Pediatria da Universidade Federal de São Paulo - São Paulo - SP - Brazil.

Correspondence to:
Andréia Regina Augusto dos Santos.
Universidade Federal de São Paulo. R. Botucatu, 598 - Vila Clementino, São Paulo - SP, 04023-062. E-mail: andreiaras92@gmail.com

Resid Pediatr. 2024;14(1). DOI: 10.25060/residpediatr-2024.v14n1-966

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy resulting from the association of the beta S gene (βS) with another abnormal gene due to a change in the structure of hemoglobin (Hb) or a defect in its synthesis. When the gene (βS) is homozygous (HbSS), the disease is called Sickle Cell Anemia (SCA), which is the most severe form of SCD. SCD is a chronic hemolytic anemia associated with acute and chronic complications. In the Brazilian population, it is estimated that 4% have the sickle cell trait (HbAS) and that 25,000 to 50,000 people have the disease in a homozygous state or as compound or double heterozygotes[1].

SCD occurs as a consequence of the replacement of a single nucleotide (adenine for thymine) in the codon with amino acid 6. The change converts a glutamic acid (GAG) codon into a valine (GTG) codon (HBB Glu6Val, βS). SCA is the most severe genotype of SCD and results from the combination of two HbβS genes. When the HbβS gene combines with other forms of hemoglobinopathy, other genotypes occur, for example HbSC, HbSβ thalassemia. The result is an Hb that is poorly soluble when deoxygenated and as a result the red blood cells polymerize, which take on a sickle shape. After repeated sickling cycles, the red blood cell membrane is ruptured, leading to hemolysis and vaso-occlusive events[2].

Among the main acute complications, vaso-occlusive crisis (VOC) is the most frequent. Several other complications occur, many exposing these patients to life-threatening risks, such as bacterial infections due to asplenia, acute chest syndrome, stroke, splenic sequestration, acute aplastic crisis due to erythrovirus B19 (parvovirus) infection, priapism, hepatobiliary complications, among others. Chronic complications can involve most organs and systems during the lives of affected individuals, the most common of which are chronic pain, avascular bone necrosis, pulmonary hypertension, renal and ophthalmological complications, lower limb ulcers and recurrent priapism[3].

The pathophysiology of vaso-occlusion has evolved from a concept based solely on polymerization to a multi-step pathway involving complex interaction between sickle red blood cells, leukocytes, endothelial cells and plasma proteins4. Painful VOC, characterized by sudden onset of pain and is the most common cause of hospitalization in patients with SCD, is generally precipitated by several known risk factors, including hypoxemia, inflammation, stress, trauma, increased blood viscosity, dehydration and exposure to cold3. When VOC presents with bone or joint pain for a prolonged period of time, without improvement with the usual measures, the diagnosis of osteomyelitis or septic arthritis should be considered as a complication of VOC[5].

Osteomyelitis (OM) is an acute or chronic infectious process of the bone, caused by bacteria or other microorganisms through three different mechanisms: hematogenous dissemination of the pathogen, which is the most frequent route, extension by contiguity or direct inoculation of the infectious agent. The occurrence of OM in patients with SCD varies between 1.4% and 12% in different studies[6]. The increased propensity for OM in patients with SCD has been attributed to asplenia, impaired complement activity, increased intestinal permeability promoting bacterial translocation and the presence of infarction and bone necrosis[7].

Although VOC is 50 times more common than OM[5,8,9,10], the differential diagnosis of OM must be considered, because delaying this diagnosis can lead to serious consequences including bone destruction, sepsis and bone deformity[11].

Both conditions present an increase in inflammatory tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), leukocyte count and fever. The gold standard for diagnosis is a positive blood culture or bone or joint secretion culture, but negative cultures do not rule out the diagnosis, since in the literature there is no identification of the infectious agent in 33% to 55% of OM cases[9].

Due to the diagnostic difficulty based on clinical and laboratory tests, imaging tests become essential for the diagnosis of OM. In the first two weeks, both bone infarction and OM present a periosteal reaction, with radiography being a limited examination to differentiate the two conditions[12]. Ultrasonography, despite not being the gold standard, is an easy-to-perform and low-cost exam, being correlated with findings such as significant periosteal elevation (>0.4 cm)[5] and associated with increased CRP and leukocytes suggest the diagnosis of OM, which can be confirmed by magnetic resonance imaging (MRI)[8].

MRI is the gold standard imaging for diagnosing OM. Early pathological changes, such as bone marrow edema, are detectable after the first 24 hours of the onset of infection, translated as a localized bone marrow abnormality with decreased signal on T1 images and increased signal on T27,10. Other secondary findings of OM, such as soft tissue collections, cellulitis and cortical bony sinus areas also have similar MR signaling characteristics. Serial MRI can present a clinical correlation with the evolution and response to treatment, without the risk of ionization[5].

Staphylococcus aureus (S aureus) is the organism most associated with OM In the general population, found in 70 to 90% of confirmed cases [13]. However, in the population with SCD the enteric bacillus Salmonella spp (70%) is more commonly isolated in relation to S aureus (16.4%)[5]. Enteric bacteria are translocated into the bloodstream through ischemic intestinal infarction during episodes of vaso-occlusion. Therefore, in suspected cases of OM in patients with SCD, empirical antimicrobial coverage should be for both S aureus and Salmonella spp to try to avoid OM complications[7].

Differentiating between OM and VOC is a challenge, as the clinical, laboratory and radiological findings are very similar.

OBJECTIVE

To identify clinical and laboratory characteristics of osteomyelitis in three patients with sickle cell disease.

METHODOLOGY

Description of three cases of children and adolescents, with SCD and OM. This is a retrospective study carried out in a

tertiary University Hospital. The data were obtained from the patient's electronic medical records, including name, age, sex, genotype, previous treatment for SCD - hydroxyurea or chronic transfusion, and comorbidities.

Data were also collected regarding hospitalization for osteomyelitis, initial symptoms, location of VOC and OM, antibiotics administered, laboratory tests (blood count, C-reactive protein, MRI) ordered by the attending physician, complications, duration of hospitalization and clinical evolution until hospital discharge.

CASES

Case 1 - Boy, twelve years old, HbSS genotype, on chronic transfusion since he was eight years old, due to a stroke. The patient's mother went to the children's emergency room (PSI), because the child complained of pain in the upper and lower limbs, which had been severe for a day. He had no trauma, fever or other complaints, improving with the use of tramadol. Admittance exams: Hemoglobin (Hb) 10.6 g/dL; Leukocytes 12600 /mm3 (6475 neutrophils; 3667 lymphocytes) and CRP 97.32 mg/L. On the 2nd day of hospitalization (DH), paresthesia began in the left mandible, with pain and hyperemia in the last left molar and phlogistic signs in the mandible. An ulectomy was performed with the release of local purulent secretion. Antimicrobial therapy was started with ceftriaxone and clindamycin. On the 5th DH, drainage of the affected molar was performed. Magnetic Resonance Imaging (MRI) showed signs of local OM (Figure 1). He remained afebrile during intravenous antimicrobial therapy for nine days. At discharge he had Hb 11.5 /g/dL; Leukocytes 12300/mm3 (7417 neutrophils; 2645 lymphocytes); CRP 6.85 mg/L. No agent was isolated. He was discharged on the 12th day of hospitalization, asymptomatic on ciprofloxacin and clindamycin, orally, for seven weeks, and advised to continue outpatient follow-up with pediatric hematology and pediatric infectious diseases experts.

Case 2 - Girl, nine years old, HbSC genotype. The patient's mother went to the ER because the child complained of severe pain in the lower back, radiating to the lower limbs, which began 2 hours after admission. She denied fever, trauma or other complaints. History of OM in the left femur at three years of age requiring surgical treatment. Entrance exams: Hb: 10.6 g/dL; Leukocytes: 15400 /mm3 (8624 neutrophils 5852 lymphocytes) and CRP 95.99 mg/L. On the 2nd DH she presented a fever spike, evolving into Acute Chest Syndrome, and ceftriaxone was introduced. On the 4th DH, she reported pain in the region of the right humerus, left shoulder, hip and bilateral femur, with restricted mobility, making the hypothesis of OM, and was started on oxacillin. The MRI showed OM of the head of the left femur and fracture of the L4 vertebra (Figure 2). She maintained feverish peaks for five days in a row. On the 6th DH she showed improvements in her pain and on the 10th DH she started walking again. She remained hospitalized for 22 days, receiving ceftriaxone to treat STA and oxacillin. At discharge she had Hb: 11.3 g/dL; Leukocytes: 6910 /mm3 (2419 neutrophils; 4077 lymphocytes); CRP 4.29 mg/dL. No agent was isolated in cultures. She was discharged on the 22nd DH with oral ciprofloxacin for 76 days. Outpatient follow-up continued with pediatric hematology and pediatric infectious diseases.

Case 3 - Girl, seventeen years old, HbSS genotype, using hydroxyurea (since April 2011 and currently at a dose of 22.5 mg/kg/day). The patient's mother brought her to the ER because the patient complained of intense pain in the left lower limb, sternum and thoracic spine, which began 3 hours ago. Entrance exams: Hb 7.8 g/dL; Leukocytes 14118/mm3 (8471 neutrophils; 3106 lymphocytes) and CRP 324.32 mg/dL. On the 2nd DH, she developed pain in the right hip and thigh joint and difficult-to-control analgesia with morphine. Due to the persistence of the pain, she received multiple therapy with baclofen, gabapentin, dipyrone and morphine. On the 4th DH she developed Acute Chest Syndrome requiring oxygen therapy and antimicrobial therapy with ceftriaxone and azithromycin was introduced. On the 6th DH,

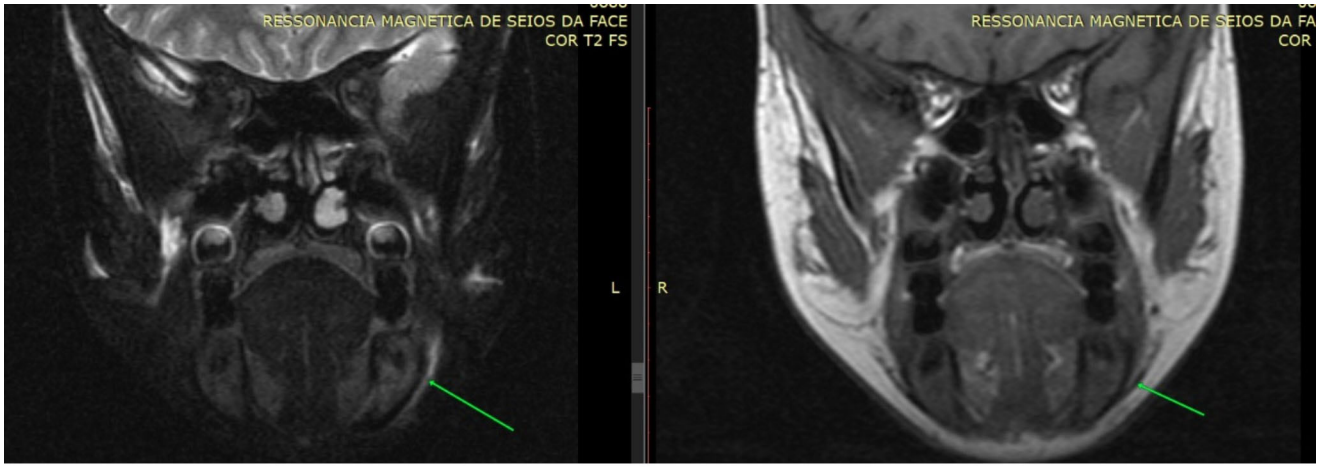


Figure 1. Case 1 - MRI of the jaw: Hypersignal of the bone marrow of the body of the mandible on the left, associated with edema of the adjacent myoadipose planes, compatible with an inflammatory/infectious process (osteomyelitis).

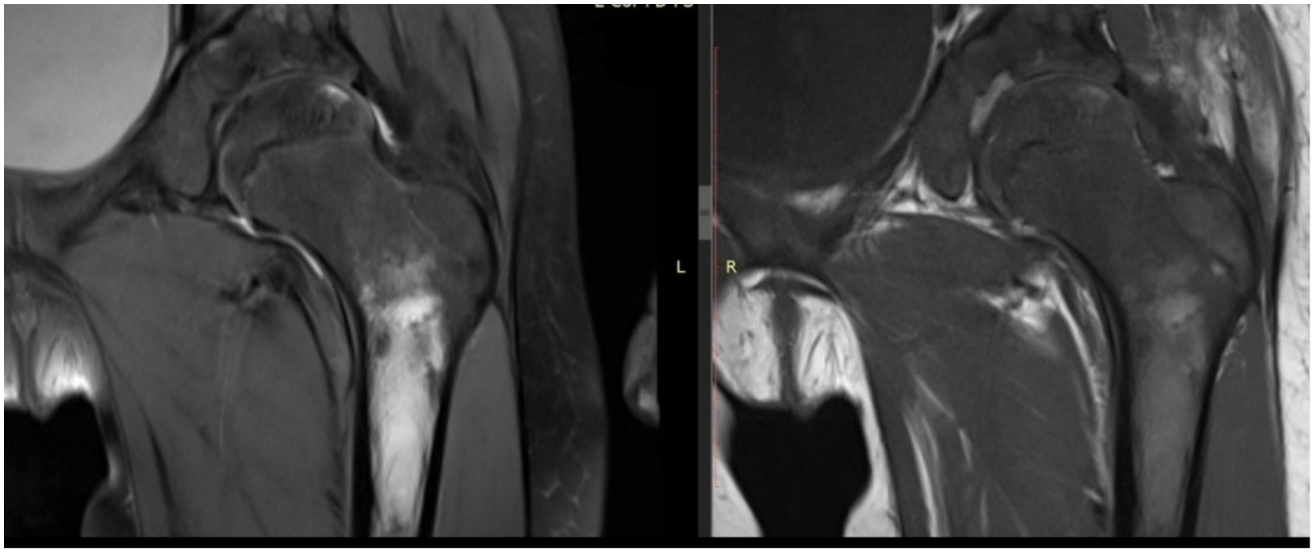


Figure 2. Case 2 - MRI of the left hip: Areas of osteonecrosis affecting the acetabular border of the ilium and pubis, the epiphysis, metadiaphyseal region of the femur.

due to persistent fever, antibiotics were changed to cefepime. On the 10th DH, fever and intense pain in the right hip and thigh still persisted, with limited walking, and the hypothesis of OM and osteonecrosis of the right hip and thigh was suggested, confirmed by MRI, which showed an acute/subacute inflammatory process in the proximal diaphysis of the femur and in the anterior aspect of the iliac, multiple bone lesions of chronic appearance (osteonecrosis) in the head and proximal diaphysis of the femur, iliac and ischium (Figure 3) and vancomycin was started. Discharged after completing 21 days of cefepime and 17 days of intravenous vancomycin, she had Hb: 9.3 g/dL; Leukocytes: 2520/mm3 (1273 neutrophils; 1081 lymphocytes) and CRP 10.85 mg/dL. No agent was isolated in cultures. Advised to complete treatment with oral ciprofloxacin for 19 weeks and continue outpatient follow-up with pediatric hematology and pediatric infectious diseases.

The clinical and laboratory characteristics of the cases described are shown in chart 1.

DISCUSSION

The study aimed to describe three patients with SCD and OM who came to the ER with painful VOC which progressed to acute OM. Differentiating between VOC and OM is a challenge in medical practice from diagnosis to treatment.

In the pediatric population, an incidence of OM is reported to be approximately eight cases per 100,000 children per year13, and in patients with SCD, OM represents a complication that affects 0.3 to 12% of the population7.

In a retrospective study with 28 children with SCD, the majority of patients diagnosed with OM were children with a

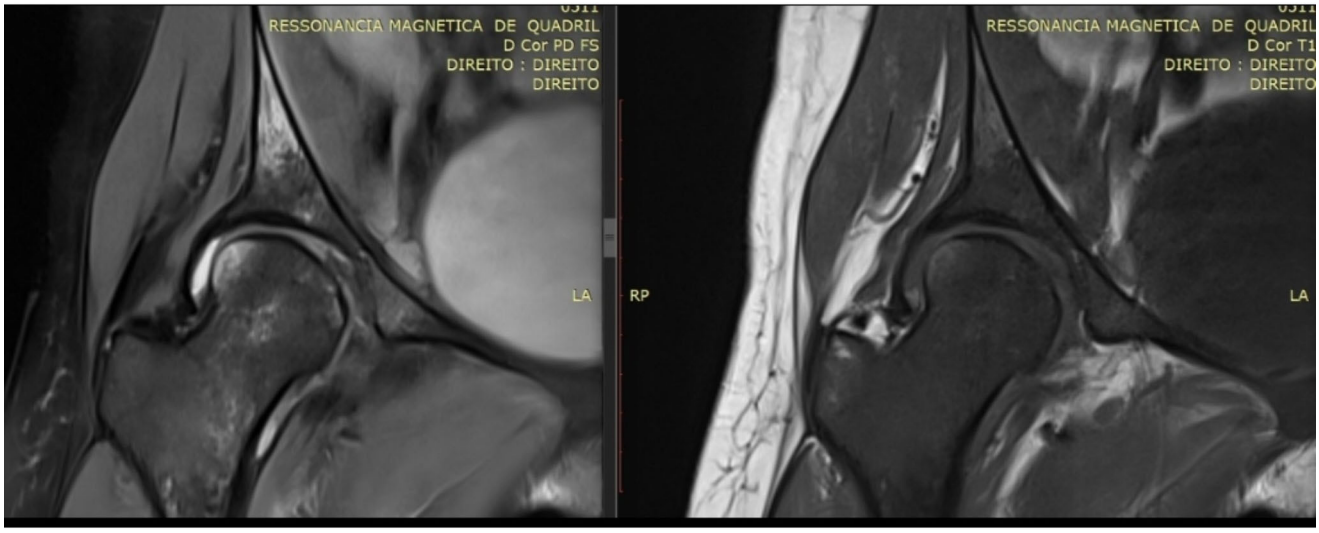


Figure 3. Case 3 - MRI of the right hip: Acute/subacute inflammatory process in the proximal shaft of the femur and the anterior aspect of the iliac bone. Multiple chronic bone lesions (osteonecrosis) in the head and proximal shaft of the femur, iliac and ischium

Chart 1. Clinical and laboratory characteristics of patients with sickle cell disease and osteomyelitis.

	Case 1	Case 2	Case 3
Identification **Genotype**	Male, 12 years old HbSS	Female 9 years old HbSC	Female 17 years old HbSS
Clinical history **Upon arrival at the ER**	Pain in the Upper and lower limbs Paresthesia and pain for1 day in the left mandible on the second hospital day	Lumbar pain irradiating to the lower limb For 2 hours	Severe pain in the left lower limb, sternum and thoracic spine for 3 hours
Osteomyelitis location	Left mandible	Left femur head	Right femoral thigh
Days of hospitalization	12 days	22 days	26 days
Fever	No	5 days	10 days
Admission lab results	Hemoglobin: 10.6 g/dL Leukocytes: 2,600/mm3 (6,475 neutrophils; 3,667 lymphocytes) CRP: 97.32 mg/L	Hemoglobin:10.6 g/dL Leukocytes: 1,540/mm3 (8,624 neutrophils 5,852 lymphocytes) 5,852 lymphocytes) CRP: 95.99 mg/L	Hemoglobin: 7.8 g/dL Leukocytes: 14,118/mm3 (8471 neutrophils; 3106 lymphocytes) CRP: 324.32 mg/L
Lab results upon discharge	Hemoglobin: 11.5 g/dL Leukocytes: 12,300/mm3 (7,417 neutrophils; 2,645 lymphocytes) CRP: 6.85 mg/L	Hemoglobin: 11.3 g/dL Leukocytes: 6,910/mm3 (2,419 neutrophils 4,077 lymphocytes) CRP: 4.29 mg/L	Hemoglobin: 9.3 g/dL Leukocytes: 2,520/mm3 (1,273 neutrophils; 1,081 lymphocytes) CRP :10.85 mg/L
Etiological agent	Not found	Not found	Not found
Antibiotic during hospital stay	Ceftriaxone Clindamycin	Ceftriaxone Oxacillin	Ceftriaxone Cefepime Vancomycin
Outpatient antibiotic	Ciprofloxacin Clindamycin 49 days	Ciprofloxacin 76 days	Ciprofloxacin 133 days
Evolution	Resolution after surgical treatment	Resolution with antibiotics	Resolution with antibiotics

Caption: CRP: C-reactive protein

mean age of 13 years, ranging between 4 and 17 years and HbSS genotype.7 Long bones were the most affected, but there were no significant differences in relation to the genotype, which is similar to the cases reported here. The cases described here were comparable with the study above regarding age and the higher frequency of long bone involvement; and 2 of the 3 patients were homozygous for SCD. In this report, we observed that one patient had jaw involvement, which is not described as a frequent site, and one patient had the Hb'SC genotype, which confirms that all patients with SCD should receive special attention for the diagnosis of OM, regardless of genotype or location.

The likelihood of OM increases by 80% for each day a child has a fever before presentation, and by 20% for each day they had pain before presentation11. Patients were 8.4 times more likely to have osteomyelitis if they had documented edema of the affected limb. The risk of osteomyelitis was reduced by 30% for each additional painful site if more than one painful site was present. A high white blood cell count was not found to be a significant prognostic factor for osteomyelitis in a multivariate analysis.

In a study, 96 patients with SCD were retrospectively evaluated, with 358 hospital admissions; with the aim of identifying the incidence of OM and the management of bone pain. The authors compared patients with OM with those with VOC, and observed that the leukocyte count showed no significant difference, while CRP and fever, when elevated, showed significance (p=0.007 and 0.010 respectively)9. The three patients described here had leukocyte counts similar to those found in the literature9, and all showed an increase in CRP as OM progressed, showing a reduction in values when treatment began. Pain and local edema were also present in the reported cases, and two of them had pain in different sites, which was diagnosed in these cases.

In this study, no agent was isolated in blood cultures – in the literature we found many studies with similar results9, while other studies showed positive cultures in 19.3% (6/31)11; 30% (6/20)6 and 32.1% (9/28)7;respectively of the cases analyzed. Both blood culture and positive local culture are gold standard tests for diagnosis; Staphylococcus aureus and Salmonella spp. are the most common agents when isolated. When the hypothesis of OM is raised, empirical antimicrobial therapy should be introduced to cover these, with a minimum duration of 4 to 6 weeks, aiming to reduce the occurrence of complications such as septic arthritis, bone deformity and chronic damage. In this report, a patient required a local surgical approach during hospitalization and none of the patients presented complications. In the three cases described here, the patients after discharge underwent follow-up with the infectious diseases and pediatric hematology teams, and the final suspension of treatment varied according to laboratory tests and clinical evolution.

Due to the clinical and laboratory diagnostic difficulties between bone infarction and OM, imaging tests have played an important role. In a retrospective study with 41 patients with SCD and a diagnosis of OM, the role of ultrasound in the diagnosis of OM was evaluated. Ultrasound was the first imaging test of choice due to its low cost and ease of performance, and it has been reported that periosteal elevation greater than 0.4 cm correlated to the clinic is a positive finding for OM8. However, MRI continues to be the gold standard imaging test for diagnosis and should be indicated when diagnostic confirmation is necessary. Initial pathological features, such as bone marrow edema, are detectable 24 hours after the onset of infection5. In case 1, the imaging exam showed the expected changes, while in cases 2 and 3, in which the patients long bones involvement, the most common sites of previous bone infarction, both acute and chronic changes were found.

The patients described did not show significant differences when compared with the literature and the correlation between clinical, laboratory and imaging aspects enabled the correct diagnosis.

CONCLUSION

Patients with SCD are at increased risk for OM, the differential diagnosis between VOC-related bone infarction is a challenge, as the initial clinical presentation is similar. OM should be suspected in patients with SCD who present with persistent painful VOC, prolonged fever, and increased inflammatory tests. Early recognition and treatment of OM with appropriate antimicrobials can prevent complications and provide a better prognosis.

REFERENCES

1. Ministério da Saúde (BR), Secretaria de atenção à saúde, Secretaria de ciência, tecnologia e insumos estratégicos. Portaria Conjunta Nº 5, de 19 de fevereiro de 2018: Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Doença Falciforme. Doença Falciforme-PCDT. Brasília: Ministério da Saúde; 2018.
2. Piccin A, Murphy C, Eakins E, Rondinelli MB, Daves M, Vecchiato C, et al. Insight into the complex pathophysiology of sickle cell anaemia and possible treatment. Eur J Haematol. 2019 Apr;102(4):319-30. DOI: https://doi.org/10.1111/ejh.13212.
3. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence--based report by expert panel members. JAMA. 2014 Sep;312(10):1033-48. DOI: https://doi.org/10.1001/jama.2014.10517.
4. Puri L, Nottage KA, Hankins JS, Anghelescu DL. State of the Art Management of Acute Vaso-occlusive Pain in Sickle Cell Disease. Paediatric Drugs. 2018 Feb;20(1):29-42. DOI: https://doi.org/10.1007/s40272-017-0263-z.
5. Al Farii H, Zhou S, Albers A. Management of Osteomyelitis in Sickle Cell Disease: Review Article. J Am Acad Orthop Surg Glob Res Rev. 2020 Sep;4(9):e20.00002-10. DOI: https://doi.org/10.5435/jaaosglobal--d-20-00002.
6. Kao CM, Yee ME, Maillis A, Lai K, Bakshi N, Rostad BS, et a. Microbiology and radiographic features of osteomyelitis in children and adolescents with sickle cell disease. Pediatr Blood Cancer. 2020 Oct;67(10):e28517. DOI: 1 https://doi.org/0.1002/pbc.28517.
7. Weisman JK, Nickel RS, Darbari DS, Hanisch BR, Diab YA. Characteristics and outcomes of osteomyelitis in children with sickle cell disease: A 10-year single-center experience. Pediatr Blood Cancer. 2020 May;67(5):e28225. DOI: https://doi.org/10.1002/pbc.28225.
8. Inusa BP, Oyewo A, Brokke F, Santhikumaran G, Jogeesvaran KH. Dilemma in differentiating between acute osteomyelitis and bone infarction in children with sickle cell disease: the role of ultrasound. PLoS One. 2013 Jun;8(6):e65001. DOI: https://doi.org/10.1371/journal.pone.0065001.
9. Fontalis A, Hughes K, Nguyen MP, Williamson M, Yeo A, Lui D, et al. The challenge of differentiating vaso-occlusive crises from osteomyelitis in children with sickle cell disease and bone pain: A 15-year retrospective review. J Child Orthop. 2019 Feb;13(1):33-9. DOI: https://doi.org/10.1302/1863-2548.12.180094.
10. Rothman JA. Osteomyelitis in sickle cell disease: You know it when you see it? Pediatr Blood Cancer. 2020 Oct;67(10):e28585. DOI: https://doi.org/10.1002/pbc.28585.
11. Berger E, Saunders N, Wang L, Friedman JN. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. Arch Pediatr Adolesc Med. 2009 Mar;163(3):251-5. DOI: https://doi.org/10.1001/archpediatrics.2008.545.
12. Vanderhave KL, Perkins CA, Scannell B, Brighton BK. Orthopaedic Manifestations of Sickle Cell Disease. J Am Acad Orthop Surg. 2018 Feb;26(3):94-101. DOI: https://doi.org/10.5435/JAAOS-D-16-00255.
13. Castellazzi L, Mantero M, Esposito S. Update on the Management of Pediatric Acute Osteomyelitis and Septic Arthritis. Int J Mol Sci. 2016 Jun;17(6):855. DOI: https://doi.org/10.3390/ijms17060855.