Osteomyelitis by *Proteus spp* after snake bite – Account of a still neglected tropical illness

Osteomielite por *Proteus spp* após mordedura de cobra - Relato de uma doença tropical ainda negligenciada

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**ABSTRACT**

Background: Serum therapy is used in accidents intervention. After the bite, the proposed treatment is based on the snake's type and size, on symptomatology for light, moderate or grave ones. Despite serum therapy's beneficial evidence, there is the need for monitoring and systematic follow-up on the first seven days after the accident. Aim: To report the case intervention with emergence of osteomyelitis by *Proteus spp.* occurred five weeks immediately after the snake bite. Methods: Case report of an adolescent individual aged 17, male, bitten at the proximal third of the lower left limb (LLL) living at rural zone at Mato Grosso (MT) countryside, Brazil. Immediate intervention was made with antiphospholipid serum 20 minutes after the bite. A single dose of Benzetacil® (Benzathine benzylpenicillin) was prescribed 48 hours after the accident, associated with anti-inflammatory and corticosteroid. The patient's re-internment with antibiotic therapy after the fifth day could not prevent the osteomyelitis at the tibia bone. To solve the case, two surgical interventions were required. For data analysis, initial and final moments of exams' values were compared, concurring to the assessment by MRI imaging. Results: It was found osteomyelitis in 3,5 cm of the tibia at nuclear MRI, in the result...
of anterior and fibular tibial muscle culture, and on the bone fragment of the tibia, by Proteus spp bacteria. Conclusions: It is possible to conclude that, in ophidic accidents, one must take into account the possibility the immune system may not respond to the bacterian microorganisms infected on the patient, being needed administration of antibiotics for either positive and negative gram. Such measures would avoid systemic wounds, longer internments and installation of physical deficiencies with increase of health costs.

Keywords: serum therapy, gram negative, Proteus spp, osteomyelitis.

RESUMO
Introdução: Na intervenção de acidentes ofídicos adota-se a soroterapia. O tratamento proposto após a picada de cobra baseia-se no tipo e tamanho da cobra, na sintomatologia para leves, moderadas ou graves. Apesar das evidências benéficas da soroterapia há necessidade de monitoramento e acompanhamento sistemático nos primeiros sete dias após o acidente. Objetivo: Relatar a intervenção de caso com surgimento de osteomielite por Proteus spp. ocorrido nas cinco semanas imediatas após picada de cobra. Métodos: Relato de caso de um indivíduo adolescente com idade de 17 anos, do gênero masculino, picado no terço proximal do membro inferior esquerdo (MIE) residente na zona rural do interior de Mato Grosso (MT), Brasil. A intervenção imediata foi feita com soro antiofídico 20 minutos depois da picada. Foi prescrita dose única de Benzetacil® (benzilpenicilina benzatina) 48 h depois do acidente associado com antiinflamatório e corticóide. A reinternação do paciente com antibioticoterapia após quinto dia não evitou a osteomielite no osso da tíbia. Para resolução do caso houve necessidade de duas intervenções cirúrgicas. Para a análise dos dados, comparou-se os momentos inicial e final dos valores do exames, concomitante a avaliação por imagens de ressonância magnética nuclear (RMN). Resultados: Encontrou-se presença de osteomielite em 3,5 cm da tíbia na imagem de ressonância magnética nuclear, no resultado da cultura do músculo tibial anterior e fibular, e do fragmento ósseo da tíbia pela bactéria proteus spp. Conclusão: Conclui-se que em acidentes ofídicos deve-se considerar a possibilidade do sistema imunológico não conseguir responder aos microrganismos bacterianos infectados no paciente, sendo necessária administração de antibióticos tanto para gram positivos e negativos. Tais medidas evitariam lesões sistêmicas, internamentos prolongados e instalação de deficiências físicas com aumento dos custos de saúde.

Palavras-chave: soroterapia, gram negative, Proteus spp, osteomielite.

1 INTRODUCTION

Worldwide, it is estimated that 5 million people are bitten by snakes every year, resulting in about 125,000 deaths and 400,000 victims deficient or scarring (1). Ophidic accidents are considered the most neglected ones from those called “tropical neglected illnesses” in the world (2)(3). Since it is a neglected and underestimated disease, there are no specific treatment protocols, specialized treatment centers and theoretical knowledge by most health professionals (4).

The incidence of snake bites varies from 5 to 62 cases/100,000 people for year in Latin America. In Brazil, about 30,000 cases of ophidic accidents are registered annually, with
incidence in about 16 cases/100,000 inhabitants. The snake bite cases occur predominantly during the seasons in hot months (5). The regions mostly attacked are North, Northeast and Midwest, and months from November to May are the ones of the most prevalence (6). Most of the victims are male, from 15 to 25 years old, from rural areas and most bites occur in inferior members (7). The economic impact is considerable, especially because most victims are young (5).

In Brazil, health professionals were obliged to notify poisoning by ophidic accidents in 1993 by National Notification System (NNS) (8). However, one can note that, in fact, there is a high rate of sub notification of the cases and many of these are not treated effectively, generating incapacities, expenses for health system with hospitalization and rehabilitation, and deaths (9). In the country, the most common genre is the Bothrops (jararaca), followed by Crotalus (cascavel) (10). Accidents by non poisonous snakes may also cause wounds, due to the lacerations caused by its teeth or by an infection resulting from the bite (7).

The botropic poisoning causes local and systemic effects. Locally, edema, hemorrhage and necrosis may lead to tissue loss and permanent incapacity (11). Treatment consists of elevation of the affected member, administration of the antiophidic serum, prescription of analgesics, physiological serum to keep the patient hydrated and to avoid the occurrence of acute renal insufficiency, and antibiotics when there are indication of infection (12). Latin America has a long history on production of anti venoms which began with the pioneer work of Vital Brazil at Instituto Butantan (13).

Therapy with antivenom is the only effective treatment for neutralizing the venom's toxins if administered precociously. However, the progression of local effects may continue despite its usage and most damage cannot be reverted (2). It has still been associated a wide variety of aerobic and anaerobic bacterias in ophidic accidents (14). Being common complication the infection at the local of the bite, due to the proliferation of microorganisms present at the snake's mouth. Therefore, it may become a grave complication of not diagnosed precociously (9). Sepsis complications are considered rare, meningitis, compartmental syndrome, osteomyelitis and pneumonia (12).

There are three types of osteomyelitis: hematogenic, by contiguity of the infection site or by direct inoculation of microorganisms in intact bone. The hematogenic long bones osteomyelitis is usually caused by only one microorganism, being the *Staphylococcus*, and from this one, the *S. aureus*, the most common agent. *S. aureus* and *S. epidermidis* are part of skin's normal flora, and it may invade the subjacent tissue after breakage of the natural barrier (15).
Osteomyelitis by *Proteus spp.* is rare, mainly in adults (16). This microorganism is mostly found in new-borns and it is associated to infections of the urinary tract (17). So, osteomyelitis' most prevalent symptoms are fever, pain and edema. Diagnosis is made through biopsy and culture of the affected bone (18).

Osteomyelitis' treatment is done with antibiotic therapy, hydration, analgesia and surgical removal of the bone and infected annexes. It is suggested that the treatment with antibiotics can be begun empirically according to the most likely pathogen, until biopsy results, and it must include *Staphylococcus aureus*. Thus, the treatment's elapsed time is usually long and varies from four to eight weeks, aiming to avoid progressive tissue necrosis and complications (19).

*Proteus spp* is an anaerobic negative gram bacteria from enterobacteria family (20). This bacteria is part of gastrointestinal tract flora and there are five species named and three unnamed, being the most common ones the *P. Mirabilis* and *P. Vulgaris*. (21). *Proteus spp* is a bacteria found in the snake's oral flora, however few people develop infection due to the antibacterial action of the venom itself (22). Besides, the own tissue inflammatory changes caused by venom make it hard to identify secondary infection (14).

In literature, the existence of deaths and amputations due to snake bites is cited (23). However, there are no reports of osteomyelitis cases by *Proteus spp* microorganism. Complications by snake bite resulting in deficiencies are a grave public health problem and must not be neglected by professionals and health systems, especially in endemic regions and tropical countries (23). Therefore, the goal of this article is to report the case intervention with osteomyelitis outbreak by *Proteus spp*. occurred at the five weeks immediately after snake bite.

2 MATERIALS AND METHODS

2.1 SAMPLE

A teen patient was studied, aged 17, resident from rural area from Midwest region, Brazil. After suffering ophidic accident, patient sought medical assistance at the local emergency department, being assessed 15 minutes after the episode. The snake bite occurred at the third proximal region of the knee, lower left limb (LLL) anterolateral face (Figure 1).
Figure 1. Soon after the snake bite.

2.2 CLINICAL INTERVENTION PROTOCOL METHOD

After initial assessment, the patient was hospitalized and received antiophidic serum according to the doctor's prescription. The next day, 23 hours after the accident, the patient was discharged, according to the doctor's decision and prescription, for the patient at home, of Nimesulida 100 mg (anti-inflammatory) and Prednisolona 20 mg (corticoid) 12/12 hours for five days. Biochemical exam was requested and a return to the on-duty doctor to reassess the exam. After the result, which presented signs of infection, the doctor added benzetacil® (Benzathine benzylpenicillin), single dose, and kept the usage of anti-inflammatory and corticoid at home.

After that, the patient presented fever and vomiting during the week and was admitted in a reference hospital, where he was submitted to wide antibioticotherapy via intravenous therapy with oxacillin 500 mg 6/6 hours for 12 days, ceftriaxone (rocefin®) 1g 12/12 hours for 3 days, metronidazol 500 mg 12/12 hours for 12 days, gentamicine in replacement to rocefin 80 mg 8/8 h for 6 days, clindamicine 300 mg 6/6 hours. In this hospital, the first surgery was performed with open drain at the local of the bite, after confirmation of intramuscular exsudate by the ultrasonography exam (USG). After surgery, the teenager remained interned for 12 days.
There was improvement of clinical status and the patient was discharged with prescription of the antibiotic clindamicine 300 mg 6/6 h, metronidazol and cimetidine.

Afterwards, the patient got discharged from the hospital after assessment from the orthopedist without being able to step, with light edemas on extremities, without fever or nausea. He presented clubfoot syndrome, without response from the fibular nerve, with absence of the dorsiflex movement. Since there was a progressive worsening after two weeks, the patient was taken to a specialist in a reference hospital, at the capital of the state. He was received by a neurosurgeon to begin the rehabilitation process. After consultation, and due to his constant sub feverish state, the doctor recommended reassessment of the infectology for follow up of the case. After thorough assessment, the infectologist diagnosed extense polymyositis and bone osteomyelitis at the tibia of the MIE.

Due to this, the patient was submitted to a new surgical procedure, wider, with bone marrow technique (BMT) and closed drain in suction on the MIE. During the surgical procedure, tibial and fibular muscles were removed due to necrosis. Then, the patient remained hospitalized for 10 days to receive intravenous antibiotic of wide coverage. Finally, on the complementary exams, the negative gram bacteria Proteus spp was verified at the bone and the muscle (Figure 2).
3 RESULTS

The patient presented signs of infection, with white blood cells at 14,700/mm$^3$, being the reference up to 10,000/mm$^3$, according to Table 1.

Table 1. Clinical Variables, biochemical markers, imaging exams of the individual submitted to bone marrow surgery (BMS) by snake bite.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial</th>
<th>Final</th>
<th>$\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>42%</td>
<td>44.8%</td>
<td>+2.8%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.8g/dL</td>
<td>15.10g/dL</td>
<td>+1.3g/dL</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>4,74 millions/mm$^3$</td>
<td>5.02 millions/mm$^3$</td>
<td>+0,28 millions/mm$^3$</td>
</tr>
<tr>
<td>Mean corpuscular Volume (MCV)</td>
<td>88.6 fl</td>
<td>89.20 fl</td>
<td>+0.6 fl</td>
</tr>
<tr>
<td>Mean Corpuscular Hemoglobin (MCH)</td>
<td>29.1 pg</td>
<td>30pg</td>
<td>+0.1 pg</td>
</tr>
<tr>
<td>Mean Corpuscular Hemoglobin Concentration (MCHC)</td>
<td>32.8%</td>
<td>33.70%</td>
<td>+0.9%</td>
</tr>
<tr>
<td>White blood cells</td>
<td>14.700/mm$^3$</td>
<td>4.700/mm$^3$</td>
<td>-10.000/mm$^3$</td>
</tr>
<tr>
<td>Basophils</td>
<td>0/mm$^3$</td>
<td>47/mm$^3$</td>
<td>+47/mm$^3$</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>735/mm$^3$</td>
<td>47/mm$^3$</td>
<td>-688/mm$^3$</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>0/mm$^3$</td>
<td>0/mm$^3$</td>
<td>0</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>0/mm$^3$</td>
<td>0/mm$^3$</td>
<td>0</td>
</tr>
<tr>
<td>Batons</td>
<td>588/mm$^3$</td>
<td>0/mm$^3$</td>
<td>-588/mm$^3$</td>
</tr>
<tr>
<td>Segmented</td>
<td>11.613/mm$^3$</td>
<td>2.068/mm$^3$</td>
<td>-9.545/mm$^3$</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.323/mm$^3$</td>
<td>2.068/mm$^3$</td>
<td>+745/mm$^3$</td>
</tr>
<tr>
<td>Monocytes</td>
<td>441/mm$^3$</td>
<td>470/mm$^3$</td>
<td>+29/mm$^3$</td>
</tr>
<tr>
<td>Small plaque count</td>
<td>150.000/mm$^3$</td>
<td>199.000/mm$^3$</td>
<td>+49.000/mm$^3$</td>
</tr>
<tr>
<td>Coagulation time – Lee White</td>
<td>7 minutes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coagulation time – Lee White</td>
<td>2 minutes</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$\Delta$ (Initial Value – final value)

For complementary assessment, imaging exams were performed, among them muscle ultrasound and MRI (Table 2).

Table 2. Complementary exams of the patient bitten by snake with osteomyelitis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial</th>
<th>Final</th>
<th>$\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia bone histology</td>
<td>Present +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RMNI</td>
<td>Present +++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Muscular Bacterioscopy MIE</td>
<td>Present +</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$\Delta$ (Initial Value – final value), RMNI= Imaging MRI.

In Figure 3, nuclear MRI presents the evolution of the osteomyelitis during treatment. The bone infection focuses are circulated in red. Letter “A” shows the initial phase of the treatment. Letter “B” has arrows pointing the OMC and letters “C” and “D” show the post-surgical evolution.
In Figure 4, there is a comparison of the evolution of the affected member since the bite until post-surgical moment. It is possible to note, in the last image, the reduction of the MIE circumference, in relation to patient's MID, due to the loss of approximately two-thirds of musculature by the infection, with the intent to avoid total amputation of the leg.
4 DISCUSSION

In this case study, positive bacteriology was found for Proteus spp. at muscle and bone, which resulted in an osteomyelitis diagnosis. The infectious state developed on the first five days after the bite. As a result, the patient lost muscles and nerves, beginning the deficiency at the foot dorsiflex movement. Osteomyelitis is a serious disease and etiologic factor for member amputation, secondary to several kinds of accidents, among them snake bites. It is not known exactly why the patient responded badly to the antibioticotherapy, but possibly some factors had their role, such as the patient's ineffective immunity at a young age.

According to data from Brazilian Institute of Geography and Statistics (IBGE), there are about 7,5 millions of underage people working, aged 10 to 17, who constitute about 11,6% of Brazilian workforce (24). Children and teenagers contaminate themselves easier by biological agents, according to the environment they work at or the activities they perform. Among the
factors that make them more susceptible to infections, there is the immaturity of the immune system and the insufficient nutritional ingestion associated to the increased caloric expense. Besides, they experience a conflicting role in the family, work and community, because, as workers, teenagers are forced to act like adults. These factors are source of emotional stress which affect mental and physical development. (25).

The usage of corticoids depresses immunity. So, treatment with only 10 mg of prednisone daily is enough to increase the risk of new infections, grave ones, or the reactivation of old ones, bacterians, either viral or fungical ones. Besides, the infection symptoms can be masked by the anti-inflammatory effect of the corticoids (26). Thus, the risks of its usage must be taken into account for prophylaxis, because other secondary factors may lead to complications.

It is also known that wounds generated by ophidic accidents are potentially contaminated, and may lead to tissue destruction and infection by bacteria (14). If there had been potent prophylaxis immediately after the snake bite, with wide spectrum antibiotic, probably the diagnosis wouldn't evolved the way it did (15). Thus, hospitalizing and monitoring patients victims of snake bite could avoid complications and deficiencies. Besides, health professionals should observe the risk of negative gram bacteria, rare, administering the use of antibiotics, for either positive and negative gram.

5 CONCLUSION

Serum therapy has shown itself effective for treatment of snake poisoning, however it does not prevent the outbreak of infections by inoculation of the bite.

Therefore, it is possible to conclude that, in ophidic accidents, hospitalization and monitoring of these patients could avoid complications. One must consider the risk of infection by negative gram bacteria, rare, by administering the use of antibiotics, for either positive or negative gram. These measures could avoid longer internments, physical deficiencies and increase of health costs.
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