Ischemic cardiomyopathy: Pathological Findings In A Case Of Stem Cell Implantation
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Citation

Abstract
The term “regenerative medicine” is a multidisciplinary field involving molecular and cell biologist, embryologist, pathologist, clinicians, bioengineers, and not to exclude ethicists. Early clinical studies, so far have indicate that, a stem cell implantation is feasible and has beneficial effect on infarcted heart. When compared to death of donor hearts for transplantation, complications associated with immunosuppression, long-term failure of transplanted organs with high morbidity and mortality rates associated with myocardial infarction, stem cells scores over organ transplant. Most of the trials to date assessed cardiac function at 4-6 months after treatment and long-term outcome have not yet been described. Here in we present histopathological findings in explanted heart in a 50-year-old male patient who had received stem cell therapy for chronic ischemic heart disease.

INTRODUCTION
Stem cell therapy is emerging as a potential therapy for infarcted heart. There is growing interest in clinical cardiology treating patients with myocardial infarction or cardiac failure with stem cells. Cardiac experiments, mainly with adult homologous stem cells, have proved that this therapy is safe and may improve myocardial vascularization and pump function.1

Stem cells are multipotent, undifferentiated cells capable of multiplication and differentiation. Four categories of stem cells have been examined for their ability to promote cardiac repair: bone marrow derived/circulating progenitor cells (BMPCs) and their subpopulation, skeletal myoblasts (SM), embryonic stem cells (ESCs) and resident cardiac stem (or cardiomyocyte progenitor) cells (CMPCs).2 Skeletal muscle cells and BMPCs are being used in clinical trials mainly because these cell types are potentially autologous. ESCs are at present the major heterologous source of cells being considered and ethically the most sensitive as their derivation requires the destruction of early human embryos.

Different techniques and routes of administering stem cells have been advocated. Although intramyocardial injection process is simple and can be performed by direct inspection of the potential target zones during cardiac surgery, it is associated with intraoperative and postoperative risks.3 Intracoronary injection has advantage because it can deliver the maximum concentration of cells to the site of infarct and peri-infarct tissue during the first passage. However, in successive days intravenous administration of stem cells will be an attractive and practical mode of delivery. There exists always a risk of micro vascular obliteration and of poor therapeutic efficiency if the stem cells are to cross the coronary wall and migrate extravascularly- especially when targeting a territory supplied by occluded coronary arteries.4 While experimental studies and early phase clinical trials tend to support that stem cell therapy enhances cardiac repair by improving myocardial vascularization and pump function. Present consensus is that stem cell have therapeutic benefit, but this is not based on the ability of these cells to Tran differentiate into cardiac myocytes. There are still several key issues still needs to be addressed like: the optimal type of donor cells in relation to the clinical profile, the mechanism by which cell engraftment improves cardiac function, development of less invasive cell delivery techniques and relevance to non-ischemic heart failure.2

CASE REPORT
He was a 50-year-old male, diabetic since 18 years old, hypertensive, and a known case of coronary artery disease. This patient had under gone coronary artery bypass graft (CABG) for triple vessel disease, with 4 grafts in 2005 in our hospital. Later, he was admitted with repeated signs of ischemia. He was offered a choice of stem cell therapy in 2006. He subsequently under went stem cell therapy in 2006. Autologous stem cells were harvested from bone marrow.
Stem cell injection was done through left coronary artery, right coronary artery, left internal mammary artery, saphaneous vein graft to diagonal-1 and saphaneous vein graft to obtuse marginal (5ml in each vessel injected slowly over 10 minutes each) and total of 25 ml was delivered to recipient. He was readmitted in 2008 with severe biventricular dysfunction and refractory heart failure.

We received an explanted heart weighting 286 grams. Grossly the grafts were near patent and at places could not be traced till myocardial entrance. The anterior wall along left anterior descending artery was thinned out (thickness-0.5cm) and undergone remodeling. The left ventricle cavity was dilated. Coronary artery showed recanalization of the lumen with intimal fibro cellular proliferation on hisopathological examination. Mild focal endocardial fibrosis was noted. Large areas of replacement fibrosis noted within the myocardium with attenuated subendomyocardial fibers(Fig.1a) & lipomatous metaplasia (Fig.1b). Section from anterior wall of left ventricle showed dense scared tissue. There was increase in capillary density (Fig.1c). At foci occasional clusters of immature myofibers were noted (Fig.1d). Over all features were consistent with ischemic cardiomyopathy with areas of lipomatous metaplasia.

**DISCUSSION**

Stem cell transplantation in acute myocardial infarction is still in its infancy. The consensus is that stem cell transplantation is feasible and may improve with beneficial effect on ventricular remodeling after myocardial infarction.\(^3\) The genetic and cellular mechanisms that initiate trans differentiation of stem cells are poorly understood. Several studies have shown that unknown paracrine mechanisms have been proposed as underlying functional improvement.
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by altering extra cellular matrix deposition and heart remodeling. While others have supported the theory of enhanced blood vessel formation and subsequent preservation of left ventricular function by increased recovery of hibernating myocardium, Neovascularization in turn may inhibit apoptosis of cardiomyocytes. Pagani and colleagues, have shown evidence of skeletal myoblast viability in scarred myocardium and differentiated into mature myofibers. It is now clear that BMPCs do not transdifferentiate into cardiomyocytes. The functional improvement in post-Myocardial infarction patients treated with stem cell therapy is probably due to subpopulation of endothelial precursor cells, enhancing angiogenesis and the local blood supply in ischemic tissue. Mesenchymal stem cells, present in BMPCs cord blood and adipose tissue; have also been described as possibly having cardiomyogenic potential. Over all their efficiency of cardiomyogenic conversion is low.

It is difficult to assess the fate of transplanted stem cells unless they are radioactively labeled with a safe and commercially available tracer substance. No technology is yet available for labeling the implanted cells and tracking their destiny in clinical setting. Noninvasive in vivo imaging techniques are needed in upcoming clinical trials to monitor and detail donor cell delivery, myocardial differentiation, integration into damaged myocardium, and contribution to cardiac function. The optimal numbers of stem cells to be transplanted have not been determined. It is still a gray zone to decide ideal strategy of delivery as well as time of delivery. Although transplanting stem cells between 7 and 14 days after myocardial infarction seems reasonable, our findings support the hypothesis that stem cells alter extracellular matrix deposition and heart remodeling through unknown paracrine mechanism. The interstitial connective tissue is greatly thickened and stiffened because of abundant collagen deposition around mummified myofibrocytes. The local cardiac skeleton and architecture have also undergone some degree of remodeling, which may involve substantial, irreversible volume expansion. Although there is increased capillary density, it will be difficult to differentiate angiogenesis Vs angiomyohyperplasia. Some are of opinion that, collateral development is not angiogenesis but angiomyohyperplasia, that is, hyperplasia of all wall components of preexisting vessels, which lead to increased diameter and length and to the remodeling of the normal wall structure in relation to enhanced flow or to endothelial growth factors or both.

We hope that the apparent lack of immediate commercial or industrial interest will not discourage the scientific community from adopting a disciplined strategy in pursuing this field. Current literatures fail to highlight the effectiveness of stem-cell transplantation alone; this is because the clinical studies have been done in conjunction with percutaneous or surgical revascularization. Most likely, recently infarcted myocardial territory has environment that expresses signals conductive to stem cell differentiation into myeloid cells or myofibrocytes. Larger double-blinded, controlled studies with clear therapeutic end points are imperative to clarify the role of stem cell transplantation for myocardial regeneration. If confirmed, the stem cell injection should be accompanied by aggressive, artificial signal enhancement designed to promote the development of myofibers or arteriogenesis.

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