A Case of Growth Failure Following Allogeneic Bone Marrow Transplantation Successfully Treated by Replacement with Recombinant Growth Hormone


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Abstract We report a case of 13-year-old boy with growth failure following allogeneic bone marrow transplantation which was performed at the age of 6 for acute lymphoblastic leukemia. The patient had been preconditioned with total body irradiation. Growth failure was observed in height and body weight, and growth hormone (GH) deficiency was confirmed by the endocrinological studies. The patient was successfully treated by replacement therapy with recombinant GH without recurrence of leukemia, the duration of administration being short and only for 1 year and 6 months.

Key Words: Bone marrow transplantation, Growth failure, Growth hormone, Leukemia

Introduction

Recently, the survival rates for children with malignant hematological disorders have been improved by bone marrow transplantation (BMT). However, late complications after BMT, such as growth failure1-8, gonadal failure1-3, hypothyroidism1-3,6 and cataracts3 have been reported. Among these complications, growth failure is common and observed in 40-60% of the patients1-9. It has been suggested that total body irradiation (TBI) for pretransplant conditioning in BMT and previous cranial irradiation for the prophylaxis of central nervous system involvement, influence the induction of growth failure1-9.

Growth hormone (GH) replacement therapy is widely performed with primary growth failure due to GH deficiency. However, there are reports that administration of GH has increased the incidence of leukemia7-12, and it is more frequent in Japan than in Europe or North America8,9,12. Hence, careful monitoring for leukemia is needed when GH is administered to children who received BMT for leukemia and develop late complications involving growth failure. We report a case of growth failure following BMT for acute lymphoblastic leukemia (ALL), which was successfully treated by GH replacement therapy without relapse of leukemia.

Case report

A 4-year-old boy was diagnosed with ALL (L1, T-cell type) and received remission induction chemotherapy with multi-antileukemic agents. Complete remission was obtained. Subsequently, he was treated
Fig. 1. Gross-sectional growth chart for boys (0-18 years). BMT and GH represents the time of bone marrow transplantation and the time of start of growth hormone replacement therapy. Solid lines are the curves for patient.

Fig. 2. Insulin loading test. The figure represents low response of growth hormone (GH) secretion. BS: blood sugar

Fig. 3. Nocturnal GH secretion. The figure represents low response of GH secretion.

Fig. 4. Growth hormone releasing hormone (GRH) loading test. The figure represents the partial response of GH secretion.
Table 1. The endocrinological study on admission

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>4.4 μU/ml</td>
<td>(0.34–3.5)</td>
</tr>
<tr>
<td>T3</td>
<td>1.0 ng/dl</td>
<td>(0.8–1.8)</td>
</tr>
<tr>
<td>T4</td>
<td>5.8 μg/dl</td>
<td>(4.6–12.6)</td>
</tr>
<tr>
<td>TBS</td>
<td>24.0 μg/ml</td>
<td>(14–28)</td>
</tr>
<tr>
<td>GH</td>
<td>1.0 ng/ml</td>
<td>(&lt;0.42)</td>
</tr>
<tr>
<td>Somatomedin-C</td>
<td>0.14 U/ml</td>
<td>(0.73–3.16)</td>
</tr>
<tr>
<td>LH</td>
<td>5.7 mIU/ml</td>
<td>(0.50–6.5)</td>
</tr>
<tr>
<td>FSH</td>
<td>15.0 mIU/ml</td>
<td>(1.23–10.5)</td>
</tr>
<tr>
<td>ACTH</td>
<td>36 pg/ml</td>
<td>(30–60)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>13 ng/ml</td>
<td>(1.5–9.7)</td>
</tr>
<tr>
<td>ADH</td>
<td>0.6 pg/ml</td>
<td>(0.3–3.5)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>9.2 μg/dl</td>
<td>(4.0–18.3)</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>79 pg/ml</td>
<td>(35.7–240)</td>
</tr>
</tbody>
</table>

by intrathecal administration of methotrexate (MTX), cytosine arabinoside (Ara-C) and hydrocortisone, cranial irradiation (24 Gy) and administration of high dose MTX (1000 mg) for the prophylaxis of CNS involvement. However, two months later ALL relapsed and reinduction chemotherapy was performed and a second complete remission was obtained. There was an HLA-identical sister, and he received allogeneic BMT in May 1985 at the age of 6. The preconditioning regimen consisted of TBI (10 Gy, fractioned over 3 days), Ara-C and cyclophosphamide. Cyclosporine A was administered for prophylaxis of graft-versus-host disease (GVHD). The hematological recovery after BMT was prompt and the clinical course was uneventful without acute or chronic GVHD. However, growth failure in height and body weight was observed after BMT (Fig. 1). The patient was born at 39 weeks gestational age with normal delivery from normally built parents. At 12 years and 10 months of age, his bone age was 9 years and height was 128 cm (below -2SD) and body weight was 25.3 kg (below -2SD) (Fig. 1). Several kinds of loading tests were performed for endocrinological evaluation. Insulin loading test (Fig. 2) and clonidine loading test (data not shown) revealed

![Fig. 5. Lutenizing hormone releasing hormone (LH-RH) and thyrotropin releasing hormone (TRH) loading tests. The figure represents high basal level of follicle stimulating hormone (FSH) followed by normal response to LH-RH (●—●), normal response of lutenizing hormone (LH) to LH-RH (○——○), and normal response of thyroid stimulating hormone (TSH) to TRH (×—×).](image-url)
impairment of GH release, and the mean nocturnal GH concentration was low (Fig. 3). The loading test of growth hormone releasing hormone (GRH) revealed a response of GH release, but was not sufficient (Fig. 4). The plasma basal levels of various hormones are shown in Table 1. Insulin like growth factor-1 (IGF-1, somatomedin C) was low, but there was no liver dysfunction. Adrenocorticotropic hormone (ACTH), thyroxin stimulating hormone (TSH), prolactin and antidiuretic hormone (ADH) were normal. T3, T4 and thyroxine binding protein (TBG) were normal, and the response of TSH to thyrotropin releasing hormone (TRH) was also normal (Fig. 5). Cortisol and adrenaline were normal. Lutenizing hormone (LH) was normal and follicle stimulating hormone (FSH) was high, and the gonadotropin release to lutenizing hormone releasing hormone (LH-RH) was almost normal (Fig. 5). According to these results, the patient was diagnosed as growth failure due to impaired GH secretion. In December 1991, at the age of 13, GH replacement therapy was started at an initial dose of 4IU/week by subcutaneous injection after the informed consent from his parents was obtained. After 1 year and 6 months of GH treatment, his height increased to 147.3 cm and weight to 30.4 kg, and the recurrence of leukemia was not observed.

Discussion

There is evidence to suggest that cranial irradiation or TBI primarily damages the hypothalamus judging by the greater GH response to GRH than to insulin-induced hypoglycemia. Our case revealed impaired GH secretion and response to GRH was partially impaired. This result suggested the hypothalamus as well as the pituitary axis of GH secretion was damaged. Multiple endocrine abnormalities such as hypothyroidism, adrenal insufficiency and gonadal failure had been reported following BMT. Our patient had normal thyroid and adrenal gland function, but had higher level of FSH. This may represent hypergonadotrophic hypogonadism, which had been observed in the majority of children who were prepubertal at the time they received TBI. There is also a report that posttransplant glucocorticoid treatment for acute or chronic GVHD itself was responsible for the growth failure. The present case did not have serious acute or chronic GVHD, thus posttransplant use of glucocorticoid was not necessary.

The frequency of leukemia occurrence among GH users is estimated to be 1 per 6,000 receiving such treatment in Japan and the observed/expected ratio of leukemia occurrence was 10 times higher than in the general population, while the rates ranged between 1 per 12,000 and 35,000 patient in the United States and Europe, giving a ratio 2.5 times higher. The risk factors for leukemia occurrence were Fanconi anemia, radiation to brain tumor, chemotherapy, myelodysplastic syndrome and Bloom's syndrome. Patients without additional strong risk factors do not represent a definitely higher leukemia incidence worldwide except for Japan. In a recent report, there was no increase in leukemia in patients with idiopathic GH deficiency among 6284 recipients monitored by the National Hormone and Pituitary Program of the United States between 1963 and 1985. However, the association of leukemia and cranioopharyngioma was significant and may be related to the radiation therapy. However, cranial irradiation was not a risk factor according to another report. The mean time between the start of GH therapy and leukemia onset was 5.0 years (0.2-18.8). The duration and total dose of GH administration did not show dose-dependent relationship with leukemia occurrence.

Results of in vitro studies revealed that GH and IGF-1 increased the proliferation of blasts in acute myeloid and lymphoid leukemia, and also in leukemic erythroid (K562), myeloid (HL60) and lymphoid (Daudi) cell lines. GH hormone receptor consists of a structurally similar subfamily that includes receptors of erythropoietin and granulocyte colony-stimulating factor etc. More proliferative and unstable reaction of white blood cells to GH administration, with rapid increase in neutrophils was a risk factor for leukemia occurrence, but lymphocyte
response was variable. In addition, a causative relationship between the occurrence of secondary leukemia and prior chemotherapy and radiotherapy in conventional chemotherapy as well as in BMT remains to be elucidated. There remains a risk of recurrence due to minimal residual leukemia especially in the patients who received BMT for acute leukemia when using GH for growth failure. The supplemental administration of GH in leukemia patients in remission must be carefully monitored for early relapse. In the present case, the velocity of increase in height and body weight was accelerated after administration of GH, but recurrence of leukemia was not observed during administration of GH, although the duration of administration was short and only for 1 year and 6 months. The early relapse of leukemia was not observed in the present case, however, careful observation for more long term in needed.

Acknowledgement

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