Bilateral Retinal Detachments After Intravitreal Injection of Adipose-Derived ‘Stem Cells’ in a Patient With Exudative Macular Degeneration

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ABSTRACT: A 77-year-old woman with exudative macular degeneration underwent bilateral intravitreal injections of “stem cells” at a clinic in Georgia. One month and 3 months after injection, she developed retinal detachments in the left and right eyes, respectively. Increased awareness within the medical community of such poor outcomes is critical so that clinics offering untested practices that have been shown to be potentially harmful to patients can be identified and brought under U.S. Food and Drug Administration oversight.


INTRODUCTION

Enthusiasm for stem cell treatment has given rise to numerous clinics in the United States offering unproven “stem cell” therapies without the oversight of the U.S. Food and Drug Administration (FDA). Though current FDA-regulated clinical trials are ongoing to evaluate the use of stem cell technology, unproven and unregulated “stem cell” therapies are already being offered to patients in hundreds of clinics in the United States. In June 2016, the American Academy of Ophthalmology published a clinical statement warning that unproven “stem cell” therapies “require further scientific evaluation to assure their safety and effectiveness to the public in well-conducted clinical trials under the aegis of the FDA.” Here, we describe a case of delayed retinal detachment with poor visual acuity and anatomical outcomes following bilateral intravitreal injection of autologous adipose tissue-derived “stem cell” therapy in a clinic in Georgia performed without FDA oversight.

CASE REPORT

A 77-year-old woman with a history of exudative age-related macular degeneration (AMD) and advanced primary open-angle glaucoma in both eyes underwent bilateral intravitreal injections of autologous adipose tissue-derived “stem cells.” Although the injected product is marketed as “stem cells,” the exact composition of the injections remains unknown, which is why the term “stem cells” appears in quotes throughout this report. Documentation confirmed that adipose tissue-derived stromal vascular fraction (SVF) was prepared for the intravitreal injection.

The patient had a history of exudative AMD for the past 10 years and had been receiving anti-vascular endothelial growth factor (VEGF) injections as needed for the last 2 years at the Florida Retina Institute. Her last recorded best-corrected visual acuity was 20/400 in the right eye and 20/200 in the left eye. Baseline optical coherence tomography (OCT) images are shown in Figures A and B. The patient opted to travel to Georgia, where she was told she would be participating in a “stem cell” study. The patient did not recall being informed of adverse risks associated with the injections, but was told there was a possibility the treatment may not result in visual gain. The patient was charged $8,900, underwent periumbilical liposuction, and received sequential bilateral intravitreal injections of “stem cells” 1 day apart, starting with the right eye. “Stem cell” material remaining after each ocular administration was then delivered intravenously. Four days
following the “stem cell” injection, she received an intravitreal injection of aflibercept (Eylea; Regeneron, Tarrytown, NY) in the right eye only. She was advised to return in 1 month to repeat the aflibercept injections.

Three weeks after “stem cell” injections, the patient returned for a follow-up visit at Florida Retina Institute with interval onset vitreous hemorrhage and cellular material collecting in the inferior vitreous of both eyes. Her visual acuity was 20/400 and 20/200 in the right and left eyes, respectively. The retina in each eye was found to be attached and a decision was made to observe at that time (Figures C and D). Two weeks later, the patient presented emerg-

Figure. A 77-year-old woman with a history of bilateral exudative macular degeneration received intravitreal adipose-derived “stem cell” injections in both eyes. Her baseline optical coherence tomography (OCT) images are shown 4 months prior to the injections in the right (A) and left (B) eyes. Three weeks after “stem cell” injections, the normal retinal contour was blunted by epiretinal membrane (ERM) formation in the right (C) and left (D) eyes. Vitreous hemorrhage and debris were noted bilaterally. Five weeks after “stem cell” injections, the ERM in the right eye progressed, resulting in progressive irregularities in the retinal contour (E). The left eye developed a tractional retinal detachment (F). By 7 months after the “stem cell” injections, the patient had undergone a retinal detachment repair in the right eye at an outside institution. Fundus photographs show recurrent rhegmatogenous/tractional retinal detachments with proliferative vitreoretinopathy in the right (G) and left (H) eyes. The view in the left eye is limited by a brunescent cataract. OCT imaging showed detachment of the right macula with a thin, hyperreflective overlying membrane (I). OCT imaging of the left eye showed thinned and atrophic retina with a thin, hyperreflective overlying membrane (J). The initial vision was 20/200 in the right eye and 20/400 in the left eye. Visual acuity 7 months after the “stem cell” injections was hand motions in the right eye and light perception in the left eye.
gently to the Florida Retina Institute with a superior visual field defect in her left eye. Her visual acuity measured counting fingers at 2 feet in the left eye (Figures E and F). Intraocular pressure (IOP) was 10 mm Hg. Slit-lamp examination was significant for a dense nuclear sclerotic cataract with no evidence of zonular weakness. Dilated funduscopic exam showed a tractional retinal detachment from 4 o’clock to 9 o’clock sparing the macula. No retinal breaks were identified. She underwent pars plana vitrectomy (PPV), membrane peel, endolaser, and silicone oil tamponade. Extensive tractional membranes were noted intraoperatively.

The retina remained attached in the left eye at the 1-week postoperative visit. However, at postoperative week 3, the patient had developed proliferative vitreoretinopathy and a recurrent combined rhegmatogenous/tractional detachment involving the macula of the left eye. The patient did not consent to repair of the recurrent detachment. Instead, she sought a second opinion from an outside ophthalmologist, where she was found to have developed a retinal detachment now in the right eye, 3 months after the “stem cell” injections. While at the outside institution, she underwent combined PPV and lensectomy for the retinal detachment and cataract in the right eye. The recurrent detachment in the left eye was not repaired.

Seven months after the intravitreal “stem cell” injections, the patient presented to Bascom Palmer Eye Institute for a third opinion. The patient’s visual acuity was hand motions in the right eye and light perception in the left eye. The patient’s chief complaint was loss of ability to ambulate independently and perform activities of daily living since her visual decline. Her IOPs were 10 mm Hg and 12 mm Hg in her right and left eyes, respectively. Slit-lamp examination showed aphakia in the right eye and a dense nuclear sclerotic cataract in the left eye. Fundus exam in the right eye demonstrated a complex tractional/rhegmatogenous retinal detachment with fibrotic bands in the posterior pole under silicone oil (Figure G). Fundus exam in the left eye was limited by cataract but was significant for a complex tractional/rhegmatogenous detachment with prominent fibrotic bands under silicone oil (Figure H). OCT showed macular detachment in the right eye (Figure I) and atrophic retina in the left eye (Figure J). Fluorescein angiography did not show signs of vasculitis or retinal vascular leakage. The patient was scheduled for surgical repair of the recurrent detachment in the right eye.

**DISCUSSION**

In a phase 1/2 clinical trial, Schwartz et al. demonstrated that subretinal transplantation of human embryonic stem cell-derived retinal pigment epithelial cells was safe and led to improvement in vision and vision-related quality of life measures at 12 months in patients with Stargardt disease and late nonexudative AMD. Although this report was promising, there is no FDA-approved stem cell therapy for retinal disease at present. However, multiple “stem cell” clinics currently offer treatments using untested techniques without FDA oversight. These clinics claim that the application of minimally manipulated cells for homologous use does not expose patients to significant risk and does not require strict regulatory oversight. The FDA has clarified that these therapies do indeed require FDA oversight.

Kuriyan et al. describe a case series of six eyes in three patients treated at a “stem cell” clinic in Florida resulting in profound vision loss. The starting vision in the better-seeing eye ranged from 20/30 to 20/50 and the final vision in the better-seeing eye ranged from 20/200 to no light perception. All but one injected eye developed a combined tractional/rhegmatogenous retinal detachment, which occurred in a delayed manner at an average of 18 days after the “stem cell” injection (range: 3 days to 38 days). The authors speculate that the mechanism for the delayed tractional detachment may be secondary to the “stem cells” themselves rather than the injection technique. One postulated mechanism was that the “stem cells” may settle on the retinal surface, improperly differentiate into myofibroblast-like cells, and produce contractile membranes similar to proliferative vitreoretinopathy. The patient in this case report similarly developed preretinal membranes followed by bilateral complex tractional retinal detachments in a delayed manner, 1 month and 3 months after “stem cell” injections in the left and right eyes respectively.

In both the current case and the cases detailed by Kuriyan et al., SVF was the intended “stem cell” preparation for injection. SVF may contain a mixture of preadipocytes, mesenchymal stem cells, endothelial progenitor cell, T-cells, B-cells, and mast cells as well as adipose tissue macrophages. All three patients described by Kuriyan et al. showed evidence of zonular weakness, including one patient with bilateral anterior displacement of the crystalline lens presumably resulting in highly elevated IOPs. In the present case, no evidence of zonular laxity was noted.

The prevalence of “stem cell” clinics is rising in the United States and internationally. A recent study reported 187 unique websites that offered interventions at 215 clinics in the United States. Another study found web-based direct-to-consumer advertis-
ing for stem-cell therapies from 351 businesses at 570 clinics. The growing prevalence of such clinics and their direct-to-consumer advertising is a concerning trend that raises ethical questions about offering therapies to patients without FDA oversight that may lead to severe vision loss. This report of a complication from a clinic in Georgia highlights the fact that the untested intraocular use of “stem cells” is not an isolated event and spans beyond the “stem cell” clinic in Florida where the three cases reported by Kuriyan et al. received treatment. Promoting increased awareness and providing patient education about proper evidence-based treatments in ophthalmologic practice will be important in preventing similar outcomes in the future. Increased awareness within the medical community is critical so that these clinics offering untested practices that have been shown to be potentially harmful to patients can be identified and brought under FDA oversight.

REFERENCES