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Autoimmune/Inflammatory Syndrome Induced by Adjuvants Causing Myositis and Pulmonary Fibrosis

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In recent years there has been an increase in breast implant surgeries. The relationship between such procedures and connective tissue disorders has caused controversy among health care professionals, and much has been written on this topic. Some studies have reported a higher risk of autoimmune events in this population, with muscle involvement as a prominent feature in the described cases. Most of these reports, however, failed to establish a clear relationship between silicone implantation and autoimmunity [1]. We present the case of a patient who developed myositis and pulmonary fibrosis in association with a breast implant rupture.

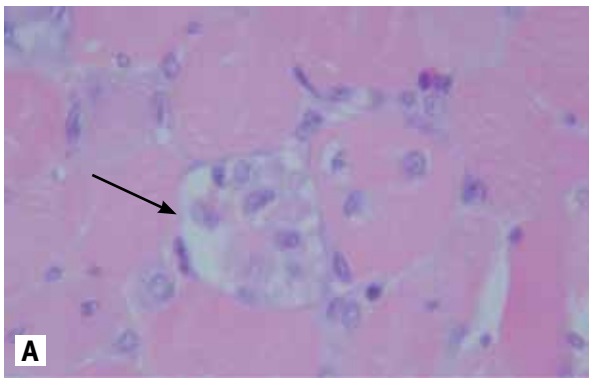
PATIENT DESCRIPTION

In our institution, a tertiary care hospital in southwestern Colombia, in 2011 we treated a 53 year old woman who presented after 1 month of intermittent fever, malaise, weight loss, and pruriginous rash on the chest, upper limbs, and face. She had undergone breast implant surgery 5 years earlier. She reported arthralgia in her hands, morning stiffness, and myalgia in her pelvic muscles and thighs. She did not report any weakness. The physical examination revealed basal rales, hand edema in the absence of synovitis, and cervical and axillary lymph node enlargement (more than 1 cm in diameter, painful, and mobile).

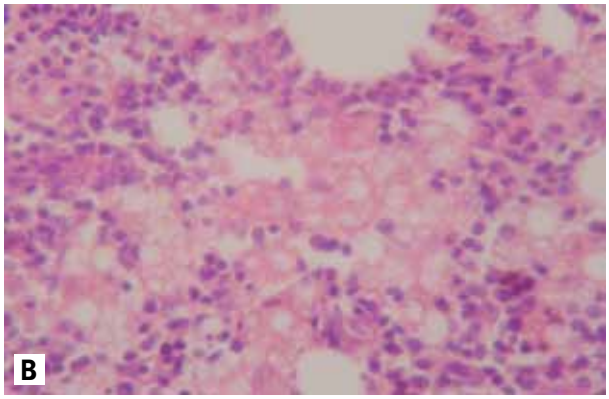
A few weeks before presentation, the patient had high levels of creatine kinase (1021 U/L, normal range 0–170 U/L) and positive antinuclear antibodies with a cytoplasmatic pattern (1:160). We performed a full blood panel workup to rule out infectious and autoimmune diseases. We found elevated alanine aminotransferase (176 mg/dl, normal range 0–33 mg/dl), aspartate aminotransferase (249 mg/dl, normal 0–32), lactate dehydrogenase (712 mg/dl, normal 135–214), creatine kinase (6239 U/L), immunoglobulin G anticardiolipin antibody (221.4 IgG GPL, normal below 15 GPL), IgM anticardiolipin antibody (17.1 IgM MPL, normal below 15 MPL), positive anti-smooth muscle antibodies (1:20), reactive rapid plasma reagin (16 dils), qualitative direct Coombs test ++++, and serum protein electrophoresis with a marked decrease in albumin and a rise in the gamma zone. In contrast, she had a negative fluorescent treponemal antibody absorption test, negative antinuclear antibody but with cytoplasmatic pattern (1:80), negative autoantibodies to extractable nuclear antigens, negative antimitochondrial antibodies, and negative anti-topoisomerase I antibodies.

Other diagnostic tests included chest computed tomography, which demonstrated pulmonary fibrosis and multiple axillary lymph nodes. Spirometry concluded that the flow/volume curve was normal, but a mild carbon monoxide diffusion capacity decrease was noted. Electromyography and nerve conduction velocity tests were normal. A skeletal muscle biopsy showed inflammatory myopathy without multifocal lymphocytic infiltrates [Figure A] and no specific findings on immunochemistry or high resolution optical microscopy. A liver biopsy was consistent with moderate cholestasis and single-cell necrosis without fibrosis, lymphocytes or plasmatic cells. A lymph node biopsy revealed silicone lymphadenitis [Figure B]; this prompted follow-up with magnetic resonance imaging of the breasts, which demonstrated rupture of the implants [Figure C].

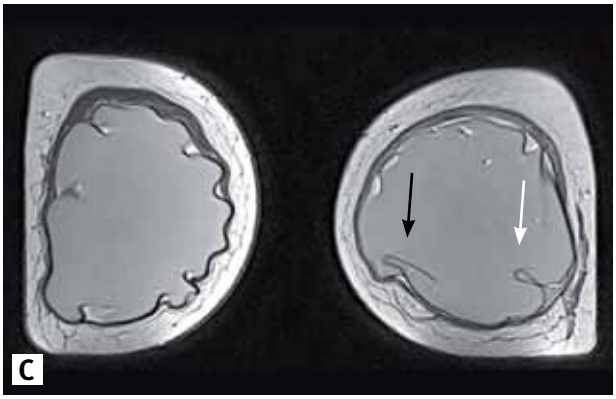
After a thorough search for infectious and neoplastic diseases, we suspected an autoimmune phenomenon with inflam-



[A] Skeletal muscle histopathology (hematoxylin & eosin, magnification x40), showing a few destroyed fibers containing lymphocytic infiltrates (black arrow)



[B] Lymph node histopathology (hematoxylin & eosin, magnification x40), showing histiocyte content refringence compatible with silicone vacuoles



[C] Breast MRI. T2 coronal slice that shows multiple radial folds in the implants with intra- and extracapsular rupture, Linguine sign (black arrow) and key hole sign (white arrow)

matory manifestations in the muscles, lung, skin and liver, but without criteria for a known rheumatic condition. We concluded that it could be related to the silicone found in the lymph nodes. Treatment with non-steroidal anti-inflammatory drugs and prednisone was started with good response, and we recommended removal of the implants.

COMMENT

Silicone in breast implants is considered an adjuvant or substance that increases antigen-antibody immune response, although it is not necessarily the primary trigger [2]. The process begins with the expression of Toll-like class IV receptors around the prosthesis, which allows recruitment of histiocytes and macrophages [3]. The former migrate into the implants (where they are activated and begin the degradation of silicone elastomers by the release of reactive oxygen molecules) and cause capsule rupture. After that, the phagocytized silicone migrates to lymph nodes where it presents as an antigen to lymphocytes. This produces an acute immune response through CD4 T cells and, in turn, CD8 T cell apoptosis is stimulated and leads to an autoimmune response. Patients who develop autoimmune phenomena mediated by silicone express histocompatibility complex-specific molecules like HLA–DQA1*0102, HLA-DRB1 and HLA-DQB1. This differentiates them from other cases in that they present with inflammatory myopathies, which express other types of antigen-presenting proteins. This specific autoimmune response could lead to clinical manifestations such as fever, myalgias, arthralgias, arthritis, fatigue, cognitive disturbances, depression, sicca symptoms, lymphadenopathies, and non-specific positive laboratory tests [2] as seen in our patient.

In addition to muscle involvement, some patients have constitutional symptoms and lymphadenopathies with biopsies revealing granulomatous caseating lymphadenitis but no demonstrable evidence of other pathologies [4]. Although the silicone-related myopathy is frequently recognized, its association with pulmonary disorders, like fibrosis, is unusual. To date there is only one reported case of a patient exhibiting lymphadenitis, myopathy and interstitial pneumonitis with lung function test abnormalities [5].

Shoenfeld and Agmon-Levin [2] describe siliconosis as the immune response to silicone and include it in a new entity called ASIA – autoimmune/inflammatory syndrome induced by adjuvants – and published the diagnostic criteria [2]; our patient met two of the major criteria. Considering all these elements we propose ASIA as the cause of our patient's symptoms. This constitutes a new kind of disease that should be taken into account as part of the differential diagnosis of autoimmune syndromes that affect muscles and lungs.

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