

## **LETTER TO THE EDITOR**

**The possible involvement of granulocyte-colony stimulating factor in IgA nephropathy which developed in a donor after undergoing allogeneic peripheral blood stem cell transplantation**

Y Funakoshi<sup>1</sup>, A Nazneen<sup>2</sup>, Y Nakashima<sup>1,2</sup>, K Nakashima<sup>1</sup>, M Okada<sup>1</sup>, T Taguchi<sup>2</sup>, and H Moriuchi<sup>1</sup>.

<sup>1</sup>Department of Pediatrics, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, Japan.

<sup>2</sup>Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Running title: Involvement of G-CSF in IgA nephropathy in a PBSCT donor

IgA nephropathy (IgAN) is the most common form of glomerulonephritis and a principal cause of end-stage renal disease (ESRD) throughout the world.<sup>1</sup> Selectins are cell-to-cell adhesion molecules involved in the leukocyte-endothelial cell interaction leading to leukocytic infiltration into tissue.<sup>2</sup> Leukocytic infiltration into the glomerulus and renal interstitium appears to be critical for the pathogenesis of IgAN.

Granulocyte-colony stimulating factor (G-CSF) is widely used to induce neutrophil production after myelosuppressive treatment and to mobilize bone marrow hematopoietic progenitors which are provided for hematopoietic stem cell transplantation (HSCT) recipients. Although G-CSF is normally safely administered, it has been associated with rare but serious toxicities including splenic rupture, allergic reactions, flares of underlying autoimmune disorders and vascular complications,<sup>3,4</sup> as previously reviewed by Tigue *et al.* in this journal<sup>5</sup>, as well as hematological malignancies<sup>6</sup>.

G-CSF induces E-selectin expression on endothelial cells<sup>7</sup> and E-selectin ligand (CD44) expression on mobilized, circulating leukocytes.<sup>8</sup> Therefore, enhanced leukocyte-endothelial cell interactions due to the upregulation of both E-selectin and CD44 may play a crucial role in the pathobiology of G-CSF-associated vascular complications. This report describes a previously healthy 7-year-old male who

developed IgAN after the administration of G-CSF.

A 7-year-old boy was hospitalized to serve as a donor for his sister with juvenile myelomonocytic leukemia and who was scheduled to undergo peripheral blood SCT. He had no significant past medical history. He had undergone regular health checkups at school, including the latest urinalysis 3 months before hospitalization, and all findings had been normal. There was no renal disorder among either his family or relatives. He was given 300  $\mu\text{g}$  (12.5  $\mu\text{g}/\text{kg}$ ) of filgrastim (GRAN®; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) on days 1 to 3 once daily, and 375  $\mu\text{g}$  (15.6  $\mu\text{g}/\text{kg}$ ) twice on day 4 subcutaneously. On day 5, he was given the final dose (375  $\mu\text{g}$ ) of filgrastim and thereafter underwent leukapheresis without any adverse reactions. He was discharged shortly after completion of the procedure.

Thirteen days after the first dose of filgrastim, he presented with general fatigue. A physical examination showed no abnormality. His blood pressure was normal and he had no fever. The hematological examination was normal. The blood urea nitrogen was 13.8 mg/dl, serum creatinine was 40.7  $\mu\text{mol}/\text{L}$ , and creatinine clearance was 51 ml/min. Serological tests for antinuclear antibody were negative. The levels of serum complement factors C3 and C4 were normal. The concentrations (normal ranges)

of the serum IgG, IgA and IgM were 776 (670-1,560), 134 (48-276), and 146 (85-337) mg/dl, respectively. The urinalysis revealed hematuria (1+) and proteinuria (3+). He underwent a kidney biopsy 33 days after the first dose of filgrastim, because of the persistent hematuria and proteinuria. Histological studies of the biopsied specimen revealed prominent IgA deposition on the mesangium with mesangial and endocapillary proliferation, which was compatible with the acute phase of IgAN. He was treated with a cocktail therapy consisting of prednisolone, azathioprine, warfarin, and dipyridamole on day 75 after the first dose of filgrastim because his urinary findings remained abnormal. He responded to the treatment quickly, and his urinalysis was normalized by day 99. His urinalysis remained normal until the latest visit on day 462 after the first dose of filgrastim.

Indirect immunofluorescence staining was performed using monoclonal antibodies P2H3 and DF1485 against E-selectin and CD44, respectively (Santa Cruz Biotechnology, Inc., Santa Cruz, California, U.S.A). The expression of E-selectin in the glomerulus was evident in this patient (**Figure 1A**), but not in any other patients with IgAN untreated with filgrastim (**Figure 1B**) or a normal control (data not shown). Furthermore, CD44 expression was also demonstrated in the glomerulus of the patient, but not in the normal control (data not shown).

G-CSF has a number of biological functions, thus providing several clinical applications. Notably, it is administered to many healthy individuals who have served as donors for HSCT; therefore, the safety issues regarding its administration are crucial. It is very important to report severe toxicities developing in G-CSF derived PBSC donors, especially in the case of children<sup>6</sup>. The reported adverse effects include bone pain, headache or general fatigue following G-CSF administration in approximately 30% of all cases.<sup>9</sup> Furthermore, although rare, vasculitic complications, such as coronary artery disease and capillary leak syndrome, and hematological malignancies can also sometimes result in a serious outcome.<sup>3-6</sup>

IgAN, initially considered to be benign, leads to ESRD within 20 years in approximately 40% of patients.<sup>1</sup> This report suggests that G-CSF administration might be linked to IgAN in a previously healthy donor, based on the chronological sequence and the recent findings that G-CSF induces the expression of E-selectin<sup>7</sup> and its ligand<sup>8</sup> which are the key factors involved in the pathogenesis of IgAN. It should be also noted that the donor was given a relatively high dose of G-CSF (31.2 µg/kg/day on day 4), because of the critical clinical condition of the recipient. This suggests that the donor in the current case may have been genetically susceptible to IgAN and thus the administration of high dose of G-CSF may have induced the donor to subsequently

develop IgAN. Although IgAN has never previously been considered to be an adverse effect of G-CSF, and it is not possible to prove this hypothesis experimentally, it is nevertheless important to note that G-CSF administration may cause IgAN, a principal cause of ESRD worldwide, in susceptible individuals.

It is important to note that selectin gene polymorphisms have been suspected to play a role in the development and/or progression of IgAN<sup>9</sup>. The establishment of a method(s) to carefully screen and identify individuals genetically susceptible to IgAN and other vascular events may help avoid this rare but serious complication of G-CSF in such donors. Furthermore, genetic susceptibility may account for the increased risk of myelodysplastic syndrome among breast cancer patients receiving G-CSF<sup>10</sup> or other G-CSF-related toxicities. Accumulation and analyses of cases are required.

Finally, while G-CSF should not be assumed to be risk-free, its benefits still outweigh the risk. Extensive investigation on its safety and toxicity in pediatric population is essential.

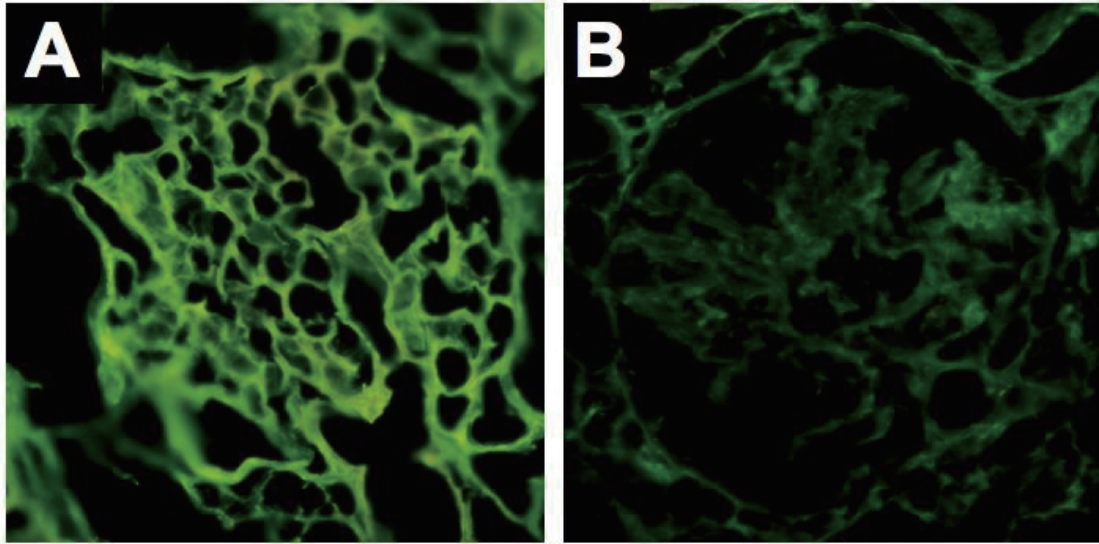
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**Figure legends**



**Figure 1.** E-selectin expression in the patient's renal section specimens.

(A) E-selectin expression is widely distributed in the glomerulus of the patient.

(B) E-selectin expression is not obvious in another IgAN patient.