Endocrine Journal 2021, **68** (4), 399-407

ORIGINAL

Metreleptin worked in a diabetic woman with a history of hematopoietic stem cell transplantation (HSCT) during infancy: further support for the concept of 'HSCT-associated lipodystrophy'

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Abstract. A 17-year-old woman with a history of childhood leukemia and hematopoietic stem cell transplantation (HSCT), preceded by total body irradiation, developed diabetes, dyslipidemia, fatty liver, and marked insulin resistance. Based on Dunnigan phenotype, HSCT-associated lipodystrophy was suspected. Because of rapid deterioration of diabetes control, metreleptin was introduced at 23 years of age upon receipt of her caregiver's documented consent. This trial was initially planned as a prospective 18 month-long study, with regular assessments of the patient's physical activity, food intake, and body composition analysis. However, because an abrupt and transient attenuation of the metreleptin effect occurred 16 months after the treatment initiation, the entire course of 28 months is reported here. Over the period, her HbA1c decreased from 10.9% to 6.7% despite no significant increase of physical activity and with a stable food intake. Decreased levels of triglyceride and non-HDL cholesterol were found. Her liver function improved, indicating the amelioration of fatty liver. In addition, a 25% reduction in the subcutaneous fat area at umbilical level was found, accompanied by a decrease in fat percentage of both total-body and trunk. The formation of neutralizing antibodies to metreleptin may be responsible for the transient loss of efficacy, considering a sudden elevation in her serum leptin level. In conclusion, metreleptin is useful for the management of HSCT-associated lipodystrophy, supporting the concept that adipose tissue dysfunction is responsible for diverse post-HSCT metabolic aberrations.

Key words: Bone marrow transplantation, Childhood cancer survivors, Dunnigan phenotype, Leptin, Total body irradiation

YOUNG ADULTS undergoing hematopoietic stem cell transplantations (HSCT) during childhood are at a high risk of developing diverse metabolic aberrations later in life. These medical conditions include diabetes [1, 2], dyslipidemia [3], fatty liver [4], central adiposity [5], and insulin resistance [2, 4, 6]. Notably, most affected patients have a normal or even low body mass index, differentiating them from obese ones who have overnutrition and/or a sedentary lifestyle [2-6]. In addition, lipodystrophy of Dunnigan phenotype has sometimes been found among these patients; it is characterized by a loss of subcutaneous adipose tissue in the buttocks and extremities, with lipohypertrophy noted in the cheeks and neck [7-10].

To elucidate the above findings rationally, we proposed the hypothesis of 'HSCT-associated partial lipodystrophy' [7, 8]. According to this, total body irradiation (TBI) as a preconditioning regimen before HSCT, damages subcutaneous adipose tissue expandability, resulting in impaired lipid storage capacity. Overflowed lipid will then accumulate as ectopic fat in muscle, liver, and visceral fat tissues, causing insulin resistance and the subsequent metabolic aberrations. In addition to this major pathway, chemotherapeutic agents, chronic graft-*versus*-host disease (GVHD), and endocrinological complications may play some role in establishing the lipodystrophic phenotype. A cross-sectional survey in our institution identified the morbidity rate of partial lipodystrophy as high as 9.2% among the childhood cancer survivors treated with HSCT [7].

Here, we report the results of a 28-month-long experience of metreleptin treatment, a recombinant analog of human leptin, in a patient with HSCT-associated partial lipodystrophy who had developed overt diabetes.

Submitted May 29, 2020; Accepted Oct. 29, 2020 as EJ20-0325
Released online in J-STAGE as advance publication Nov. 21, 2020
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Patients and Methods

Patient report

The female patient developed acute myeloid leukemia with multiple extra-marrow involvements when she was one year old. The first two bone marrow transplantations were unsuccessful; however, the third one leveraged by TBI achieved long-term remission. She has suffered from diverse post-transplant complications, including extensive chronic GVHD, leukoencephalopathy, intractable epilepsy, moderate intellectual impairment, cataract, GH deficiency, hypothyroidism, and hypogonadism. When first evaluated in the Endocrine Unit at 17 years of age, she was found to have a typical Dunnigan phenotype. Laboratory findings revealed a diabetic response to oral glucose tolerance test (fasting blood glucose [FBG] of 100 mg/dL and blood glucose 231 mg/dL at 120 min.) with extraordinary hyperinsulinemia (basal and peak insulin: 53.9 and 717 μIU/mL, respectively), hypertriglyceridemia (490 mg/dL), fatty liver, increased visceral fat area, and hypoadiponectinemia (1.6 μg/mL). Comprehensively, she was diagnosed with partial lipodystrophy. Recombinant GH therapy had never been provided because GH deficiency was diagnosed late, and because GH is contraindicated to diabetes in Japan. Her final height was 130 cm. Over the next 6 years, she had an increasing HbA1c level despite lifestyle modification and the later introduction of glibenclamide and metformin (Fig. 1). Thus, she fulfilled the diagnostic criteria of overt diabetes developed by the Japan Diabetes Society [11]. An add-on of insulin treatment was withheld because it may be challenging for her to manage hypoglycemia properly owing to her intellectual burden. We considered metreleptin to be suitable for her because severe hypoglycemia is less likely to occur as its side effect. Another reason is that metreleptin is expected to have a beneficial effect also against hypertriglyceridemia, which is severe and persistent in the patient. In addition, her caregiver hoped to avoid the increase in oral administrations, as the patient was already prescribed many oral medications including: glibenclamide, metformin, thyroid hormone, and some anti-epileptic agents. Moreover, in Japan, metreleptin is approved to treat both generalized and partial lipodystrophy. With the caregiver's documented consent, the trial of metreleptin was initiated at 23 years of age.

Method

The metreleptin therapy protocol was planned initially as a prospective study consisting of an observational period of 3 months, titration of 6 months (period A), and maintenance of 12 months (period B). An approved metreleptin dose is 0.08 mg/kg/day, namely 0.56 mg/kg/week, administered subcutaneously once daily. However, because of the patient's and her caregiver's strong aversion to self-injection, metreleptin was administered four times a week by visiting nurses. Therefore, the daily dose was gradually increased to 0.14 mg/kg during period A, and was stabilized thereafter. The doses of oral hypoglycemic agents were fixed throughout the study, with glibenclamide 2.5 mg a day and metformin 500 mg a day. The combination and amounts of antiepileptic drugs were determined by the corresponding neurologist based on the patient's epileptic symptoms. The L-thyroxine dose was adjusted according to the thyroid function tests. Monthly blood sampling was performed following overnight fasting, and blood pressure was recorded in a sitting position. Daily food intake in calories was calculated by a certified dietitian using photographs of consumed food. The number of steps recorded using a pedometer was adopted as an index of the patient's daily exercise amount, as walking was her main physical activity. Serum leptin levels were determined using a Human-Leptin radioimmunoassay (EMD Millipore, Darmstadt, Germany). Visceral and subcutaneous fat areas by single slice CT scans at the umbilical level were measured at 6-month intervals using FatVizCalc® version 1.1 (Lisit Co. Ltd., Tokyo, Japan). Discovery® DXA System A (Hologic, Inc. Massachusetts, USA) was utilized to analyze the body fat mass at 6-month intervals. For statistical analysis, IBM SPSS Statistics version 24 (IBM Corporation, New York, NY, USA) was used with a p-value of less than 0.05 considered to be significant. To compare the results obtained during each period to those in the observational period, an unpaired t test or Mann-Whitney U test was employed according to the parametric (HbA1c, blood pressure and liver function tests) or non-parametric (body weight, abdominal circumference, lipids and adipokines) nature of the data.

Results

As initially planned, the metreleptin dose of 0.14 mg/kg four times a week, which is equivalent to the authorized dose of 0.56 mg/kg/week, was achieved at the end of period A without any discernible adverse events. As described below, near the end of the study, a sudden deterioration in diabetes control was noted. Therefore, an additional 10 months was added to the study (period C). Unfortunately, fasting blood sampling, recording of food consumption and the number of steps, and body composition analysis could not be carried out during period C upon the caregiver's request.

Effects of metreleptin on carbohydrate metabolism

During the observational period, the patient's HbA1c

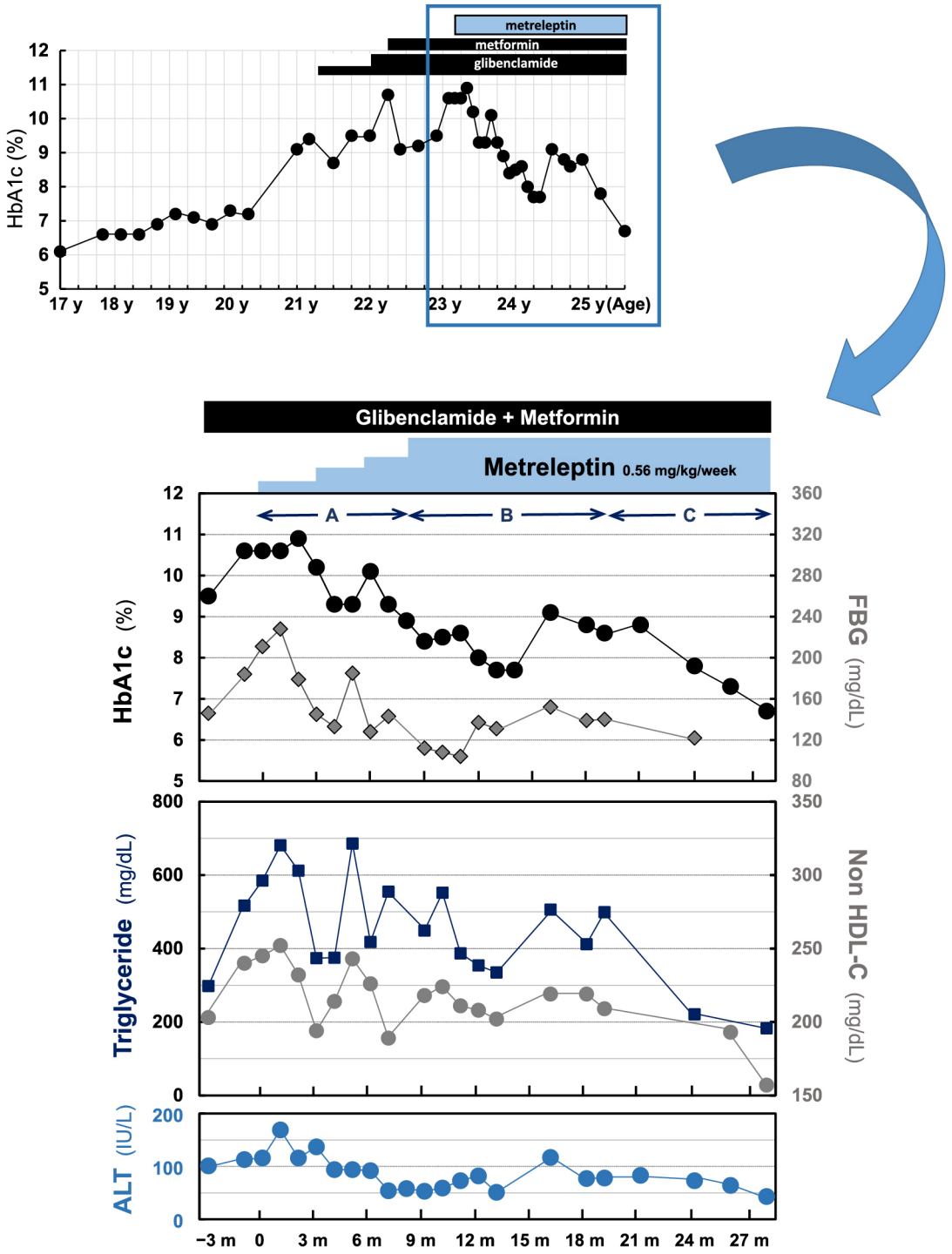


Fig. 1 Treatment course, with changes in major laboratory tests
Top panel: Long course since the diagnosis of lipodystrophy
Second panel: Indices of glycemic control during the study. A, B, and C corresponds to the three periods described in the text.
Third panel: Changes in triglyceride and non-HDL cholesterol levels
Bottom panel: Changes in ALT levels
FBG, fasting blood glucose

level ranged from 9.5% to 10.6%. During period A and the first half of period B, HbA1c level decreased gradually from the highest value of 10.9% to 7.7% (Fig. 1). Similarly, FBG levels also decreased. The fasting insulin level during the observational period, *i.e.*, 67.0, 83.7, and 90.6 μIU/mL, remained unchanged during the first half of period B with 77.4, 75.8, and 63.6 μIU/mL. By virtue of decreased FBG, homeostasis model assessment of

insulin resistance (HOMA-IR) decreased from 36.5 to 22.0 (3-month average during the observation period and period B before deterioration, respectively). 16 months after treatment initiation, the patient's HbA1c level suddenly deteriorated to 9.1%, while the fasting insulin level increased to 131.6 μIU/mL, resulting in a concomitant increase in HOMA-IR to 45.5 at 19 months. The patient's caregiver reported no significant change in both food consumption and physical activity. In fact, estimated consumed calories remained unchanged during periods A and B (Table 1). In addition, although once restricted due to impaired visual acuity, the patient's walking activity had recovered at the time of HbA1c deterioration, thanks to the successful cataract surgery. Instead, following the deterioration, the plasma leptin level unexpectedly increased to 409 ng/mL, whereas the mean leptin level during the observational period, period A, and period B before deterioration, was 21.3, 29.3, and 34.9 ng/mL, respectively (Table 1). At the end of the initial protocol of 1.5 years, her HbA1c was stable at around 8.6% and further deterioration seemed unlikely. Therefore, metreleptin treatment was continued at the same dose thereafter, and the study was extended by 10 more months (period C). Fortunately, her HbA1c levels during period C were significantly lower than those in the observational period (7.9 ± 0.9 *vs.* 10.2 ± 0.6; $p < 0.01$), and the latest HbA1c was 6.7%.

Effects of metreleptin on lipid metabolism

During predetermined 18-month-long protocol (periods A and B), fasting triglyceride levels, as well as those of HDL-cholesterol and non-HDL-cholesterol, showed no significant improvement. However, at the end of the additional 10 months (period C), fasting triglyceride

Table 1 Anthropometric, biochemical, radiological, and other indices during metreleptin treatment

	Observational period [–3 to –1 m]	Metreleptin treatment			
		Period A	Period B		Period C
		[0 to 6 m]	[7 to 15 m]	[16 to 19 m]	[20 to 28 m]
Body weight (kg)	27.5 (27.2–27.9)	27.4 (26.6–27.9)	26.8 (26.3–27.5)	*26.3 (26.1–26.4)	26.1 (25.6–26.7)
Systolic blood pressure (mmHg)	104 (98–107)	104 (99–114)	108 (99–120)	107 (103–110)	105 (98–111)
Diastolic blood pressure (mmHg)	69 (65–75)	70 (64–81)	69 (61–76)	73 (67–80)	63 (50–73)
Abdominal circumference (cm)	64.7 (64.0–65.8)	65.6 (64.6–66.3)	63.5 (62.5–65.0)	63.0 (61.5–64.5)	ND
Daily caloric intake (Cal/day)	1,088	1,117	1,508	1,047	ND
Daily walk (steps/day)	5,375	2,662	1,294	5,452	ND
Liver function tests					
ALT (IU/L)	110 (101–116)	108 (54–169)	†63 (51–82)	91 (77–117)	†66 (43–83)
γGTP (IU/L)	177 (144–220)	159 (129–196)	*121 (93–159)	*120 (108–137)	†71 (43–101)
Lipid profile					
Triglyceride (mg/dL)	467 (298–585)	529 (374–686)	415 (335–552)	472 (412–506)	*202 (183–221)
HDL-cholesterol (mg/dL)	37 (36–38)	35 (29–39)	34 (32–36)	*34 (33–35)	*35 (34–35)
Non-HDL cholesterol (mg/dL)	229 (203–245)	221 (189–252)	213 (202–224)	216 (209–219)	*175 (157–193)
Leptin (ng/mL)	21.3 (18.0–23.6)	29.3 (22.0–43.0)	34.9 (32.1–37.6)	338 (267–409)	ND
Adiponectin					
Total (μg/mL)	1.8 (1.6–1.9)	1.6 (1.5–1.8)	1.7 (1.6–1.7)	1.8 (1.7–1.8)	ND
High molecular weight (μg/mL)	0.39 (0.32–0.45)	0.35 (0.33–0.37)	0.40 (0.35–0.44)	0.45 (0.42–0.48)	ND
Fat area at the umbilical level					
Visceral fat (cm^2)	89.1	103.2	90.7	85.1	ND
Subcutaneous fat (cm^2)	84.5	82.3	76.0	63.7	ND
DEXA analysis					
Percent fat in total body (%)	33.9	33.3	ND	29.4	ND
Percent fat in trunk (%)	37.7	37.9	ND	33.3	ND

Mean and range (in parenthesis) are shown when more than two data are available. DEXA, dual-energy X-ray absorptiometry; ND, not determined

Period B is subdivided into two terms before and after the attenuation of the metreleptin effect. * $p < 0.05$, † $p < 0.01$ compared to the observational period.

levels decreased to just above the normal range. Whereas HDL-cholesterol had remained unchanged, non-HDL-cholesterol reached its lowest value at the end of period C (Fig. 1).

Effects of metreleptin on body composition

Fig. 2 shows the CT images at the umbilical level, with the results of visceral and subcutaneous fat area measurements. Compared to pretreatment, a 25% reduction in the subcutaneous fat area was found after 18 months of treatment. In accordance with this finding, the patient's body weight and abdominal circumference experienced a downward trend during period B. In addition, the fat percentage was minimal when evaluated at the end of period B in both the total-body and the trunk (Table 1).

Effects of metreleptin on other aspects

The patient's blood pressure remained consistently normal throughout the study period. Her daily caloric intake, estimated by photo records of the foods consumed for two days, was also unchanged (Table 1). As stated earlier, the reduced number of steps during period B might be a result of her impaired visual acuity caused by advanced cataracts. ALT and γGTP levels significantly declined, except for the temporary deterioration of ALT that occurred at the end of period B (Fig. 1 and Table 1). Regrettably, an imaging study for hepatic steatosis was not included in the study protocol. However, the ultrasonography performed recently at her 25 years of age revealed substantial improvement of fatty liver, compared to the prior study conducted when she was 17 years of age. Although the leptin level initially increased in parallel with metreleptin dose increments, the adiponectin levels remained low in both the total and high-molecular-weight forms (Table 1).

Safety issues

Metreleptin treatment has been well tolerated, and no regional reactions were ascertained. No other adverse events related to metreleptin were observed. Adverse events unrelated to metreleptin included a subdural hematoma following a fall caused by epileptic seizures and a deterioration of cataract necessitating surgery. An abruptly increased leptin level was observed in period B, accompanied by a sudden deterioration of diabetic control, suggesting the formation of anti-metreleptin antibodies with neutralizing activity. However, it is currently infeasible to determine the antibody titer because of the high cost.

Discussion

Interventions for lipodystrophy are challenging because high doses of insulin and/or antidiabetic drugs may be required to overcome severe insulin resistance [12]. In addition, hypertriglyceridemia tends to be refractory to various pharmacological agents such as fibrates, statins, and niacin [12]. In this situation, metreleptin has emerged as a revolutionary treatment option for both generalized and partial lipodystrophy with low leptin levels [13-15]. The metreleptin trial in our patient was

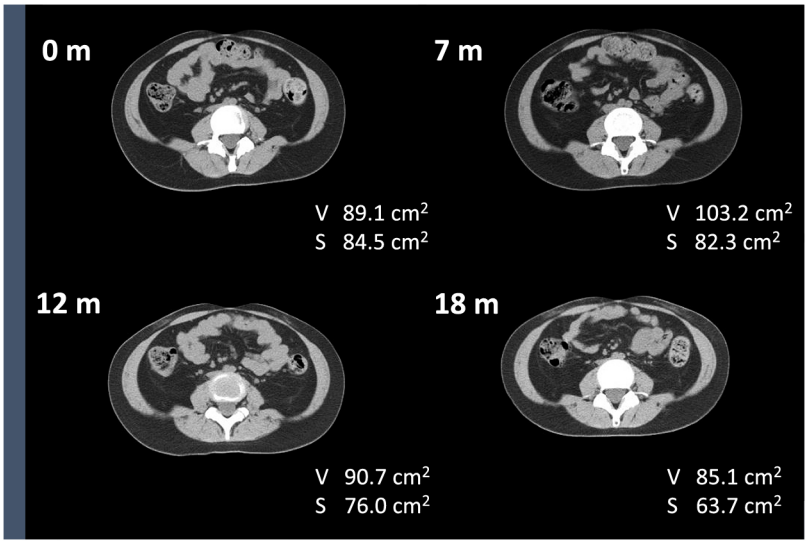


Fig. 2 Computed tomography images at the umbilical level, with the results of visceral and subcutaneous fat area measurements. Note a 25% reduction in the subcutaneous fat area at 18 months compared to pretreatment.

V, visceral fat area

S, subcutaneous fat area

planned because she had worsened glycemic control and persistent severe hypertriglyceridemia.

Having completed 28-months of treatment, the favorable effect of metreleptin on our patient's glycemic control is obvious. An absolute reduction of 4.2% in her HbA1c level was observed, although transient deterioration had occurred. Considering her intellectual difficulty, it seems unlikely that her own motivation to control diabetes significantly improved by participation in the trial. In addition, her appetite was stable, but her physical activity even decreased transiently due to her visual problem. Besides, her thyroid function remained stable, and the number and amount of anti-epileptic drugs decreased over time. Lastly, the patient's and her caregiver's adherence to the protocol was excellent, which can be further substantiated by the fact that visiting nurses were involved in both metreleptin injection and the checking of all other medications. Therefore, we assumed that the decline in the patient's HbA1c level resulted from the inherent metabolic effect of metreleptin. In particular, the decline in HOMA-IR might imply that metreleptin had ameliorated the severe insulin resistance. Besides the glycemic control, the patient's liver function also improved, indicating the alleviation of fatty liver. Also, metreleptin seems to be beneficial in reducing triglyceride and non-HDL cholesterol levels, whereas the HDL-cholesterol level did not respond. The subcutaneous fat mass at the umbilical level and fat percentage in DEXA analysis also decreased.

The sudden and unexpected deterioration of the patient's glycemic control occurred at 16 months, near the end of the initially planned protocol. This coincided with an upward trend in triglyceride and ALT levels. Considering the concomitant elevation in the serum leptin level, it seems most likely that the effect of metreleptin was cancelled out by the anti-metreleptin antibody. Although its precise frequency is unknown, the development of antibodies with neutralizing potency, coupled with resultant loss of clinical efficacy, has been described previously in patients with lipodystrophy, obesity, or congenital leptin deficiency [16-18]. In most cases with neutralizing antibodies, the circulating leptin levels were high, determined by either radioimmunoassay or enzyme-linked immunosorbent assay, suggestive of a delayed clearance of antibody-bound metreleptin. In addition, as observed in our patient, some patients with neutralizing antibodies experienced a spontaneous restoration of the clinical effect of metreleptin, as well as a decrease in antibody titer, during the continuation of metreleptin treatment [17, 18]. The decrease, or even disappearance, of anti-drug antibodies is also observed in other peptide drugs, including vatreptacog alfa [19], adalimumab [20], and infliximab [21].

The effectiveness of metreleptin treatment strengthens our hypothesis of HSCT-associated lipodystrophy. In addition to our own trial, two recently published reports also described favorable effects of metreleptin on both glycemic and lipid control in patients who developed lipodystrophy following HSCT [22, 23]. By adhering to the predetermined 18-month-long protocol, consisting of periods A and B, our trial may be unique in excluding both the possible anorexic effect of metreleptin and lifestyle change during the trial. It was unfortunate that during period C, some of the planned measurements were refused by the caregiver. Nevertheless, cumulative evidence on the effectiveness of metreleptin in treating diabetes patients following HSCT indicates that HSCT-associated lipodystrophy is a real clinical entity and that dysfunctions of adipose tissue, including adipose tissue expandability and insufficient adipokine production, are among the main causes of HSCT-associated lipodystrophy.

The concept of HSCT-associated partial lipodystrophy is shown in Fig. 3. We, and other authors [7, 8, 24, 25], have speculated that adipose tissue injury caused by TBI is the major cause of severe insulin resistance with Dunnigan phenotype. In accordance with this assumption, a significant correlation between the post-HSCT period and the risk for developing lipodystrophy or diabetes [7, 26], as well as the adiponectin level [6], has been demonstrated, indicative of progressive adipocyte damage induced by TBI. In addition, TBI was found to be the independent risk factor for diabetes after HSCT [2]. However, it is acceptable that some potential factors may expedite the impact of TBI. These include chemotherapeutic agents used during first-line treatment and/or transplantation preconditioning, cranial or abdominal irradiation [27], endocrinological complications (including hypothyroidism, hypogonadism, and GH deficiency), sarcopenia [5, 6], chronic GVHD (especially GVHD-related scleroderma [7, 10]), and immunosuppressants used for GVHD treatment. Among these, GH status may be of particular importance because adults with GH deficiency are at risk of insulin resistance and increased visceral fat, which may temporarily worsen when GH treatment is initiated [28]. In addition, estrogen deficiency may be related to the limited storage capacity of subcutaneous adipose tissue. As for our patient, the additional complexity of high-dose chemotherapy, extensive GVHD, hypogonadism, and untreated GH deficiency may be relevant to the extreme phenotype.

Nevertheless, the main role of TBI is supported by the following findings. First, among the survivors of childhood leukemia, those with HSCT/TBI had substantially worse metabolic outcomes compared to those treated solely by chemotherapy [3]. In the same study, a worsening metabolic outcome with time elapsed since primary

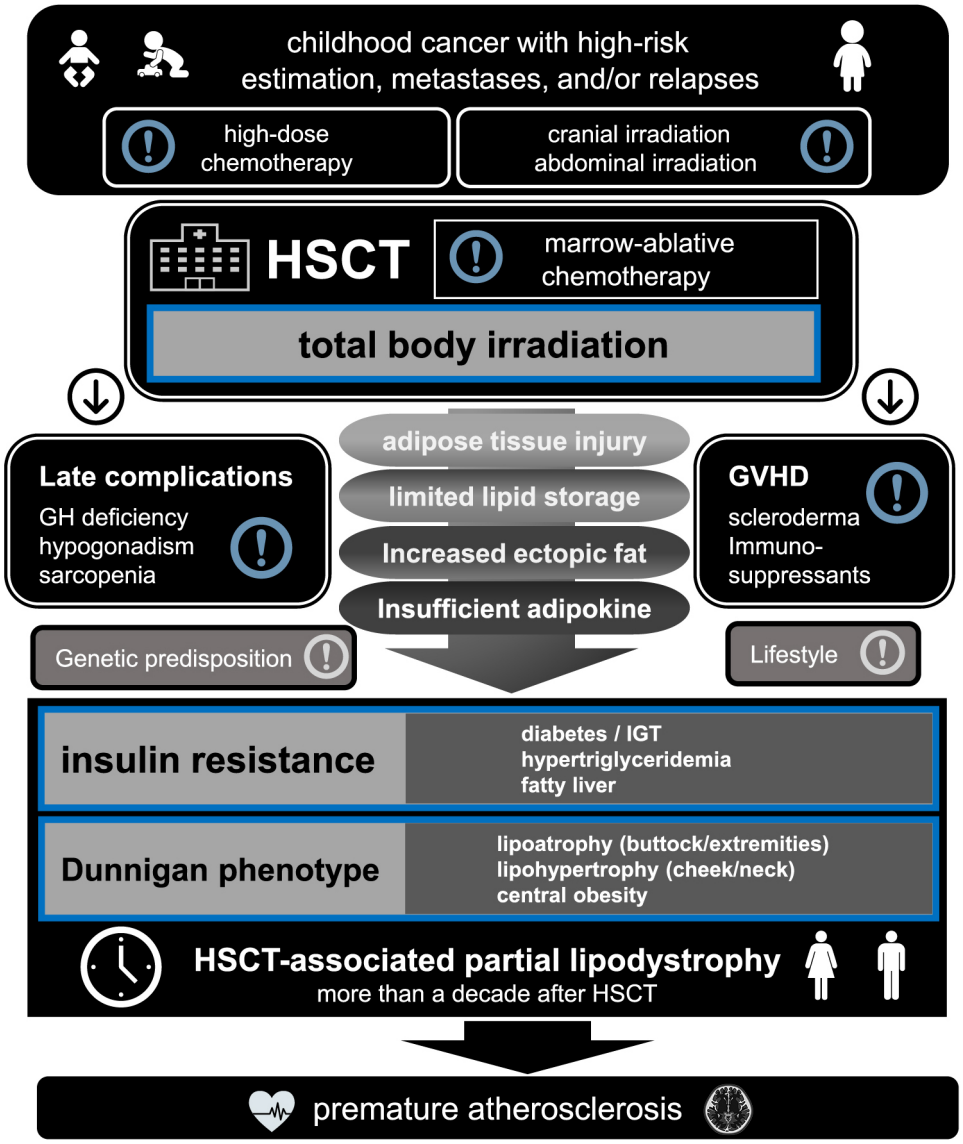


Fig. 3 Concept of HSCT-associated partial lipodystrophy. The severe insulin resistance with Dunnigan phenotype of partial lipodystrophy usually occurs more than a decade after HSCT. The main culprit for this serious complication, which may lead to premature atherosclerosis, is the adipose tissue damage induced by total body irradiation. In addition, other factors, indicated by exclamation points in this figure, may be involved in the development of lipodystrophy. These include chemotherapeutic agents, cranial or abdominal irradiation, endocrinological complications, sarcopenia, GVHD, lifestyle, and genetic predisposition.

HSCT, hematopoietic stem cell transplantation
GVHD, graft-*versus*-host disease
IGT, impaired glucose tolerance

treatment was found only in HSCT/TBI survivors and not in the chemotherapy-only group [3]. Second, no causative link between lipodystrophy and any endocrinopathies listed above has been established. In addition, one study comparing patients with HSCT/TBI with or without GH deficiency showed no difference in body composition, prevalence of abnormal glucose tolerance, adiponectin, or fat deposition pattern [6]. Lastly, 3 out of 6 patients with lipodystrophy identified through our institutional survey were free from GVHD [7]. Similar cases of lipodystrophy without GVHD have also been found [24, 25]. In addition, no impact of GVHD or post-transplantation steroid dose was shown to affect any components of metabolic syndrome among the survivors of childhood leukemia [29].

Our patient's pretreatment leptin level was relatively high, compared to that in the inclusion criteria of the National Institute of Health pilot study for partial lipodystrophy (*i.e.* <12.0 ng/mL in females and <8.0 ng/mL in males) [14]. The favorable effect of metreleptin in our

patient may indicate that it can exert its metabolic effect not only in individuals with low leptin levels but also in those with rather high leptin levels, by virtue of a supra-physiological metreleptin level.

Whether or not lipodystrophy will develop in a given patient following HSCT may depends on the combination of above-mentioned factors that might expedite the impact of TBI. In addition, lifestyle diversity and/or genetic variation predisposing to metabolic disorders may also be involved (Fig. 3). This assumption implies that the severity of HSCT-associated lipodystrophy differs widely among patients: in contrast to a full-blown patient like ours, mildly affected patient may develop metabolic derangement with subtle Dunnigan phenotype. If this assumption holds true, metreleptin may be a treatment option for post-HSCT metabolic complications regardless of the severity of lipodystrophy.

Conclusion

Metreleptin substantially improved glycemic control in a young female with partial lipodystrophy with Dunnigan phenotype that developed after HSCT preceded by TBI. This finding reinforces the concept of 'HSCT-associated lipodystrophy'. Metreleptin may be a treatment option for HSCT-associated lipodystrophy, regardless of pre-treatment leptin levels.

Acknowledgements

The authors would like to thank Mrs. Miki Koba for her dedication in the calculation of daily caloric intake. In addition, we are grateful to Dr. Satoshi Takakuwa, Department of Pediatrics, Hyogo Prefectural Nishinomiya Hospital (Hyogo, Japan), for his valuable comment on anti-metreleptin antibody formation.

Ethical Approval and Consent to Participate

All procedures were in accordance with the national ethical standards of human clinical study and with the 1964 Helsinki Declaration and later versions. This study was approved by the Institutional Review Board at Kanagawa Children's Medical Center as 1707-02 in December 2017, and written informed consent for the publication of the details of study results was obtained from the patient's caregiver.

Disclosure

The authors declare no conflicts of interest.

Author Contributions

MA, KM, and JH attended to the patient; MA wrote the manuscript; KM and YA provided conceptual advice. All authors have read and approved the final manuscript.

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