Acute Respiratory Failure in a Patient with IPF following Experimental Nebulized and Intravenous Stem Cell Therapy

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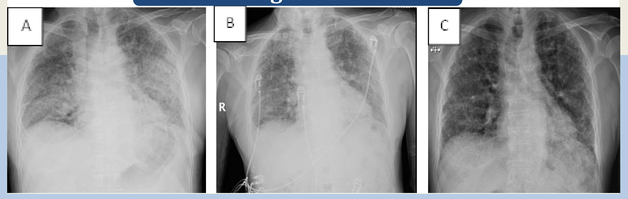
Introduction :

- Given the limited treatment options and poor prognosis of idiopathic pulmonary fibrosis (IPF), patients and their families are drawn to experimental and off-label treatments to help prolong life and improve symptoms. This may occur both in and out of the context of a formal clinical trial.
- Stem cell therapy is a newly emerging option that is available through a limited number of centers, some through experimental programs and some as unproven treatments (i.e. not approved by the FDA but not as part of a formal research study).
- Most published information regarding stem cell use in IPF is from pre-clinical studies. Due to the small number of published trials in patients with IPF, and the wide range of techniques used for the procedure, little is known about potential adverse effects.
- Several editorials and guidance have been recently published regarding the use of stem cells in patients with orphan diseases, such as IPF. These have focused on the appeal of stem cells to patients, but also on the concerns about what stem cells have been proven to offer and how patients understand stem cell "therapy."

Case Description:

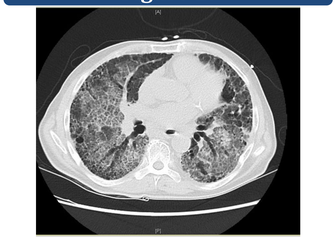
- A 72-year-old male diagnosed with IPF 4.5 years prior to presentation and maintained on home oxygen presented with progressively worsening shortness of breath and cough over 1 week. He denied fever, chills, sputum production and chest pain. He had no prior IPF exacerbations.
- The patient reported receiving intravenous and nebulized stem cell therapy through an experimental program 4 weeks prior to and again 2 weeks prior to the current admission. The procedures were completed as part of a patient-funded experimental program where stem cells were harvested from adipose tissue.
- On EMS arrival he was tachypneic and tachycardic with an oxygen saturation of 68% on 2L nasal cannula; 100% non-rebreather facemask improved saturation to 85%. On exam, he appeared malnourished and fatigued. Lungs had bilateral lower lobe rales, without wheeze or evidence of consolidation.
- Labs were significant for WBC=17.6 (4.8-10.8 K/uL), mild anemia, glucose=299 (74-106 mg/dL), BUN=32 (7-17 mg/dL), creatinine=1.2 (0.5-1.0 mg/dL), anion gap=21 (5-16 mEq/L), and lactic acid=6.5 (0-2.10 mmol/L). Rapid influenza, urine *Legionella* antigen, and urine *Streptococcal pneumonia* antigen were negative.
- Chest radiograph revealed diffuse infiltrates in both lungs, much increased from last study 12 months earlier (Figure 1A). The patient was started on methylprednisolone 40mg q8h, vancomycin, piperacillin/tazobactam and levofloxacin. High resolution CT scan showed extensive ground glass attenuation in a "crazy paving" pattern in a perihilar distribution superimposed on extensive interstitial lung disease (Figure 2). The apices were spared.

Figure 1:



- Lactate rapidly improved and normalized within 5 hours. He was maintained on BIPAP and demonstrated significant improvement in oxygenation within 12 hours. By day 2 the patient reported feeling less dyspneic and his chest X-ray demonstrated improvement in the bilateral infiltrates (see Figure 1B).

Figure 2:



- He remained on BIPAP for 3 days. Cultures were unrevealing and antibiotics were narrowed. Intravenous corticosteroids were continued for 5 days at which time oral prednisone was started. By day 5 oxygen saturation had improved to 96% on 2L via nasal cannula at rest.
- The patient was discharged on 40mg prednisone and supplemental oxygen at 2L NC. Prednisone was tapered down over several weeks with close follow-up. Chest X-ray 10 days after discharge revealed complete resolution of the alveolar infiltrates (Figure 1C).

Discussion:

- When appropriately selected, screened, and implanted, stem cells may have the ability to repair and regenerate damaged tissues in the body. One theory of IPF pathogenesis is that epithelial injury, abnormal reepithelialization, deposition of fibroblasts and microfibroblasts, and scarring of the lung parenchyma contribute to the disease. Hypothetically, stem cell treatment could contribute to cell repair and regeneration [1,2].
- There has been a paucity of studies published in patients with IPF who have received stem cell therapy and few trials registered in clinicaltrials.gov.
- In the small number of IPF patients whom have been reported on, there have been no serious adverse events identified. One patient in the Serrano-Mollar study developed a transitory alveolar infiltrate and hypoxemia after cell instillation that responded rapidly to steroids [3]. Chambers et al. reported only mild adverse events, including a transient decrease in arterial oxygen saturation [4]. Recent results of the AETHER study revealed 2 deaths during the study period, neither reported as related to the intervention [5].
- Given our patient's rapid improvement and possible link to stem cell inhalation or infusion, one could speculate that pathologically he had an organizing pneumonia, a hypersensitivity reaction or an eosinophilic pneumonia (though peripheral eosinophils were normal).
- The above case raises concerns over the safety of stem cell therapy in IPF. Patients seeking stem cell therapy should only do so in the context of a reputable clinical research program. Clinicians must be diligent in explaining the unproven nature of stem cell therapy and the potential unknown side effects of this newly emerging option.

References:

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3. Serrano-Mollar A et al. Chest 2016;150:533-543.
4. Chambers DC et al. Respirology. 2014;19:1013-1018.
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