Original Article

Abnormal Adipose Tissue Distribution with Unfavorable Metabolic Profile in Five Children Following Hematopoietic Stem Cell Transplantation: A New Etiology for Acquired Partial Lipodystrophy

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Abstract. We report five consecutive patients who underwent hematopoietic stem cell transplantation (HSCT) to treat leukemia or neuroblastoma early in their lives and later manifested abnormal patterns of adipose tissue distribution. Lipoatrophy was remarkable in the gluteal regions and extremities, whereas subcutaneous fat was preserved in the cheeks, neck, and abdomen. In addition, visceral fat deposition, fatty changes in the liver, and metabolic derangements such as insulin resistance and hypertriglyceridemia were evident. These features resemble Dunnigan-type familial partial lipodystrophy, which is a rare condition caused by LMNA gene mutation. These patients shared a common medical history involving HSCT, including conditioning with total body irradiation (TBI). They also received intensive chemotherapy because of multiple metastases (n = 3), relapse (n = 3), and repetitive HSCT (n = 3). We propose HSCT as a new etiology for acquired partial lipodystrophy and recommend that patients who undergo HSCT with TBI and intensive chemotherapy early in their lives must receive careful observation for the possible development of lipodystrophy and metabolic complications.

Key words: chemotherapy, dyslipidemia, hypertriglyceridemia, insulin resistance, total body irradiation

Introduction

Partial lipodystrophy refers to a pathological and unique fat distribution, characterized by lipoatrophy (loss of adipose tissue) and lipo hypertrophy (abnormal fat accumulation) (1, 2). Metabolic complications such as insulin resistance, diabetes, hypertriglyceridemia, and fatty changes in the liver are additional hallmarks of partial lipodystrophy (1–4).

Familial partial lipodystrophy (FPLD) arises from genetic mutations, including mutations in the LMNA (5–7), PPARγ (8–10), AKT2 (11) and CIDEC (12) genes. Specifically, FPLD caused by a LMNA mutation is referred to as Dunnigan-type FPLD, or FPLD2, and is characterized by lipoatrophy in the extremities and buttocks combined with fat accumulation in the face, neck
and intra-abdominal areas. Among the acquired forms of partial lipodystrophy, the most prevalent one is highly active antiretroviral therapy (HAART)-associated lipodystrophy syndrome found in HIV-infected individuals (13, 14). Acquired partial lipodystrophy can also develop following viral infection, autoimmune disease or membranous proliferative glomerulonephritis (1).

We treated 5 consecutive patients who had previously undergone hematopoietic stem cell transplantation (HSCT) to treat malignancies at a younger age. These patients, later in their lives, manifested aberrant fat distribution patterns similar to those occurring in patients with FPLD2, as well as severe metabolic abnormalities.

Case Series

All the study procedures, including the control subjects in body composition analysis, were reviewed and approved by the ethics committee of Kanagawa Children’s Medical Center. Patients 2, 3, 4, and 5 and the mother of patient 1 provided written informed consent for publication of their facial photographs.

Patient 1, female, acute myeloid leukemia (AML)

As a result of an evaluation of walking difficulties and repetitive, febrile episodes, a 1-yr-old girl was diagnosed with AML, classified as M4, with multiple extra-marrow involvements, including the central nervous system. Following successful induction chemotherapy, bone marrow transplantations (BMTs) from her mother were attempted twice, but were rejected. A third allogeneic BMT, with conditioning that included total body irradiation (TBI) of 10 Gy, was successful and resulted in long-term remission. However, the patient developed chemotherapy-related leukoencephalopathy, and suffered from intractable epilepsy. To suppress extensive, chronic, graft-versus-host disease (GVHD) (15), she had received steroid therapy for 3 yr (Table 1).

At 17 yr of age, the patient underwent her first endocrinological evaluation (Table 2) because she was short [130.3 cm, –5.3 SD for Japanese standards (16)] and prepubertal. Subcutaneous fat was rather abundant in her cheeks and neck, which resulted in a moon-face appearance (Fig. 1a). In addition, the patient exhibited remarkable abdominal distension, with an abdominal circumference of 69 cm at the navel level. However, both her extremities and buttocks showed marked reductions in subcutaneous fat tissue (Fig. 1b).

An oral glucose tolerance test (OGTT) showed a diabetic blood glucose pattern with tremendous hyperinsulinism (Fig. 2). Mildly elevated alanine aminotransferase (ALT) (56 IU/L) and γ glutamyl transpeptidase (γ GTP) (387 IU/L) levels were found, and fatty changes in the liver were suspected based on abdominal ultrasonography (US). Dyslipidemia was also evident, with fasting triglyceride (TG) levels of 675 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 39 mg/dL and low-density lipoprotein cholesterol (LDL-C) of 168 mg/dL (Table 3).

A magnetic resonance imaging scan revealed a small pituitary gland, and the patient was found to have GH deficiency, subclinical hypothyroidism (TSH, 5.45 µIU/L; free T4, 0.93 ng/dL), and primary ovarian insufficiency (FSH, 60.9 IU/L) (Tables 1 and 2).

Patient 2, female, AML

An 8-yr-old girl was diagnosed with AML (M2) through an evaluation for petechiae and epistaxis. Six mo after the first remission was achieved by chemotherapy, a marrow relapse was found. A BMT from a human leukocyte antigen (HLA)-identical donor was conducted, following conditioning that included TBI of 12 Gy. Chronic GVHD with pneumonitis, joint contractures and liver dysfunction required immunosuppressive treatment lasting more than a decade. She also suffered from right-sided femoral neck necrosis (with an onset at age 12), transient aplastic anemia following a parvovirus infection (at age 13) and multiple hepatic angiomas (at age 17).
<table>
<thead>
<tr>
<th>Pt (sex)</th>
<th>Primary disease (onset)</th>
<th>Treatment</th>
<th>Radiation (site)</th>
<th>Transplantation (conditioning#)</th>
<th>Chronic graft-versus-host disease classification and treatment@</th>
<th>Treatment-related complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F)</td>
<td>AML (1 yr)</td>
<td>VP-16, Ara-C, MIT, THP-ADR, ACR, VCR, MTX (it), HC (it)</td>
<td>ND</td>
<td>Failed 2 consecutive allogeneic BMTs (BSF, VP-16, L-PAM)</td>
<td>Extensive (skin, liver) CSa (for 1.5 yr), PSL (for 3 yr)</td>
<td>GH deficiency (untreated), hypothyroidism (treated from age 17 yr), leukoencephalopathy, epilepsy, primary hypogonadism (treated from age 17 yr)</td>
</tr>
<tr>
<td>2 (F)</td>
<td>AML (8 yr)</td>
<td>VP-16, Ara-C, MIT, IDR, MTX (it), HC (it)</td>
<td>ND</td>
<td>Unrelated BMT following marrow relapse (TBI 12 Gy, BSF, L-PAM)</td>
<td>Extensive (lung, joint, liver) PSL (for 12 yr), FK-506 (for 12 yr)</td>
<td>Femoral neck necrosis, aplastic anemia, hepatic angioma, hypothyroidism (treated from age 15 yr), primary hypogonadism (treated from age 19 yr)</td>
</tr>
<tr>
<td>3 (M)</td>
<td>ALL (0 yr)</td>
<td>VCR, THP-ADR, L-ASP, MTX, CPM, Ara-C, 6-MP, PSL, DEX</td>
<td>18 Gy (cranial)</td>
<td>2 consecutive allogeneic BMTs following marrow relapse [1) TBI 12 Gy, VP-16, Ara-C, CPM 2) BSF, VP-16, Ara-C, CPM]</td>
<td>Extensive (skin, joint) CSa (for 4 yr), AZa (for 9 yr), PSL (for 12 yr), MTX (for 1 yr)</td>
<td>GH treatment (from age 11 to 17 yr), chronic thyroiditis (no treatment)</td>
</tr>
<tr>
<td>4 (M)</td>
<td>NB (1 yr)</td>
<td>CPM, VP-16, THP-ADR, CDDP, CBDCA</td>
<td>23.4 Gy (cranial), 18 Gy (right orbit)</td>
<td>Scheduled PBSCT (TBI 12 Gy, CBDCA, VP-16, L-PAM)</td>
<td>None</td>
<td>Hypothyroidism (treated from age 4 yr), empty sella, GH deficiency (treated from age 14 to 20 yr), hypogonadism (treated from age 18 yr)</td>
</tr>
<tr>
<td>5 (F)</td>
<td>NB (1 yr)</td>
<td>CPM, VP-16, THP-ADR, CDDP, DTIC, IFM</td>
<td>19.8 Gy (epigastrium), 30 Gy (right iliac)</td>
<td>2 consecutive autologous BMTs [1) CBDCA, THP-ADR, L-PAM, 2) CBDCA, VP-16, THP-ADR, CPM], allogeneic BMT following regional and marrow relapse (TBI 12 Gy, TT, VP-16)</td>
<td>Extensive (liver, intestine) FK-506 (for 3 yr), PSL (for 3 yr)</td>
<td>GH deficiency (treated from age 11 to 17 yr), primary hypogonadism (treated from age 15 yr), high-frequency deafness, cataract</td>
</tr>
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</table>

F, female; M, male; ND, not done; it, intrathecal injection; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; rt, right. *Abbreviations for agents: VP-16, etoposide; Ara-C, cytarabine; MIT, mitoxantrone hydrochloride; THP-ADR, tetrahydropyranlyadriamycin; ACR, aclarubicin hydrochloride; VCR, vincristine sulfate; MTX, methotrexate; HC, hydrocortisone; IDR, idarubicin hydrochloride; L-ASP, L-asparaginase; CPM, cyclophosphamide; 6-MP, 6-mercaptopurine; PSL, prednisolone; DEX, dexamethasone; CDDP, cisplatin; CBDCA, carboplatin; DTIC, dacarbazine; IFM, ifosfamide. BSF, busulfan; L-PAM, melphalan; ATG, antithymocyte globulin; TT, Thio-TEPA; CSa, cyclosporin A; FK-506, tacrolimus; AZa, azathioprine.
When the patient was 15 yr old, abnormal fat distribution was ascertained by whole body computed tomography (CT) (Fig. 1c). An OGTT showed a normal blood glucose response but with hyperinsulinism (Fig. 2). Dyslipidemia and fatty changes in the liver were also noticed. An endocrinological evaluation revealed mild hypothyroidism (TSH, 9.28 µIU/mL; free T4, 0.89 ng/dL) with primary hypogonadism (FSH, 217.9 IU/L; E2, 5.6 pg/mL).
Patient 3, male, acute lymphoid leukemia (ALL)

This patient was diagnosed with unclassified ALL at 11 mo of age as a result of an evaluation of petechiae. His first remission was achieved by chemotherapy and 18 Gy cranial radiation. A year later, marrow relapse was found. Following chemotherapy, two consecutive allogeneic BMTs were conducted, with 12 Gy TBI conditioning being provided before the first round of BMT (Table 1).

Chronic GVHD, with major symptoms of joint contractures and scleroderma, was treated with immunosuppressants. In accordance with
his wishes, GH treatment was conducted for 6 yr beginning at age 11 despite normal GH secretion. Nevertheless, his final height was 142.4 cm (–4.9 SD).

Thinning of the extremities, due to subcutaneous fat loss, and a moon-face appearance were noticed when the patient was 13 yr old. A whole body CT scan taken at age 19 revealed fatty changes in the liver and an abnormal pattern of subcutaneous fat distribution (Fig. 1c). Dyslipidemia and hyperinsulinism were also evident.

### Table 2 Current status and information relevant to the etiology of lipodystrophy in the 5 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Current status</th>
<th>At diagnosis of lipodystrophy</th>
<th>Estimated onset of lipodystrophy* (yr)</th>
<th>LMNA mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yr)</td>
<td>BMI (kg/m²)</td>
<td>Typical fat distribution$^*$</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>17.7</td>
<td>+</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>12.2</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>16.5</td>
<td>+</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>18.3</td>
<td>+</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>14.1</td>
<td>+</td>
<td>17</td>
</tr>
</tbody>
</table>

+, present; BMI, body mass index; ND, not determined. $^*$Typical fat distribution denotes lipoatrophy in the gluteal region and extremities coupled with preserved, or even prominent, subcutaneous fat in the cheeks, neck and abdomen. *Onset of lipodystrophy as deduced from the emergence of an elevated triglyceride level. (For details, refer to the Methods section.) $^#$GH treatment was conducted from 11 to 17 yr of age despite normal GH secretion.

**Fig. 2.** Results of a 75-g oral glucose tolerance test in the 5 patients. Left panel, blood glucose (BG) response; right panel, insulin response. In the criteria developed by the Japanese Diabetes Society, the diabetic pattern is defined as the fasting blood glucose being higher than 126 mg/dL or the blood glucose level at 120 min being higher than 200 mg/dL. The normal pattern is defined as a fasting blood glucose less than 110 mg/dL and a blood glucose level of less than 140 mg/dL at 120 min.
Patient 4, male, neuroblastoma

A 1-yr-old boy developed exophthalmos and neuroblastoma, originating from the left adrenal, with multiple bone and marrow metastases (stage IV\textsubscript{A}). Following total resection of the primary lesion, complete remission was obtained by chemotherapy and radiation (whole skull, 23.4 Gy; right orbit, 18 Gy). Eight months after diagnosis, peripheral blood stem cell transplantation (PBSCT) was carried out, with conditioning that included 12 Gy TBI.

Since age 4, the patient has been receiving L-thyroxine because of primary hypothyroidism (TSH, 22.0 μIU/mL; free T4, 0.78 ng/dL). At age 14, an evaluation for growth failure revealed severe atrophy of the pituitary gland. At that time, abdominal US demonstrated fatty changes in his liver. After a diagnosis of complete GH deficiency, GH treatment was started. At age 18, testosterone administration was introduced due to primary hypogonadism (LH, 7.6 IU/L; FSH, 26.6 IU/L; testosterone, 51 ng/dL).

At 19 yr of age, abnormal liver function tests, dyslipidemia and a moon-face appearance prompted a metabolic reevaluation. Although the degree of aberrant fat distribution was modest compared with other patients, a CT scan demonstrated increased visceral fat with a markedly fatty liver. A diabetic pattern of blood glucose response was observed in an OGGT, as well as pronounced hyperinsulinism.

Patient 5, female, neuroblastoma

A neuroblastoma, with multiple bone metastases (stage IV\textsubscript{A}), was diagnosed in a 1-yr-old female during the evaluation of an abdominal mass. Following total removal of the primary tumor and chemotherapy, two consecutive autologous BMTs, without TBI, were performed 3-mo apart. A regional relapse in the right iliac bone, as well as marrow relapse, was found one year later. The patient was treated with an allogeneic BMT, the donor being her 2-locus mismatched sister, following 12 Gy TBI conditioning. Thereafter, complete remission was obtained, and immunosuppressants were withdrawn at age 8.

Partial GH deficiency was diagnosed at age 12, and GH treatment was conducted for 5 yr. The patient also exhibited primary hypogonadism, high-frequency deafness and the presence of cataracts. At around age 17, fatty
changes in the liver and hypertriglyceridemia developed, followed by a mild, abnormal pattern of subcutaneous fat distribution. An OGTT showed normal blood glucose responses, but with hyperinsulinism.

**Methods and Results**

Body composition analysis with dual-energy X-ray absorptiometry was performed in patient 1 using a Discovery® A Densitometer (Hologic, Inc., Bedford, MA, USA) in fan beam analysis mode and software version 13.3.0.1 (Fig. 1b). To illustrate fat distribution abnormality clearly, a 25-yr-old obese woman and a 29-yr-old healthy nonobese woman served as controls. In the former, this analysis was carried out as one of the routine medical evaluations for obesity.

Visceral fat area at the 4th lumbar spine level was determined with FatVizCalc® (LISIT Co., Ltd., Tokyo, Japan) using the CT images of each patient (Fig. 1c).

Written informed consent for LMNA gene analysis was obtained from patients 2, 3 and 5 and from the mother of patient 1. Patient-specific gDNA was extracted from a nail specimen, and the common mutations in exons 8 and 11 of the LMNA gene, associated with FPLD2, were studied, as previously described (17). The mutation was absent in these patients (Table 2).

The onset of lipodystrophy is difficult to ascertain because the attending hematologists, as well as the patients themselves, are unaware of fat distribution abnormalities. Because serum triglyceride levels were routinely measured in the patients, we deduced the onset of lipodystrophy based on the timing of emergence of an elevated triglyceride level. As listed in Table 2, lipodystrophy seemed to develop about a decade after HSCT.

**Discussion**

All the described patients demonstrated a characteristic adipose tissue distribution pattern. Lipoatrophy was remarkable in the gluteal region and extremities, whereas subcutaneous fat was preserved, or even prominent, in the cheeks, neck and abdomen. Visceral fat deposition, as well as fatty changes in the livers of these patients, was also evident. This particular distribution pattern resembles that seen in FPLD2, which is caused by a LMNA gene mutation (1, 2, 5–7). Patients with this rare entity, which has an estimated prevalence of 1 in 15 million individuals (1), manifest a peculiar lipodystrophy after adolescence. In addition, metabolic complications, including insulin resistance, diabetes, hypertriglyceridemia, low HDL cholesterol levels and fatty liver, are prevalent in FPLD2 patients (3, 4). Female patients also have an increased risk for developing polycystic ovary syndrome and infertility (18). Compared with generalized lipodystrophy and other types of partial lipodystrophy, leptin and adiponectin levels in FPLD2 are only modestly decreased (19). However, FPLD2 is unlikely the cause of lipodystrophy in these patients, considering its low prevalence and the absence of LMNA gene mutations in the 4 patients tested.

Our patients and those with FPLD2 share similarities in fat distribution patterns and in metabolic derangements. Pronounced hypertriglyceridemia, coupled with decreased HDL cholesterol levels, was present in the 5 patients; elevated LDL cholesterol, defined as levels above 150 mg/dL, was present in 4 patients. The patients had high homeostasis model assessment ratios (HOMA-Rs), indicating insulin resistance, although acanthosis nigricans was not observed in any patients. Two patients had OGTTs that categorized them into the diabetic pattern according to the criteria developed by the Japanese Diabetes Society (see Fig. 2 legend). The patients with the diabetic pattern were found to have pronounced hyperinsulinemia with a peak insulin level exceeding 700 µIU/mL. In the present cases, the levels of leptin and adiponectin were modestly decreased.

The patients described in this report shared a common medical history that included HSCT
and conditioning with 10–12 Gy TBI. All of them also received intensive chemotherapy because of the severe nature of their diseases, including widespread metastases (patients 1, 4 and 5) and early relapses (patients 2, 3 and 4), and/or repetitive HSCT (patients 1, 3 and 5). Major surgery, however, was only conducted on those with neuroblastomas. Cranial radiation was performed on only 3 patients.

Based on the above observations, we propose HSCT as a new etiology for acquired partial lipodystrophy. Partial lipodystrophy seems to develop following HSCT, including TBI, especially in conjunction with intensive chemotherapy. This outcome appears to occur irrespective of other interventions such as surgery and cranial radiation. Younger age at the time of HSCT may be of significance, considering that 4 patients received transplants during infancy.

We speculate that TBI and/or intensive chemotherapy may damage the function of adipocytes in the subcutaneous fat, thereby limiting their lipid-storage capacity. This may lead to ectopic deposition of fat in visceral adipose tissue, muscle and liver. This hypothesis is reasonable because adipose tissue fibrosis, and the resultant ectopic lipid accumulation, has been demonstrated in obese individuals (20). Although the mechanism for the characteristic pattern of lipodystrophy is unclear, it may reflect the site-specific adipose tissue functions. In a subset of partial lipodystrophy accompanying glomerulonephritis, differential expression of complementary D by various adipose tissues is considered to cause the different degrees of lipodystrophy among the body (21).

It is essential to consider other potential factors that may be relevant to the development of lipodystrophy. Rooney and Ryan (22) reported a female patient who underwent allogeneic HSCT for relapsed ALL and developed partial lipodystrophy, with overt diabetes, 9 yr later. This patient had GVHD-associated scleroderma, and these authors speculated that there was a causative relationship between partial lipodystrophy and scleroderma. This hypothesis is very intriguing considering that decreased adiponectin levels have been described in systemic sclerodermas with autoimmune origins (23, 24). However, the severity of the GVHD varied among our patients, and scleroderma was present only in patient 3. GVHD was entirely absent in patient 4, who underwent autologous HSCT. Therefore, GVHD and GVHD-related scleroderma may not be a prerequisite but may be a predisposing factor for the development of partial lipodystrophy.

Another factor that should be considered is endocrinopathy. Four patients had endocrinological complications such as GHD, hypothyroidism and hypogonadism (Table 2). Although some of these endocrinopathies had been treated at the time of the investigation, hormone deficiency must be present for a significant period before the initiation of hormonal therapy. At present, endocrinopathy, per se, is not regarded as a definite cause of lipodystrophy (1, 2). However, endocrinological complications may be likely to modify the development and/or progress of lipodystrophy, considering that each hormone has its own receptor in the adipose tissue (25, 26), and the relationship between hormonal deficiency and metabolic complications is well-known (27, 28).

A causative relationship between HSCT and lipodystrophy may be disputed based on the absence of reports other than that of Rooney and Ryan (22). However, in accordance with our proposal, a high incidence of fatty liver was also reported in individuals who have undergone HSCT (29). In addition, radiation therapy, including TBI, is an established risk factor for developing metabolic syndrome (30, 31). Moreover, impaired glucose tolerance and dyslipidemia have been described as late complications following HSCT (32–34). We infer that a substantial number of partial lipodystrophy patients may have gone undiagnosed because careful observations are necessary to detect abnormal fat distribution.
and because lipodystrophy is not a well-known condition, especially among pediatricians.

To clarify the incidence of HSCT-related lipodystrophy, as well as the contributions of GVHD, GVHD-scleroderma and endocrinopathies, further studies are clearly needed. Lipodystrophy appears to develop more than a decade after HSCT. In addition, the progress of lipodystrophy may be slow, considering that the OGTT results did not differ over a 10-yr interval in patient 3 (Table 3). Thus, prospective studies with long observation periods may be needed to clarify the reality of this potentially life-threatening complication in childhood cancer survivors.

**Conclusion**

Five pediatric patients manifesting aberrant fat distribution patterns similar to those observed in FPLD2 patients and severe metabolic abnormalities were described. Patients undergoing HSCT, especially when performed early in their lives and in conjunction with TBI and intensive chemotherapy, warrant careful observation for the potential development of partial lipodystrophy.

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Lipodystrophy after stem cell transplant


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