Original Article

Partial lipodystrophy in patients who have undergone hematopoietic stem cell transplantation during childhood: an institutional cross-sectional survey

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Abstract. Partial lipodystrophy (PD), a condition similar to metabolic syndrome without obesity, is one of the late complications of hematopoietic stem cell transplantation (HSCT) performed during childhood. We aimed to investigate the prevalence and risk factors of PD. A cross-sectional survey was performed in a children's hospital, targeting patients treated for a malignancy or hematological disorder, and who were disease-free for > 24 mo. PD was defined as gluteal lipoatrophy and lipohypertrophy of the cheeks or neck associated with diabetes and/or fatty liver disease. In total, 65 patients were enrolled. Six patients (9.2%) were judged to have PD, all of whom had received 10–14 Gy total body irradiation. Compared with the patients without PD, patients with PD were older at investigation (P < 0.01), had a longer elapsed time following HSCT (P < 0.01), had more frequent disease recurrence (P < 0.05), and were more likely to have undergone multiple HSCT (P < 0.05). In addition, they had higher blood pressure and showed higher levels of low-density lipoprotein-cholesterol and triglycerides, whereas their adiponectin levels were significantly lower. In conclusion, a large number of patients developed PD following HSCT, with unfavorable metabolic profiles at a later age, especially when they experienced a complex disease course.

Key words: childhood cancer survivors, fatty liver disease, insulin resistance, metabolic syndrome, total body irradiation

Introduction

Patients who have undergone radiotherapy and/or chemotherapy, including childhood cancer survivors (CCS), are predisposed to various endocrinological complications (1, 2). In addition, those who received hematopoietic stem cell transplantation (HSCT) are considered to be at high risk for developing endocrinopathies, including GH deficiency, primary hypothyroidism, and primary hypogonadism (2–4).

In addition to endocrinopathies, metabolic derangements have emerged as important, under-recognized, late complications in patients who underwent HSCT. In 2000, impaired glucose intolerance and dyslipidemia were discerned as late effects of HSCT in children (5). Furthermore, reports have confirmed the
association between HSCT and aberrations in glucose/lipid metabolism (6–11), which include central or abdominal obesity (5, 7, 10), insulin resistance (5, 8, 9), diabetes (5, 6, 10, 11), hypertriglyceridemia (5, 9, 10), and fatty liver disease (8, 10). These metabolic derangements can develop in the absence of obesity or a high body mass index (BMI) (5, 7, 8, 11), and are associated with total body irradiation (TBI) performed for HSCT conditioning, but not with chemotherapeutic agents (6, 7, 11).

An analysis by Wei et al. (12) of 30 CCS with acute lymphoblastic leukemia (ALL) who had undergone HSCT demonstrated a higher incidence of glucose intolerance with insulin resistance compared with non-HSCT CCS with ALL and obese controls. They also identified a lower lean mass, and higher visceral and lower subcutaneous fat among the patients following HSCT, describing their phenotype as “lipodystrophic and sarcopenic” (12). In our previous study (13), we reported five CCS who developed severe insulin resistance and hypertriglyceridemia following HSCT, with a partial lipodystrophic phenotype that markedly resembled Dunnigan-type familial partial lipodystrophy (familial partial lipodystrophy type 2, OMIM #151660).

Despite the aforementioned studies, partial lipodystrophy following HSCT has rarely been reported (13, 14). The difficulty in diagnosing partial lipodystrophy, mainly due to the absence of both diagnostic criteria and biomarkers, is likely the main reason for limited reports. However, we consider that the lipodystrophic phenotype is an important study target, as it indicates that adipose tissue has become damaged through HSCT, and adipocyte dysfunction is closely related to the pathogenesis of metabolic derangements following HSCT (6, 7, 9, 11).

The present study aimed to investigate the prevalence of partial lipodystrophy among patients following HSCT by performing a cross-sectional survey in a local children’s hospital. In addition, an extraction of risk factors was attempted for the development of partial lipodystrophy following HSCT.

Materials and Methods

Study population

The target population in this study was patients who had undergone HSCT to treat malignant disease or benign hematological disorders, such as pure red-cell anemia, aplastic anemia, or myelodysplastic syndrome. Those patients whose latest HSCT was < 24 mo from study initiation were excluded, to avoid confusing poor nutrition immediately following HSCT with the lipodystrophic phenotype.

In April 2014, the candidate patients were extracted from the institutional medical record database. After excluding the patients who showed relapse and/or died and those lost to follow-up, 110 patients were confirmed as the primary target population. Of these 110 patients, 108 underwent HSCT in our hospital. Two patients who had undergone HSCT in other hospitals were also included in the study. Three patients with Down syndrome were excluded, in an attempt to depict the metabolic characteristics clearly in the patients with lipodystrophy. Three patients with severe medical conditions, including chronic heart failure (n = 1) with cardiomyopathy and chronic respiratory failure (n = 2) due to pulmonary fibrosis, were considered unsuitable for study participation. Therefore, 104 patients were asked to participate in this study.

Experiments

An experienced clinician (MA) evaluated the study participants in the outpatient setting of the Pediatric Endocrinology Clinic from April 2014 to March 2016. Height and weight were measured in the upright position using a certified electronic scale. Waist circumference was measured using a measuring tape at the umbilical level. Blood pressure (BP) was recorded in the sitting position. Pediatric radiologists evaluated the presence of fatty liver disease using ultrasonography or
computed tomography (CT) imaging. Patient histories were obtained by searching medical records. Prolonged immunosuppressant administration was arbitrarily defined as the administration of any immunosuppressant for >37 mo, based on the finding that the median duration of immunosuppresson therapy for chronic graft-versus-host disease (GVHD) among the study participants was 20.3 mo (range: 4.0–155 mo, n = 36).

The diagnostic criteria for partial lipodystrophy were based on our previous observation that five patients developed partial lipodystrophy resembling Dunnigan-type familial partial lipodystrophy following HSCT (13). First, on a clinical inspection, partial lipodystrophy was suspected when definite lipohypertrophy of either the cheek or neck was recognized by findings such as a Cushingoid appearance or double chin (15), as well as simultaneous recognition of definite lipoatrophy of the gluteal region. The diagnosis of partial lipodystrophy was confirmed when overt diabetes and/or ultrasonography- or CT-proven fatty liver disease were detected.

To define overt diabetes, the diagnostic criteria of the Japan Diabetes Society were adopted (16). Patients with a fasting blood glucose level of 126 mg/dL and concomitant elevated glycated hemoglobin (HbA1c) levels (≥ 6.5%) were diagnosed with overt diabetes. In cases where the HbA1c level was < 6.5%, a repeatedly high fasting blood glucose level was sufficient for the diagnosis of overt diabetes.

A high BMI was defined as > 22 kg/m² in adults and > 90th percentile in children using national standards (17). Hypertension was defined according to the Guideline for the Management of Hypertension 2014, developed by the Japanese Society of Hypertension (18).

After obtaining patient consent, fasting blood samples were collected. For patients receiving antidiabetics or lipid-lowering medications, a 3-month cessation of medication was requested before sampling. Low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, HbA1c, and insulin were measured at an in-house laboratory. Serum leptin levels were determined using a Human-Leptin radioimmunoassay (EMD Millipore, Darmstadt, Germany). Total adiponectin was measured with a latex turbidimetric immunoassay using a Human Adiponectin Latex Kit (LSI Medience Corporation, Tokyo, Japan). Serum levels of tumor necrosis factor-alpha (TNF-α) were measured with the Human TNF-alpha Quantikine HS ELISA (R&D Systems, Inc., Minneapolis, USA). The homeostatic model assessment of insulin resistance (HOMA-R) was calculated by the following formula: fasting glucose (mg/dL) × insulin (µIU/mL)/405

Statistics

Normally distributed data are presented as the mean with standard deviation; non-normally distributed data are presented as the median with range. To compare the clinical properties between participants and non-participants, as well as those between patients with and without lipodystrophy, an unpaired T-test, Mann-Whitney U-test, Chi-square test, or Fisher’s probability test was performed according to the parametric/non-parametric nature of the data and the number of samples. Parametric data included the age at recruitment and the age at evaluation. To compare the metabolic profiles between patients with and without lipodystrophy, an unpaired T-test, Mann-Whitney U-test, or Fisher’s probability test was employed, where triglycerides, HOMA-R, and leptin concentrations were treated as non-parametric data. Statistical analysis was performed using the IBM SPSS Statistics version 23 (IBM Corporation, New York, NY, USA). A P-value of < 0.05 was considered significant.

Ethical issues

The study design was approved by the Institutional Ethical Committee of Kanagawa Children’s Medical Center in January 2014.
(permission number 82-06). This study was registered in the University Hospital Medical Information Network Clinical trial registry in February 2014 as UMIN000013087. Written informed consent was obtained from the patients and/or their caregivers depending on the patient’s age and cognitive ability.

### Results

#### Participant clinical profiles

Of the 104 patients who were asked to participate in the study, 65 agreed to enroll until March 2016. Ten patients showed relapse and/or died during the study period. The remaining 29 patients did not participate due to patient’s or parental refusal. The profile of the participants compared with that of the non-participants is described in Table 1. Although male predominance was observed in the non-participants, no other differences were noted between the participants and non-participants.

#### Incidence of partial lipodystrophy

Nine patients were suspected to have a lipodystrophic phenotype resembling Dunnigan-type familial partial lipodystrophy based on the findings of gluteal lipoatrophy and lipohypertrophy of the cheeks and/or neck. Of these patients, six were found to have fatty liver disease and, therefore, were regarded as having developed partial lipodystrophy according to our criteria. Among the six patients with partial lipodystrophy, three patients met the criteria for overt diabetes. The profile of these six patients is described in Table 2, as compared with the profile of those who did not meet the criteria.

#### Clinical characteristics of the patients with partial lipodystrophy

Patients with partial lipodystrophy were significantly older at evaluation compared with those without partial lipodystrophy (Table 2 and Fig. 1; P < 0.01). Similarly, patients with partial lipodystrophy showed a significantly longer

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**Table 1** Comparison of the profiles between study participants and non-participants

| Characteristic                  | Participants (n = 65) | Non-participants (n = 29) | P-value |
|--------------------------------|----------------------|--------------------------|---------|
| Sex                            | Male                 | 29                       | 21      | 0.013   |
|                                | Female               | 36                       | 8       |         |
| Age at recruitment# (yr)       | 15.3 ± 5.1           | 15.0 ± 7.0               | 0.88    |
|                                | 15.0 (6.6–27.9)      | 14.2 (3.9–28.5)          |         |
| Disease category               |                      |                          |         |
| Acute lymphoblastic leukemia    | 20                   | 8                        |         |
| Acute myeloid leukemia          | 11                   | 8                        |         |
| Chronic myelogenous leukemia    | 0                    | 1                        |         |
| Neuroblastoma                   | 16                   | 1                        | 0.066   |
| Brain tumor                     | 8                    | 2                        |         |
| Sarcoma                         | 3                    | 3                        |         |
| Lymphoma                        | 2                    | 2                        |         |
| Hematological diseases*         | 5                    | 4                        |         |
| Age at initial HSCT## (yr)      | 4.8 (1.0–14.3)       | 6.5 (1.1–21.1)           | 0.175   |

#For the age at recruitment, both the mean ± standard deviation and the median (range) are shown, whereas only the median (range) is provided for the age at initial HSCT.

*Hematological diseases included aplastic anemia (n = 4), pure red cell anemia (n = 1), myelodysplastic syndrome (n = 3), and hemophagocytic syndrome (n = 1). HSCT, hematopoietic stem cell transplantation.
elapsed time following the first HSCT compared with those without partial lipodystrophy (Table 2 and Fig. 2; P < 0.01).

In addition, recurrence of the underlying malignant disease (P < 0.05) and multiple HSCTs (P < 0.05) were frequently observed in patients with partial lipodystrophy, as compared with those without partial lipodystrophy.

Disease category, types of HSCT, TBI, cranial irradiation, and prolonged immunosuppressant administration were not significantly different between the patients with lipodystrophy and those without (P > 0.05). However, all patients with lipodystrophy had received TBI.

**Table 2** Comparison of the clinical profiles between patients with and without lipodystrophy

|                      | With lipodystrophy (n = 6) | Without lipodystrophy (n = 59) | P-value |
|----------------------|----------------------------|--------------------------------|---------|
| Sex                  |                            |                                |         |
| Male                 | 3                          | 26                             | 0.555   |
| Female               | 3                          | 33                             |         |
| Age at evaluation# (yr) | 22.8 ± 4.2                 | 15.5 ± 4.7                     | 0.001   |
|                      | 23.8 (15.5–26.6)           | 15.4 (7.0–28.7)                |         |
| Disease category     |                            |                                |         |
| Acute lymphoblastic leukemia | 3 (50.0%)              | 15 (25.4%)                     | 0.161   |
| Acute myeloid leukemia    | 2 (33.3%)             | 9 (15.3%)                      |         |
| Neuroblastoma         | 1 (16.7%)                 | 15 (25.4%)                     |         |
| Others               | 0                          | 20 (33.9%)                     |         |
| Age at initial HSCT# (yr) | 3.7 (1.9–10.0)          | 4.4 (1.0–14.2)                 | 0.749   |
| Time after first HSCT# (yr) | 18.3 (10.8–24.6)      | 8.2 (3.3–26.2)                 | 0.002   |
| Total body irradiation | 6/6 (100%)               | 39/59 (66.1%)                  | 0.099   |
| Cranial irradiation   | 3/6 (50.0%)               | 10/59 (16.9%)                  | 0.089   |
| Type of HSCT*         |                            |                                |         |
| Autologous           | 1                          | 24                             | 0.561   |
| Allogeneic           | 2                          | 12                             |         |
| Unrelated            | 3                          | 23                             |         |
| Prolonged immunosuppressant | 3/6 (50.0%)          | 8/59 (13.6%)                   | 0.056   |
| Disease recurrence   | 4/6 (once 2, twice 2)     | 14/59 (once 12, twice 2)       | 0.045   |
| Multiple HSCTs       | 4/6 (twice 3, thrice 1)  | 11/59 (twice 10, thrice 1)    | 0.022   |

#For the age at evaluation, both the mean ± standard deviation and the median (range) are presented, whereas only the median (range) is provided for the age at initial HSCT and time after first HSCT.

*If the patient underwent multiple HSCTs, the mode of HSCT where total body irradiation was performed was selected. HSCT, hematopoietic stem cell transplantation.

**Metabolic aspects of the participants**

As is shown in Table 3, approximately two-thirds of the participants agreed to undergo fasting blood sampling. Compared with the patients without lipodystrophy, those with lipodystrophy were found to have significantly elevated systolic and diastolic BP (P < 0.01), a high incidence of hypertension (P < 0.05), significantly elevated LDL-C levels (P < 0.01), and significantly elevated triglyceride levels (P < 0.01).

Adiponectin levels were significantly lower in patients with lipodystrophy compared with the patients without lipodystrophy (P < 0.01), whereas serum leptin and TNF-α levels were not significantly different between the two groups. HOMA-R was significantly higher in patients...
Three of the six patients with lipodystrophy had developed overt diabetes: at the time of investigation, one patient was on metformin (500 mg a day with HbA1c 6.5%), whereas the remaining two patients were instructed to modify their lifestyle. One lipodystrophic patient without overt diabetes was on statin therapy, and her fasting glucose levels were mildly elevated (111 mg/dL). Among the patients without lipodystrophy, only one patient had diabetes and was treated by lifestyle modification.
**Discussion**

The present study performed a cross-sectional survey in a local children’s hospital in Japan and demonstrated that the prevalence of partial lipodystrophy resembling the Dunnigan-type was 9.2% among CCS and the patients with hematological disorders who have undergone HSCT. In addition, HSCT-related lipodystrophy was frequently found in the patients of older age, in those with longer elapsed time following HSCT, in those with a history of disease recurrence, and multiple HSCTs. This is the first systematic study to investigate the lipodystrophic phenotype in this population.

The absence of a gold standard diagnostic method, as well as the absence of useful diagnostic biomarkers, confounds the confirmation of partial lipodystrophy, especially in its acquired form where gene analyses serve no purpose (15, 19–22). In this study, criteria for the diagnosis of partial lipodystrophy were devised as follows: affirmation of abnormal subcutaneous fat distribution evidenced by lipohypertrophy in the cheek and/or neck as well as gluteal lipoatrophy, and the presence of fatty liver disease and/or overt diabetes.

Of the nine patients with suspected lipodystrophy, six were shown to have fatty liver disease, thus confirming that the clinical assessment had a high specificity for ascertaining lipodystrophy, and that over-diagnosis of lipodystrophy was unlikely. In addition, three of the four patients with overt diabetes were judged as having lipodystrophy, indicating high sensitivity. Accordingly, we assume that our criteria for the diagnosis of partial lipodystrophy were acceptable. Possibly, overt diabetes may not be necessary for the diagnostic criteria, considering that diabetes is not directly related to abnormal fat distribution.

The 9.2% prevalence of lipodystrophy in this study may be an overestimation since a substantial number of the patients had moved to adult hospitals or were lost to follow-up. There is also the potential that patients with any concurrent medical problems, such as dyslipidemia, would have preferred to stay in the hospital where HSCT was performed. In addition, those with a history of disease recurrence and those who had undergone multiple HSCTs showed a higher incidence of lipodystrophy. Those patients with a complicated disease course may also have preferred to undergo follow-up in the children’s hospital. We have no reasonable explanation for the difference in sex proportions between the participants and non-participants. Obviously, the true incidence of lipodystrophy should be determined through a large-scale, prospective study.

All patients with lipodystrophy had received TBI of 10–14 Gy as the conditioning procedure prior to HSCT. In previous reports of HSCT-related lipodystrophy (9, 10, 12, 14), including our study (13), all patients had undergone TBI. Mayson et al. (9) suggested that TBI might deplete the number of pre-adipocytes, which would inhibit fat-tissue expandability, leading to severe insulin resistance and hypertriglyceridemia. In addition, the association between TBI, but not chemotherapeutic agents, and diabetes and/or dyslipidemia following HSCT (6, 7, 11) supports the causative role for TBI in the development of lipodystrophy. An animal study suggested that subcutaneous adipose tissue is very sensitive to TBI (23). In addition, ob/ob mice that received 8 Gy TBI developed reduced body-fat mass with more severe insulin resistance and hepatic steatosis compared with controls (24). Together, these results suggest that TBI is a prerequisite for the development of HSCT-related partial lipodystrophy.

The present study aimed to identify other risk factors for the development of partial lipodystrophy among patients following HSCT. Although a multivariate analysis could not be applied due to the small sample size, a significant difference in the elapsed time following HSCT, as well as in the age at evaluation, was observed between patients with and without
This suggests that the probability of developing partial lipodystrophy increases as a patient ages and that a long latent period is required to develop a lipodystrophic phenotype. Consistent with this, in our six patients with lipodystrophy, > 9 yr had elapsed since the initial HSCT. This observation is in accordance with previous reports, in which almost a decade was necessary for either lipodystrophy or diabetes to develop following HSCT (9, 10, 12–14).

Here, we discuss the relationship between HSCT-related partial lipodystrophy and hitherto reported metabolic aberrations following TBI. Previous studies have recurrently demonstrated that TBI can cause central obesity (5, 7, 10), insulin resistance (5, 8, 9), diabetes (5, 6, 10, 11), hypertriglyceridemia (5, 9, 10), and fatty liver disease (8, 10), even in patients with a low-to-normal BMI (5, 7, 8, 11). Some authors have suggested that these features resemble the phenotype of partial lipodystrophy. However, partial lipodystrophy following HSCT has rarely been reported (9, 10, 12–14). We suggest that this discrepancy derives from both the poor recognition of lipodystrophy as a disease entity and the challenges associated with the diagnosis of partial lipodystrophy. Accordingly, the metabolic aberrations and partial lipodystrophy following HSCT may be the same condition caused by adipocyte damage from TBI.

Disease recurrence and multiple HSCTs were more common in patients with lipodystrophy compared with patients without lipodystrophy. In addition, although not significant, a history of prolonged immunosuppressive treatment was also recurrently found in patients with lipodystrophy. Collectively, patients with lipodystrophy tended to have a complicated disease course. While TBI may be the main culprit for adipose tissue damage, chemotherapeutic agents, chronic GVHD itself and/or immunosuppressants may have had some role in the disease progression.

Our study indicates that patients with partial lipodystrophy following HSCT are at a high risk of developing metabolic complications, including elevated BP, higher LDL-C and triglyceride levels, elevated HOMA-R, diabetes, and fatty liver disease. These results indicated that HSCT-related partial lipodystrophy might influence the development of premature atherosclerosis, as with other forms of lipodystrophy (15, 21).

Patients with lipodystrophy had decreased adiponectin levels, which is consistent with a previous report showing low adiponectin levels in ALL patients following HSCT compared with those treated with chemotherapy only (12). Considering that hypoadiponectinemia plays a pivotal role in the development of insulin resistance, dyslipidemia, and hypertension in metabolic syndrome (25), it is tempting to believe that hypoadiponectinemia is one of the major factors to induce metabolic complications found in partial lipodystrophy following HSCT. Although we measured TNF-α as a representative inflammatory cytokine, no difference in circulating TNF-α levels was observed between the patients with lipodystrophy and those without. However, marked metabolic derangements found in our patients strongly suggest an involvement of inflammatory cytokines. A more comprehensive evaluation is needed for determining the causative role of cytokines.

The present study had several limitations. First, our study population was rather small and considerably heterogeneous in terms of age and elapsed time period from HSCT. Second, as mentioned previously, the incidence of lipodystrophy (9.2%) may have been biased. Third, although endocrinological complications may have some roles in the development of lipodystrophy, a thorough analysis of endocrinopathies was not possible because of limited access to the patients. However, thyroid and gonadal function were routinely screened in the majority of the patients. Therefore, the presence of severe hypothyroidism or untreated hypogonadism does not seem likely.

The reliability of the diagnosis of partial lipodystrophy is the final limitation of this
A novel mutation of NR3C2

study. As discussed previously, we assume that our criteria for partial lipodystrophy had satisfactory sensitivity and specificity. However, the judgment of regional lipoatrophy and lipohypertrophy depended solely on subjective observation. Development of a new biomarker for partial lipodystrophy, which is more accurate than plasma adiponectin or lipid levels, will be very helpful. This biomarker will also facilitate an early ascertainment of lipodystrophy, coupled with the increased recognition of partial lipodystrophy as a disease entity among clinicians caring for patients following HSCT.

**Conclusion**

A substantial number of patients developed partial lipodystrophy resembling the Dunnigan-type at a later period following HSCT, and this was associated with unfavorable metabolic profiles. All patients with lipodystrophy had received TBI, which may be the main cause of adipose tissue dysfunction.

**Conflict of Interest:** None of the authors have any potential conflicts of interest associated with this research.

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**References**

1. Rose SR, Horne VE, Howell J, Lawson SA, Rutter MM, Trotman GE, et al. Late endocrine effects of childhood cancer. Nat Rev Endocrinol 2016;12: 319–36. [Medline] [CrossRef]
2. Nandagopal R, Laverdière C, Mulrooney D, Hudson MM, Meacham L. Endocrine late effects of childhood cancer therapy: a report from the Childrens Oncology Group. Horm Res 2008;69: 65–74. [Medline]
3. Gunasekaran U, Agarwal N, Jagasia MH, Jagasia SM. Endocrine complications in long-term survivors after allogeneic stem cell transplant. Semin Hematol 2012;49: 66–72. [Medline] [CrossRef]
4. Orio F, Muscogiuri G, Palomba S, Serio B, Sessa M, Giudice V, et al. Endocrinopathies after allogeneic and autologous transplantation of hematopoietic stem cells. Scientific World Journal 2014;2014:282147.
5. Taskinen M, Saarinen-Pihkala UM, Hovi L, Lipsanen-Nyman M. Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet 2000;356: 993–7. [Medline] [CrossRef]
6. Baker KS, Ness KK, Steinberger J, Carter A, Francisco L, Burns LJ, et al. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. Blood 2007;109: 1765–72. [Medline] [CrossRef]
7. Neville KA, Cohn RJ, Steinbeck KS, Johnston K, Walker JL. Hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus in survivors of childhood cancer: prevalence and risk factors. J Clin Endocrinol Metab 2006;91: 4401–7. [Medline] [CrossRef]
8. Tomita Y, Ishiguro H, Yasuda Y, Hyodo H, Koike T, Shimizu T, et al. High incidence of fatty liver and insulin resistance in long-term adult survivors of childhood SCT. Bone Marrow Transplant 2011;46: 416–25. [Medline] [CrossRef]
9. Mayson SE, Parker VE, Schutta MH, Semple RK, Rickels MR. Severe insulin resistance and hypertriglyceridaemia after childhood total body irradiation. Endocr Pract 2013;19: 51–8. [Medline] [CrossRef]
10. Rajendran R, Abu E, Fadl A, Byrne CD. Late effects of childhood cancer treatment: severe hypertriglyceridaemia, central obesity, non alcoholic fatty liver disease and diabetes as complications of childhood total body irradiation. Diabet Med 2013;30: e239–42. [Medline] [CrossRef]
11. Meacham LR, Sklar CA, Li S, Liu Q, Gimpel N, Yasui Y, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk
associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med 2009;169: 1381–8. [Medline] [CrossRef]

12. Wei C, Thyagiarajan MS, Hunt LP, Shield JP, Stevens MC, Crowne EC. Reduced insulin sensitivity in childhood survivors of haematopoietic stem cell transplantation is associated with lipodystropic and sarcopenic phenotypes. Pediatr Blood Cancer 2015;62: 1992–9. [Medline] [CrossRef]

13. Adachi M, Asakura Y, Muroya K, Goto H, Kigasawa H. Abnormal adipose tissue distribution with unfavorable metabolic profile in five children following hematopoietic stem cell transplantation: a new etiology for acquired partial lipodystrophy. Clin Pediatr Endocrinol 2013;22: 53–64. [Medline] [CrossRef]

14. Rooney DP, Ryan MF. Diabetes with partial lipodystrophy following sclerodermatous chronic graft vs. host disease. Diabet Med 2006;23: 436–40. [Medline] [CrossRef]

15. Garg A, Misra A. Lipodystrophies: rare disorders causing metabolic syndrome. Endocrinol Metab Clin North Am 2004;33: 305–31. [Medline] [CrossRef]

16. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus: revision for international harmonization of HbA1c in Japan. J Jpn Diabet Soc 2012;55: 485–504 (in Japanese).

17. Kato N. Construction of BMI for age references for Japanese children from the 2000 national growth survey. J Jpn Assoc Hum Auxol 2009;15: 37–44.

18. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, et al. Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res 2014;37: 253–390. [Medline] [CrossRef]

19. Vantyghem MC, Balavoine AS, Douillard C, Defrance F, Dieudonne L, Mouton F, et al. How to diagnose a lipodystrophy syndrome. Ann Endocrinol (Paris) 2012;73: 170–89. [Medline] [CrossRef]

20. Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. Medicine (Baltimore) 2004;83: 18–34. [Medline] [CrossRef]

21. Fiorenza CG, Chou SH, Mantzoros CS. Lipodystrophy: pathophysiology and advances in treatment. Nat Rev Endocrinol 2011;7: 137–50. [Medline] [CrossRef]

22. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. J Clin Endocrinol Metab 2016;101: 4500–11. [Medline] [CrossRef]

23. Poglio S, Galvani S, Bour S, André M, Prunet-Marcassus B, Pénicaud L, et al. Adipose tissue sensitivity to radiation exposure. Am J Pathol 2009;174: 44–53. [Medline] [CrossRef]

24. Ablamunits V, Weisberg SP, Lemieux JE, Combs TP, Klebanov S. Reduced adiposity in ob/ob mice following total body irradiation and bone marrow transplantation. Obesity (Silver Spring) 2007;15: 1419–29. [Medline] [CrossRef]

25. Maeda N, Funahashi T, Shimomura I. Cardiovascular-metabolic impact of adiponectin and aquaporin. Endocr J 2013;60: 251–9. [Medline] [CrossRef]