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.

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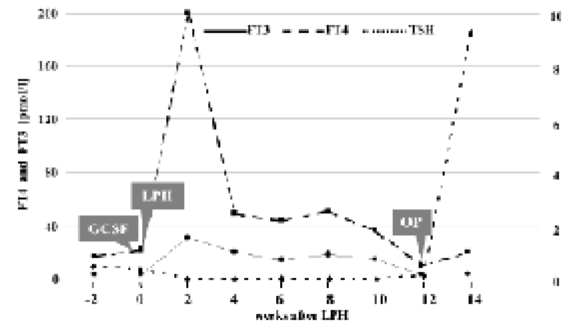
A 53-year-old obese man (body weight 125 kg, height 187 cm) presented to the emergency unit with dyspnea and tachyarrhythmia. A few days before, he had undergone a leukapheresis of allogeneic PBPC for an unrelated recipient. The harvest had been preceded by treatment with glycosylated rhG-CSF (Lenograstim, Chugai Pharmaceutical Inc., Tokyo, Japan) which was administered subcutaneously for five consecutive days at a dose of 7.5 µg/kg/day (total 894 µg/day Lenograstim). A sufficient yield of 5.5×10^8 CD34-positive cells (corresponding to 8.5×10^6/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 cardiosonography showed a dilated and hypokinetic left ventricle (enddiastolic diameter, 69 mm; endsystolic 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 triiodthyronine, FT3; free thyroxine, FT4) as well as antibodies to thyreoglobuline, thyroid peroxidase and TSH-receptors (Figure 1). There was a homogenous tracer-uptake to the gland in thyroid scanning.

Thyreostatic treatment was initiated with oral carbimazol, but had to be changed to intravenous thiamazol due to a worsening of symptoms. Furthermore, the patient received metoprolol, digoxin, enalapril, diuretics and heparin. After 10 weeks of conservative treatment, thyroid and cardiac dysfunction persisted and the patient developed a demyelinating polyneuropathy with paresthesias and muscle weakness. Surgical thyroidectomy was performed. After surgery, TSH and thyroid hormones normalized and levothyroxin substitution was started. Heart failure and the patient´s condition improved, tachyarrhythmia converted to sinus rhythm, but left-ventricular dilatation and hypokinesia remained unchanged. Symptoms of polyneuropathy could be reduced by intravenous immunglobulin infusions.

Although the current evidence for a role of rhG-CSF in thyroid dysfunction and autoimmunity is poor, the short interval between PBPC donation and manifestation of hyperthyreosis is suggestive for a causative association. To date, only one patient was reported, who received subcutaneous rhG-CSF 10 µg/kg/day after chemotherapy



	Normal Range	Pre-examination	Leuk-apheresis	Hospitalization	Discharge	Follow up week 26
TSH	0.25-4.22 mU/l	0.54	0.41	0.00	12.01	13.83
Free T4	10-25 pmol/l	17.2	21.9	205.0	10.7	16.7
Free T3	2.4-7.1 pmol/l	3.39	5.73	30.8	3.20	3.69
Antibodies to:						
- thyroid peroxidase	<60 U/ml	213	15	581	n.d.	771
thyroglobuline	<60 U/ml	<20	<20	49.2	n.d.	<20
- TSH-receptors	0.3-1.0	<0.3	0.9	2.5	n.d.	0.0

Figure 1. **Thyroid function and thyroid antibodies before rhG-CSF treatment, at leukapheresis and during symptomatic hyperthyreosis (n.d. – not done).**

for breast cancer, and developed reversible hypothyreoidism with microsomal and thyroglobulin antibodies.[1] Two more cases of thyroid dysfunction have been described among 25 cancer patients who were treated with intravenous granulocyte-macrophage colony stimulating factor (GM-CSF).[2] Thyroid function and antibodies was examined systematically in two small studies with 20 and 33 patients, respectively, who were given subcutaneous rhG-CSF to accelerate myeloid recovery after chemotherapy.[3,4] The results indicated, that rhG-CSF administration does not induce thyroid dysfunction or autoimmunity in these patients, even in those with preexisting thyroid antibodies. To our knowledge there are no reports about thyroid dysfunction in the setting of allogeneic PBPC mobilization.

In our patient, euthyroidism was documented at preexamination 4 weeks prior to stem cell mobilization and on the day of leukapheresis. Antibodies to thyroid peroxidase were already detectable in retrospectively analysed cryopreserved samples from these time points (Figure 1), whereas TSH receptor stimulating immunglobulins appeared only after PBPC harvest accompanied by symptoms of hyperthyroidism. If there was a contribution of G-CSF to the pathogenesis of this complication, the mechanism of action remains hypothetically. Nevertheless, in addition to hematopoietic properties, the cytokine is also known to exert pleotropic effects on different types of cellular and humoral immune effectors. RhG-CSF treatment for PBPC mobilization is accompanied by a significant expansion of all lymphocyte subsets. Monocytes and T- and B-lymphocytes express G-CSF receptors and therefore may be direct targets of G-CSF action.[5,6] In blood dendritic cells, G-CSF stimulation leads to altered expression of adhesion molecules and chemokine receptors.[7]

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.[8] 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 antibod-

ies.[9] Recently, an increase in circulating endothelial adhesion molecules during rhG-CSF mobilization was reported.[10] 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 immunmodulatory 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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