Temporomandibular joint arthritis in sickle cell disease: a case report

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We report a rare case of aseptic arthritis in the temporomandibular joint of a patient with sickle cell anemia. A 22-year-old woman with sickle cell disease, in the 18th week of gestation, was referred by her hematologist to investigate a sudden mouth opening limitation and severe pain on her left cheek. The patient received a standard pain assessment protocol, clinical examination, and complementary exams (complete blood count, hemoglobin electrophoresis, blood solubility test, panoramic radiograph, and magnetic resonance imaging [MRI]). The blood results were consistent with a sickle cell crisis and the MRI showed an inflammatory process around the left temporomandibular joint. Treatment with opioid analgesics and blood transfusion provided good results. Sickle cell anemia is a disease that can cause arthritis of the temporomandibular joint, and although it is rare, clinicians should be attentive to the differential diagnosis in patients with this disease. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e31-e35)

Sickle cell anemia is an autosomal recessive disease with high prevalence in the world as well as in Brazil (1 in every 200 births)¹ and consists of the clinical expression of a homozygous hemoglobin S gene, where polymerized hemoglobin leads to chronic hemolytic anemia.² It is characterized by vaso-occlusive crises that affect many organs and manifests primarily by crises of acute pain.³ The triad of ischemia, infarction, and inflammation contributes to the pathophysiology of pain in this condition.⁴

The interaction between erythrocytes and the vascular endothelium is critical in the pathogenesis of painful crises that occur during sickle cell anemia. This process involves hemoglobin S polymerization, subsequent red cell distortion, interaction of erythrocytes with adhesion proteins of the vascular endothelium, and an ensuing inflammatory response that further increases cellular adhesiveness. In sickle cell disease, erythrocytes upregulate the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in vascular endothelial cells in vitro. Heme and heme oxygenase, the heme-degrading enzyme, are also potent inducers of inflammation and endothelial cell adhesion, as is phosphatidylserine when exposed on the surface of red cells. Increased adhesion and the subsequent inflammatory response decrease blood flow, leading to further sickling in an increasingly hypoxic and acidic environment. These vaso-occlusive crises are typically manifested by pain. Repeated episodes of decreased blood flow can lead to the impaired nourishment of critical structures (e.g., femoral head, vertebral bodies, or joint), leading to bony lesions with loss of trabeculae (e.g., avascular necrosis, vertebral collapse).⁵⁻¹³

Nearly half of sickle cell patients (49%) experience orofacial pain. Sixty-eight percent experience pulpal necrosis without apparent cause and 77% experience headaches.¹⁴ Complications such as mandibular osteomyelitis and neuropathy, fibrous ankylosis, and asymptomatic pulpal necrosis have been reported.¹⁵⁻¹⁸ Limb joint pain is common, but temporomandibular joint (TMJ) pain is rare.¹⁹ Here, we report a patient who had aseptic arthritis of the TMJ and sickle cell anemia, focusing mainly on a multidisciplinary assessment and the treatment outcome of the patient.

CASE REPORT

A 22-year-old woman in the 18th week of pregnancy was admitted to the hematology ward after experiencing a throbbing pain for 2 days in the left preauricular region. The pain was constant and severe, scoring 10 on the Visual Analog

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Scale, which ranges from 0 (no pain) to 10 (worst pain). The pain increased when she reclined, chewed, or talked and only subsided with parenteral opioid analgesia. She denied fever or trauma.

Her medical history at the time of her pregnancy included various complications associated with sickle cell anemia: frequent hospitalizations caused by painful crises and episodes of pneumonia since childhood; ischemic stroke at 10 years old without sequelae; cholecystectomy for cholelithiasis; femoral and humeral head osteonecrosis; transfusional iron overload; and a recent splenic sequestration crisis. Apart from folic acid supplementation and iron chelation therapy, she had been treated with hydroxycarbamide for 3 years.

Findings at physical examination included mild edema, allodynia, and hyperalgesia in the left preauricular region, hyperalgesia of the left masseter muscle, limited interincisal mouth opening (11 mm), and pain upon mandibular movement. Only 1 tooth was missing, a maxillary left premolar. No other dental or periodontal abnormalities were observed during the visual examination, with thermal or percussion testing, or on panoramic radiograph (Figure 1).

The following complementary tests were performed: complete blood count, biochemical tests, hemoglobin electrophoresis (Tables I and II), and magnetic resonance imaging (MRI; Figure 2). Arthritis in the left condylar head secondary to a sickle cell crisis was diagnosed after the analysis of the laboratory tests and images. The final diagnosis rendered was aseptic arthritis of the left mandibular condyle secondary to a sickle cell crisis.

**Treatment**

The patient was admitted to the hematology ward and received standard analgesia recommended for treatment of severe pain: parenteral opioid analgesia and nonsteroidal anti-inflammatory drugs (NSAIDS; naproxen). She also received a blood transfusion because of worsening anemia.

The pain gradually subsided after 2 days of hospital stay, allowing progressive weaning from the analgesic treatment. Mouth opening amplitude improved substantially to 28 mm interincisal opening (initially 11 mm). After 1 week, there was resolution of facial pain and edema; thus, the analgesic and anti-inflammatory medications were discontinued at this time. The patient was followed for 6 months without relapse of facial pain.

**DISCUSSION**

This rare case of arthritis of the left condylar head illustrates an uncommon situation of joint pain of systemic origin, although vaso-occlusive crises associated with sickle cell anemia often cause pain. The pain lasted 10 days and was accompanied by leukocytosis. The clinical signs and symptoms were consistent with the diagnosis of sickle cell crisis.20,21

The patient had a systemic disease that affects bones and joints, including TMJ. According to the diagnostic criteria of the American Academy of Orofacial Pain, the diagnosis requires the presence of a clearly documented disease or event associated with osteoarthritis, functional pain, local tenderness, limited TMJ movements and deviation to the affected side, crepitation or multiple joint noises,22 and manifestations of arthritis and necrosis in other joints. The present case met all these criteria. Although the classification of polyarthritids does not contemplate sickle cell disease, it should be...
considered in the differential diagnosis, and similar findings have been reported in another case report of a patient with chronic TMJ pain.\textsuperscript{23} Of note, in this report the patient was pregnant. Pregnancy has been shown to worsen sickle cell anemia, increasing its severity and the frequency and severity of pain crises and infection.\textsuperscript{24} In fact, our patient had 3 vaso-occlusive crises in the prior 3 months.

Bone and joint areas affected by hypoxia may initially cause bone hypervascularization and significant inflammatory processes (osteitis and arthritis), visible as hyperintensity in MRI in T2 (T2 brightens liquids and bone edema). Unfortunately, MRI imaging in T2 in this patient could not be fully appreciated and completed because of the patient’s level of pain. However, persistent hypoxia and inflammation result in aseptic bone necrosis, which appears as a hypointense signal in T2.

Our patient was treated with parenteral opioid analgesia and blood transfusion to prevent progression of the disease. This treatment reduced pain and improved joint function, without the need for antibiotics, suggesting that this was probably an acute inflammatory phenomenon with features of aseptic osteonecrosis.

Sickle cell vaso-occlusive episodes require a multidisciplinary approach.\textsuperscript{25} It is important to remember that these patients have chronic organ damage, such as diastolic dysfunction, that is often unnoticed and that improper crisis management may precipitate a serious acute pulmonary disease (i.e., acute chest syndrome). Patients are hydrated with dual goals: correct the hypovolemia caused by hyposthenuria and insensible losses and assure intracellular hydration, reducing the polymerization of desoxihemoglobin S. This aim can be achieved through hydration with hypotonic saline, avoiding volume overload that could lead to pulmonary congestion.\textsuperscript{26}

Pain control is achieved through the judicious use of analgesics. In inpatients opioid analgesia is recommended, with careful titration of doses to achieve pain control while avoiding excessive sedation, which could result in hypoventilation, triggering acute chest syndrome. Some patients can be treated with continuous infusion of morphine using patient-controlled analgesia. NSAIDs can be used in the treatment of acute pain because they inhibit endovascular inflammation by blocking cyclo-oxygenase. Because the kidney is a target organ for damage in sickle cell disease, NSAIDs should be used cautiously and dosage should be restricted. Pain management is often frustrating and stressful, requiring education of the patient and the health care team to reduce acute and chronic complications.\textsuperscript{26,27}

Red blood cell transfusion is recommended when there is worsening of anemia. Transfusion does not reduce the duration of existing painful episodes, but can prevent and treat clinical complications, such as acute chest syndrome, and restore the proper oxygen transport. Red blood cell transfusion, however, is not innocuous and it is important to remember the acute and chronic transfusion-related complications such as volume overload, infections, alloimunization, and iron overload.\textsuperscript{28}

### Table I. Laboratory data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference range, adults</th>
<th>Basal status</th>
<th>On admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12-16</td>
<td>9.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35-47</td>
<td>28.9</td>
<td>24.2</td>
</tr>
<tr>
<td>Mean corpuscular volume (mm(^3))</td>
<td>80-100</td>
<td>96.3</td>
<td>97.1</td>
</tr>
<tr>
<td>White cell count (per mm(^3))</td>
<td>4,000-11,000</td>
<td>14,000</td>
<td>14,700</td>
</tr>
<tr>
<td>Differential count (per mm(^3))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1,600-7,000</td>
<td>8,700</td>
<td>9,100</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>900-3,400</td>
<td>4,300</td>
<td>4,400</td>
</tr>
<tr>
<td>Monocytes</td>
<td>200-900</td>
<td>800</td>
<td>900</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>50-500</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Basophils</td>
<td>0-200</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smear description</td>
<td></td>
<td>Sickled cells</td>
<td>Sickled cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poikilocytosis</td>
<td>Poikilocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycromasia</td>
<td>Polycromasia</td>
</tr>
<tr>
<td>Platelet count (per mm(^3))</td>
<td>140,000-450,000</td>
<td>230,000</td>
<td>157,000</td>
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<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>240-480</td>
<td>571</td>
<td>574</td>
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<tr>
<td>Indirect bilirubin (mg/dl)</td>
<td>0.10-0.60</td>
<td>0.68</td>
<td>0.61</td>
</tr>
<tr>
<td>Reticulocytes (per mm(^3))</td>
<td>27,000-134,000</td>
<td>208,000</td>
<td>Not available</td>
</tr>
<tr>
<td>C-reactive protein (mg/liter)</td>
<td>Less than 3.0</td>
<td>13.2</td>
<td>34.1</td>
</tr>
</tbody>
</table>

### Table II. Hemoglobin electrophoresis\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient (%)</th>
<th>Reference range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin S</td>
<td>83.10</td>
<td>0</td>
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<tr>
<td>Hemoglobin A2</td>
<td>2.30</td>
<td>2.0-3.5</td>
</tr>
<tr>
<td>Fetal hemoglobin</td>
<td>14.60</td>
<td>Less than 1.2</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Electrophoresis on cellulose acetate, pH 9.1.
In conclusion, clinicians should be aware that aseptic arthritis may occasionally be caused by sickle cell disease. The differential diagnosis should include avascular necrosis of the condylar head, manifestation of rheumatoid arthritis in the TMJ, and lupus arthritis of the TMJ. Laboratory tests and diagnostic imaging remain important for proper assessment because clinical manifestations of TMJ arthritis are similar. Treatment often involves a multidisciplinary team and effective communication with the patient.

We are grateful to Dr. Maria Paula Peres for her support of the Dentistry Division of Hospital das Clínicas and Dr. Juliana Bertoldi Franco for her interest and referral of this complex case to our group.

Fig. 2. Magnetic resonance imaging of the face shows a signal change at the condylar head and neck of the left jaw, suggesting bone edema (A) with T2 hyperintensity and obliteration of the fat planes in the adjacent masticatory muscles (masseter and lateral pterygoid, also suggesting edema/inflammatory process; B and C).
REFERENCES
7. Hebbel RP, Vercellotti GM. The endothelial biology of sickle cell disease. J Lab Clin Med 1997;129:288-93.

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