



## Association of silicone breast implants and acute renal allograft rejection

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### ABSTRACT

Silicone may, like any other adjuvant, induce an inflammatory reaction and diseases. There is no data about its use in renal transplant recipients.

Increased immunogenicity of silicon may manifest by activation of both the innate and the adaptive immune system cells what promotes a chronic pro-inflammatory response. Dendritic cells, macrophages, fibroblasts and T-cells have all been found at the capsule/silicone implant contact zone. Additionally, silicon may induce mononuclear cells to secrete proinflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . Herein, we present two patients who developed acute rejection after breast augmentation and reconstruction with silicone-gel implants.

By influencing the immunological and inflammatory response, silicone-gel may be involved in promotion of acute allograft rejection in renal transplant recipients. Further studies are needed to prove our hypothesis.

### Introduction

Silicone gel breast implants have been employed for many years for augmentation or postmastectomy reconstruction. Although silicone was considered to be an inert material, it may, like any other adjuvant, induce an inflammatory reaction and diseases. While previous epidemiological meta-analyses have failed to show a significant association between silicone breast implants and autoimmune diseases [1,2], an association between silicone and immune related diseases has been reported in numerous cases and in the latest analysis of 24 651 silicone breast implants recipients [3].

Renal transplantation is method of choice for treatment of end-stage renal disease. It required permanent use of immunosuppressive drugs for prevention of acute rejection. Although antigen-dependent immune responses have traditionally been considered to be critical for induction of both acute and chronic allograft rejection, there is accumulating evidence supporting the observation that antigen-independent injury and subsequent inflammation may trigger allograft rejection [4,5].

There is no data on the use of silicone breast implants in renal transplant recipients. Herein, we present a hypothesis of increased risk of allograft rejection based on our experience with two patients.

### Case-reports

A 36-year-old female patient with end-stage renal disease of unknown etiology underwent preemptive living donor renal transplantation in May 2012. She received basiliximab induction with tacrolimus, mycophenolate and steroid maintenance. Posttransplantation course was uneventful with stable allograft function (serum creatinine 110  $\mu$ mol/l, no proteinuria). Despite the advices from nephrologists, she underwent bilateral breast augmentation with silicone-gel implants in March 2016. Six months later she developed proteinuria 1.74 g/day with increase in serum creatinine to 184  $\mu$ mol/l. Renal biopsy revealed acute cellular rejection (Banff g1, i2, t1, v0, ptc0, c4d0) with mild chronic changes (cg2, mm0, ci0, ct0, ah3, cv1, ti2) and development of de novo DQ5 donor specific antibody (DSA) (MFI 15000). C4d negative acute humoral rejection was suspected so she received 5 steroid pulses of 500 mg each, 5 plasma exchanges and intravenous immunoglobulins 2 g/kg body weight. Her serum creatinine returned to initial values, proteinuria decreased to 0.6 g/day, and DQ5 fell to 13.500 MFI. She refused to remove breast implants. One year later, she has stable serum creatinine but is maintained on the higher steroid dose (10 mg per day) with stable level of DQ5.

Another patient was 52-year-old woman with end stage renal disease of unknown etiology who received a renal allograft from the deceased donor in April 2008 after three months of treatment with

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hemodialysis. Her immunosuppressive protocol included basiliximab induction, cyclosporine, mycophenolate and steroids. Posttransplantation course was complicated with pneumonia and urinary tract infections. Graft function was stable with no proteinuria. In February 2012 she was diagnosed invasive lobular breast carcinoma and underwent mastectomy and received radiotherapy and tamoxifen. In April 2015 she underwent breast reconstruction, but one month later developed acute cellular rejection Banff IA without chronic changes which was treated with 5 steroid pulses of 500 mg each. Creatinine returned to initial values, and she remained with stable allograft function.

## Discussion

The number of women receiving silicone gel breast implants for augmentation or reconstruction of the breast is increasing due to increase in number of patients with breast cancer but also to increase number in cosmetic procedures. Silicone gel breast implants have been claimed to induce different clinical problems which may be local or systemic and include capsular formation, fibromyalgia, autoimmune collagen vascular disease, granulomatous disease, arthritis, arthralgia and silicone-related disease [3,6]. However, systemic consequences of silicone breast implants are still subject of controversies.

We present two patients with stable renal allograft function who developed acute rejection shortly after the breast implant surgery. We suggest association between exposure to silicone gel and induction of the immunological response and provide possible explanations for our hypothesis.

Silicone is an adjuvant that may 'leak' and subsequently induce chronic immune system stimulation. It may spread throughout the body what was proven by detection of silicone in different tissues [7,8]. Besides the induction of autoimmune diseases, silicon degradation products have been shown to be associated with development of anaplastic large T-cell lymphoma in the capsule surrounding the breast implants [9]. Additionally, silicone degradation products may activate both the innate and the adaptive immune system cells what promotes a chronic pro-inflammatory response [10]. Data were derived from both experimental and clinical studies. Dendritic cells, macrophages, fibroblasts and T-cells have all been found at the capsule/silicone implant contact zone by the immunohistochemical analysis. In this zone, activated CD4+ T-cells mainly expressed CD25 and CD45RO markers [11]. In the further analysis by the flow cytometry, the same group showed a preponderance of effector T cells which were mainly TH17 cells, while regulatory T cells were decreased [12]. An increasing body of evidence has been accumulated to support the critical role of regulatory T cells in the suppression of alloimmune responses [13]. Thus, by influencing the balance between different T-cell types, silicone may promote allograft rejection.

However, it seems that different types of silicone behave differently while Meza Britze et al. found increased numbers of CD3+ T cells and also of cellular infiltrates (macrophages) in capsular biopsies recovered from textured rather than smooth implants and concluded that textured silicone might induce a local T-cell response [14]. In another study, nanosilicone reduced secretion of the proinflammatory cytokines IL-6, TNF- $\alpha$  and IFN- $\gamma$  compared to silicone microparticles used at the same concentration [15]. Not only cellular, but also humoral responses may be induced by silicone-gel. Namely, some silicone-gel surfaces may

induce mononuclear cells to secrete proinflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$  [16].

In a retrospective single center study of 36 non-selected women with silicone breast implants and 36 sex- and age-matched controls, autoimmune reactions were evaluated by measuring antinuclear antibodies, rheumatoid factor and thyroid gland antibodies, along with angiotensin-converting enzyme and C-reactive protein. Only 8% of women in the control group had detectable antibodies compared to 33% of patients from the group with silicone implants, but none of them had clinical symptoms or signs of connective tissue disease [17].

We report two cases of acute renal allograft rejections in adult female patients after breast augmentation and reconstruction with silicone-gel implants. Nephrologists should be familiar with the possible immunological disorders related to silicone breast implants including the possibility of acute allograft rejection. Further studies are needed to prove our hypothesis.

## Conflict of interests

None.

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