Case Report

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Long-Term Follow-Up of Cadaveric Breast Augmentation: What Can We Learn?

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Abstract

Breast augmentation with cadaveric fat graft has long been available to patients in Eastern European countries, primarily in the Soviet Union and Eastern Germany. Most such procedures were performed from the 1970s to the 1990s. Although only a few case reports have been published, all of which involved complications that appeared several years after the procedure, it appears that, surprisingly, this nonvascularized and incompatible immunologic tissue is relatively well tolerated. We present the case of a 45-year-old Russian woman who underwent breast explantation, due to breast hardness and pain, 15 years after breast augmentation with cadaveric fat grafting. Through genetic studies, we confirmed that the host and the graft were HLA incompatible. Moreover, results of analyses excluded the possibility of an acute or chronic immunologic rejection by the host. We suppose that the early complications that often occur in such cases might result from a nonspecific, inflammatory reaction induced by acute tissue ischemia and necrosis, and the late local complications that occur years later may relate more to chronic inflammation, due to nonvascularized tissue, than to immunologic rejection. Therefore, we propose that different mechanisms may explain how this allogenic fat tissue could have been tolerated by the patient's immune system. We particularly underline the immunomodulatory effect of mesenchymal stem cells, which are abundant in adipose tissues. This characteristic of fat tissue should be investigated further to assess its potential in treating autoimmune diseases or reducing the likelihood of allograft rejections.

Level of Evidence: 5

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Before the advent of silicone prostheses, numerous materials were utilized for breast augmentation, including ivory, glass, cellulose, sponges, rubber, plastic, and paraffin. From the 1970s to the 1990s, even cadaveric fat allografts were used in Eastern European countries, particularly the Soviet Union.[1-8] Our knowledge of this procedure is limited to the few complications that have been reported; we found no technical description of the surgery itself in the international medical literature. However, our research indicates that in this technique a fat block harvested from the buttocks of a cadaver is transplanted to the patient's breast through a submammary incision, similar to the implantation technique for silicone prostheses.

Through a case study of breast augmentation with a homologous cadaveric fat graft, we attempt to understand how this nonvascularized and immune-incompatible fat tissue could be tolerated for many years.

CASE PRESENTATION

A healthy 45-year-old Russian woman was referred to our department by an oncologist in 2005. At presentation, she

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was free of infection and immune disease (eg, human immunodeficiency virus). According to the patient, she had undergone bilateral augmentation mammaplasty in 1990 in the Soviet Union via "a specific technique without breast implant." The immediate postoperative period had been marked by signs of local inflammation of the breasts, accompanied by fever and asthenia, which resolved without any treatment (eg, antibiotics, immunosuppressors) by 3 months postoperatively. Since 1991, she presented sporadic subcutaneous nodules, which disappeared spontaneously, and progressive breast hardness. While breastfeeding 9 years after the procedure, the patient had episodes of mastitis that resolved with antibiotic therapy. Beginning in 2002, her breasts became painful, and occasional sterile discharge emerged from subcutaneous nodules. Malignancy was excluded by biopsy and ultrasonography findings.

Our first visit with the patient occurred 15 years after her breast augmentation procedure. We noted that the breasts were hard and deformed, with inframammary scars on both sides. In the right breast, we detected a subcutaneous

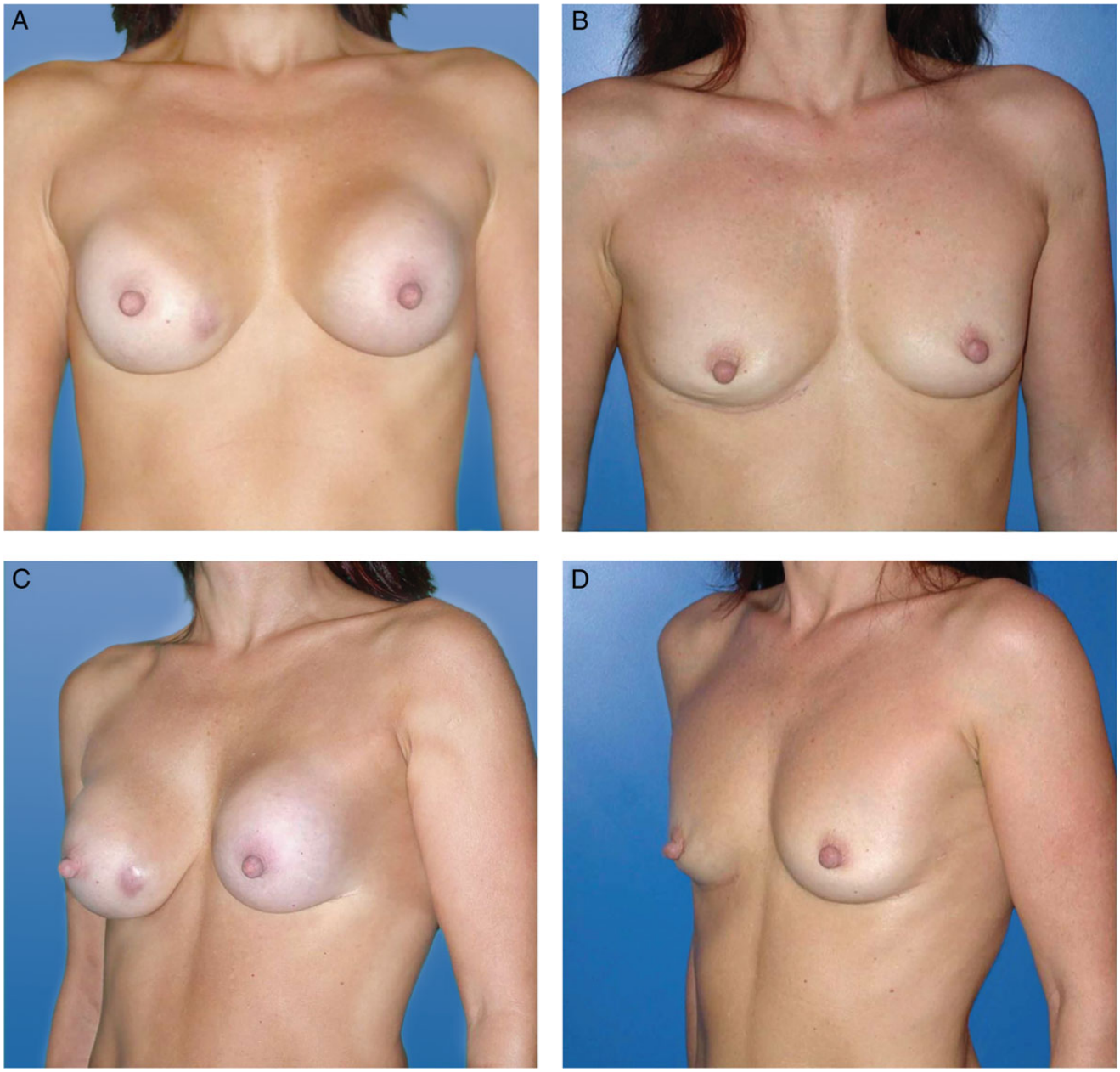

Figure 1. (A, C) Pre-explantation images of the 45-year-old woman, obtained 15 years after breast augmentation with cadaveric fat grafting. (B, D) Two years after explantation.

fluctuating nodule, measuring 2 × 3 cm, which was covered by inflamed skin (Figure 1A,C).

Magnetic resonance imaging of each breast revealed a subglandular mass with heterogeneous signal on T1/T2, compatible with fat tissue and some vacuoles in the center (Figure 2). Each mass was surrounded by a thick capsule. On the right breast a herniation of this tissue to the skin was noted.

Bilateral explantation of these "breast implants" was performed. A yellowish mass (measuring 7.5 × 5 × 4.5 cm), compatible with necrotic fat tissue, was excised from each breast. These masses were surrounded by a hard and calcified capsule, which was difficult to dissect from the breast gland (Figure 3). The large subcutaneous nodule in the right breast, corresponding to herniated necrotic fat, was excised. Immediate and 1 year post-operatively was free of any medical event and patient didn't present any discomfort. The breasts were ptotic and empty in the upper pole, with a retracted scar in the internal quadrant on the right breast where the herniated nodule had been excised (Figure 1B,D).

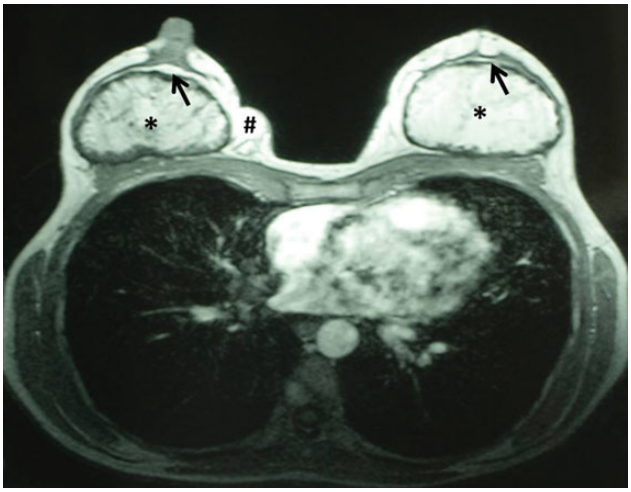

Figure 2. Pre-explantation magnetic resonance image (obtained 15 years after cadaveric fat breast augmentation procedure) demonstrates bilateral subglandular masses (*), each measuring 8 × 7 × 5 cm, compatible with fat tissue signal. The masses are heterogeneous, including some vacuoles in the center, and are surrounded by an intact thick capsule (arrow). On the right breast, note the herniation of this tissue to the skin (#).

Macroscopic examination showed a thick, 2 mm, calcified capsule surrounding necrotic adipose tissue. The internal part included focal areas of calcification and a central cystic degeneration that contained oils (Figure 4A).

Microscopic analysis confirmed a calcified capsule rich in collagen and devoid of inflammation. This capsule delimited a 6 × 5 cm mass of adipose tissue, which was completely mummified and necrotic. The mass contained several cysts and no inflammatory cells (Figure 4B). Focally, on the periphery of the capsule, in the breast parenchyma that was minimally resected with the mass, synovial metaplasia with a xanthogranulomatous inflammation was observed; it was rich in macrophages but poor in lymphocytes (Figure 4C). A specimen obtained intraoperatively for bacterial analysis tested negatively.

All information concerning the donor was unknown to the patient, and therefore to us. Hence, to confirm the allogenic origin of the fat graft, genetic studies were ordered. Results showed that the excised grafted fat was HLA-incompatible. In the effort to determine a potential immunologic reaction between the host and the graft, anti-HLA antibody analysis was conducted by enzyme-linked immunosorbent assay. In cases of graft-vs-host rejection, these antibodies usually are positive. Interestingly, in our patient, the biopsy specimen and blood testing were negative for anti-HLA class I and II antibodies.

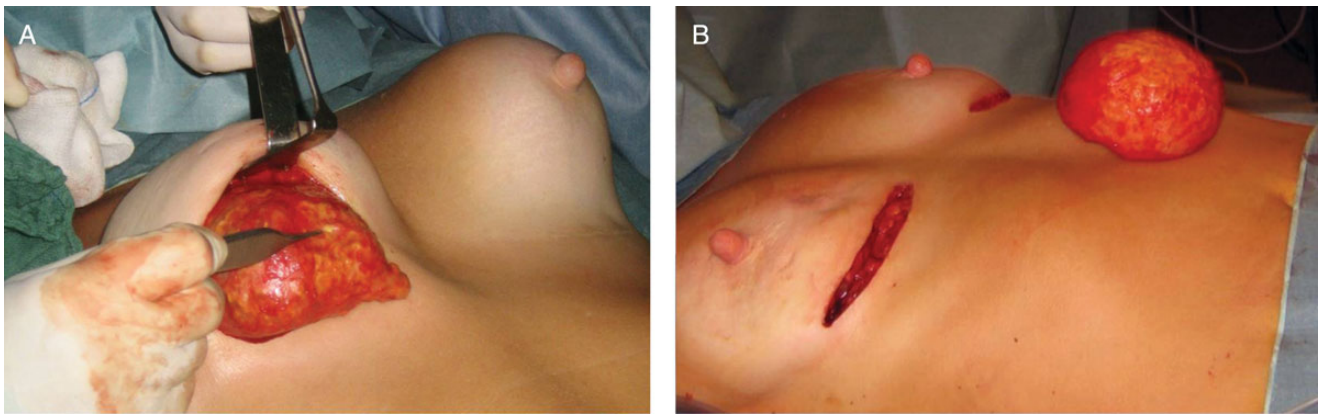

Figure 3. Intraoperative images. (A) Difficult dissection of the right cadaveric fat implant, which was surrounded by a thick capsule from the mammary tissue. (B) Appearance after bilateral explantation.

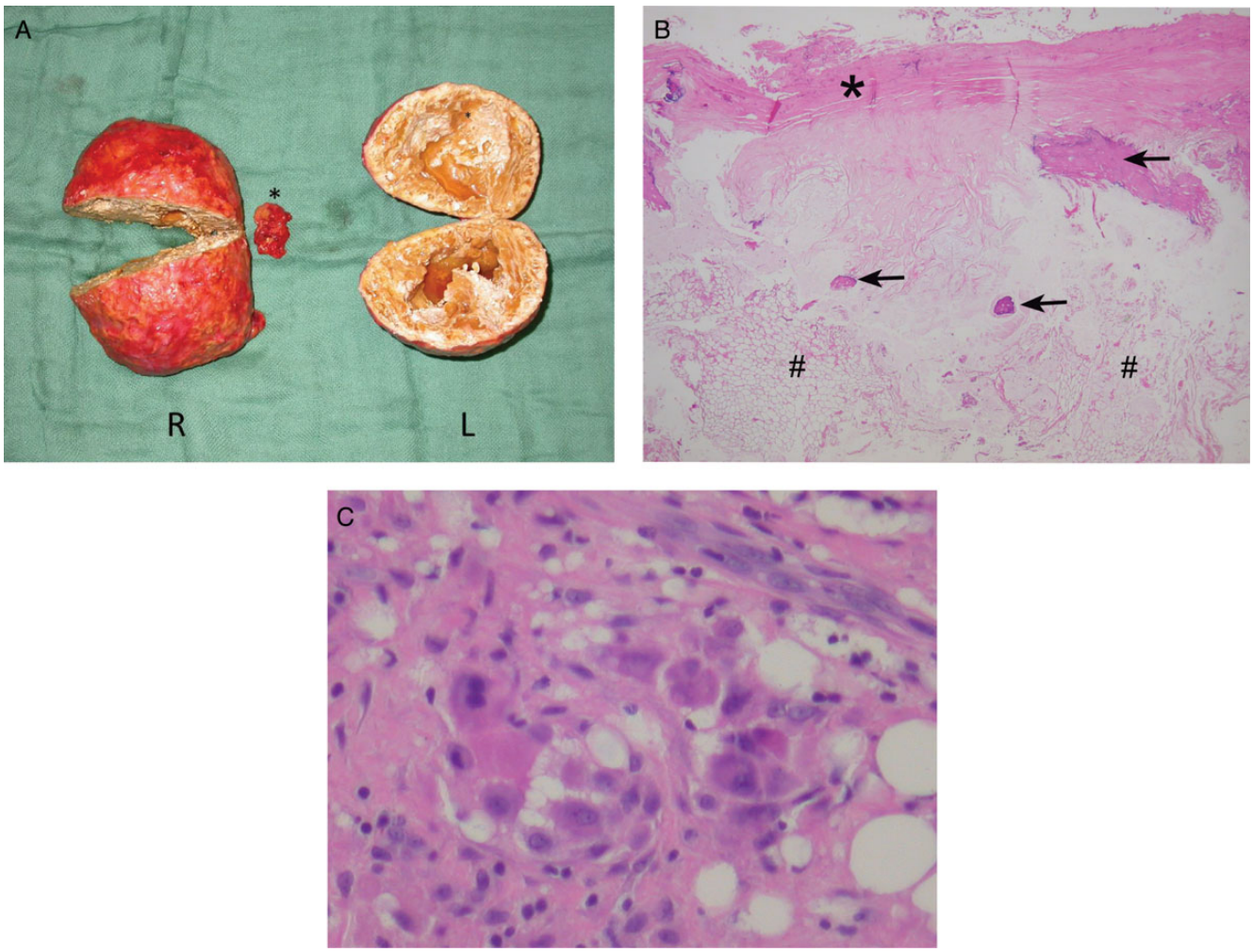

Figure 4. Histopathologic images. (A) Macroscopic view of the right (R) and left (L) masses after a difficult cut, due to the hard calcified capsule. In the center, note the complete necrotic adipose tissue with focal areas of calcification and a central cystic degeneration containing oils. An additional piece, corresponding to the herniated mass, was resected from the right breast (*). (B) Microscopic view of the thick fibrous capsule (*) surrounding the mummified cadaveric tissue (#) and containing dead adipocytes and calcification (arrow). Hematoxylin and eosin stain, original magnification × 20. (C) Breast tissue at the periphery of the graft demonstrates a macrophagic and giant cell reaction (xanthogranulomatous) poor in lymphocytes. Hematoxylin and eosin stain, original magnification × 400.

DISCUSSION

In a review of the literature, we found only 6 articles (representing 26 cases) on patients who underwent breast augmentation with allograft fat between 1966 and 1991, most of which were from the Soviet Union and Eastern Germany. As in the present case, the fat was not injected but rather implanted through a 4 to 6 cm submammary incision. In all 6 reports, complications that required postoperative management were described.[1-8] Interestingly, the complaints in most of these cases were similar to those of our patient: moderate local and systemic inflammatory reactions occurred within several months of the surgery, followed by local pain and hardness many years later, ultimately leading to excision.

To our knowledge, the present case is the first in which genetic studies were performed to confirm HLA incompatibility between the host and the graft. Subsequently, to investigate the presence of an immune response against the graft, immunologic testing was conducted. However, we did not detect any antibody against the graft, which excludes acute or chronic immunologic rejection by the host. Furthermore, histopathologic analyses demonstrated only macrophages (a nonspecific immune reaction) and no lymphocytic reaction was noted, as is usually present in host-against-graft rejection. This observation of probable immunotolerance of an implanted allogenic tissue in the absence of immunosuppressor therapy is surprising. We hypothesized different possibilities that might explain this phenomenon:

(1) *The isolation of grafted tissue from the patient's immune system.* Because the fat graft was nonvascularized, initially only the surrounding part was exposed to the patient's immune cells, which could stimulate an immunologic reaction. Later, the thick fibrotic capsule developed around the allogenic tissue, which could isolate it further from the patient's immune system.
(2) *The low immunogenicity of fat tissue*. Because the literature concerning the specific immunogenicity of fat tissue is very limited, further assessments are needed.
(3) *The immunomodulatory property of adipose-derived mesenchymal stem cells (MSCs)*. This has been demonstrated recently in the literature and, in our opinion, is the most interesting explanation.

MSCs are stromal cells known for their limitless capacity for differentiation into bone, fat, muscular, nervous, or endothelial cells, according to their environment.[9] They are present in most tissues (including bone marrow, adipose tissue, skin, placenta, and heart) and are key elements of tissue regeneration. Recently, it has been shown that adipose tissue contains 1000 times more MSCs than the bone marrow, which initially was regarded as the best source of stem cells.[10] The immunogenicity of MSCs is low due to their low expression of the HLA class I cell marker and lack of the class II marker on their cell surface.[11] Moreover, recent studies have demonstrated the potent capacity of MSCs to inhibit the activation and proliferation of immune cells involved in both acute and chronic phases of immunologic rejection of noncompatible tissue by the host. Lymphocytic reaction is primordial, with T cells and B cells playing key roles. In a variety of experimental conditions, MSCs have suppressed this lymphocyte proliferative response to allogenic or xenogenic antigens through a number of mechanisms.[12-16]

MSCs modulate the activation, proliferation, and functioning of T cells.[17-19] Although MSCs strongly suppress $CD8^+$ cytotoxic T lymphocytes (CTL), they themselves are resistant to CTL-mediated lysis.[14,20,21] In addition to their effects on naïve T-cell populations, MSCs inhibit the proliferation of memory T cells.[19,20] Some investigators have found that MSCs effectively inhibit B-cell proliferation, differentiation, and antibody production,[22] as well as suppress the production of interferon-gamma and interleukin-2, which normally stimulate natural killer cells.[20,23]

Based on these data, it has been proposed that MSCs can contribute to controlling auto-immune diseases such as rheumatoid arthritis and multiple sclerosis. Their effectiveness in humans is under investigation in different clinical trials. The immunomodulatory properties of MSCs suggest that they may play a role in bone marrow and solid-organ transplantation by preventing rejection. This ability has been demonstrated by MSCs infusions to murine models of allogenic bone marrow,[24] skin,[12] and liver[25] grafts, where graft-versus-host disease was prevented.

The application of MSCs to bone marrow transplantation has also been investigated in human studies: various groups have shown that administration of MSCs not only increases bone marrow engraftment after hematopoietic stem cell transplantation, but also reduces conventional therapy-resistant host-versus-graft disease.[26,27] The effectiveness of MSCs in solid-organ transplantation is a relatively new area of research.[28] Therefore, the immunomodulatory effect of MSCs that is present abundantly in the fat graft might be responsible, in part, for the immuotolerance of the allogenic fat implanted in the breast. Furthermore, it can be supposed that fat tissue was in some way isolated from the immunologic reaction: the grafted tissue was not vascularized and, except for the periphery, was not in contact with the immune system. Later, the nonvascularized capsule isolated the grafted tissue from the immunologic reaction. Some investigators purport that the grafted tissue had been embedded in a plastic sac in order to isolate it from the immune system.[3]

Although breast augmentation by homologous fat tissue appears to provide seemingly satisfactory immediate results, complications may arise after several years. Late complications of this procedure have been attributable more so to fat necrosis than to immunologic reaction. The physiologic turnover of adipocytes is 3 months. As demonstrated by Eto et al;[29] most graft adipocytes that are further than 3 mm from a vessel begin to die in the first 24 hours. Stem cells better support the ischemia; they survive up to 5-7 mm from an oxygen source. Thus, when a big piece of fat is transplanted as a prosthesis rather than being injected during a cadaveric breast augmentation procedure, it is not surprising that most adipocytes will die within 3 days but some stem cells will survive. Except for cells in the periphery, grafted tissue is isolated from oxygen and undergoes necrosis during the first postoperative days, especially in the center. This narcotization provokes oil cysts and a chronic nonlymphocytic immune reaction, resulting in multiple granulomas, as we have demonstrated by histopathologic analysis. We suppose that the early complications that often occur in such cases might result from a nonspecific, inflammatory reaction induced by acute tissue ischemia and necrosis. However, the late local complications that occur years later as mastitis, nodules, pain, and breast hardness, without systemic reaction, may relate more to chronic inflammation, due to nonvascularized tissue, than to immunologic rejection.

CONCLUSIONS

Although cadaveric breast augmentation likely has been abandoned entirely, the existing case reports have raised interesting questions about the potential immunomodulatory effect of fat tissue. This characteristic of fat tissue should be investigated for its potential in the treatment of autoimmune disease (eg, scleroderma) and in reducing the likelihood of allograft rejection (eg, facial transplantation).

Disclosures

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