Multifocal lipoatrophy secondary to insulin injection in a patient with type 2 diabetes, hepatitis B virus infection, and liver cirrhosis

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Abstract
Lipoatrophy secondary to insulin injection is a rare complication of insulin use. Localized lipoatrophy is recognized by a loss of subcutaneous fat caused by insulin injection. We report the case of a 69-year-old non-obese female patient with type 2 diabetes mellitus, decompensated liver cirrhosis, and hepatitis B virus (HBV) infection who developed multifocal lipoatrophy during the administration of human insulin and an insulin analog.

Keywords
Lipoatrophy, type 2 diabetes mellitus, hepatitis B virus, liver cirrhosis, human insulin, insulin analog

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Introduction
Insulin-induced lipoatrophy is a rare complication of repeated insulin injection that manifests as a reduction in local subcutaneous adipose tissue mass. Many factors are involved in the etiology of lipoatrophy, including adverse immunological side-effects of insulin therapy and anaphylaxis connected with impurities in the preparations. With the development of high-purity insulin and its analogs, insulin-induced lipoatrophy has become less common and multifocal lipoatrophy is even rarer. Here, we report a case of multiple localized lipoatrophy in a patient with type 2 diabetes mellitus (T2DM),
decompensated liver cirrhosis, and hepatitis B virus (HBV) infection who was administering premixed insulin and an insulin analog.

Case presentation

We report the case of a 69-year-old woman who was diagnosed with type 2 diabetes when she was 65 years old, had had HBV infection for 10 years, and who presented with a blood glucose concentration of 21.3 mmol/L and decompensated liver cirrhosis. According to the patient, she had vomited ~500 mL fresh blood twice a day 10 years previously. After treatment by esophageal and gastric fundic vascular ligation to provide hemostasis (details unknown), the patient’s hematemesis was significantly ameliorated. Hepatitis screening showed positivity for hepatitis B virus surface antigen (HBsAg), hepatitis B virus core antibody IgG (HBcAb IgG) and hepatitis B virus e antibody IgG (HBeAb IgG), but not for hepatitis B virus surface antibody (HBsAb) or hepatitis B virus e antigen IgG (HBeAg). The HBV DNA concentration was within the normal range, as were the circulating aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities and the total bilirubin concentration (21 IU/L, 29 IU/L, and 11 μmol/L, respectively). Elastography showed the presence of severe liver fibrosis, with a stiffness of 16.5 kPa. The patient had not undergone any antiviral therapy, but had taken some Chinese medicinal herbs 2 years after the onset of diabetes. Since then, she had been under the care of the Department of Endocrinology of Dongyang People’s Hospital.

After her first hospital stay, the patient weighed 56 kg, was 158 cm tall, and had a body mass index (BMI) of 22.4 kg/m². She was administering 30 units daily of recombinant NovoRapid® 30Mix (BIAsp30). Lipoatrophy developed at the insulin injection site on the right side of her abdominal wall 1 year after the start of insulin therapy (Figure 1a), and during this period she was not admitted to hospital because of liver cirrhosis decompensation or other problems. Furthermore, after she started administering insulin on her left side, a second lesion developed there. She next started to rotate her injection sites, including both sides of her thighs (Figure 1b), buttocks (Figure 1c), and arms (Figure 1d), but lipoatrophic defects developed at all these injection sites, which were confirmed ultrasonographically (Figure 2). The ultrasonographic examination showed that her skin was normal (Figure 2a), the underlying adipose tissue was dystrophic (Figure 2b), and the underlying muscle was normal (Figure 2c). The size of all the lesions increased steadily, and 1 year after starting insulin therapy, indentations of various sizes had developed. The dimensions of the smallest indentation were 0.4 cm × 1 cm (left arm) and those of the largest were 5 cm × 12 cm (thigh), with depths of 0.2 to 2 cm. The lipoatrophic lesions expanded around the insulin injection site. According to the patient, she had sought medical assistance in the city of Dongyang, and many attempts were made to ameliorate the lesions, mainly comprising changes in the injection site and insulin type, including a switch to Novolin 30R (an insulin mix consisting of 30% R/neutral insulin and 70% neutral protamine Hagedorn [NPH]). However, these measures failed to stop the development of lipoatrophic lesions or ameliorate the existing lesions. Four years after starting insulin therapy, when the patient was last examined, she had lost 2 kg of body mass, such that she weighed 54 kg and had a BMI of 21.6 kg/m², with no ascites. Routine laboratory testing showed that her white blood cell count was within the normal range. Her circulating procalcitonin
concentration was within the normal range (0.17 ng/mL), but those of interleukin-6 (IL-6) and C-reactive protein (CRP) were high (16.83 pg/mL and 8.13 ng/L, respectively).

She stopped injecting insulin for 6 months after visiting her physician, at the end of which she had a glycated hemoglobin (HbA1c) concentration of 8.3%, a fasting blood glucose concentration of 21.3 mmol/L and normal concentrations of relevant autoantibodies, including versus glutamic acid decarboxylase (GAD), islet cell cytoplasmic autoantibodies (ICAs), insulinoma-associated-2 autoantibodies (IA-2As), and insulin autoantibodies (IAAs).

At this time, the patient was instructed to stop her insulin injections and to start oral antidiabetic drugs (OADs; an alpha-glucosidase inhibitor [acarbose] and a sulfonylurea [glimepiride]). This treatment was successful because 1 month after discharge she had an HbA1c of 7.2% and there had been no deterioration in her liver indices. In addition, after 6 months of this regimen, there had been no deterioration of the lipoatrophy and no more new sites of lipoatrophy had developed.
Discussion

We have reported a case of severe multiple localized lipoatrophy in a patient with T2DM, decompensated liver cirrhosis, and HBV infection, who was being treated with premixed insulin and an insulin analog. After switching the patient to OADs, there was no further deterioration of the lipoatrophy and no more lesions developed.

Various pharmaceutical preparations, including glucocorticoid hormone preparations and papillomavirus vaccines, can cause localized insulin-induced lipoatrophy. Furthermore, liver diseases, including virus hepatitis, liver cirrhosis, and fatty liver, can also be associated with partial or generalized acquired lipoatrophy. In the patient reported herein, we do not know whether the pathogenesis of the lipoatrophy was related to the HBV infection or liver cirrhosis. To determine this, further clinical characterization and laboratory work will be required.

Ramos et al. reported lipoatrophy in a patient with type 1 diabetes mellitus who was administering a recombinant human insulin preparation. This problem was successfully managed by the administration of daily NPH insulin mixed with betamethasone. However, in the patient reported herein, neither changing the insulin type nor the injection site was effective at ameliorating the lipoatrophy. Instead, glycemic control was achieved using OADs in this patient. In adult patients, insulin-induced lipoatrophy rarely resolves spontaneously, and in the patient reported herein, the lipoatrophy did not resolve after insulin injection was stopped, but also did not progress. However, ongoing monitoring will be required to determine the long-term effects of the insulin injection.

The circulating IL-6 concentration of the present patient was high. Previous studies have shown that the basal serum IL-6 concentration is high in type 2 diabetic patients. IL-6 may directly or indirectly contribute to muscular atrophy, but whether IL-6 signaling is sufficient for and/or has a direct role in the induction of muscle atrophy remains controversial. The neutralization of extracellular IL-6 prevents adipose tissue lipolysis, because in cachectic mice that are administered an anti-IL-6 receptor antibody, white adipose tissue (WAT) lipolysis and browning are inhibited. However, we were unable to determine whether the high IL-6 concentration played a role in the insulin-induced lipoatrophy in the present case.

Previous studies have shown that visceral and subcutaneous WAT have differing biology. Visceral adipose tissue is characterized by greater lipolysis and less lipogenesis, such that expansion of this depot promotes the portal delivery of lipid to the liver. In contrast, subcutaneous adipose tissue is a more metabolically neutral store for excess lipids, whereby it protects insulin-sensitive tissues from lipotoxicity. The release of cytokines and lipid metabolites is increased by lipolysis, and this plus impaired lipogenesis in adipose tissue leads to the development of insulin resistance. Insulin resistance, excess fat accumulation, and inflammation promote lipid influx into the liver and are key participants in the pathogenesis of diabetes and liver disease. Furthermore, because adipose tissue regulates many immune mechanisms, substances released by atrophic adipose tissue in response to insulin injection at these sites may have played a role in the liver cirrhosis of the present patient.

Autoimmunity, especially mediated through hyperactivation of the complement pathway, has been reported in most cases of acquired partial lipoatrophy. However, the mechanism whereby such autoimmunity induces adipose tissue abnormalities remains to be identified. Recently, the pathology associated with some genetic disorders of glycosylation have been shown to
involve autoinflammation that arises because of a proteasomal anomaly. These also result in a lipoatrophic syndrome, which is characterized by fever, dermatosis, and panniculitis.\textsuperscript{24} This is likely to be an autoimmune disorder, because it resembles other autoimmune disorders that have been previously reported.\textsuperscript{25} However, further research is required to characterize the links between autoimmunity and lipoatrophy.

Limitations
Because of the rarity of the reported phenomenon, it is difficult to make a more extensive evaluation.

Conclusions
We have reported a case of severe multifocal lipoatrophy that developed following the administration of a premixed insulin preparation comprising an insulin analog and human insulin at multiple sites, which is rarely encountered at present. This is the first case of lipoatrophy that has been described in a patient with T2DM, combined with decompensated liver cirrhosis and HBV infection, and it was first diagnosed 1 year after starting the insulin therapy. Switching the treatment to OADs maintained the patient’s glycemic control and there was no further deterioration of the lipoatrophy.

Ethics statement
All the patient’s details were de-identified and she provided her written informed consent. The investigation was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Dongyang Hospital (2018-XY-003).

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Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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Author contributions
Y.W. and X.L. conceived and supervised the project. Y.W. conducted the data analysis. Y.W. wrote the manuscript. X.L. reproduced the data analysis. Y.W. and X.L. revise the manuscript. Both authors discussed the results and commented on the manuscript. Both authors agree to be accountable for the work and to ensure the accuracy and integrity of all parts of the work.

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