Severe autoimmune hyperthyroidism after donation of rhG-CSF-primed allogeneic peripheral blood progenitor cells

The administration of recombinant human granulocyte-colony stimulating factor (rhG-CSF) to healthy related or unrelated donors has become a standard procedure for mobilization and collection of allogeneic peripheral blood progenitor cells (PBPC). We report a patient, who developed severe autoimmune hyperthyroidism with secondary congestive heart failure after an unrelated PBPC donation.

A 53-year-old obese man (body weight 125 kg, height 187 cm) presented to the emergency unit with dyspnea and tachyarrhythmia. A few days before, he had undergone a leukapheresis of allogeneic PBPC for an unrelated recipient. The harvest had been preceded by treatment with glycosylated rhG-CSF (Lenograstim, Chugai Pharmaceutical Inc., Tokyo, Japan) which was administered subcutaneously for five consecutive days at a dose of 7.5 µg/kg/day (total 394 µg/day Lenograstim). A sufficient yield of 5.5x10^10 CD34-positive cells (corresponding to 8.5x10^10/kg of the recipient’s body weight) could be harvested by a single large-volume, continuous-flow apheresis (Cobe Spectra 7.0, Gambro BCT Inc.) on day 5.

Two weeks after PBPC harvest, the patient had to be hospitalized. He was pale and short of breath at slight exertion (NYHA stage III). In chest x-ray, there was pulmonary congestion. The ECG registered continuous tachyarrhythmia (heart rate up to 180/min) with atrial fibrillation, and cardioangiography showed a dilated and hypokinetic left ventricle (enddiastolic diameter, 69 mm; endysystolic diameter, 58 mm; fractional shortening, 16 %). A moderate reduced cardiac contractility was already diagnosed ten months before, when the patient had undergone a cardiological evaluation because of arterial hypertension and ventricular extrasystoles.

The laboratory findings revealed a hyperthyroidism with suppressed thyroid stimulating hormone (TSH), elevated peripheral thyroid hormones (free triiodothyronine, FT3; free thyroxine, FT4) as well as antibodies to thyroid and cardiac dysfunction persisted and the patient received metoprolol, digoxin, enalapril, diuretics and tachyarrhythmia (heart rate up to 180/min) with atrial fibrillation, and cardioangiography showed a dilated and hypokinetic left ventricle (enddiastolic diameter, 69 mm; endysystolic diameter, 58 mm; fractional shortening, 16 %). A moderate reduced cardiac contractility was already diagnosed ten months before, when the patient had undergone a cardiological evaluation because of arterial hypertension and ventricular extrasystoles.

The laboratory findings revealed a hyperthyroidism with suppressed thyroid stimulating hormone (TSH), elevated peripheral thyroid hormones (free triiodothyronine, FT3; free thyroxine, FT4) as well as antibodies to thyroglobulin, thyroid peroxidase and TSH-receptors (Figure 1). There was a homogenous tracer-uptake to the gland (Cobe Spectra 7.0, Gambro BCT Inc.) on day 5. There was a homogenous tracer-uptake to the gland (Cobe Spectra 7.0, Gambro BCT Inc.) on day 5.

Additional evidences suggest a role of G-CSF in pathogenesis of Graves’ hyperthyroidism. First, endogenous G-CSF serum levels were observed to be significantly increased in patients with Graves’ disease, as compared to healthy controls. Second, in patients with toxic nodular goiter, serum concentrations of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) correlate with titres of TSH receptor antibodies and thyroid peroxidase antibo-
ies. Recently, an increase in circulating endothelial adhesion molecules during rhG-CSF mobilization was reported. A 4-fold- and 6-fold-increased concentration of sICAM-1 and sVCAM-1 was also found in our patient.

In addition, the individual pattern of human leukocyte antigen (HLA) expression could be a very important feature. A known phenomenon is, that patients with Graves’ disease often express HLA-B8 and HLA-DR3. Interestingly, both alleles were present in our patient.

Finally, the induction of autoimmunological hyperthyroidism by rhG-CSF in this patient can not be proven. Nevertheless, the short interval to cytokine treatment and the immunomodulatory properties of the agent remain suspicious features. Doctors should be aware of this potential problem and carefully observe donors of allogeneic PBPC for symptoms of autoimmune disorders.

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References