Siliconosis: Autoimmune/Inflamatory Syndrome Induced by Adjuvants (ASIA)

Mónica Caldeira MD and António Caldeira Ferreira MD

Internal Medicine Department, Hospital Central do Funchal, Madeira Island, Portugal

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For Editorial see page 121

Recently a very interesting syndrome called ASIA (autoimmune/inflammatory syndrome induced by adjuvants) was described by Shoenfeld in an article published in the *Journal of Autoimmunity* regarding "the integration of the pre-existing evidence into the autoimmune/inflammatory syndrome induced by adjuvants" [1]. Diagnostic criteria have been suggested for ASIA syndrome. The major criteria are the presence of "typical" clinical manifestations such as myalgia, myositis, muscle weakness, arthralgia and/or arthritis, chronic fatigue, unrefreshing sleep or sleep disturbances, neurological manifestations (especially associated with demyelination), cognitive impairment and memory loss, pyrexia and dry mouth, after a systemic exposure to external stimuli, such as adjuvants, infections, vaccines and silicone. Amelioration of symptoms after removal of the inciting agent and a typical biopsy of involved organs are also major criteria. Minor criteria include the appearance of autoantibodies or antibodies directed at the suspected adjuvant, other clinical manifestations (irritable bowel syndrome), specific HLA (HLA DRB1, HLA DQB1), and evolution of an autoimmune disease (multiple sclerosis, systemic sclerosis) [1,2].

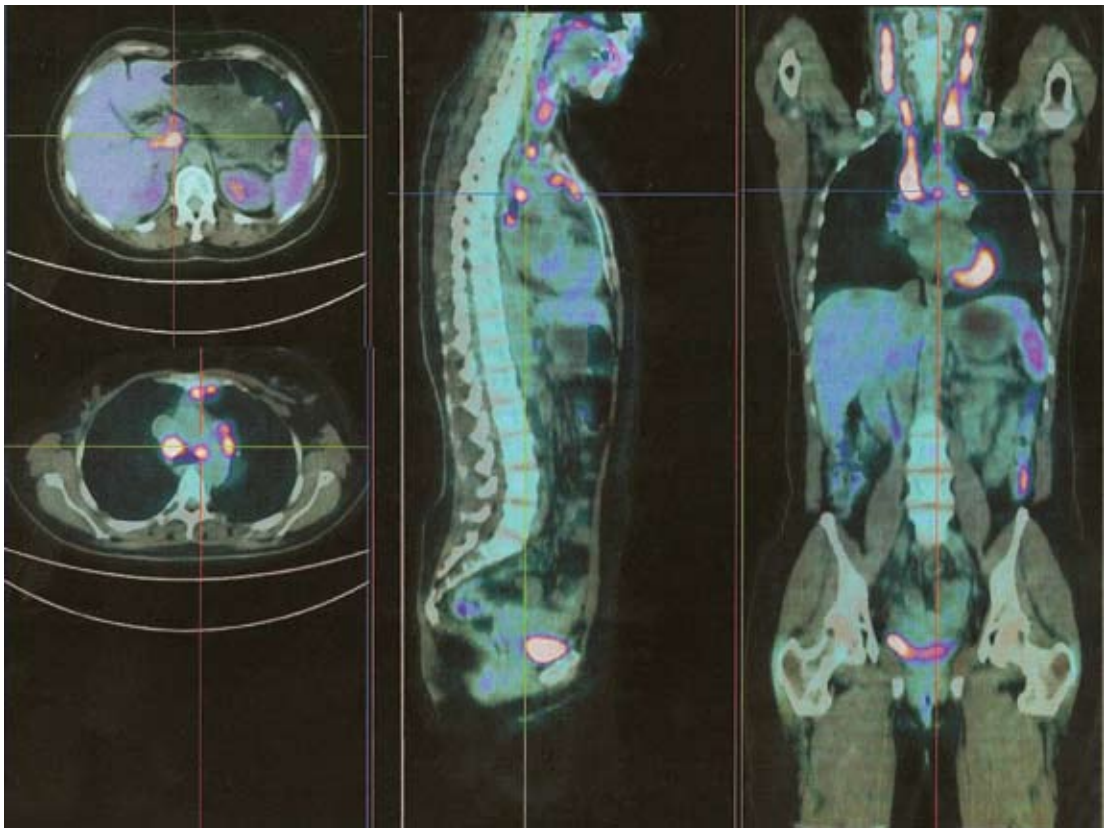
Silicone elastomer (silastic) is one of the three common forms of silicone, the other two being liquid and gel. Silicone has been widely used in the manufacture of medical implants such as artificial joints, tubings, and breast implants. The side effects of silicone have attracted much attention in recent years. Local cutaneous inflammation and siliconomas of the breast, plus regional lymphadenopathy characterized by silicone granuloma have been reported after breast reconstruction with prostheses containing silicone gel. Lofgren syndrome and neurosarcoidosis have been reported as late complications of augmentation mammoplasty using silicone gel. Remission of sarcoidosis following removal of silicone gel breast implants has been reported in a patient with debilitating multisystem sarcoidosis. Though these adverse reactions have been notoriously associated with silicone gel, silicone granulomatous lymphadenopathy secondary to a silastic joint prosthesis has also been reported. Silicone was considered an inert material and thus unable to induce immune reactions [3]; however, like other adjuvants, it is capable of inducing autoimmune-like phenomena called in the early 1990s "the adjuvant disease" [4].

The risk of developing a diffuse connective tissue disease among silicone-exposed (breast implants) individuals is only 0.8%, not significantly higher than the risk in the general population. However, that is not the case for less specific symptoms such as arthralgia and myalgia and even some diffuse neurologic manifestations that appear to be more common in individuals exposed to silicone implants. Although the silicone autoimmune-induced syndrome does not fulfill any diagnostic criteria for a defined connective tissue disease, the relationship is unequivocal [2] and the role for an adjuvant mechanism has been suggested.

PATIENT DESCRIPTION

This report refers to a Caucasian female, 53 years old, with a past medical history of right breast cancer who underwent surgery (T2N0M0) in 2001, has been in remission since then (after chemotherapy and radiotherapy), and had a reconstruction of that breast with a silicone prosthesis (2003). In 2007 she had an anterior uveitis. In 2008 she experienced constitutional symptoms such as anorexia, loss of 5 kg in 3 months (7% of her body weight), extreme fatigue, and a left cervical node. The routine blood tests for autoimmune disease were negative. Cervical computed tomography scan showed multiple cervical non-necrotizing lymphadenopathies. The fine node needle aspirate showed granulomatous non-necrotizing lymphadenitis, but the biopsy revealed granulomatous caseating lymphadenitis. The chest X-ray was normal. At this time she started empiric antituberculosis treatment but stopped 5 months later due to a poor response.

Considering the medical history of the patient, malignancy spread could not be excluded. The tumor markers were normal (including CA 15.3). The thoracic-abdominal CT scan confirmed multiple lymphadenopathies and added some micronodular images in the upper lobe of the right lung. The whole-body positron-emission tomography scan [Figure] showed multiple cervical, intrathoracic and intra-abdominal metastatic lymphadenopathies. The blood tests showed elevated levels of angiotensin-converting enzyme (90.3 U/L) in several



Whole-body PET (positron-emission tomography) scan showing multiple cervical, intrathoracic and intra-abdominal lymphadenopathies

measurements. A bronchoalveolar lavage was performed, showing CD4/CD8 ratio > 3.5. Pulmonary function tests were normal. Gram stain and Ziehl-Neelsen stain and culture of sputum and bronchoalveolar lavage for fungus and mycobacteria yielded no growth. The possible diagnosis of sarcoidosis was made and she was managed conservatively with corticotherapy. She is taking deflazacorte 3 mg/day with a good response and partial adenopathy regression.

COMMENT

The authors present this patient to call attention to this puzzling case. The patient´s past medical history of breast cancer had made the differential diagnosis difficult in view of the clinical presentation and test results. A possible metastatic spread could explain the case, although the biopsies showing granulomatous non-necrotizing lymphadenitis challenged this hypothesis. Tuberculosis was excluded due to failure of the empiric therapeutic course. Siliconosis was the most probable diagnosis in view of the presence of two major criteria, although the favorable response after removing the possible adjuvant has not been tested because the patient refused.

Earlier reports that silicone is biologically relatively inert have recently been challenged with the description of ASIA syndrome.

Corresponding author:
Dr. M. Caldeira
Rua da Olaria, Edifícios Jardins do Oceano II, Bloco A, 4ºM, Garajau, 9125-043 Caniço, Santa Cruz, Madeira Island, Portugal
Phone: (351-96) 278-1940
email: monica.caldeira@netmadeira.com

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"An eye for an eye would make the whole world blind"

Mahatma Ghandi (1869-1948), Indian political and ideological leader during the Indian independence movement and pioneer of resistance to tyranny through mass civil disobedience