

Prolonged Fever due to Silicone Granulomatosis

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Silicone lymphadenopathy is a rare complication of breast implants and is often confused with metastases from breast carcinoma. Silicone breast implants have been associated with connective tissue inflammatory syndromes; however, silicone is not inert, and silicone from breast implants “bleeds” through the surrounding envelope and is present in the surrounding capsule or migrates to other distant locations. We present a patient who was admitted to the hospital for investigation of prolonged fever and was eventually diagnosed with silicone granulomatous lymphadenopathy that responded to treatment with doxycycline.

Patient Description

A 50 year old woman was admitted because of high fever for 3 weeks (up to 38°C at night, every night, without shivering or sweating), fatigue, severe headache and malaise. There was no history of travel abroad in the preceding 12 months; she did not keep animals at home, had not visited caves, insisted on drinking only pasteurized milk, and had not had any contact with patients with contagious diseases. She was not losing weight and slept well at night. Her medical history included bilateral silicone breast implant surgery 10 years earlier. The physical examination was perfectly normal except for a regional non-tender lymph node enlargement (about 3 x 3 cm) in the right axilla. She did not have skin rash or signs of splinter hemorrhages; Roth spots were not seen in the retina, and she did not have hepatosplenomegaly. There were no signs of uveitis or episcleritis, and no joint deformity or swelling. Laboratory findings were normal except for an elevated sedimentation rate of 90 mm in the first hour. All hematologic and biochemi-

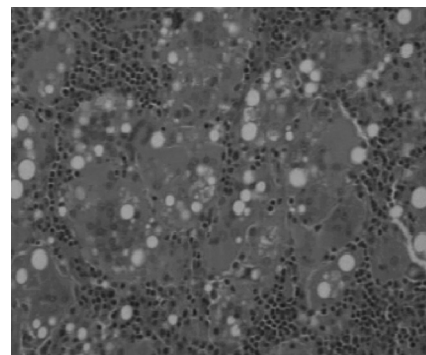
cal parameters were normal. Serology was normal including viral antibody titers against cytomegalovirus, adenovirus, Epstein-Barr virus, Q fever, Rickettsia, human immunodeficiency virus, hepatitis A, B and C, Brucella and Bartonella species. All blood and urine cultures were negative. Antinuclear antibodies, cytoplasmic antineutrophil cytoplasmic antibody and p-ANCA autoantibodies were negative, as was VDRL.

Chest X-ray and whole-body computerized tomography were normal except for the right axillary lymphadenopathy mass (35 x 35 x 40 mm) with irregular borders and the silicone implants in both breasts. Transesophageal echocardiography was normal without vegetation or an atrial mass. Because of the continuous fever accompanied by severe headache, treatment with doxycycline tablets 100 mg twice a day was instituted. Twelve hours after starting this treatment she developed fever of 39.5°C accompanied with chills, but after 24 hours the fever returned to normal values and remained normal for more than 3 months of follow-up. The erythrocyte sedimentation rate (90 mm/hr on admission) returned to normal values (20 mm/hour). Before starting the treatment a lymph node biopsy from the right axilla was performed, which revealed numerous giant cell granulomas accompanied by multiple vacuoles. The vacuoles partly contained an unstained non-birefringent refractile “oily” material compatible with silicone [Figure].

Comment

We describe a patient who presented with prolonged fever without known cause that

p-ANCA = perinuclear antineutrophil cytoplasmic antibody



Lymph node biopsy from the right axilla showing silicone granules. Giant cells create granulomatous structures that encapsulate the silicone particles.

was eventually diagnosed as related to silicone granulomatous lymphadenopathy. Silicone medical devices have been associated with various complications that may involve an immune reaction to silicone [1]. Silicone implants may cause local complications (capsular contraction, rupture, gel “bleed,” and nodular foreign body granulomas in the capsular tissue and lymph nodes), or general symptoms including high sedimentation rate with high C-reactive protein levels, high fever, arthralgia and myalgia, and positive antinuclear antibodies [2]. Silicone granulomatous lymphadenopathy is a rare complication in patients with breast implants, and is often confused with metastases from breast carcinoma. Several case reports have described “silicone-induced granulomatous adenitis” that necessitated removal of the silicone implants, and this surgical procedure was considered routine management of local and systemic reactions to silicone “leak” [3]. However, it was recently found that patients who developed “silicone granulomas of the face” were successfully treated with minocycline [4].

Tetracyclines have anti-inflammatory as well as antibacterial properties. They reduce the activity of collagenase, phospholipase A2, several matrix metalloproteinases, as well as the production of interleukin-1 beta and tumor necrosis factor-alpha in a wide range of tissues. At high concentrations tetracyclines inhibit staphylococcal exotoxin-induced cytokines and chemokines [4]. Recent research of the immunomodulatory properties of tetracyclines suggests that they may have a previously unknown short-term biphasic effect on inflammatory modulation; namely, enhancement of host defense mechanisms shortly after initial administration, followed by curtailment of local infection/inflammation in the subsequent period [5]. This short-term effect with

inflammatory reaction enhancement may explain the sudden abrupt development of fever with chills within the first 12 hours of treatment, followed by long-term clinical recovery.

In conclusion, granulomatous giant cell lymphadenopathy is a rare phenomenon and usually not accompanied by systemic inflammatory reactions. Treatment with tetracyclines may offer a medical alternative to the more common surgical management of this rare disorder and for other silicone implants.

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People hate as they love, unreasonably

William Makepeace Thackeray (1811-1863), British novelist, whose most famous work is *Vanity Fair*

Capsule

Vaccines, adjuvants and TLR

After vaccination, the efficiency with which protective antibodies are produced often depends on the presence of an adjuvant, a substance that promotes activation of antibody-producing B cells. It has been anticipated that Toll-like receptors (TLRs) might be major players in mediating the effects of adjuvants. However, Gavin et al. found that the known TLR pathways do

not modulate B cell responses and so adjuvants containing TLR ligands must depend on other properties. Such a revision to thinking about the effects of TLR on B cell responses will likely refocus current thinking about vaccine development.

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Eitan Israeli

Capsule

Progesterone and breast cancer

Mutations in the breast cancer susceptibility gene *BRCA1* greatly increase a woman's risk of developing breast and ovarian cancers. Why do these mutations predominantly affect hormone-responsive tissues when the mutant gene is widely expressed throughout the body? Poole and associates suggest that this tissue specificity is caused in part by *BRCA1*-mediated effects on signaling by the hormone progesterone. Mammary epithelial cells (MECs) of *Brcal*/

p53-deficient mice accumulated high levels of progesterone receptors, probably through defective degradation by the proteasome, and developed aberrant proliferation of the MECs. Treatment with the progesterone antagonist mifepristone (RU 486) prevented or delayed mammary tumor development in the mice.

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