Osteonecrose Multifocal e Síndrome de Guillain Barré

Multifocal Osteonecrosis and Guillain Barré Syndrome

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Resumo

A osteonecrose multifocal, definida pelo envolvimento de 3 ou mais sítios anatómicos, é incomum, sendo observada em apenas 3% a 11% dos doentes com diagnóstico de osteonecrose. A síndrome de Guillain-Barré é uma doença de início agudo, habitualmente monofásica, imune mediada, que afeta o sistema nervoso periférico. O objetivo deste artigo é relatar um caso clínico de osteonecrose associado a síndrome de Guillain-Barré com revisão da literatura.

Apresentamos o caso de um doente do sexo masculino, de 40 anos, com sintomas e sinais neurológicos, que se apresenta no Serviço de Urgência uma semana após uma síndrome gripal. Por suspeita inicial de mielite, foi iniciada corticoterapia. O diagnóstico de síndrome de Guillain-Barré foi mais tarde confirmado e iniciou tratamento com imunoglobulinas. Um ano depois, o doente desenvolveu artralgias da anca e ombro bilateralmente.

O diagnóstico de osteonecrose multifocal foi estabelecido por ressonância magnética. Foi realizada artroplastia total da anca direita e programada a da esquerda. O doente foi submetido a um programa de reabilitação visando alívio da dor e melhoria funcional com bom resultado.

Nos últimos dez anos de revisão da literatura, não existem casos descritos da associação entre síndrome de Guillain-Barré e osteonecrose multifocal.

Palavras-chave: Osteonecrose; Síndrome Guillian-Barre.

Abstract

Multifocal osteonecrosis, defined by the involvement of 3 or more anatomic sites, is unusual, being observed in only 3% to 11% of patients diagnosed with osteonecrosis. Guillain–Barré syndrome is an acute onset, usually monophasic immune-mediated disorder of the peripheral nervous system.

The aim of this article is to report a clinical case of multifocal osteonecrosis and Guillain–Barré syndrome with review of the literature.

We present a case of a 40-year-old male, with neurological symptoms who presented to the Emergency Department one week after a flu like syndrome. Myelitis was firstly suspected and corticosteroids were started. Diagnosis of Guillain–Barré syndrome was later confirmed and he underwent treatment with immunoglobulins. One year later, the patient developed bilateral hips and shoulders arthralgia. The diagnosis of multifocal osteonecrosis was established by magnetic resonance imaging. Total right hip arthroplasty was performed and a left one was planned. The patient underwent a rehabilitation program aiming pain relief and function improvement with a good outcome.

In the last ten years literature review, there were no reports of the association between Guillain–Barré syndrome and multifocal osteonecrosis.

Keywords: *Guillain-Barre Syndrome; Osteonecrosis.*

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Introdução

Osteonecrosis (ON) is an ischemic process in the juxta-articular bone. Two forms of osteonecrosis are distinguished, one in which infarction occurs in bone marrow, causing no clinical signs, and another involving the cortical medulla, with a more florid clinical picture. Although it can occur in any bone, typical predilection sites are the hip and knee. [1] Associated conditions include hypercoagulability,[1] corticosteroids (CS), hyperlipidemia, excessive alcohol consumption, smoking,[2] systemic lupus erythematosus (SLE), pancreatitis, chemotherapy,[3] and hematological diseases.[4] Multifocal or multiple osteonecrosis (MON), defined by the involvement of 3 or more anatomic sites, is unusual, being observed in only 3% to 11% of patients diagnosed with ON.[5,6] Guillain–Barré syndrome (GBS) is an acute onset, usually monophasic immune-mediated disorder of the peripheral nervous system. The term GBS is often considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the increasing recognition of variants over the past few decades.[7] There are no reports of the association between GBS and MON, however, as these patients may be exposed to CS or to other risk factors of ON, this complication should be kept in mind in GBS patients with persistent joint symptoms. The aim of this article is to report a clinical case with literature review about MON and related conditions.

Case Report

We report a case of a 40-year-old healthy male, gardener, who presented one week after a self-limited flu like syndrome, with a clinic of paresthesia and hypoesthesia starting in the toes, which progressed proximally till the hips and hands; he was unable to walk. He denied motor deficits, pain and bowel or urinary disturbances. At physical examination, his Glasgow Coma Scale was 15 out of 15. His speech and higher mental functions were normal. There was horizontal left gaze nystagmus with no other cranial nerve involvement. Muscle tone was normal in all limbs with increased deep tendon reflexes. Hip flexors and knee extensors muscle power was four out of five proximally and the other segments were normal. Pinprick sensation revealed hypoesthesia with stocking and glove distribution, with the other sensory functions normal. Loss of ankle proprioception. Vibration proprioception tests were abnormal. Plantar reflexes were normal. Oral temperature, oxygen saturation, and systemic examination were all within normal limits.

Complementary diagnostic exams were performed. Blood tests revealed normal hemoglobin, normal leucocyte and platelet counts and renal function, liver tests, C- reactive protein and sedimentation rate, also within the normal range. Cerebral computing tomography (CT) scan did not show any cranial lesions, neither ischemic nor hemorrhagic. Lumbar puncture was performed and cerebrospinal fluid (CSF) revealed increased protein (98 mg/dL) and slightly increased white blood cell count (15 cells, mononuclear) with normal glucose (inferior to 60% of the serum value). The electromyography did not reveal any abnormal conduction parameters.

A diagnostic of an infectious transverse myelitis was presumed and the patient was admitted to the Infectious Diseases Department. An antimicrobial regimen was started with ceftriaxone plus acyclovir with the duration of two weeks without any improvement of the neurological deficits. HIV- check was negative. The DNA of Borrelia spp, herpes virus and enterovirus were all negative in the CSF. Serological tests (herpes, cytomegalovirus, Borrelia) performed in the CSF were negative for acute infection. No other microbiological agents were isolated in the CSF. A magnetic resonance imaging was performed and showed diffuse posterior disc osteophytes in L5-S1 of right predominance, disc protrusion, with narrowing of the intervertebral space.

Due to the lack of clinical improvement, methylprednisolone, 1g per day, was started and maintained for an eight-day course. Again, the neurological deficits persisted and a second electromyography was performed in the Neurology Department, which revealed decreased of motor unit potentials, establishing the diagnosis of GBS.

Treatment with intravenous immunoglobulin infusion and an intensive physiatric rehabilitation plan were then initiated in a Rehabilitation Centre outside our institution and clinical outcome was favorable, with full recovery.

After two years, the patient was referred to the Physical and Rehabilitation

Medicine Department of our institution, complaining about hips and shoulders joints pain and movement restriction, with an insidious onset. At the shoulders physical examination, there was deep, difficult to localize, shoulder and arm pain elicited by motion. The average range of motion (ROM) for the right shoulder was 140º for flexion, 130º for abduction, 70º for external rotation and 40º for internal rotation. Considering the left shoulder, ROM was 80º for flexion, 60º for abduction, 50º for external rotation and 20º for internal rotation.

At the hip physical examination, there was anterior tie and groin pain with hip bilateral loss of external and internal rotation; bilateral short swing and stance phase.

The average range of motion (ROM) for the right hip was 90º for flexion, 20º degrees for abduction, 30º for external

rotation and 10º for internal rotation. Considering the left hip, ROM was 110º for flexion, 30º for abduction, 30º for external rotation and 10º for internal rotation.

The diagnosis of MON was established by magnetic resonance imaging (MRI) two years after the GBS diagnosis. The joints involved were the hips (Fig.1) and shoulders (Fig. 2). Radiographs of other asymptomatic joints were performed (knees) and no signs suggestive of MON were found.

There was no history of smoking, alcohol abuse, pancreatitis, chemotherapy or hematological diseases. The clinical history and the auto-immunity exams were not compatible with an auto-immune disease [namely SLE or antiphospholipid syndrome (APS)]. The laboratory results excluded a hypercoagulability state, hyperlipidemia or

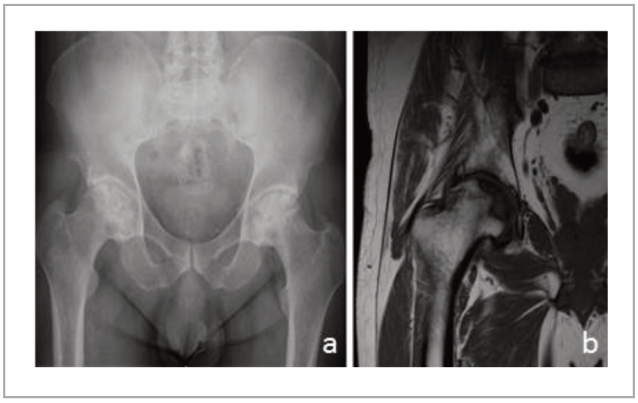

Figure 1 - Radiographic findings compatible with ON; the loss of femoral head sphericity is observed bilaterally (a). T1-weighted image of right femoral head with signal changes compatible with ON (b).

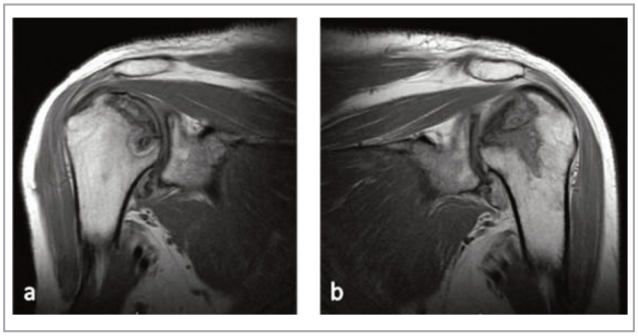

Figure 2 - T1-weighted image showing depression of both humeral heads (a and b).

human immunodeficiency virus infection.

Total right hip arthroplasty was performed and a total left hip arthroplasty was then scheduled. The patient started a standard total hip arthroplasty protocol and simultaneously, a rehabilitation program, three times a week for four months, aiming pain relief and shoulder function improvement, including: weight restriction, ice, heat, ultrasound and other electrotherapy modalities, gentle mobilization of the shoulder joint; once the pain was controlled the patient started rotator cuff strengthening and proprioceptive exercises for better scapulothoracic motion control, through the available range of movement.

After four months of physical rehabilitation, the patient had improved in pain, range of motion and ability to perform daily activities. He had improved his shoulder abduction range of motion by 40º in the right shoulder and by 30º in the left shoulder; his shoulder flexion had improved by 20º bilaterally; internal rotation by 20º bilaterally; external rotation by 10º in the right shoulder and 20º in the left.

Concerning the hip, patient had improved in pain and in range of motion exclusively in the hip that underwent surgery: 20º of flexion, 5º of abduction, 5º of external rotation and 10º of internal rotation.

Discussion

In a Cochrane systematic review of 6 trials with 587 patients it has been shown that corticosteroid therapy is ineffective for treating GBS.[7] However, in clinical practice, CS still remain present in some clinical cases and, as they could lead to several side effects, the clinician need to be aware about this issue. In this particular case, CS were used before the diagnosis of GBS was established and before the therapy with human immunoglobulin was initiated. Although there are no reports about increased risk of ON with immunoglobulin therapy, CS are well established risk factors for this condition. Moreover, in those patients in whom osteonecrosis is steroid-induced, there is evidence that the number of affected sites is related to the dose of steroids which has been given.[8]

During the severe acute respiratory syndrome epidemic in China (2003), Zhang *et al* aimed to determine the relationship between the dosage of steroids and the number and distribution of osteonecrotic lesions in patients treated with CS. They confirmed that the number of osteonecrotic lesions was directly related to the dosage of CS and that a very high dose (a peak dose of more than 200 mg) or a cumulative methylprednisolone-equivalent dose of more than 4000 mg, is a significant risk factor for multifocal osteonecrosis with both epiphyseal and diaphyseal lesions. In this study, patients with diaphyseal osteonecrosis received a significantly higher cumulative methylprednisolone-equivalent dose than those with epiphyseal osteonecrosis. They suggested that MON should be suspected if a patient is diagnosed with osteonecrosis in the shaft of a long bone.[9]

We performed a literature review on Medline for MON and included case reports, case series or reviews in the last ten years. Articles enrolled had at least an abstract available in

English or Spanish with information on number of joints affected, age, gender and known risk factors. The results are reported in Table 1.[6,10,13-33]

We identified 165 patients with MON, the mean age was 42.83, 55.7% were female, and the mean number of sites affected was 5.20. The hips were the joints more frequently

Table 1 - Results of the literature review (165 patients with MON found).

Study	Nº of patients reported	Age	Gender	Nº of joints affected	Associated pathology	Reference
1	87	NA	NA	5.2 (mean)	Sickle cell disease	[10]
2	26	46	16 F 10 M	5.2	Idiopathic, CS use, alcohol abuse	[6]
3	26	48.4 (mean)	7F 19 M	5.2 (mean)	Previous CS use, APS, coagulopathy, liver transplantation, COPD, dermatomyositis, bone marrow transplant, HIV, kidney transplant, prolactinoma, mastocytosis/acute myeloid leukemia, lymphoma, sickle cell disease, autoimmune hepatitis	[14]
4	6	43	6 F	9.5	Hypogammaglobulinemia, alcohol abuse, sickle cell anemia, SLE, leukemia, ulcerative colitis, liver transplant	[15]
5	2	38 and 27	2 F	6 and 5	SLE and septic arthritis	[16]
6	1	24	F	6	SLE and APS	[17]
7	1	32	F	4	Panhypopituitarism	[18]
8	1	14	F	5	Acute lymphoblastic leukemia	[19]
9	1	49	M	8	HIV	[20]
10	1	56	F	4	HIV	[21]
11	1	31	M	5	Liver transplantation and APS	[22]
12	1	NA	F	3	Multiple sclerosis	[23]
13	1	13	F	4	Dermatomyositis	[24]
14	1	25	F	6	SLE/systemic sclerosis (overlap syndrome)	[25]
15	1	37	M	8	SLE, alcohol abuse	[26]
16	1	21	F	4	SLE	[27]
17	1	10	F	8	Juvenile dermatomyositis	[28]
18	1	20	M	6	Ulcerative colitis	[29]
19	1	15	F	3	Tuberculous encephalitis	[30]
20	1	57	F	3	Alcohol abuse	[31]
21	1	31	M	3	Vibration-induced	[13]
22	1	32	M	4	Alcoholism	[32]
23	1	52	F	6	APS	[33]

CS-corticosteroids; APS-anti phospholipid syndrome; COPD-chronic obstructive pulmonary disease; HIV- human immunodeficiency virus; SLE-systemic lupus erythematous.

affected, followed by knees and shoulders (Table 2). CS use was reported in 60.30% of cases (Table 3). The results were comparable with those of a multicenter study of Collaborative Osteonecrosis Group which identified 101 MON patients from 21 different centers. Overall, 631 joints were involved (6.2 lesions per patient) and all 101 patients had femoral head involvement.

Osteonecrosis also was seen in the knee (96%), shoulder (80%), ankle (44%), and seven other sites. The percentage of patients that underwent CS therapy was higher than in our review [92 of the 101 patients (91%)]. Twelve patients (of 14 tested) were found to have a coagulation disorder. All 101 patients had femoral head involvement.[8] Of note is that this study, published in 1999, was not taken into account in our literature review since we considered only studies of the last ten years.

In our review, sickle cell disease was the condition most frequently associated with MON (Table 4). The main contribution for those data was provided by C. Flouzat-Lachaniete *et al* who described a cohort of patients with sickle cell disease who developed MON. They concluded that in patients with sickle cell disease, the risk of MON was very high.[10]

Regarding the distribution and frequency of joints affected, there is some evidence in

literature advising that, in patients with hip ON, the other joints should be evaluated with radiography and MRI if the joint is symptomatic. In patients with ON of other joints rather the hips, evaluation by radiography or MRI of the hips should be performed, regardless of whether the hip is symptomatic.[8,10] Before the adoption of MRI, bone scanning was considered a more sensitive diagnostic test than standard radiographs for early disease detection.[11] Mont *et al* concluded in 2008, that bone scanning has a low sensitivity for diagnosing symptomatic ON, especially for early-stage lesions, and joints other than the hip.[12]

Regarding the clinical case that we presented, the major factors that contributed to the MON were the high CS dose and, possibly, the exposition to vibration in the patient professional activity (gardening equipment). Besides the association between CS therapy and MON was well established in the literature, we found only one report of vibration-induced MON.[13]

MON is a major cause of disability and this complication should be kept in mind in patients treated with CS and persistent articular symptoms. As take home messages we would like to emphasize that:

- GBS is not usually associated with MON
- Patients with risk factors for this condition and articular symptoms suggestive of MON should underwent an appropriated clinical and radiological examination (including X rays and MRI if necessary)
- In patients with hip ON, the other joints should be evaluated with radiography and MRI if the joint is symptomatic
- In patients with ON of other joints rather the hips, evaluation by radiography or MRI of the hips should be performed, regardless of whether the hip is symptomatic.
- MRI has largely replaced radionuclide bone scanning because of its greater sensitivity

Table 2 - Patients characteristics in the cases of MON reported in the literature review.

		n available (n total – 165)
Age, mean (SD)	42,83 (13.63)	78
Female, nº (%)	44 (55.7%)	79
Number of sites affected per patient, mean (SD)	5.20 (1.21)	165
Sites affected, nº		140
• Hips	240	
• Knees	204	
• Shoulders	196	
• Others	122	

Table 3 - Steroids use, coagulopathy and antiphospholipid syndrome reported in the cases of MON reported in the literature review

	Nº of cases (valid %)
Steroids use	47 (60.30)
Coagulopathy	12 (23.50)
Antiphospholipid syndrome	6 (4.3)

Table 4 - Comorbidities reported in the cases of MON reported in the literature review

Comorbidity (n – 165)	Nº of cases (%)
Sickle cell disease	89 (53.6)
HIV	9 (5.4)
Alcohol consumption	8 (4.8)
Systemic lupus erythematosus	5 (3.0)
Leukemia	4 (2.4)
Liver transplant	4 (2.4)
Bone marrow transplant	3 (1.8)
Dermatomyositis	3 (1.8)
Ulcerative colitis	2 (1.2)
Others*	12 (7.2)
Idiopathic MON	14 (8.4)

*Including: autoimmune hepatitis, chronic obstructive pulmonary disease, hypogammaglobulinemia, juvenile dermatomyositis, kidney transplant, systemic sclerosis, lymphoma, multiple sclerosis, panhypopituitarism, previous prolactinoma, tuberculous encephalitis, vibration-induced.

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