Mod Rheumatol (2003) 13:73–75

CASE REPORT

Miyuki Bohgaki · Masaya Mukai · Atsushi Notoya
Michifumi Kohno · Akio Takada

Vasculitis following implantation of a ventriculoperitoneal shunt tube made of silicone

Received: December 19, 2001 / Accepted: June 11, 2002

Abstract A 56-year-old man presented with hyperproteinemia and renal dysfunction associated with antineutrophil cytoplasmic antibodies (ANCA). He had had a ventriculoperitoneal shunt tube made of silicone implanted 4 years earlier. In his renal biopsy, necrotizing crescentic glomerulonephritis was identified: tests for both myeloperoxidase ANCA and proteinase 3 ANCA were initially weakly positive. Antinuclear and other autoantibodies were also present. We diagnosed ANCA-associated vasculitis, probably induced by the silicone tube.

Key words Adjuvant disease · Antineutrophil cytoplasmic antibody (ANCA) · Silicone · Vasculitis syndrome

Introduction

There have been a number of reports in which autoimmune syndromes have occurred following implantation or injection of various chemicals, including silicones or paraffins. In 1964, Miyoshi et al.[1] described two patients with connective-tissue-like disease identified after mammoplasty with paraffin- or silicone-related substances. This report considered that the implants played an adjuvant role as self-antigens, and that autoimmune syndromes developed. This was later called "human adjuvant disease."[2]

Silicone is derived from silica (SiO_2), and is widely used in medical implants and ventriculoperitoneal (VP) shunts. Here, we report on a patient who presented with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis following implantation with a VP shunt made of silicone.

M. Bohgaki · M. Mukai (✉) · A. Notoya · M. Kohno
Division of Clinical Immunology and Hematology, Department of Medicine, Sapporo City General Hospital, Kita 11, Nishi 13, Chuo-ku, Sapporo 060-8604, Japan
Tel. +81-11-726-2211; Fax +81-11-726-9541
e-mail: masaya-mukai@hokkaido.med.or.jp

A. Takada
Department of Pathology, Sapporo City General Hospital, Sapporo, Japan

Case

A 56-year-old Japanese man was referred to this hospital on May 2, 2000, because of hyperproteinemia, anemia, and renal dysfunction identified during a routine health examination. He showed no sclerosis or any other skin lesions. He had no previous history of renal dysfunction until that time. He had been given a VP shunt tube implant (containing silicone) for a subarachnoid hemorrhage in 1996. This implanted tube had been maintained without any complications or reactions.

On admission, his laboratory values were as follows: erythrocytes $224 \times 10^4/\mu l$, hemoglobin 6.9 g/dl, and hematocrit 20.2%. Serum total protein was 9.0 g/dl (γ-globulin 48.9%), and serum albumin was 2.9 g/dl. C-reactive protein (CRP) was 4.77 mg/dl, and IgG was 4960 mg/dl. Serum creatinine was 3.0 mg/dl, blood urea nitrogen 52 mg/dl, and creatinine clearance 24.5 ml/min. Urinary protein was 0.8 g/day. Urinary occult blood was 3+. Serological studies showed rheumatoid factor (RF) positive (246 IU/ml; normal range up to 35 IU/ml), and the titre of antinuclear antibodies was 1:320 with a nucleolar pattern (in immunofluorescence). Antinuclear ribonucleo protein (RNP), anti-Scl 70, anti-SS-A (Ro), and anti-SS-B (La) antibodies were positive (measured by enzyme linked immunosorbent assays). Antidouble-stranded DNA antibody was negative. Proteinase 3 (PR-3) ANCA was 16 EU (normal range up to 10 EU), and myeloperoxidase (MPO)-ANCA was 12 EU (normal range up to 10 EU). IL-6 was 8.5 pg/ml (normal range up to 4 pg/ml), and circulating immune complex (CIC) (by the Clq method) was 11.2 μg/ml (normal range up to 2.9 μg/ml). Cryoglobulin was negative and other blood chemistry results were normal.

A lip biopsy, salivary gland scintigraphy, and Schirmer's test showed no abnormalities, and Sjögren's syndrome was ruled out. The patient showed no pulmonary or nasal

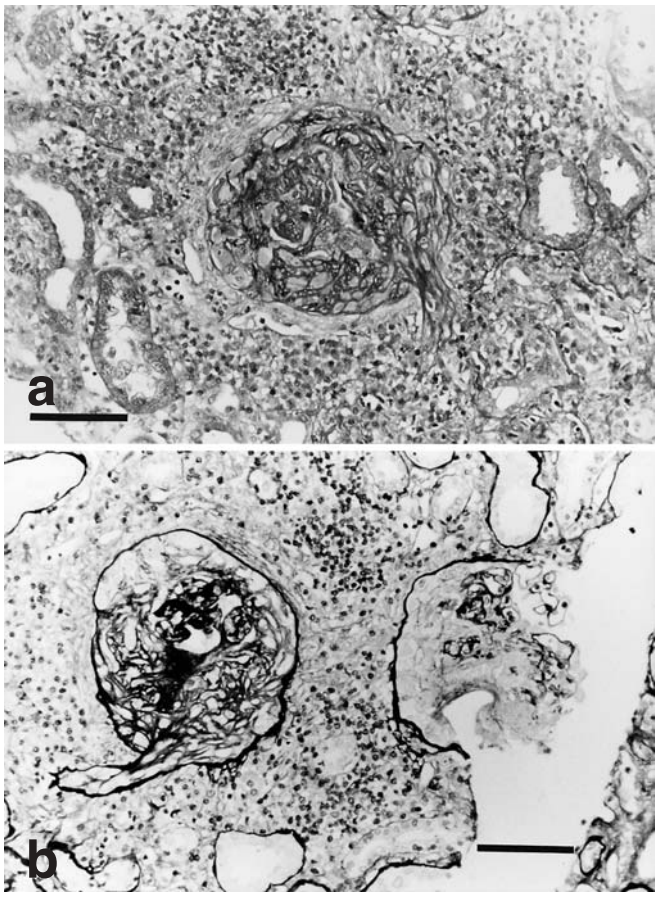

Fig. 1. Renal biopsy showed necrotizing crescentic glomerulonephritis. **a** A large fibrocellular crescent with a destroyed and compressed tuft. Extensive periglomerular interstitial cellular infiltrates and tubular atrophy were also found. *Bar* 100 μm (Masson trichrome stain; original magnification ×200). **b** Two large fibro-cellular crescents with destroyed and compressed tufts. Extensive peri-glomerular interstitial cellular infiltrates and tubular atrophy were also found. *Bar* 100 μm (periodic acid and methenamine silver staining; original magnification ×200)

lesions. A renal biopsy showed necrotizing crescentic glomerulonephritis (NCGN) but no granulomatous lesions (Fig. 1). Fifty-seven per cent and 14% of glomeruli formed cellular crescent and global necrosis, respectively. Plasma cells, lymphocytes, and other inflammatory cellular bodies infiltrated the interstitium around the glomeruli. Mild ischemic wrinkling was found in the glomeruli, but no proliferation of mesangeal cells, mesangeal matrix, or capillary basement membranes was found. Immunofluorescence detected faint, nonspecific IgM, C3, and Clq deposits on the mesangial area. Lupus nephritis was ruled out completely.

In this patient, hypergammaglobulinemia and other inflammatory laboratory indices were found, and glomerulonephritis occurred subsequently, with faint ANCA positivity. Following a diagnosis of systemic vasculitis syndrome (Wegener's granulomatosis, which is limited to the kidney) because he was continuously positive for PR-3-ANCA, the patient was treated with steroid pulse therapy (methylprednisolone 1 g/day for 3 days). Subsequently, high-dose oral prednisolone (60 mg/day) was started. His CRP and erythrocyte sedimentation rate (ESR) improved immediately. One month later, oral cyclophosphamide (100 mg/day) was started. He was discharged 3 months after admission. At discharge, his creatinine clearance was 46.9 ml/min, serum creatinine concentration was 1.5 mg/dl, and blood urea nitrogen concentration was 20 mg/dl. Only PR-3-ANCA remained continuously positive; other autoantibodies became negative by the time of his discharge. His titre of PR-3-ANCA increased to 43 EU as the steroid therapy was tapered down in November 2001.

Discussion

The relationship between silicone implants and autoimmune disease is disputed. Some experimental studies have shown silicone to be immunologically active, and it may, in fact, act as an adjuvant against self-antigens.[3] Naim et al.[3] described silicone-induced autoantibody and immunoglobulin production, as well as overproduction of IL-6 and IL-1β, and activation of macrophages in female A.SW mice. They speculated that IL-6 and IL-1β might mediate the inflammatory response to silicones. White et al.[4] assessed the autoimmunity-inducing potential of silicone gel in Brown Norway rats, which provide a model for systemic lupus erythematosus following exposure to certain chemicals. They reported that silicone gel does not induce autoimmunity in this model.

In clinical studies, Goldblum et al.[5] reported two cases of specific immune reactions, with abdominal pseudocyst formation and hypergammaglobulinemia, associated with a VP shunt made from silicone. Press et al.[6] reported that 11 women with silicone breast implants developed autoimmune disease. They suggested the possibility of a relationship between the symptoms and 9–10 years of silicone exposure. However, to date, many clinical studies have concluded that there is little association between autoimmune disease and silicone.[7–11] Gabriel et al.[7] and Sánchez-Guerrero et al.[8] reported that silicone breast implants do not cause autoimmune disorders or overproduction of autoantibodies. Metaanalyses of nine cohort studies, nine case–control studies, and two cross-sectional studies have shown that silicone breast implants are not associated with the development of connective tissue diseases.[9] We suspect that silicone may induce autoimmune diseases in patients who have a particular genetic background. However, there is no report of silicone-induced rheumatic diseases associated with genetic background.

On the other hand, it has been suggested that glomerulonephritis or small-vessel vasculitis might be elicited by silica dust or exposure to compounds containing silicon.[12] Several case reports and case–control studies have concluded that silicon exposure may be related to the development of renal lesions, usually associated with MPO-ANCA.[13] In most cases, these would involve pauciimmune NCGN. Patients had usually been suffering from low-grade fever, arthralgia, hemoptysis, purpura due to leukocytoclastic angiitis, renal insufficiency with microscopic hematuria, and proteinemia.

They usually responded well to prednisolone and cyclophosphamide treatment. Cheviller et al.[13] reported that the overall incidence of patients with silicon exposure and renal involvement among their ANCA-positive patients was 5.5% (8/145). All had MPO-ANCA.

Mechanisms by which silicon-containing compounds can induce ANCA-associated disease have been suggested in several reports.[13–15] First, the material may stimulate lymphocytes via a T-cell receptor Vβ-specific T cell activation pathway.[14] This activation could cause a patient with an appropriate genetic background to produce autoantibodies leading to autoimmune disease. Second, silica may activate monocytes and macrophages, causing IL-1 or tumour necrosis factor-α, oxygen-derived free radicals and lysosomal enzymes such as PR-3 or MPO to be released.[11] Nuyts et al.[15] reported that 7 of 16 patients with Wegener's granulomatosis had exposure to silicon-containing compounds, resulting in a significantly elevated odds ratio of 6.5 (95% confidence interval 1.3–13.5).

In our patient, although titres of various autoantibodies were initially increased, the patient presented only with signs of ANCA-associated vasculitis, and was continuously positive for PR-3-ANCA. The many autoantibodies initially present were considered to be the result of hypergammaglobulinemia due to polyclonal activation by the silicone. We believe that the implanted VP shunt initially activated cytokines such as IL-6 nonspecifically to induce hypergammaglobulinemia, and that these later switched to activate PR-3-ANCA specifically by releasing PR-3 from neutrophils. The implanted shunt may have triggered immunological abnormalities through stimulation of the immune system, eliciting his autoimmune disease. However, his symptoms responded well to steroid and immunosuppressant therapy. Although we planned to remove the VP shunt to exclude the possibility of releasing PR-3 from neutrophils by the stimulation of the tube, we had to abandon the idea because of the need to retain the shunt function. An accumulation of such cases and further studies are necessary to clarify whether long-term exposure to silicon-containing compounds or implants made with silicone is related to the development of autoimmune disease.

References

1. Miyoshi K, Miyaoki T, Kobayashi Y. Hypergammagloblinemia by prolonged adjuvanticity in man: disorders developed after augmentation mammoplasty (in Japanese). Nihon Iji Shinpo 1964;2122:9–14.
2. Kumagai Y, Abe C, Shiokawa Y. Scleroderma after cosmetic surgery: four cases of human adjuvant disease. Arthritis Rheum 1979;22:532–7.
3. Naim JO, Satoh M, Buehner NA, Ippolito KML, Yoshida H, Nusz D, et al. Induction of hypergammaglobulinemia and macrophage activation by silicone gels and oils in female A.SW mice. Clin Diagn Lab Immunol 2000;7:366–70.
4. White KL Jr, David DW, Butterworth LF, Klykken PC. Assessment of autoimmunity-inducing potential using the Brown Norway rat challenge model. Toxicol Lett 2000;112–113:443–51.
5. Goldblum RM, Pelley RP, O'Donell AA, Pyron D, Heggers JP. Antibodies to silicone elastomers and reactions to ventriculoperitoneal shunts. Lancet 1992;340:510–3.
6. Press RI, Peebles CL, Kumagai Y, Ochs RL, Tan EM. Antinuclear autoantibodies in women with silicone breast implants. Lancet 1992;340:1304–7.
7. Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LJ III. Risk of connective-tissue diseases and other disorders after breast implantation. N Engl J Med 1994;330:1697–702.
8. Sánchez-Guerrero J, Schur PH, Sergent JS, Liang MH. Silicone breast implants and rheumatic disease: clinical, immunologic, and epidemiologic studies. Arthritis Rheum 1994;37:158–68.
9. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 2000;342:781–90.
10. Bar-Meir E, Teuber SS, Lin HC, Alosacie I, Goddard G, Terybery J, et al. Multiple autoantibodies in patients with silicone breast implants. J Autoimmun 1993;8:267–77.
11. Zazgornik J, Piza H, Kaiser W, Bettelheim P, Steiner G, Smolen J, et al. Autoimmune reactions in patients with silicone breast implants. Wien Klin Wochenschr 1996;108:781–7.
12. Sanchez-Roman J, Wichmann I, Salaberri J, Varela JM, Nuñez-Roldan A. Multiple clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica. Ann Rheum Dis 1993;52:534–8.
13. Chevailler A, Carrere F, Renier G, Hurez D, Subra JF, Reboul P, et al. Silicone nephropathy and myeloperoxidase antibodies. Ann Rheum Dis 1994;53:781–2.
14. Ueki A, Yamaguchi M, Ueki H, Watanabe Y, Ohsawa G, Kinugawa K, et al. Polyclonal human T-cell activation by silicate in vitro. Immunology 1994;82:332–5.
15. Nuyts GD, van Vlem E, de Vos A, Daelemans RA, Rorive G, Elseviers MM, et al. Wegener granulomatosis is associated to exposure to silicon compounds: a case–control study. Nephrol Dial Transplant 1995;10:1162–5.