

of the extraperitoneal space to obtain enough room for graft implantation or during closing the incision when one improper stitch can tear the peritoneum leading to a defect. Careful dissection should be performed in all cases, and if a peritoneal defect is found, it should be closed regardless of its size to avoid the occurrence of a PH.

All in all, PH is a relatively uncommon but potentially fatal complication after renal transplantation, and its non-specific symptoms may lead to misdiagnosis. Physician awareness, prompt diagnosis, and early surgical intervention are crucial. Additionally, meticulous surgical technique during transplantation may help avoid this complication.

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Treatment of Knee Osteoarthritis With Autologous Mesenchymal Stem Cells: Two-Year Follow-up Results

Osteoarthritis is the most prevalent joint disease and a frequent cause of joint pain, functional loss, and disability (1). Osteoarthritis often becomes chronic, and conventional treatments have demonstrated only modest clinical benefits, without lesion reversal (2). Cell-based therapies have shown encouraging results in both animal studies and a few human case reports. We have recently published the results of a pilot clinical trial designed to assess the feasibility and safety of osteoarthritis treatment with bone marrow–derived mesenchymal stromal cells (MSCs) in 12 patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of osteoarthritis (3). The patients were treated with autologous expanded bone marrow MSCs by intra-articular injection (40×10^6 cells), and clinical outcomes, including evaluations of pain, disability, and quality of life, were followed up for 1 year. Articular cartilage quality was assessed by quantitative magnetic resonance imaging (MRI) T2 mapping (3).

Feasibility and safety were confirmed, and strong indications of clinical efficacy were identified. Patients exhibited rapid and progressive improvement of algofunctional indexes that approached 65% to 78% by 1 year. This outcome compared favorably with the results of conventional treatments. In addition, MRI T2 relaxation measurements demonstrated

a significant improvement of cartilage quality, in 11 of 12 patients (3).

Now, we report the results of follow-up at 2 years from the intervention. No serious adverse effects appeared during the second year. Figure 1A–D summarizes the evolution of the clinical results. The pain improvement observed by the end of the first year was maintained with no significant modifications 1 year later, as exemplified for the Visual Analogue Scale (VAS) measurements during both daily and sport-associated activities (Fig. 1A). The therapeutic efficiency estimated from the pain relief–versus–initial pain score plot (4) was 0.71 (over a maximum of 1) for VAS (Fig. 1B). For Lequesne severity index, the efficiency was 0.66 (Fig. 1C). Regarding the Western Ontario and McMaster Universities Osteoarthritis Index, the estimated therapeutic efficiency varied between 0.44 and 0.78 for the different components of the test (Fig. 1D).

The cartilage quality evolution is shown in Figure 1E–F. The values of the Poor Cartilage Index (PCI; maximum value, 100; normal value, 5) (3) improved during the second year from 14.3 ± 1.8 (36% of maximum) to 13.0 ± 1.7 (45% of maximum) (Fig. 2A). This decrease of PCI was not statistically significant, but the overall improvement with regard to the baseline value (19.5 ± 2.3) was highly significant ($P < 0.001$). The PCI improvement–versus–initial PCI plot (4) is

shown in Figure 2(B). There was a significantly ($P < 0.01$, $r = 0.70$) positive correlation between both parameters, with a slope of 0.57. The fitted line cut the abscissa axis at PCI of 8%, a value not far from the theoretical one of 5% (3).

The results of the 2-year follow-up reaffirm the conclusions from the first-year results on the feasibility and safety of our MSC treatment. A recent meta-analysis gathering together 844 procedures with a mean follow-up of 21 months also concluded that the procedure is safe (5). We also find strong indications of clinical efficacy with improvements of the algofunctional indexes that reach 65% to 78% 1 year after the intervention and are maintained during the second year. The results of other clinical trials on treatment of osteoarthritis with expanded MSC declared in the data base clinicaltrials.gov have not been published yet, but the results of several series and case reports (6–8) were generally optimistic and consistent with our results.

The quantitative MRI results on cartilage quality improvement are especially encouraging. There was a significant improvement 1 year after the intervention (3), and we find now at the 2-year follow-up that the quality of cartilage has further improved. Although the difference with the 1-year value was not statistically significant, the profile of the improvement, affecting 11 of the 12 patients was very convincing (Fig. 2B).

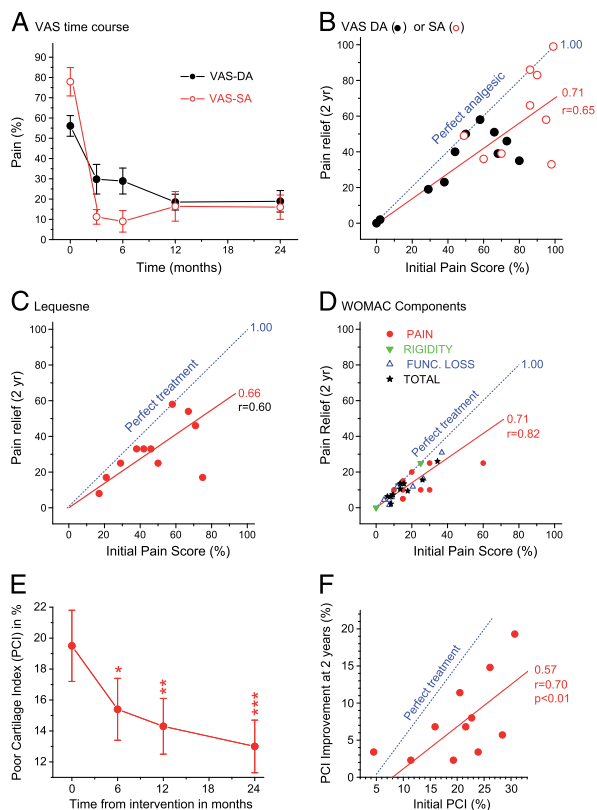


FIGURE 1. Pain and cartilage quality improvement resulting from MSC treatment. (A) Graph showing evolution of knee pain, as measured by VAS, over time. Mean \pm SE of the values of daily activity of 11 patients (VAS-DA, filled circles) or the values of sports activity of 7 patients (VAS-SA, open circles). All the values at 3, 6, 12, and 24 months were significantly smaller than the baseline value ($P < 0.001$ in all the cases; analysis of variance; Bonferroni test). (B–D) Correlation between improvement of knee pain 2 years after treatment with MSCs and initial pain score, as measured with different tests. The “perfect” treatment (dotted line with a slope of 1) is shown for comparison. The best-fitting lines are shown with values for the slope and linear regression coefficient (r) at the right. In case D, the four components of the Western Ontario and McMaster Universities Osteoarthritis Index test are shown with different signs (codes at top). The fitted line shown corresponds to the “total” component. (E and F) Cartilage quality was assessed by MRI T2 mapping and is quantified as the Poor Cartilage Index (PCI) (computed as the percentage of sample points with a T2 relaxation value > 50 milliseconds). The worse possible value for PCI is 100, and healthy cartilage should approach 5. (E) Graph showing the temporal evolution of PCI; mean \pm SE values of 12 patients treated with MSCs. Significance for differences with baseline value: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (analysis of variance; Bonferroni test for paired values). (F) Correlation between PCI improvement at 2 years and initial PCI for the 12 patients included in this study. The best-fitting line is shown with values for the slope and linear regression coefficient (r) at the right. The “perfect” treatment (dotted line with a slope of 1) is shown for comparison.

Overall, our results reaffirm that MSC may be a valid alternative for the treatment of knee osteoarthritis because it attains effective and durable pain relief and objective cartilage improvement. The intervention is simple, but cell preparation is expensive. Future research should confirm results in large series of patients and look for modifications of

cell production to make possible generalization of cell therapy.

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Postirradiation Cutaneous Angiosarcoma Mimicking a Cyst in a Heart Transplant Recipient

Angiosarcomas (AS) are rare malignancies developing from blood or lymphatic endothelial cells. They account for approximately 2% of skin sarcomas and present usually in elderly patients as red violaceous plaques or tumors developing over the scalp, trunk, or limbs. Their cause is unknown; in contrast to Kaposi sarcoma, they are not linked with human herpesvirus (HHV)-8 infection. Risk factors include radiation therapy, chronic lymphedema, toxins (e.g., vinyl chloride), and some cancer-prone syndromes (e.g., neurofibromatosis and mutated BRCA1 or BRCA2 syndromes) (1). Immunosuppression may favor AS development through decreased immunosurveillance and destruction of malignant cells (2). Some cases of AS have been reported in patients with acquired immunodeficiency syndrome, and 20 cases of AS have been reported in renal transplant recipients (RTRs). We present here the first case of AS with a misleading clinical appearance developing in a heart transplant recipient after radiotherapy for a preceding anal carcinoma.

A 73-year-old French man sought advice for a lesion in the pubis, which had appeared some weeks before consultation. The patient had a history of melanoma of the buttock (malignant transformation of a congenital naevus – Breslow thickness 18 mm, Clark level IV, Stage T2b N0 M0) excised 12 years ago. Two years later, he received a heart transplant because of cardiomyopathy. Initially, he received tacrolimus (2.5 mg/d), steroids (2.5 mg/d), and azathioprine (150 mg/d). Six years after receiving the graft, he developed moderate acute cellular rejection. During the fifth year after receiving the graft, he developed an ulcerated, vegetating, microscopically moderately differentiated epidermoid anal carcinoma measuring 4.5 cm; it infiltrated the smooth and (focally) the striated muscle layers and invaded one inguinal lymph node with extracapsular spread. The tumor was treated with surgery and

radiotherapy. The patient was progressively weaned off tacrolimus and switched to everolimus (4.25 mg/d; trough levels, 8.8 ng/mL).

Physical examination revealed an asymptomatic, pinkish white firm nodule of 2 cm on the pubis (Fig. 1A). The clinical appearance was consistent with an epidermoid cyst or an adnexal tumor, although the history of anal carcinoma arose suspicion for a cutaneous metastasis. Microscopic examination of a skin biopsy taken from the nodule showed a diffuse dermal infiltration with atypical, large, pleomorphic polygonal cells with large basophilic nuclei. The cells occasionally lined optically empty slits (Fig. 1B). Areas of necrosis and some hemorrhage were seen in the dermis. Immunohistochemically,

tumor cells expressed strongly the proliferation-associated antigen Ki-67 and the endothelial antigens thrombomodulin, CD31, podoplanin/D2-40 and ERG (Fig. 1C–E) but were negative for keratins (pan-keratin, K5, K6, K7, K19, K20), p63, HHV-8, S-100 protein, Melan-A/MART1, CD30, CD43, CD45, CD34, CDX-2, and von Willebrand factor. These findings were diagnostic of poorly differentiated AS. A positron emission tomography performed 6 weeks after the diagnosis showed metabolic hyperactivity at the site of the tumor and the anal border, scrotal edema and right necrotic lymph node enlargement, but no evidence of distant metastasis. Chemotherapy with paclitaxel (given once weekly for 8 weeks) had to be discontinued because

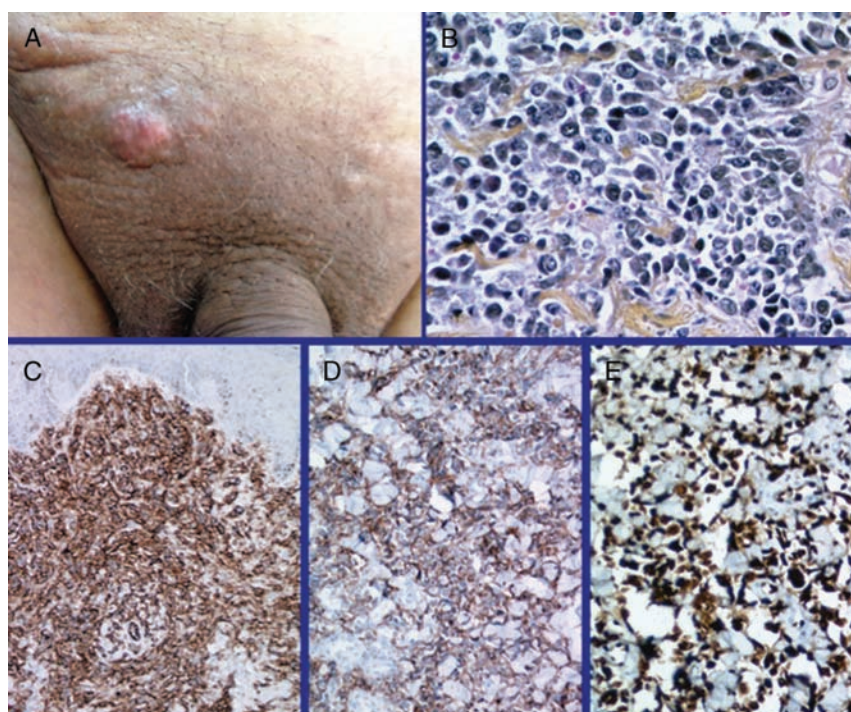


FIGURE 1. A, Clinical appearance of the lesion: a 2-cm firm, pinkish white nodule on the pubis. B, Microscopic examination of a skin biopsy showing monomorphous, polygonal tumor cells with large basophilic nuclei, occasionally lining slit-like spaces (hematoxylin-eosin stain). Tumor cells express the vascular markers CD31 (C), D2-40/podoplanin (D), and ERG (E) (streptavidin-biotin-immunoperoxidase revealed with diaminobenzidine counterstaining with Meyer hematoxylin).