THE LONG TERM EFFECT OF STEM CELL TRANSPLANTATION IN MICE MODEL OF ACUTE KIDNEY INJURY

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INTRODUCTION:
Stem cell research has received a great amount of attention in the last decade. Today, mesenchymal stem cells (MSCs) therapy is recognized as a potentially useful innovative therapeutic strategy in various degenerative and immuno/inflammatory diseases. Despite many beneficial effects of MSCs, concern about potential long-term side effects of MSCs therapies, particularly tumorigenicity, still exists.
In the light of above mentioned concerns the aim of this presentation is to briefly describe our observations found 3 months after intravenous infusion of human MSCs.

METHODS:
The efficacy of human MSCs transplantation in a lethal mouse model of cisplatin toxicity was tested. To avoid acute cellular graft rejection polyclonal antithymocyte globuline (ATG), a pharmacologic agent with marked and sustained suppressive effect on peripheral T lymphocytes population, was used prior to MSCs transplantation. Although study was designed to evaluate the short-term effect of MSCs therapy, two survived and clinically completely recovered mice were monitored for long-term effect of cisplatin toxicity and MSCs therapy: one treated with saline (control mouse) and another treated with MSCs (MSCs mouse). Both were preconditioned with ATG.

CASE REPORTS:

Control mouse: three months after MSCs therapy, sudden clinical deterioration was found associated with significant decrease of body weight. Autopsy revealed no signs of chronic kidney injury. Instead, completely atrophic thymus and enlarged spleen, liver and heart were found, adhesion of the loops of small intestine on the diaphragma (Fig 2A). The histological examination revealed penetrating ulcus in the jejunum. In spleen pronounced lymphatic proliferation and decreased number of erytrocytes in red pulpa was found. Lung tissue showed focal emphysema. In kidney lympho-, plasmo- and histiocytic infiltrates were disseminated. Focal tubular degeneration with pigment inclusions besides individual lymphocytes were noticed. Histological analysis of the heart revealed thrombus in the small brunch of right coronary artery (Fig 1C). Liver sinusoids were dilated due to blood stasis. Histological results together with blood results (marked trombocitosis and anemia) (Table 1) indicated that mouse had sepsis and associated disseminated intravascular coagulation.

MSC mouse: was vivacious, showing no signs of illness or body weight loss, but was euthanized at the same day as control mouse to compare and evaluate potential changes. Surprisingly, at autopsy thymus and spleen was of normal size and shape (Fig 2B). Although no other macroscopically visible lesion was observed histology revealed that mouse had moderate chronic jejunitis. In the mucosa atrophy of crypt epithelium and reduced number of moderately differentiated villi enterocytes was seen, lamina propria was infiltrated with mononuclear cells (Fig 1D). In addition, subpleural tumor 0.5mm in diameter was found (Fig 1A). Tumor cells were quite uniform with small round nuclei, rare mitosis and eosinophilic cytoplasm suggesting neuroendocrine origin. Tumor showed expansive type of growth. In lungs there were rare disseminated lymphohistiocytic infiltrates. Likewise, in the kidneys rare small lymphohistiocytic infiltrates were found, which were located periglomerularly and perivascularly (Fig 1B).

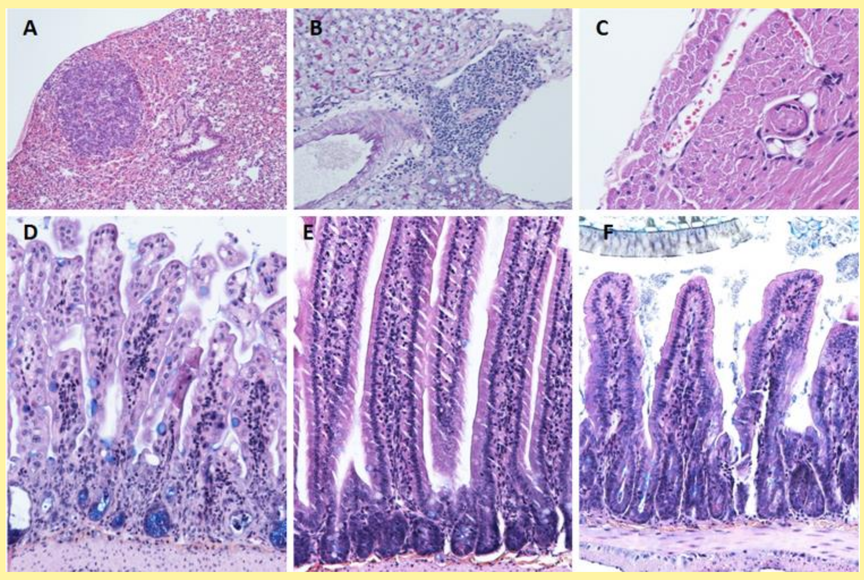

Figure 1: A) MSCs mouse; Balb/cOlaHsd male. Subpleuraly, homogenous solid tumor (diameter 0.5 mm) with rare mitosis and uniform nuclei, sharply demarcated from the surrounding tissue. Tumor is composed of cells of neuroendocrine type (HE, magnification 100x). B) Inflammatory cells (lymphocytes, plasma cells, hystiocytes) surrounding the arteriola and vein in the kidney of MSC mouse (PAS, magnification 200). C) Thrombus in the small artery of the right ventricle wall of control mouse (HE, magnification 400x). D) Moderate chronic jejunitis in MSC mouse – note atrophy of crypts and loss of architecture of villi (Kreyberg, magnification 400x) E) Jejunum in the healthy untreated mouse (Kreyberg, magnification 400x). F) Jejunum of the control mouse. Restitution of the mucosa is seen, however, the height of villi is decreased compared to healthy mice (Kreyberg, magnification 400x)

Table 1: Body weight, relative weight of organs and blood parameters.

Parameter	Control mouse	MSCs mouse	Healthy mouse
WBC (10^3/mm^3)	8,1	10,9	10,1
RBC (10^6/mm^3)	7,46	10,35	9,46
PLT (10^3/mm^3)	1303	773	789
Body weight (g)	23,7	31,4	31,6
RW of spleen	0,877	0,42	0,35
RW of liver	6,9	5,0	4,7
RW of kidney	1,5	1,36	1,82
RW of lungs	1,14	1,14	1,25
RW of heart	0,96	0,67	0,59

Abbreviations: WBC-white blood cells; RBC-red blood cells; PLT-platelets; RW-relative weight (weight of organ divided by body weight *100).

Table 1: Body weight, relative weight of organs and blood parameters.

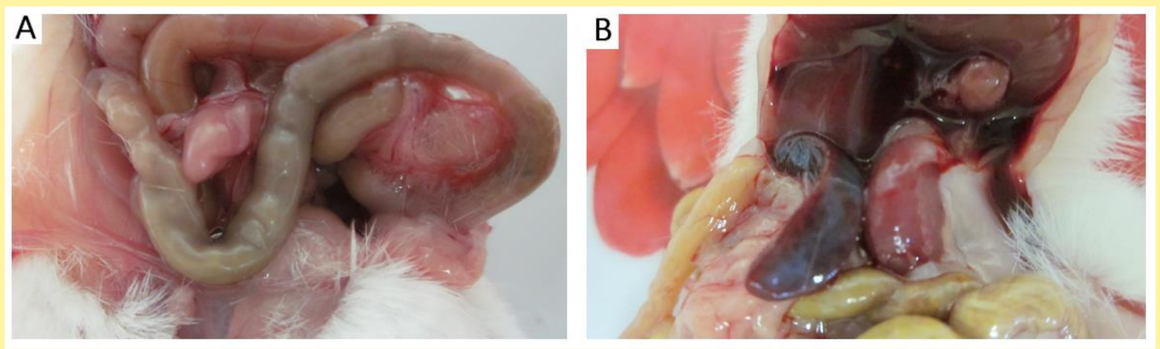

Figure 2: A) Adhesion of the loops of small intestine in control mouse. B) Thymus and spleen of normal size and shape in MSC mouse.

CONCLUSIONS: this cases demonstrate that studying long-term human MSCs therapeutic effect in immuno-competent mouse is challenging and may raise additional questions, including the neccessity to use immunosupression to overcome immune rejection and reevaluation of possible tumorigenicity on the long term.

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