Acute venous thrombosis as complication and clue to diagnose a SAPHO syndrome case. A case report

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ABSTRACT

This report concerns a male adult admitted for sternal and left arm pain, who was diagnosed and treated for acute deep venous thrombosis in the left subclavian and axillary veins. X-ray and a hybrid single photon emission tomography and computed tomography (SPECT-CT) scintigraphy scan revealed high intensity uptake in both sternoclavicular joints, which corresponded to hyperostosis, thereby suggesting a SAPHO syndrome. Upon reviewing the patient's medical history, we found dermatological pustulosis disease and an intermittent sternal chest pain untreated since 10 years ago. In the biochemical study we found erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) elevation, hyperglobulinemia, and mild anaemia. Initial treatment included nonsteroidal anti-inflammatory drugs (NSAIDs) with low response, which then changed to methotrexate, sulfasalazine, and prednisone. The patient's pain was controlled almost completely in 10 months. A control bone scan revealed a marked decrease in intensity of bone deposits according to clinical response. To our knowledge, there are only a few cases of SAPHO and thrombosis and none are followed up with a bone SPECT-CT scan.

Keywords: SAPHO syndrome; Venous thrombosis; Bone scintigraphy; Dupuytren disease.

INTRODUCTION

SAPHO is a rare syndrome that is characterized by synovitis, acne, pustulosis, hiperostosis and osteitis, affecting mainly the anterior chest wall. Its etiology remains unknown. However, several hypotheses have been proposed suggesting a multi-causal origin with a probable genetic and immunologic basis, which could be exacerbated or triggered by infection. The treatment is mostly symptomatic and based on nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, bisphosphonates and other disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine. Anti–tumor necrosis factor (anti-TNF) agents have also been shown to benefit some patients[1].

We report a new case of this syndrome in a patient with deep vein thrombosis as a complication and manifestation of an unknown SAPHO syndrome. Bone SPECT-CT scan scintigraphy aided in the follow-up, according to a clinical improvement.

CASE REPORT

In October 2011, a 56-year-old Caucasian male patient was admitted in our hospital with symptoms of pain and swelling in the left arm and sternal pain diagnosed of an acute episode of deep venous thrombosis (DVT), confirmed in the axillary and left subclavian veins on ultrasound. A chest X-ray and CT were performed to rule out malignancy. The chest X-ray and CT suggested sternoclavicular sclerosis and joint fusion with increased retrosternal density with soft tissue thickening. These findings were suggestive of a SAPHO syndrome (Figure 1). Biochemical and haematological tests revealed mild anemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), prothrombin time, D-dimer, and fibrinogen. The patient had anticoagulation medication (enoxaparine 60 mg bid) during hospitalization and continued outpatient treatment with acenocumarol. He was then referred to a rheumatologist. In the first clinic in our service, a complete medical history revealed an intermittent sternal chest pain of 10 years of evolution which improved on rest and in some periods of NSAID use due to other

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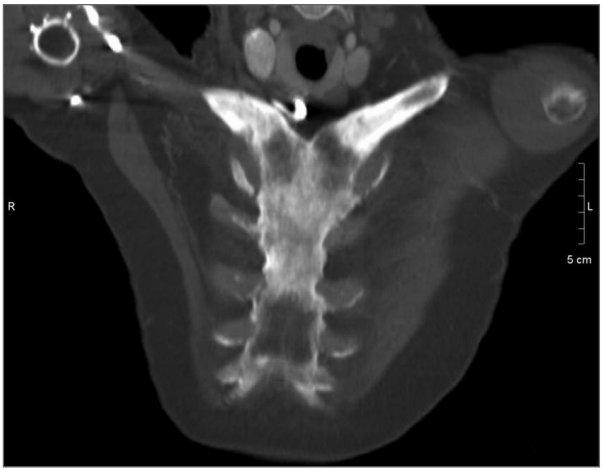

FIGURE 1. CT: Coronal reconstruction image of sternum, showing bone sclerosis at the medial end of both clavicles and sternum (manubrium most striking) with ankylosis of the sternoclavicular joint and sternum

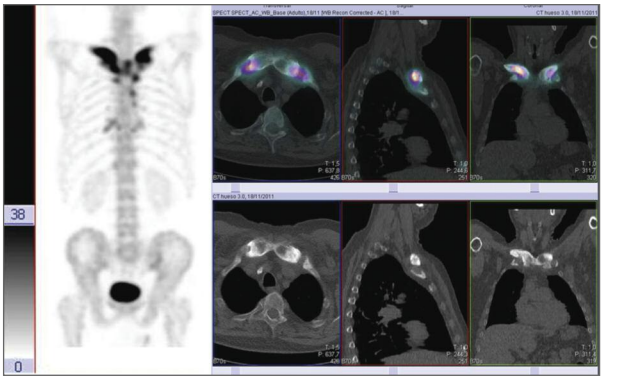

FIGURE 2. A) Maximum intensity projection image of SPECT, which shows the "bull's head" consisting of high increased uptake images and diffuse morphology manubrium and sternoclavicular joints. B) SPECT-CT scan: fusion images of a coronal and sagittal reconstruction show radiotracer increased uptake with marked sclerosis areas in the front and end of both clavicles and the manubrium, also fusion of the sternoclavicular joint and high retrosternal density in relation to hyperostosis in the CT images

pathologies. In addition to that, pruritic, keratotic papules on hand and scalp were treated 4 years ago without new episodes. Finally the patient was treated surgically for bilateral Dupuytren s disease 18 years ago. No history of chronic diseases of another surgical procedure were found.

Laboratory tests confirmed persistent elevation of CRP (3.2 mg/dL), ESR (37 mm/hr), mild microcytic hypochromic anemia, and alfa and beta hyperglobulinemia. Normal tumoral markers as Prostate-specific antigen (PSA), Carcinoembryonic antigen (CEA), Alpha-1 fetoprotein, cytokeratin fragment (CYFRA) 21--1, cancer antigen (CA 15-3, CA 19-9, and CA 125, Beta-2 microglobulin). Normal immunologic markers as rheumatoid factor, Antinuclear Antibodies (ANAs), extractable nuclear antigens (ENAs), anti-citrullinated peptide antibodies, anti-phospholipid antibodies, anti-cardiolipin and anti-B2-Glicoprotein I. No serologic evidence of hepatitis A virus (HAV) or hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Negative human leukocyte antigen B27 (HLA-B27). Negative autoimmune liver antibodies as Anti-straight muscle, Anti-mitochondrial and Anti-Liver Kidney Microsomal Antibodies (Anti-LKM). Laboratory tests also revealed normal thrombophilia genotype (Factor V Leiden and Factor II 20.210), normal thrombophilia phenotype (antithrombin III, Functional PC-Crom, Homocysteine and activated protein C resistance ratio (aPCR)). Normal levels of thyroid hormones, and a normal echocardiogram.

A diagnostic whole body SPECT-CT scan with 99mTc-HDP showed high increased uptake in the manubrium and sternoclavicular joints, typically described as the "bull head" sign corresponding with the CT hyperostosis and osteitis (Figure 2). These findings confirmed a SAPHO syndrome diagnosis with marked metabolic activity.

This patient was initially treated with NSAID (diclofenac 150 mg/day) and shoulder physiotherapy for 3 months with partial response. This leaded to a change to methotrexate 15 mg/week, prednisone 5 mg/day, folic acid 5 mg/day and sulfasalazine (increasing doses to achieve therapeutic levels of 2 gr/day for another 4 months). He also continued the anticoagulation treatment and its biochemical control were performed every two months.

A new bone scintigraphy was performed after 10 months of treatment, showing decreased uptake of 99mTc-HDP in the manubrium and sternoclavicular joint, according to a significant pain reduction (Figure 3).

DISCUSSION

The diagnostic criteria of SAPHO syndrome are basically clinical, and the symptoms usually occur asynchronously over time, (often with differences of more

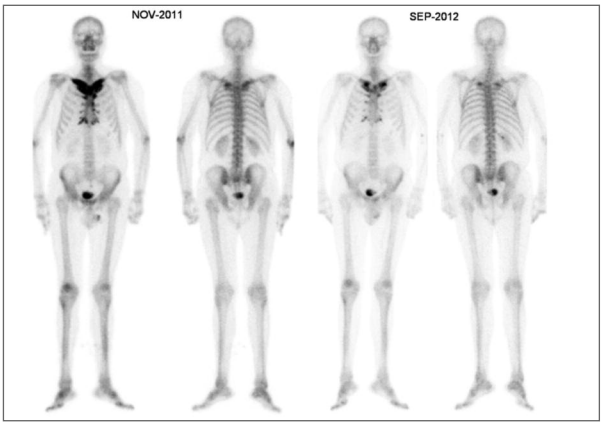

FIGURE 3. Whole-body bone scintigraphy with 99mTc-HDP images befores and after treatment. A) Shows the characteristic manubrium and sternoclavicular joints affectation. B) Marked decrease in the activity of the lesions consistent with pain relief

than 10 years). The skin lesions are minor or virtually absent in some cases[2]. The bone lesions are localized mainly in the anterior chest wall but could appear in the spine and some extrathoracic involvement with oligoarticular and asymmetric arthritis is also observed and commonly involves the knees, hips and ankles; small joints of hand and feet[3] and bilateral sacroiliac joint[4] may also be involved. Supporting diagnostic tests such as X-rays are usually nonspecific and overlap with findings suggestive of osteomyelitis. CT demonstrates musculoskeletal injuries and MRI differentiates an active process of chronic lesions[3]. Bone scintigraphy with technetium-99m diphosphonates is highly sensitive in detecting lesions of the anterior chest wall, and the characteristic "bull's head" could obviate biopsy[5] as well as a completed whole body scan would be beneficial to find additional articular lesions. Blood tests usually show elevated acute phase reactants such as CRP and ESR, mild anemia of chronic inflammatory type, and there are some mixed hyperglobulinemias cases, such as the case in this report.

Venous thrombosis as a complication of SAPHO syndrome is uncommon. We found only ten cases reported in the literature of patients with SAPHO syndrome and venous thrombosis. Six patients had subclavian vein thrombosis[6-10], one of which also had iliac vein thrombosis associated with lumbar vertebral osteitis and soft tissue mass surrounding the vein[10]; two cases of superior vena cava obstruction[11-12] and only one case of pulmonary embolism[13]. In a series of 120 patients with this syndrome, only one patient presented subclavian thrombosis[2]. The pathogenesis of venous thrombosis on SAPHO syndrome has not yet been clearly elucidated, but is believed to be due to either venous compression by the hyperostosis or caused by inflammation in the surrounding soft tissues. It has also been hypothesized that the systemic inflammatory state contributes to the hypercoagulability. Nevertheless, the pathophysiology of this complication remains unclear.

The coexistence of these two pathologies (SAPHO and Dupuytren disease) has not been described before; hence we reviewed the genetic and the inflammatory characteristics of both to assess a new possible association. Even though some genetic component had been suggested in SAPHO syndrome, as the HLA, PSTPIP2 gene and NOD2/CARD15 related with Crohn's disease (which occurs in about 10% of SAPHO patients), and LPIN2 (clinical similarities of SAPHO with Majeed syndrome), the results of the studies are contradictory. In a cohort of 38 patients with SAPHO, Hurtado-Nedelec et al. observed the 3 aforementioned genes and found no major pathogenetic role in the onset of SAPHO syndrome[14]. Genetic studies of HLA antigen genes confirm the lack of association. However, other previous studies found a positive association between them and SAPHO. In any event, it is also known the lack of information about the familiar history in the major series of cases reported in the literature.

On the other hand, the Dupuytren disease had been associated with a strong genetic component. Numerous studies tested a wide variety of genes and complex model of genetic aberrations had been proposed. These genes involve a wide range of possible pathogenic pathways, such as PRKX, which is implicated in angiogenesis, endothelial cell stimulation, proliferation and migration and vascular-like structure formation, or MAFB, which is associated with the determination of haematopoietic cells in fibromatosis[15].

The immune dysfunction in SAPHO syndrome suggested a hyperstimulation of innate immune response by increased production of interleukin (IL)-8 and TNF-α by neutrophils, and a decreasing circulating IL-10 suggests an imbalance between pro- and anti-inflammatory mediators. IL-8 has a key role in recruiting phagocytes to inflammatory sites and TNF-α plays a role in osteitis [14]. As in Dupuytren's tissue immunological mediators such as IL-l, basic fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and transforming growth factor β (TGF- β), which enhances production of collagen and other extracellular ma-

trix proteins, have a relevant role[16].

Taking everything into account, and even though these two diseases share an abnormal inflammatory/immune response, the inflammatory pathways and the genetic studies did not show common findings to support the possible relation of both diseases.

In conclusion, this case describes an uncommon disease with acute and chronic symptoms, which often occurred asynchronously in time and delaying the correct diagnosis and the initiation of treatment.

Thromboses as a complication of SAPHO syndrome have been infrequently reported and also have an unclear phatophysiology. Nevertheless, in this specific case, this complication helped to discover an undiagnosed and long evolutioned SAPHO syndrome. We also suggested bone scintigraphy as a potential marker in the activity and a useful tool in the diagnosis incorporating the SPECT-CT bone scintigraphy to complete a whole body scan assessment of the skeletal manifestations of SAPHO syndrome. We also rule out the possible association with Dupuytren's disease, but due to the known connection with other pathologic entities as Crohn's disease, we encourage further investigations that contribute to the elucidation of the mechanisms underlying SAPHO syndrome.

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