

# Case of lipoatrophic diabetes induced by juvenile dermatomyositis

Yusuke Baba<sup>1</sup>, Hiyori Kaneko<sup>1</sup>, Minoru Takemoto<sup>1,2\*</sup> , Kana Ide<sup>1</sup>, Yuki Haga<sup>3</sup>, Tatsuo Kanda<sup>3</sup>, Shinsuke Akita<sup>4</sup>, Yoshitaka Kubota<sup>4</sup>, Masayuki Kuroda<sup>5</sup>, Yutaka Kitagawa<sup>6</sup>, Koutaro Yokote<sup>1</sup>

<sup>1</sup>Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Chiba, <sup>2</sup>Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, International University of Health and Welfare, Narita, Departments of <sup>3</sup>Gastroenterology and Nephrology, <sup>4</sup>Plastic, Reconstructive, and Aesthetic Surgery, Chiba University Graduate School of Medicine, <sup>5</sup>Center for Advanced Medicine, Chiba University Hospital, Chiba, and <sup>6</sup>Numazu City Hospital, Shizuoka, Japan

## Keywords

Lipodystrophy, Metreleptin, Pioglitazone

## \*Correspondence

Minoru Takemoto  
 Tel.: +81-476-20-7701  
 Fax: +81-476-20-7702  
 E-mail address:  
 minoru.takemoto@iuhw.ac.jp

## ABSTRACT

Lipodystrophy is a rare condition that is often accompanied by one or more metabolic diseases. Here, we report a case of lipoatrophic diabetes induced by juvenile dermatomyositis. Although pioglitazone was not effective for lowering blood glucose levels, our observation suggested that it improved liver function slightly. The effectiveness of metreleptin for lowering blood glucose levels could not be determined, as we administered it in a short period. Liver biopsy showed burned-out non-alcoholic steatohepatitis. The present results show that the successful treatment of lipoatrophic diabetes induced by juvenile dermatomyositis requires an early diagnosis and therapeutic intervention.

*J Diabetes Investig* 2018; 9: 632–635

doi:10.1111/jdi.12745

## INTRODUCTION

Lipodystrophy is a rare condition that is characterized by severe loss of subcutaneous fat tissue from the face, arms and legs; it is often accompanied by metabolic diseases<sup>1</sup>. We observed a case of generalized lipodystrophy caused by juvenile dermatomyositis, and accompanied by diabetes and liver cirrhosis. Here, we report the effects of treatment with pioglitazone and metreleptin on glycemic control and liver function.

## CASE REPORT

A 19-year-old man was admitted to the Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, Chiba, Japan, for close examination and treatment of poorly controlled diabetes. He was diagnosed with juvenile dermatomyositis at 3 years-of-age. Immunosuppressive therapy with prednisolone had been initiated, and the dermatomyositis had improved; however, muscle atrophy and joint contracture appeared at 5 years-of-age. He was diagnosed with diabetes at age 9 years-of-age, and given acarbose at 9 years-of-age; metformin was then added at 18 years-of-age. Juvenile dermatomyositis completely resolved at 15 years-of-age, and the prednisolone was discontinued. However, his blood glucose control did not improve.

On admission, the patient's height was 165 cm, weight was 40.8 kg and body mass index was 15.0 kg/m<sup>2</sup>. He had no obvious diabetic complications, such as retinopathy or nephropathy, but he lost a considerable amount of subcutaneous fat and peripheral muscle, particularly in his extremities, and his knee joints were contracted (Figure 1). The initial examination findings are shown in Table 1. He also showed decreased levels of adipocytokines (Table 1). A 75-g oral glucose tolerance test revealed relatively severe insulin resistance (Figure S1). Computed tomography at the umbilical level showed very low amounts of subcutaneous fat tissue (6.4 cm<sup>2</sup>; Figure S2), but no liver abnormalities. At birth, his weight and appearance were both normal, and he had no family history of lipodystrophy. These findings led to a prior diagnosis of acquired generalized lipodystrophy (AGL) induced by juvenile dermatomyositis.

Considering the patient's lipodystrophy and diabetes, he was prescribed 15 mg pioglitazone daily. After receiving pioglitazone for 18 months, his blood glucose and glycated hemoglobin (HbA1c) levels remained unchanged, but his transaminase levels slightly attenuated (Table 1). Changes in transaminase levels and HbA1c from 8 years-of-age are also shown in Table S1. Additionally, his levels of type IV collagen, hyaluronic acid and value of Fibroscan<sup>®</sup> (indicative of liver fibrosis) were all slightly attenuated. Computed tomography scan showed a few changes in the amount of subcutaneous fat after 18 months

Received 10 April 2017; revised 26 August 2017; accepted 30 August 2017



**Figure 1** | Patient appearance.

of pioglitazone treatment (Table 1). As his liver transaminase levels were still abnormal, we therefore carried out a liver biopsy, and diagnosed the patient with type 4 non-alcoholic fatty liver disease<sup>2</sup> (Figure 2; Figure S3).

To determine why pioglitazone did not sufficiently increase the fat mass to reduce blood glucose levels, we obtained subcutaneous fat tissue from the patient's right breast after obtaining his informed consent. We compared the expression levels of adipocyte differentiation markers with those isolated from the subcutaneous fat tissue of a non-diabetic patient. As shown in Figure S4, adipocyte differentiation markers were severely attenuated in the present patient. We also tried to culture preadipocytes and compare their proliferative activities without success (data not shown), showing that the proliferation and differentiation capacities of the patient's subcutaneous fat tissue were severely attenuated.

As pioglitazone did not improve his blood glucose levels, we administered 0.02 mg/kg metreleptin to control blood glucose. We examined the short-term effects of metreleptin through a 75-g oral glucose tolerance test. Compared with baseline levels, the glucose area under the curve decreased by 10.9% after 8 days of metreleptin treatment. Although metreleptin might have lowered his blood glucose levels, this treatment was terminated because of patient non-compliance due to difficult and painful self-injections.

**DISCUSSION**

Juvenile dermatomyositis complicated by lipodystrophy has a prevalence of 10–40%<sup>3</sup>. The severity of juvenile dermatomyositis

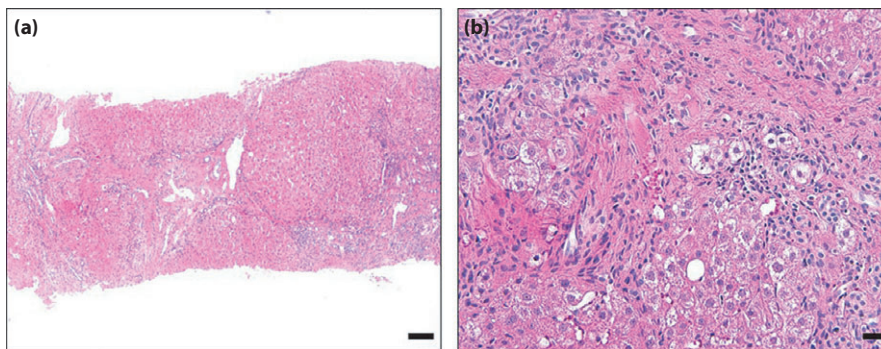
**Table 1** | Laboratory findings at initial visit and after pioglitazone treatment

	Initial visit	After pioglitazone treatment		
		3 months	6 months	18 months
Bodyweight (kg)	40.8			41.4
BMI (kg/m <sup>2</sup> )	15.0			15.2
HbA1c (%)	8.6	8.6	9.6	8.8
FBS (mg/dL)	197		190	205
IRI (μU/L)	25.6			41.2
CPR (ng/mL)	3.64			4.25
Total cholesterol (mg/dL)	206			203
HDL cholesterol (mg/dL)	26	27	28	25
LDL cholesterol (mg/dL)	169	164	168	169
Triglyceride (mg/dL)	130	246	196	132
AST (U/L)	61	64	89	44
ALT (U/L)	132	111	125	101
γGTP (U/L)	60	47	60	51
Albumin (g/dL)	4.7	4.3	4.4	4.6
Total bilirubin (mg/dL)	0.9			0.7
Platelet (10 <sup>4</sup> /μL)	15.5	14.1	14.8	16.7
Serum creatinine (mg/dL)	0.12	0.10	0.14	0.17
Fasting leptin (ng/mL)	2.8			3.2
Fasting adiponectin (μg/mL)	2.5			2.9
Visceral fat area (cm <sup>2</sup> )	44.7			79.2
Subcutaneous fat area (cm <sup>2</sup> )	6.4			12.0
HBsAg				(-)
HCV antibody				(-)
Anti-mitochondrial antibody	<1.5			
Type IV collagen (ng/mL)	6.5			6.1
Hyaluronic acid (ng/mL)	21			11
Fibroscan (kPa)	13.2			11.4

Reference values for type IV collagen, hyaluronic acid, and fibroscan are <6 ng/mL, <50 ng/mL and <7 kPa, respectively. γGTP, gamma-glutamyltransferase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CPR, C-peptide reactivity; FBS, fasting blood glucose; HbA1c, glycated hemoglobin; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein; IRI, immunoreactive insulin; LDL, low-density lipoprotein.

is related to lipodystrophy. Particular risk factors for lipodystrophy include panniculitis, calcinosis, joint contracture, and muscle atrophy<sup>3</sup>. Lipodystrophy leads to the development of metabolic diseases and an average lifetime expectancy of 30–40 years because of metabolic disease complications. The present patient underwent a liver biopsy, but, unexpectedly, the steatohepatitis had already progressed to hepatic cirrhosis, despite his young age. Therefore, it was important to control his hepatic disease to improve his prognosis.

The present case showed a relatively milder phenotype than that of the reported typical AGL (i.e., milder insulin resistance). This is probably because the patient had relatively preserved



**Figure 2** | Liver biopsy specimen showed burned-out non-alcoholic steatohepatitis. (a) Distortion of hepatic lobular architecture was extensively observed (hematoxylin–eosin stain; lower-power view). (a,b) Although few lipid droplets (<5%) were observed, burned-out non-alcoholic steatohepatitis<sup>10</sup> was considered, because pericellular and perivenular fibrosis were prominent, and other causes of liver diseases were ruled out in the present case. Scale bars represent (a) 100  $\mu$ m and (b) 20  $\mu$ m.

subcutaneous fat, whereas typical AGL shows a nearly complete absence of adipose tissue.

We examined two different agents (pioglitazone and metreleptin) to improve the patient's blood glucose control. Previous reports suggested that pioglitazone is an effective treatment for lipotrophic diabetes<sup>4</sup>, as it promotes preadipocyte differentiation. Previous reports showed that pioglitazone increased fat mass in non-lipotrophic body regions in patients with familial partial lipodystrophy<sup>4</sup>. However, pioglitazone did not reverse subcutaneous fat loss in lipotrophic body regions<sup>5</sup>. We administered pioglitazone, with the expectation that it would sufficiently increase the amount of fat tissue to reduce blood glucose levels, but without success. As the patient experienced full-body fat tissue loss, the number of preadipocytes might have been insufficient to respond to the pioglitazone treatment. Indeed, isolated subcutaneous fat tissue showed severely attenuated levels of adipocyte differentiation markers and proliferation capacity. These results show that the present patient should have been diagnosed and treated with pioglitazone earlier in the course of his disease.

Although pioglitazone was not effective for lowering HbA1c levels, our observation suggested that it improved liver function slightly. His aminotransferase levels attenuated after 18 months of pioglitazone treatment. As we did not carry out a liver biopsy before pioglitazone treatment, we are unable to conclusively show that pioglitazone had favorable effects on his non-alcoholic steatohepatitis (NASH). However, several reports showed that pioglitazone effectively treats liver disease caused by lipodystrophy<sup>6</sup>. We resume pioglitazone therapy so that it ameliorates liver function. Furthermore, as none of the markers of liver function predicted the presence of burned-out NASH in the present case, liver biopsy can be carried out at an early time-point when patients with lipodystrophy show liver dysfunction.

Metreleptin replacement therapy is a reportedly effective treatment for lipodystrophy<sup>7</sup>. A 9-year-old girl with AGL as a

result of active juvenile dermatomyositis was reported to be successfully treated with metreleptin. Not only did her triglyceride and HbA1c levels improve, but also her liver transaminase levels reportedly improved. She developed AGL when she was 7 years-of-age, and metreleptin treatment was started after 2 years<sup>8</sup>. Furthermore, it improves approximately two-thirds of NASH cases induced by lipodystrophy<sup>9</sup>, making it superior to pioglitazone treatment. Therefore, metreleptin replacement therapy in the early phase in this case might be effective for lowering blood glucose levels and preventing NASH. Unfortunately, we were unable to continue the metreleptin treatment because of patient non-compliance. Therefore, transplantation of fat tissue might be a suitable, alternative treatment for similar cases.

#### ACKNOWLEDGMENTS

We thank Mrs Aki Watanabe and Mrs Naoko Koizumi (Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine) for their valuable technical assistance.

#### DISCLOSURE

The authors declare no conflict of interest.

#### REFERENCES

1. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004; 350: 1220–1234.
2. Matteoni CA, Younossi ZM, Gramlich T, *et al.* Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; 116: 1413–1419.
3. Bingham A, Mamyrova G, Rother KI, *et al.* Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. *Medicine (Baltimore)* 2008; 87: 70–86.
4. Sleilati GG, Leff T, Bonnett JW, *et al.* Efficacy and safety of pioglitazone in treatment of a patient with an atypical partial lipodystrophy syndrome. *Endocr Pract* 2007; 13: 656–661.

5. Simha V, Rao S, Garg A. Prolonged thiazolidinedione therapy does not reverse fat loss in patients with familial partial lipodystrophy, Dunnigan variety. *Diabetes Obes Metab* 2008; 10: 1275–1276.
6. Cusi K, Orsak B, Bril F, *et al.* Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016; 165: 305–315.
7. Oral EA, Simha V, Ruiz E, *et al.* Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002; 346: 570–578.
8. Lebastchi J, Ajluni N, Neidert A, *et al.* A report of three cases with acquired generalized lipodystrophy with distinct autoimmune conditions treated with metreleptin. *J Clin Endocrinol Metab* 2015; 100: 3960–3970.
9. Safar Zadeh E, Lungu AO, Cochran EK, *et al.* The liver diseases of lipodystrophy: the long-term effect of leptin treatment. *J Hepatol* 2013; 59: 131–137.
10. Ong J, Younossi ZM, Reddy V, *et al.* Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl* 2001; 7: 797–801.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1** | The 75-g oral glucose tolerance test before treatments.

**Figure S2** | Computer tomography image at the umbilical level.

**Figure S3** | Liver biopsy specimen showed burned-out non-alcoholic steatohepatitis.

**Figure S4** | The expression of adipocyte differentiation markers in isolated subcutaneous fat tissue.

**Table S1** | Changes in transaminase levels and glycated hemoglobin from 9 years-of-age.

**Table S2** | Primer sequences for real-time polymerase chain reaction.