Focosi Daniele
Papineschi Federico
Petrini Mario
Division of Hematology
Azienda Ospedaliera Universitaria
Santa Chiara
Pisa, Italy

Paumgardhen Elena
Ghimenti Massimo
Division of Laboratory Analysis
University of Pisa, Italy

The first two authors contributed equally to this manuscript.
Address correspondence to: Maggi Fabrizio, M.D., Ph.D., Virology Unit, Azienda Ospedaliera Universitaria Pisana, Via San Zeno, 35-37, 56127 Pisa, Italy.
E-mail: maggif@biomed.unipi.it
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Ectopic Fibrogenesis Induced by Transplantation of Adipose-Derived Progenitor Cell Suspension Immediately After Lipoinjection

Adipose tissue has its own tissue-specific progenitor cells, a subpopulation of which has been shown to have multipotency and called adipose stem cells or adipose-derived mesenchymal stem cells (*1*,*2*). During a clinical trial in which soft tissue is augmented by transplantation of progenitor-enriched adipose tissue (cell-assisted lipotransfer), we have encountered incidence of an unexpected complication: local ectopic subcutaneous fibrogenesis. Patients participating in the trial did so under informed consent approved by individual review boards.

Cell-assisted lipotransfer was designed based on the finding that aspirated fat tissue contains many fewer vessels and adipose progenitor cells than intact fat tissue. This may explain the tendency of transplanted aspirated fat tissue to atrophy during the first 6 months posttransplantation (*3*). In the relevant clinical trial, the stromal vascular fraction (SVF) comprising 10% to 40% adipose progenitor cells was freshly isolated from aspirated fat by means of collagenase digestion and transplanted together with aspirated fat tissue grafts (*4*).

In 146 cases, SVF cells were used as a cell pellet, mixed with and attached to aspirated fat tissue grafts before injecting into fatty and muscular layers of breast mounds. On the other hand, in two cases, SVF cells isolated from 600 mL aspirated fat were separately injected as a cell suspension in 60 mL of saline into both breast mounds (30 mL/side) immediately after conventional lipoinjection. Although grafted fat survived well and fibrogenesis in the breasts or surrounding tissues was not seen in the former group, fibrous tissue formation was observed in both cases of the latter group 3 months after treatment. In the two cases, breast mounds were somewhat hard to the touch; inspection by CT scan detected unexpected fibrosis in the subcutaneous fat layers. In the thinner patient of the two (Fig. 1), fibrous tissue approximately 10 mm thick had formed on the sternum and caused anterior elevation of the skin, which was treated with local injections of triamcinolone acetonide at 6 and 8 months. Furthermore, lymphadenopathy was seen at the left abdominal wall and the left inguinal region at 3 months and gradually disappeared by 12 months.

Fibrogenesis results from persistent inflammation, in which tissue remodeling and repair processes are impaired and injured cells are replaced not with cells of the same type but with connective or scar tissue (*5*). As fibrogenesis was seen only when SVF cells were injected separately as a cell suspension, a nonphysiological microenvironment in which adherent adipose progenitor cells are suspended in saline solution may give rise to the unexpected differentiation and migration of the cells. After large-volume lipoinjection, tissue injury, edema, hemorrhage, and local inflammation are commonly seen, and transplanted adipose progenitor cells are temporarily placed in and stimulated by ischemic and inflammatory microenvironments.

These findings provide some insights into a therapeutic strategy for future cell-based therapies involving adherent stem/progenitor cells. Previous experimental studies demonstrated that transplanted bone marrow-derived mesenchymal stem cells differentiated into myofibroblasts and contributed to liver fibrosis after acute or chronic liver injury (*6*,*7*). In cell-based therapies using adherent mesenchymal stem cells, the possibility of unfavorable behaviors such as differentiation into myofibroblasts should be taken into account, even if the cells are derived from adult tissue and have not been substantially manipulated. It may be a resolution to adhere adipose-derived adher-

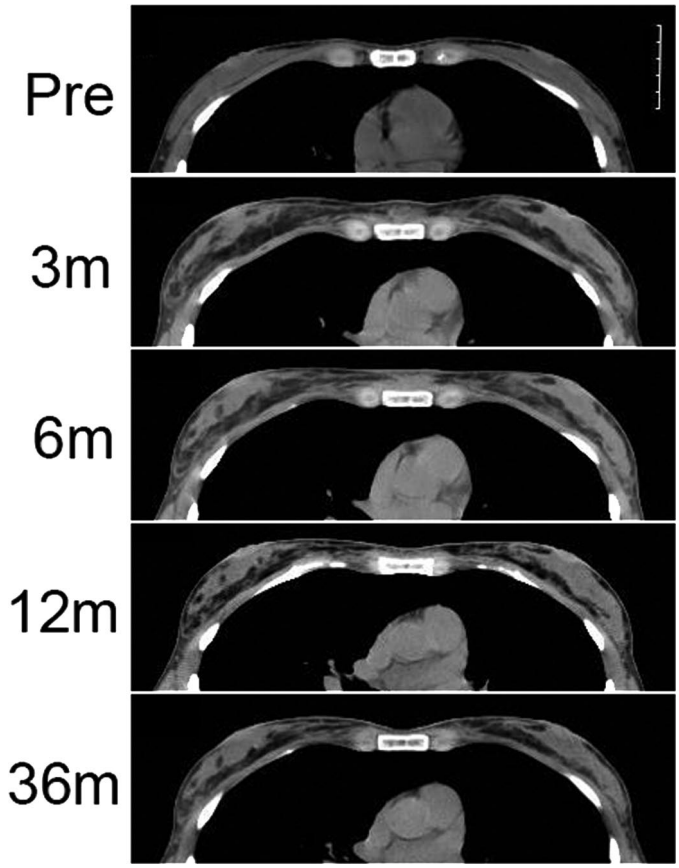

FIGURE 1. CT scan images taken before (Pre) and 3, 6, 12, and 36 months after treatment. Normal mammary glands and the thin fatty layers around them are visible before treatment. Substantial fibrosis had occurred, both diffusely in the transplanted fat surviving around the mammary glands and in the subcutaneous layer over the sternum, at 3 months. The fibrotic mass over the sternum was treated twice with local injections of triamcinolone acetonide at 6 and 8 months and dissipated, but diffuse fibrosis in the breasts remains at 36 months.

ent stem or progenitor cells to cells, tissue, extracellular matrix, or biological scaffold before administration to avoid their unexpected behaviors.

Kotaro Yoshimura
Noriyuki Aoi
Hirotaka Suga
Keita Inoue
Hitomi Eto
Department of Plastic Surgery
University of Tokyo School of Medicine
Tokyo, Japan

Katsujiro Sato
Cellport Clinic Yokohama
Yokohama Excellent III Building 2F
Kanagawa, Japan

Masakazu Kurita
Kiyonori Harii
Department of Plastic Surgery
Kyorin University School of Medicine
Tokyo, Japan

Toshitsugu Hirohi
Ritz Cosmetic Surgery Clinic Tokyo
Shinagawa-ku, Tokyo, Japan

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Address correspondence to: Kotaro Yoshimura, M.D., Department of Plastic Surgery, University of Tokyo School of Medicine, 7-3-1, Hongo, Bunkyo-Ku, Tokyo 113-8655, Japan.
E-mail: yoshimura-pla@h.u-tokyo.ac.jp
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Toward "No Age Limit" For Liver Transplant Donors

On November 2006 (more than a year ago), we transplanted a liver retrieved from a 94-year old donor who died for cerebral hemorrhage. Donor liver function test were normal. There was no history of cardiac arrest or hypotension. Donor operation was performed according to standard technique. Microscopic examination revealed minimal macrovesicular steatosis, diffuse hepatocellular ballooning, and no portal tract abnormalities. Recipient was 61-year old with a clinical history of hepatitis C virus cirrhosis with hepatocellular carcinoma.

Liver transplant was performed with a conventional technique without using veno-venous by pass. Cold ischemia and warm ischemia times have