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CASE REPORT

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Microscopic polyangiitis after silicone breast implantation

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Abstract
We describe the case of a patient who developed microscopic polyangiitis (MPA) after silicone breast implantation. A 60-year-old woman who had undergone silicone breast implantation was admitted to our hospital with complaints of general malaise and hematoproteinuria. She was diagnosed as having MPA with evidence of acute progressive renal failure, pulmonary hemorrhage, and positivity for myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA). A renal biopsy showed severe necrotizing and crescentic glomerulonephritis with arteriolitis. The patient received high-dose steroids and plasma exchange treatment, but died of progressive pulmonary hemorrhage and multiple cerebral hemorrhage. Silicone implantation is associated with scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. This case report indicates the possibility of the development of MPA after silicone breast implantation.

Key words Microscopic polyangiitis · Human adjuvant disease · Silicone breast implantation · Silica · ANCA

Introduction

In 1964, Miyoshi et al.[1] introduced the term human adjuvant disease (HAD) in their description of two patients who developed it after undergoing cosmetic surgery. The authors referred to it as a clinical syndrome resembling adjuvant arthritis in rats following paraffin injection. Since this first observation, there have been a number of published reports associating silicone breast implantation with scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, and mixed connective tissue disease.[2] We report the case of a patient who developed microscopic polyangiitis (MPA) after silicone breast implantation.

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Case report

A 60-year-old woman was admitted to our hospital in April 2003 after being ill for 2 months with general malaise and loss of appetite. In 1973, the patient had bilateral breast augmentation using silicone gel-filled implants that had been maintained without any complications or reactions. On admission, her body temperature was 36.5°C and her blood pressure was 174/97 mmHg. She complained of having a purpuric rash around her breasts. This occurred first on the inferior border of the breasts, and extended progressively around the breasts. She did not have any symptoms or signs of rheumatic diseases. Her family medical history was negative for autoimmune diseases. The results of laboratory tests were as follows: white blood cell (WBC) count, 16400/mm^3; red blood cell (RBC) count, 318×10^4/mm^3; hemoglobin level, 8.7 g/dl; hematocrit, 27.6%; platelet count, 43.2×10^4/mm^3; total protein level, 6.9 g/dl; albumin level, 2.1 g/dl; serum creatinine level, 5.7 mg/dl; serum urea nitrogen level, 68.4 mg/dl, and C-reactive protein level, 24.5 mg/dl. Her erythrocyte sedimentation rate was 131 mm/h. Rheumatoid factor (RF) was present (254 IU/ml, normal <7 IU/ml), and the titer of antinuclear antibody (ANA) was 1:20 with a diffuse staining pattern. Her levels of serum immunoglobulins were: IgG, 2279 mg/dl; IgA, 201 mg/dl; IgM, 164 mg/dl. Her myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA) titer was high (1230 EU, normal <10 EU). Proteinase 3-ANCA and antiglomerular basement membrane antibodies were absent. Urinalysis showed mild proteinuria (0.69 g/day) and hematuria (>100 RBC per high-power field). Her creatinine clearance rate was 3.75 ml/min. Sputum culture revealed the presence of *Staphylococcus aureus* (*S. aureus*). Chest radiography findings were unremarkable, whereas a chest

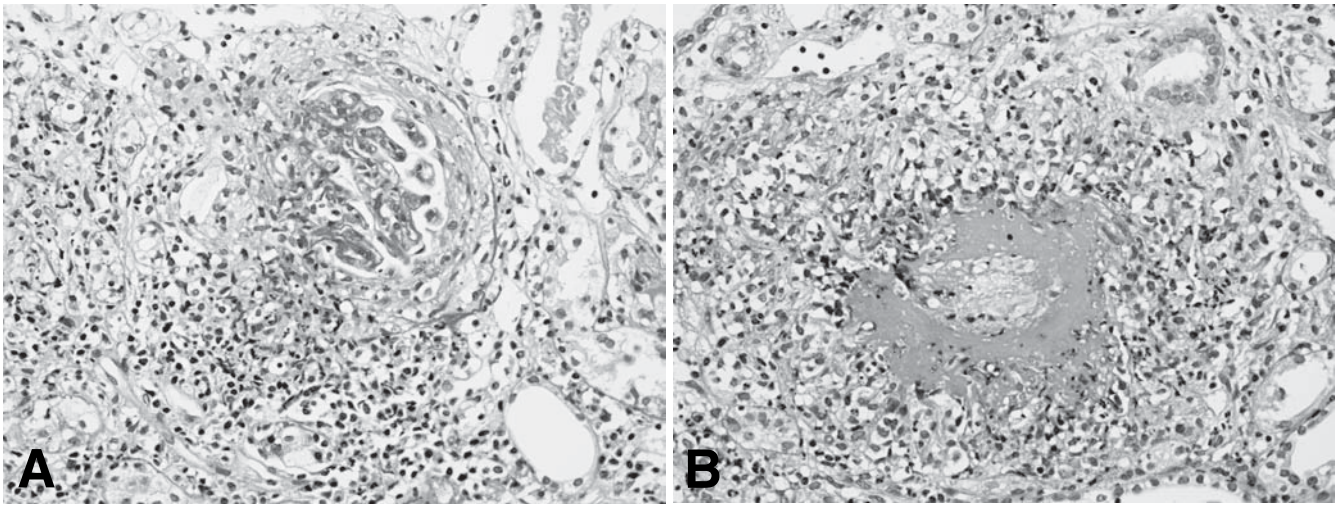

Fig. 1. **A**. Glomerulus showing cellular crescent formation. The disruption of Bowman's capsule was also observed (periodic acid-Schiff stain; original magnification ×40). **B** Renal arteriolitis with fibrinoid necrosis was observed (periodic acid-Schiff stain ×40)

computed tomography showed hazy infiltration in the posterior surfaces of the middle and lower lobes of the right lung, which was consistent with pulmonary hemorrhage.

A renal biopsy was performed on the second day after admission. Light microscopy showed a cellular crescent formation of all 11 glomeruli sampled, and the Bowman's capsule was disrupted in 10 glomeruli (Fig. 1A). Renal arteriolitis with fibrinoid necrosis and marked tubular damage associated with mononuclear cell infiltration were also observed (Fig. 1B). Immunofluorescence microscopy revealed faint deposits of IgA and C3 in the mesangial area. No electron-dense depositions were detected by electron microscopy. On the basis of these findings, a pathological diagnosis of necrotizing crescentic glomerulonephritis (GN) with arteriolitis was made. Thus, our patient was diagnosed as having MPA. She was treated with prednisolone followed by methylprednisolone pulse therapy. In addition, plasma exchange was initiated, but the patient suddenly developed multiple hemorrhage of the cerebral cortex. Because of the exacerbation of pulmonary hemorrhage and hypoxia, mechanical ventilation was initiated. We did not use cyclophosphamide because the patient developed bilateral pneumonia, and she died of sepsis due to *S. aureus* on the 26th day after admission. A renal necropsy showed the remission of disease activity; fibrous crescents were observed in 7 of 11 glomeruli, and the interstitial damage had markedly improved. We could not examine the association between purpuric rash and the disease because her family rejected cutaneous examination.

Discussion

Miyoshi et al.[1] first described HAD after breast augmentation. Thereafter, more than 100 cases of connective tissue diseases, such as scleroderma, SLE, and RA that developed after cosmetic surgery have been reported. However, in a recent metaanalysis by Janowsky et al.,[3] no correlation between silicone breast implantation and the risk of rheumatic or other autoimmune diseases was found. However, the improvement of symptoms observed following the removal of implants[4] indicates a causal relationship between the presence of silicone breast implants and autoimmune phenomena. On the other hand, epidemiological evidence exists between environmental exposure to silica, which is one of the components of silicone, via the lungs and ANCA-associated vasculitis. Chevailler et al.[5] reported that the incidence of patients with silica exposure and renal involvement among ANCA-positive patients was 5.5% (8 of 145). Gregorini et al.[6] found that 5 of 11 patients with ANCA-positive necrotizing crescentic GN had had a significant silica exposure. A more recent study showed that ANCA was detected in 17.1% of patients exposed to silica dust at work.[7]

We have described the case of a patient who developed MPA after silicone breast implantation. In our patient, the implants did not show signs of rupture of the envelope. However a silicone breast implant has been found to bleed through its envelope over the period of time[8] because the silicone elastomer envelope is semipermeable.[2] Although silicone contains 30% silica by weight, the silica within breast implants is chemically fused to the silicone polymer and does not have the same reactivity as free silica. However, several possibilities have been suggested as to how silica can be liberated from its bond to silicone, for example, following macrophage phagocytosis, but clearly documented evidence has yet to be presented.[8] Recently, Bohgaki et al.[9] have reported a case of ANCA-associated necrotizing crescentic GN after the implantation of a ventriculoperitoneal (VP) shunt tube composed of silicone. They speculated that the implanted VP shunt containing silicone initially activated cytokines nonspecifically to induce hypergammaglobulinemia, and that these later

switched to activate ANCA specifically. In addition, silicone-gel breast implants usually have a silicone elastomer envelope, known as a silicone rubber, filled with viscous silicone gel. Amorphous silica is generally used to increase the hardness of the elastomer envelope. Thus, there is a possibility that long-term exposure to the silica contained in the outer envelope of breast implants can also induce ANCA-associated diseases.

However, because no typical symptoms were observed in ANCA-positive patients professionally exposed to silica at work,[7] silica exposure only is insufficient to induce vasculitis. The presence of multiplex families and the difference in disease prevalence among populations suggest the involvement of genetic predisposition in the pathogenesis. Recently, Tsuchiya et al.[10] reported the association of HLA-DRB1*0901 with MPA and MPO-ANVA-positive vasculitis in Japanese patients. Unfortunately, we did not perform genotyping in this patient. Bacterial infections have also been postulated as one of the triggering factors in ANCA-associated diseases. In our case, sputum culture revealed the presence of *S. aureus* throughout her clinical course. The role of *S. aureus* in ANCA production was demonstrated by a study in which the immunization of rats with *S. aureus* produced circulating ANCA and caused pauciimmune segmental glomerular sclerosis.[11] In addition, a case of MPO-ANCA-positive MPA following subacute bacterial endocarditis caused by *S. aureus* has been reported.[12] Therefore, this suggested a combination of genetic susceptibility, bacterial infections, and silica exposure as a cause of MPA.

To our knowledge, this is the first report of MPA after silicone breast implantation, but the causal relationship remains unclarified. It is necessary to study the presence of ANCA and the genetic background of patients with silicone breast implantation in older to establish whether there is indeed a causal relationship.

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