Multifocal avascular osteonecrosis despite appropriate anticoagulation therapy in a patient with systemic lupus erythematosus and antiphospholipid syndrome

Title: Multifocal avascular osteonecrosis despite appropriate anticoagulation therapy in a patient with Systemic Lupus Erythematosus and Antiphospholipid Syndrome: a case report.

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[1] Center of Research of Immunopathology and Rare Diseases-Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences, San Giovanni Bosco Hospital, Turin, Italy

[2] Rheumatology Unit/University Hospital Reina Sofía of Córdoba, Córdoba, Spain

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Corresponding Author:

Savino Sciascia, MD PhD

Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, and SCDU Nephrology and Dialysis, S. Giovanni Bosco Hospital

Piazza del Donatore di Sangue 3, 10154, Turin, Italy

E-mail savino.sciascia@unito.it Tel +390112402056 Fax +390112402052

Summary

Multifocal Avascular Osteonecrosis (AON) is a serious manifestation of Systemic Lupus Erythematosus (SLE). Pro-thrombotic factors, especially antiphospholipid antibodies (aPL), have been associated with the development of AON; therefore, attenuating the pro-coagulant state while balancing the haemorrhagic risks might have a rational when managing this condition.

We report a case of a 37-year SLE patient, treated with low doses of corticosteroids and immunosuppressive therapy, who was started on vitamin K antagonist (VKA) after developing an episode of deep vein thrombosis in the presence of persistent positivity for aPL. After 2 years, he presented with a case of multifocal AON, involving both femurs and shoulders. The patient underwent a bilateral hip replacement, but after 2 years he developed another episode of AON at both distal epiphysis of femurs and proximal epiphysis of tibias, despite appropriate anticoagulation therapy.

Multifocal AON need to be suspected especially in the presence of aPL positivity. its aetiology is still unknown, and most likely multifactorial. Its management is challenging and requires combined approached.

Background

Avascular osteonecrosis (AON) is a serious medical condition which can lead to severe complications and cause long-term disability. The exact pathogenesis remains unclear, but it seems

to be multifactorial as several risk factors have been associated with AON, such as trauma, chronic use or high dose of corticosteroids (CS), infections, haemoglobinopaties, and alcohol abuse among others [1].

The presence of an autoimmune connective tissue disease has been proven to be associated *per se* with a higher risk of AON development, which is considered to be a well-known manifestation in Systemic Lupus Erythematosus (SLE) patients with a prevalence ranging from 3 to 30% [2].

Even if the exact pathogenesis of AON is partially unknown, the pathologic cascade includes, especially when involving the head of the femur, primarily venous obstruction, interrupting venous outflow, leading to the reduction of the arterial supply, ischaemia, necrosis, bone damage, and eventually collapse [3][4].

Multifocal AON, which is a more severe and dramatic presentation of AON, and is defined as the occurrence of osteonecrotic lesions in 3 or more separate anatomic sites, is unusual and only a few cases are reported in the literature [5]. Interestingly, even less data is available regarding the occurrence of multifocal AON in Antiphospholipid Syndrome (APS) setting and the impact of antiphospholipid antibodies (aPL) in the development of this medical condition.

Herein, we present a case of multifocal AON in a SLE patient with APS despite anticoagulation therapy with vitamin K antagonist (VKA) and satisfactory time in therapeutic range (TTR).

Case presentation

A 37-year-old Caucasian man was admitted to our centre and diagnosed with SLE according to the American College of Rheumatology classification criteria [6] in July 2004, when he presented with fever, severe asthenia, skin rash, pleuritis, and inflammatory polyarthritis. Serological evaluation and laboratory tests demonstrated leukopenia, elevated levels of erythrocytes sedimentation rate (ESR), anti-nuclear and anti-double stranded DNA (anti-dsDNA) antibodies positivity, and high titer anti-cardiolipin (ACA) antibodies IgM isotype. The patient also presented hyperlipidaemia, treated with fenofibrate, and smoke habit. No family history of immune-rheumatic diseases. No personal history of diabetes, previous cardiovascular events, renal disease, chronic infections, arterial hypertension, and alcohol abuse.

Initially, the patient was treated with medium doses of oral CS (prednisone 30 mg/daily) with tapering down in 9 months to the daily dose of 5 mg, associated with immunosuppressive therapy with methotrexate 15 mg/weekly and chloroquine.

In 2005, the patient developed an episode of deep vein thrombosis (DVT) and it was therefore started on anticoagulation therapy with VKA (acenocumarol, INR target 2-3).

For the following 2 years the patient's medical conditions remained clinically and serologically stable, and he continued taking low doses of CS (prednisone 5 mg/daily) and immunosuppressive therapy as previously described.

In January 2007 the patient manifested a sudden onset of severe pain in both hips, and milder pain in both shoulders. No previous trauma was reported by the patient. Physical examination showed

intense tenderness and movement limitations at those levels. No other clinical signs and symptoms of disease activity were present.

Investigations

A serological evaluation showed a normal complete blood count, including the absence of anaemia, platelets and leukocytes count were in range. The patient had normal complement and ESR levels. The C reactive protein value was slightly elevated (3.5 mg/dl), and anti-dsDNA were negative. Moreover, no serological sign of systemic infection was detected.

Radiography and magnetic resonance (MRI) were performed, pointing out the presence of multifocal areas consistent with multiple foci of AON, located at the proximal epiphysis of the right femur, at the head of the left femur and at both shoulders (Fig. 1 and 2).

Differential diagnosis comprehended: inflammatory synovitis, osteomyelitis, neoplastic bone conditions, and osteoarthritis.

Treatment

Non-steroidal anti-inflammatory drugs and immobilization were prescribed. Subsequently the patient underwent a bilateral hip replacement surgery with excellent pain relief and good outcome (Fig. 3).

Outcome and follow-up

In 2009 the patient presented with rapid onset of intense pain at both knees and the MRI showed the occurrence of a new episode of AON at both distal epiphysis of femurs and both proximal epiphysis of tibias. The clinical setting was managed with a conservative approach, and pain management was planned. The patient was kept on CS at low doses (prednisone 5 mg/daily), chloroquine, and VKA antagonist, and his conditions remain stable for nine years.

Discussion

This case report supports the multifactorial pathogenesis of AON, as our patient showed the concomitant presence of aPL positivity, the connective tissue disease, the ongoing CS treatment [7], and the traditional cardiovascular risk factors (hyperlipidaemia and smoking) [8,9].

According to the "second-hit theory" [10], the presence of aPL is necessary but not sufficient to induce thrombosis. Our patients was tested positive only for ACA IgM isotype, conferring an overall lower risk for clinical manifestation when compared to other aPL profiles (e.g. triple positivity) [11]. One could speculate that the pro-thrombotic status was only partially responsible for the AON and therefore the anticoagulation therapy with VKA (despite being well conducted, >75% over 2 years) was not enough to prevent further recurrences. A better management of all the potential risk factors (e.g. use of statins, counselling for smoking cessation, the use of steroid sparing agents to control the activity of the connective tissue disease) are therefore mandatory to improve the outcome in these complex patients. Recently, several scoring models have been

suggested for clinical risk assessment in patients with aPL. Among other, the global APS score, the GAPSS, was shown to be a useful tool when computing the likelihood of new clinical manifestations [12] in patients with SLE. Our patient scored 8 in GAPSS, conferring up to a medium risk of new events, and underlining the need for a tailored approach.

In conclusion, our case shows, in addition to the available data of the literature, that multifocal AON represent a serious cause of morbidity in SLE patients. The association with APS and aPL positivity, as well as the presence of traditional cardiovascular risk factors, seems to play a significant role in the multifactorial and complex pathogenesis of multifocal AON.

AON and osteonecrosis in multiple sites need to be suspected in all SLE patients, especially when in association with APS, despite the ongoing anticoagulation therapy, who present with sudden onset of articular pain, and diagnostic assessment should be performed in order to ensure an earlier diagnosis and treatment.

Take home messages:

- Multifocal avascular osteonecrosis (AON) is an unusual and serious manifestation of Systemic Lupus Erythematosus

- The pathogenesis of multifocal AON seems to be multifactorial, and the ongoing anticoagulant therapy in the presence of aPL positivity, can not prevent the development of new osteonecrotic events
- A careful assessment and management of traditional cardiovascular risk factors is highly recommended in patients with autoimmune diseases

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