Autologous Mesenchymal Stem Cells Foster Revascularization of Ischemic Limbs in Systemic Sclerosis

TO THE EDITOR: The case report by Guiducci and colleagues (1) presents the therapeutic potential of autologous mesenchymal stem cells (MSCs) for patients with systemic sclerosis. The authors suggest that factors expressed from MSCs and the ability of MSCs to differentiate into endothelial and vascular smooth muscle cells account for the observed revascularization. The potential immunosuppressive effect of MSCs also may have contributed to the positive outcome.

It is well-documented that MSCs suppress inflammation through soluble factors and direct physical contact, affecting the innate as well as the adaptive immune system (2). Researchers report that patients with systemic sclerosis may retain this feature (3). Investigators know less about whether MSCs have intact function in terms of endothelial differentiation and promoting angiogenesis in systemic sclerosis. Because reports show defects of endothelial progenitors in patients with systemic sclerosis (4), it would be interesting to test the immunomodulatory function, as well as the endothelial-differentiating capacity, of the MSCs derived from this patient to obtain further insight into the mechanism of treatment with MSCs.

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Potential Conflicts of Interest: None disclosed.

References

IN RESPONSE: We agree with Dr. Yun’s observation that an immunosuppressive effect of expanded autologous MSCs may have contributed to the positive outcome in our patient with systemic sclerosis. Previous data suggest that subpopulations within MSCs may have an immunomodulating role in the host, without provoking immunologic responses from alloreactive T cells or other effector cells (1). Moreover, MSCs may also have a “regenerative” role, thus contributing to the repair of damaged vessels.

Recent studies (2) have shown that MSCs derived from the bone marrow of patients with systemic sclerosis exhibit the same phenotypic, proliferative, and differentiation potential and immunosuppressive properties as healthy MSCs. These findings make MSCs derived from bone marrow attractive in a therapeutic autologous setting. Experimental data (3) have also provided evidence that MSCs can produce various cytokines and chemokines involved in the regulation of the migratory properties, differentiation, and proliferation of cells.

In addition, MSCs may play a crucial role in the modulation of angiogenesis (3). The proangiogenic effect of MSCs was demonstrated in a murine model of hind limb ischemia (3). Furthermore, cultured MSCs produce and release high amounts of proangiogenic and antiapoptotic factors that inhibit apoptosis of endothelial cells that are cultured under hypoxic conditions and promote the formation of capillary-like structures in vitro.

Mesenchymal stem cells derived from bone marrow have been shown to support the formation of vessel-like structures in vitro through paracrine effects on endothelial cells in a medium devoid of vascular endothelial growth factor and basic fibroblast growth factor (3). In this system, MSCs provided soluble proangiogenic factors and extracellular matrix components that serve as a substrate for sprouting endothelial cells. Furthermore, the potential transition of MSCs to pericytes on newly formed vessels may serve to stabilize the neovascular structure.

As Dr. Yun correctly pointed out, previous studies (4) showed that MSCs from patients with systemic sclerosis did not differentiate into endothelial cells in vitro. Therefore, autologous systemic sclerosis MSCs might not be able to incorporate into damaged or newly formed vessels but rather could participate in vascular repair through paracrine effects by releasing a wide array of proangiogenic factors. Recent experimental data from our group (Guiducci S, Manetti M, Romano E, Ibba-Manneschi L, Matteucci-Cerinich M. Bone marrow–derived mesenchymal stem cells from early diffuse systemic sclerosis exhibit a paracrine machinery and stimulate angiogenesis in vitro. In preparation.) demonstrate that MSCs from patients with systemic sclerosis, including the patient described in our case report, produce and release large amounts of proangiogenic factors, such as vascular endothelial growth factor and stromal cell–derived factor-1, and potentiate dermal endothelial cell angiogenesis in vitro.

The possible involvement of MSCs in wound repair and the topical delivery of MSCs remain unexplored areas and future challenges in systemic sclerosis (5). As for the use of autologous MSCs for treating systemic sclerosis, further functional studies are needed to investigate the participation of MSCs in mechanisms of this disease, such as the angiogenic, fibrotic, and immune processes.

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References

**Observation**

**Actinomyces-Induced Inflammatory Pseudotumor of the Lymph Node Mimicking Scrofula**

**Background:** Inflammatory pseudotumor is a rare condition characterized by an aberrant immunologic response that manifests as tumor-like masses in various anatomical locations. Two previous case reports described *Actinomyces* as a trigger for abdominal inflammatory pseudotumor (1, 2).

**Objective:** To report what we believe is the first case of *Actinomyces*-induced inflammatory pseudotumor with primary lymph node involvement.

**Case Report:** A 34-year-old woman with a history of systemic lupus erythematosus presented to an outpatient clinic with painful swelling on the left side of the neck, a 7-day history of temperatures up to 39.4 °C, and a 3-day history of cough. Her systemic lupus erythematosus was controlled with methotrexate and hydrochloroquine. She received antibiotic therapy for presumed lymphadenitis.

She returned to the clinic 3 days later with no improvement in her symptoms. At that time, physical examination was notable for a firm, tender left submandibular mass without erythema or fluctuance and decreased breath sounds at the right lung base. Chest computed tomography showed a consolidation in the right lower lobe (Figure, A). Further history revealed that the patient had a positive purified protein derivative test several years earlier but did not begin antituberculous therapy. She was admitted to the hospital for suspected reactivation mycobacterial tuberculosis causing pneumonia and lymphadenopathy (scrofula).

Fine-needle aspiration biopsy of the lymph node showed reactive features. Transbronchial biopsy of the lung lesion showed chronic inflammation without granulomas. Neither biopsy culture yielded fungal or bacterial growth, including acid-fast bacilli. Results of tests for legionella, histoplasma, and blastomycosis antigen were negative.

Pathologic examination of an excisional biopsy specimen of the lymph node revealed preserved architecture with focal paracortical hyperplasia and inconspicuous lymphoid follicles. In addition, there was expansion of the capsule, trabeculae, and hilum by sclerosed mesenchymal tissue that contained scattered spindly and polygonal cells; small blood vessels; and inflammatory cells, including plasma cells, histiocytes, and lymphocytes, without evidence of organisms, granulomas, or necrosis (Figure, B and C). Immunohistochemistry revealed no phenotypical abnormalities. These findings were consistent with inflammatory pseudotumor of the lymph node (3).

The patient began methylprednisolone therapy, and her neck swelling decreased substantially. After 12 days, the culture from her biopsy specimen yielded *Actinomyces* species. She started a 12-month course of amoxicillin therapy. Methylprednisolone therapy was switched to prednisone therapy, and she was discharged receiving a regimen of prednisone with a plan to taper the dosage over 3 months.
months. Three months later, she was asymptomatic and repeated computed tomography showed complete resolution of her lung lesion.

Discussion: Inflammatory pseudotumor is a histologic diagnosis characterized by a proliferation of myofibroblasts with an infiltrate of inflammatory cells, such as lymphocytes, histiocytes, and plasma cells (3, 4). Affected patients commonly present with constitutional symptoms and masses in the lungs, spleen, liver, gastrointestinal tract, bladder, orbit, or lymph nodes (4). Inflammatory pseudotumor encompasses a wide spectrum of conditions, including inflammatory myofibroblastic tumor, plasma cell granuloma, or xanthofibroma (5).

Inflammatory pseudotumor may be a primary immunologic lesion in some cases and a reaction to an infection in others. In rare cases, this condition has been linked to neoplastic processes. Inflammatory pseudotumor of the lymph node is a reactive process centered on the connective tissue framework of the lymph node (3). The disease course is usually benign, and this condition is managed with excision or steroids plus treatment of any underlying cause.

In this patient, actinomycosis was the trigger. Actinomyces are gram-positive, filamentous, commensal bacteria normally found in the human gastrointestinal tract. Actinomyces infection generally occurs in immunosuppressed patients or when the integrity of the gastrointestinal mucosal layer is compromised.

Conclusion: Inflammatory pseudotumor represents a diagnostic conundrum, because its clinical features can be consistent with cancer, infectious disease, or primary immunologic disease. No radiologic or laboratory tests are specific for this condition. This case highlights the diagnostic importance of biopsy and cultures in patients who present with fever and unexplained lymphadenopathy.

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Potential Conflicts of Interest: None disclosed.

Figure. Odds of fatal and nonfatal ischemic heart disease with metformin monotherapy and metformin plus rosiglitazone.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Met Events, n</th>
<th>Patients, n</th>
<th>Met + Rosi Events, n</th>
<th>Patients, n</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>Stewart et al, 2006 (3)</td>
<td>0 272</td>
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<td>4 254</td>
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<td>Jones et al, 2003 (5)</td>
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<td>1 162</td>
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<td>Fonseca et al, 2000 (6)</td>
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<td>1 232</td>
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<tr>
<td>Weissman et al, 2005 (7)</td>
<td>3 384</td>
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<td>5 382</td>
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<td>0.60 (0.14 to 2.52)</td>
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<td>Gómez-Perez et al, 2002 (2)</td>
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<td>2 77</td>
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<td>1.13 (0.10 to 12.92)</td>
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<td>Rosenstock et al, 2006 (8)</td>
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<td>2.01 (0.18 to 22.43)</td>
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<td>Overall</td>
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<td>0.46 (0.18 to 1.19)</td>
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Pooled Odds Ratio (95% CI) for Fatal and Nonfatal Ischemic Heart Disease

Error bars represent 95% CIs. Met = metformin; Rosi = rosiglitazone.

References

Correction

Correction: Comparative Effectiveness and Safety of Medications for Type 2 Diabetes

TO THE EDITOR: We would like to correct a pooled odds ratio published in our systematic review on the comparative effectiveness and safety of medications for type 2 diabetes mellitus (1). The article states, “Seven short-duration RCTs [randomized, controlled trials] reported a lower risk for fatal and nonfatal ischemic heart disease with metformin than with the combination of metformin and rosiglitazone (pooled odds ratio, 0.43 [95% CI, 0.17 to 1.10]), but event rates were low and the confidence bounds were wide and overlapped 1.0.” However, we identified an error in data abstraction from Gómez-Perez and colleagues’ study (2) and recalculated the pooled odds ratio for this comparison.

We used the denominator of 76 patients in the metformin and rosiglitazone group; the correct denominator is 77 patients. This has
Letters

been corrected in the online version of Appendix Figure 3 (available at www.annals.org).

Furthermore, the correct total pooled odds ratio and 95% CI are 0.46 (0.18 to 1.19), not 0.43 (0.17 to 1.10). This has been corrected in the revised Figure shown here.

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References

Manuscript Processing and Turnaround

Annals sends about half of submitted manuscripts for peer review and publishes about 10% of submitted material. The 2010 processing and notification turnaround time for manuscripts that were rejected without external peer review was within 1 week for more than 95% of submitted manuscripts. The processing and notification turnaround time for manuscripts that were received and rejected after external peer review was within 4 weeks for 50% and within 8 weeks for 98%.