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Sarcoidosis secondary to autoimmune/ inflammatory syndrome induced by adjuvants in a patient with HIV

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Abstract

We present the case of a 36-year-old male patient from Venezuela with a history of HIV(undetectable viral load, CD4 661) who developed skin and soft tissue infection in thegluteal region secondary to iatrogenic allogenosis. With anemia, renal failure, andhypercalcemia in whom B-cell neoplasia was ruled out, on physical examination withcervical and inguinal lymphadenopathies, in the context of immunosuppression andconstitutional syndrome. Studies requested for Mycobacterium tuberculosis andHistoplasmosis, which were negative, a biopsy of the inguinal lymph node taken with areport of non-caseating or necrotizing granulomatous disease. In addition to anencapsulated cystic lesion of the foreign body type without evidence of lymphoproliferativedisease, the ACE level as a differential shows significant elevation, confirming sarcoidosisas a manifestation of the autoimmune/inflammatory syndrome induced by adjuvants.

Introduction

Adjuvant-induced autoimmune/inflammatory syndrome (ASIA) is a rare manifestation, first proposed in 2011 by Shoenfeld and Agmon-Levin, characterized by the presence of varied manifestations and non-specific symptoms that may represent rheumatological entities and generate an immune response after the application of a substance that acts as an adjuvant or materials for aesthetic purposes 1 among the most frequent are hyaluronic acid, methacrylate compounds, various oils and silicone that has been used in prostheses articular, mammary and laryngeal 1,2.

There are four types of conditions associated with this syndrome: silicosis, Gulf War syndrome, macrophage myofasciitis syndrome and post-vaccination phenomenon 3 The above conditions share common characteristics with chronic fatigue syndrome, fibromyalgia, associated with symptoms and signs of immune response aberrant symptoms such as fever, arthralgia, myalgia, and autoantibody positivity, among others.4

Adjuvants are commonly used in medications to stimulate the immune response since they contain components that mimic microbial agents, such as lipopolysaccharide from bacterial cell walls, binding to toll-like receptors, which activate both the innate and adaptive responses 1, 2 also increase the activities of dendritic cells, lymphocytes, macrophages and activate intracellular Nalp3, which generates a local reaction to antigens and subsequently releases chemokines, cytokines and mast cells. 4

Siliconosis (exposure to silicone) first named in 1990 as ''adjuvant disease'' and exposure to mineral oil has been associated with autoimmune manifestations such as lupus erythematosus, rheumatoid arthritis, hemolytic anemia, sarcoidosis, and ulcerative colitis 5,7 since it can activate patterns

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of pattern recognition and release of proinflammatory cytokines such as IL-6, IL-1B, IFN-, the latter induces monocyte maturation, which increases the expression of the major histocompatibility complex and favors the secretion of antibodies generating capsule formation as part of the chronic inflammatory response. It has been shown that patients who develop this syndrome have a higher prevalence of the HLA-DQ2 and DRW53 alleles, demonstrating a genetic predisposition. 5.6

Below is a case report of a patient with sarcoidosis secondary to immune reconstitution syndrome (ASIA).

Clinical case

A 36-year-old male patient who consulted due to a long-standing clinical picture consisting of intermittent fever spikes, erythema, redness, and discharge of purulent secretion in the gluteal region secondary to mineral oil placement 7 years ago without immediate clinical reaction. It required multiple surgical interventions and systemic antibiotics. (Fig. 1) He has a history of HIV 4 years ago, a study requested due to clinical suspicion, on antiretroviral treatment with adequate adherence to it (undetectable viral load, CD4 661) On physical examination the patient had a heart rate of 120 with pain at gluteal palpation.

During hospitalization initial blood count (leukocytes 11,260 cells/mm3 N 72.20% L 17.70% hb 8.6 g/dl hto 27.60% VCM 85 platelets 395,000) Renal function (CR 5.87, BUN 49) ionogram (serum calcium 12) decreased parathyroid hormone (PTH 3.70). Therefore, they are classified as a probable plasma cell neoplasm since it presented a slight elevation of lambda and kappa light chains (serum lambda 142 -kappa 199.2), however protein electrophoresis with alpha 1 monoclonal peak, immunoglobulins with elevated IgG and studies negative serum immunofixation.

Given that he manifested chronic fatigue and joint pain, extension immunological studies were requested, within which ANAS was found positive 1/80 fine granular pattern, DNA and negative rheumatoid factor.

Upon physical examination with cervical and inguinal adenopathies and in the context of immunosuppression and constitutional syndrome due to weight loss of 20 kg in the last year, studies for Mycobacterium tuberculosis were requested, blood PCR, negative ppd, and negative urinary antigen of Histoplasmosis For this reason, an inguinal lymph node biopsy was performed, which documents non-caseating or necrotizing granulomatous disease with negative Ziehl-Neelsen (ZN) staining and without identification of acid-fast bacilli (AFB), in addition, evidence of foreign body-type encapsulated cystic lesion without findings of lymphoproliferative disease or bone scintigraphy report (Fig. 2) with B2 microglobulin and negative endoscopic studies. Regarding hypercalcemia, a neoplastic cause or a cause related to hyperparathyroidism was ruled out, so as a differential, studies were started for sarcoidosis as a probable origin of granulomatous disease, ACE levels were taken, which were elevated (ACE 102 U/l) for which we started management with systemic steroids.

Abnormal concentration of tracer in bilateral lung tissue, abnormal concentration of soft tissue in the gluteal region due to chronic inflammatory involvement

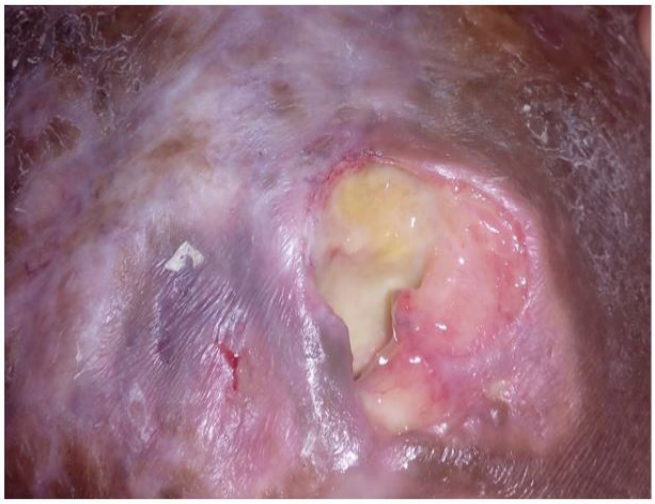

Figure 1: *Right gluteal región.*

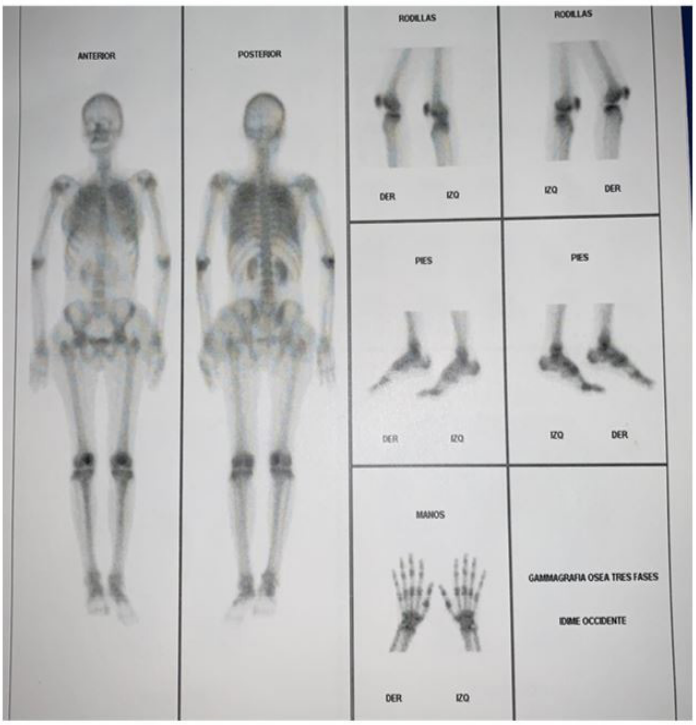

Figure 2: *Bone scintigraphy*

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Criterios diagnósticos de ASIA propuestos por Shoenfeld y Agmon-levin

Criterios mayores

1.Exposición a un estímulo externo (infección, vacuna, silicón adyuvante) previo a las manifestaciones clínicas.

2. Aparición de manifestaciones clínicas típicas: mialgias, miositis, debilidad muscular, artralgias y/o artritis, fatiga crónica, trastornos del sueño, manifestaciones neurológicas, especialmente asociadas a desmielinización, alteraciones cognitivas, pérdida de memoria, pirexia, boca seca

3. La eliminación del agente desencadenante provoca mejoría.

4. Biopsia típica en los órganos involucrados

Criterios menores:

1. Aparición de autoanticuerpos o anticuerpos dirigidos

2. Otras manifestaciones clínicas

3. HLA especificas (HLA DRB1, HLA DQB1)

4. Evolución a alguna enfermedad autoinmune

Se requiere la presencia de 2 criterios mayores o uno mayor y dos menores para el diagnostico de ASIA

Figure 3: *ASIA diagnostic criterio*

Discussion

The diagnosis of ASIA is difficult and exclusionary, infrequent without exact data on incidence or prevalence 4,5 however, 12 criteria proposed by Shoenfeld and Agmon-Levin in 2011 have been used, making the diagnosis with 2 major criteria. or one major and two minor (Fig.3) but since some are very subjective, recently Alijotas-rieg proposed new criteria based on objective data, however both criteria must be validated. In our report, the patient met the criteria to define ASIA syndrome given the presence of two major criteria: exposure to an external stimulus, in this case mineral oil and silicone, as well as lymph node biopsy with foreign body material, with the presence of manifestations symptoms such as arthralgia, myalgia and the presence of elevated ACE levels as part of the diagnostic criteria for sarcoidosis. Within the extension studies of our patient, unlike most cases reported in the literature, no autoantibody positivity was found.

The autoimmune/inflammatory syndrome induced by adjuvants can trigger autoimmune manifestations, with clinical criteria associated with an autoimmune disease such as sarcoidosis, this being a multisystem disease characterized by a response in which CD4 lymphocytes and macrophages accumulate, resulting in the formation of noncaseating granulomas. in tissues 9 which, although it is rare in patients with HIV given the decrease in CD4 counts, we present a patient with CD4 counts greater than 500 in whom cultures for mycobacteria and fungi were negative, excluding these diagnoses9,11

Sarcoidosis has a universal distribution more common in developed countries and in most cases are young adults. The incidence and prevalence are difficult to determine since most patients are asymptomatic 9 Within its pathogenesis, genetic susceptibility to environmental antigenic stimuli is postulated. His clinic includes non-specific systemic symptoms including weakness, fever, weight loss, arthralgia and peripheral lymphadenopathy, affecting the cervical, axillary and inguinal regions to a greater extent 8,10

Most of the patients have alterations in the chest X-ray, where bilateral hilar and paratracheal adenopathies are evident. There may also be an increase in uric acid levels, alkaline phosphatase, with elevated angiotensin-converting enzyme activity above two standard deviations as a reflection of the increase in macrophage activity 9,12 Histopathology reveals granulomas that are not caseating or caseating, with negative Ziehl-Neelsen staining and no identification of acid-alcohol resistant bacteria (AFB). In our patient we found significantly elevated ACE levels greater than 5 times their normal value and that although this can be elevated in diseases such as histoplasmosis, miliary tuberculosis, hepatitis and lymphoma, all this was ruled out in the reported case. In addition, biopsy confirms noncaseating granulomas.

The treatment of ASIA is based on the elimination of the external stimulus with an adequate response, however in cases of evolution to autoimmune diseases, immunomodulatory treatment is necessary 8 in our case, removal of the gluteal regions with mineral oil is indicated, in addition, treatment with systemic steroids such as prednisolone was started. these being the mainstay of treatment in sarcoidosis 10

Conclusion

In conclusion, ASIA syndrome is a rare pathology that can be associated with various autoimmune entities. We present the clinical case of a patient with sarcoidosis secondary to ASIA syndrome, which was confirmed by clinical, paraclinical and histological criteria in whom the main infectious diseases in patients with HIV were ruled out as the cause of the granulomatous disease presented.

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