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

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This article on long-term follow-up of cadaveric breast augmentation is admirable, for the authors not only report their observations on an interesting and (to me) hitherto unknown procedure, but also take the next step in the spirit of the surgeon-scientist in postulating a hypothesis and posing research questions arising from their observations.1

Macroscopic autologous fat grafts, more commonly dermis-fat grafts, were the standard method of soft tissue filler from early times, and although high failure rates were doubtless anticipated, compared to the complex multi-staged tube pedicle migration and its associated scarring and morbidity, the free graft seems to have been a reasonable reconstructive option. Free microsurgical one-stage transfers wrote the death knell for large-segment free-fat grafting. Knowing that autografts fared poorly and that immune rejection could only worsen the anticipated survival rates, allografts of non-vascularized whole fat pieces seem optimistic. The authors trace the main practitioners of the procedure to Russia and Eastern Europe, where there was perhaps less structured training and less scrutiny at that time. Naïve painters were similarly ignorant of the rigid tenets of the academy, but under such freedom original ideas take flight, some with a core of genius. The authors have sought to unravel the question: was this procedure naive, foolish, or genius?

From the clinical photographs 15 years post-transplantation, it appears that a large amount of tissue has been retained bilaterally, irrespective of its complications, perhaps more than might have been expected even with an autograft, although there is no information or record of pre-operative breast size or implanted volumes. From this one anecdotal case of “probable immunotolerance” the authors pose several hypotheses that might explain this tolerance. Without a literature report of a series of these allograft procedures and a comparable report of fat autografts, the question remains: is this case exceptional or the norm for fat allografts? Unfortunately, the basic premise on which these hypotheses are based is questionable, as are the investigations to determine whether the surviving graft is host or foreign and whether the histology distinguishes inflammation from rejection. Is this “the pearl of ornament forming around a grit of truth”?2

What exactly has survived? MRI suggests a fat signal, but at explantation a yellowish mass “compatible with necrotic fat” was observed. Macroscopic cross-section showed a calcified scar capsule and “necrotic fat and cystic degeneration”. Microscopy confirmed a calcified capsule surrounding adipose tissue that was “completely mummified and necrotic.” Staining the tissue with perilipin could have identified living and non-living fat. It would appear that the dead fat is providing volume but that the living tissue, comprising blood vessels, fibrotic capsule, and inflammatory cells, is most likely host-derived. If rejection had occurred, would lymphocytes continue to be dominant when the graft is totally mummified and necrotic? The clinical post-operative symptoms of inflammation, fever, and asthenia over 3 months are consistent with rejection. Therefore, is this really a successful transplant that has avoided an immune response or simply the aftermath of immune rejection followed by a standard macrophage dominant inflammatory response to necrotic tissue?

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For the sake of scientific pursuit, let us assume we accept that this is indeed allograft and that there has been little or no rejection: how could the survival of such a large, foreign, non-vascularized piece of tissue be explained? We have studied the fate of human fat grafting in small animals using species-specific cell markers, and found that when human fat is inserted into severe combined immunodeficiency mice, the adipocyte fraction dies but the volume of graft is retained as lipid-filled ghost cells along with the tissue-specific scaffold matrix. The inflammation that ensues, driven largely by host macrophages, signals stem cell and preadipocyte migration to the adipogenic wound environment. Gradually, over the course of two months, revascularization occurs and the dead cells are replaced by host adipocytes. We found similar results in the rat model where fresh non-vascularized muscle allografts were replaced by host fat, which suggests that adipose may be a default tissue for differentiating mesenchymal stem cells (MSCs) in an ischaemic-stressed environment. When fluorescence-activated cell sorting-sorted human adipose derived stem cells (ASCs) were implanted, fat also formed, although occasionally bone and cartilage were detected. A minority of the neo-vasculature contained human cells in the perivascular region (unpublished). As the authors point out, we have also described a similar fate of fat grafts. Most of the MSCs in the fat (ASCs) probably also die, but in the process secrete growth factors, cytokines, and enzymes, which produce a paracrine response stimulating angiogenesis, cell survival, migration and proliferation, and inhibition or modulation of immune responses. Eventually, once inflammation subsides, adipogenesis proceeds.

Given that most of the grafted content dies from inadequate vascularization, the active component of the graft is inflammatory signaling. It could be argued that, as the fat and stem cells are destined to only short-term survival, rejection is not an issue and allograft cells can fulfill the same role in initiating paracrine responses as autografts. Furthermore, the authors rightly highlight the mounting evidence for the immune modulatory capacity of ASCs and their relative lack of antigenicity. Mesoblast (Mesoblast.com) markets banked allograft immunoselected MSC precursors for clinical and research purposes, mostly targeting the cardiac, orthopaedic, and immunology arenas. They highlight their immune privilege and short-term viability as positives to avoid immune responses. Stem cell therapies are now proposed for a myriad of clinical applications, but to date there has been little convincing evidence of stem cell survival and differentiation into tissues. Most concede that the cells do not survive, but act by paracrine activity. Indeed, the very efficacy of stem cell therapy in cardiac disorders, which has shown impressive preclinical results, is currently under question.

The apparent survival of fat in this clinical case could be explained on the basis that both the fat and the stem cells have died through ischaemia (and perhaps immune rejection), but the adipocytes largely remain as lipid-filled globules and maintain the adipogenic-specific matrix space while the dying stem cells signal the host to regenerate the graft with endogenous cells. Mostly, these are destined to an adipogenic fate, but occasional differentiation into bone is consistent with the pluripotent capacity of MSCs and would explain the calcification within the graft. This could only be a credible explanation if some of the fat in the graft was living and if it was of host origin, not allograft. My hypothesis, alas, is no less flawed than I am claiming of the authors, as I am basing it on the above assumptions, which cannot be proven.

Plastic surgery is fun because of its technical and creative fundamentals, but advances come from observing and recognizing the unexpected and then taking the next step in asking why. In plastic surgery, nothing ruins a good result like a long-term follow-up, and it is only by asking why that we will progress. The authors have asked why, and in doing so invite discussion and further questions. This is the other half of the fun of our specialty, and even if the answers remain unresolved it is the intellectual engagement and banter with the academy and the naifs that will forever drive us on.

Disclosures
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REFERENCES
