〈Case Reports〉

Insulin administration to an abdominal insulin ball that triggered the onset of diabetic ketoacidosis accompanied by Hamman's syndrome in a patient with type 1 diabetes mellitus

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ABSTRACT A 41-year-old man with type 1 diabetes mellitus was referred to our hospital because of diabetic ketoacidosis accompanied by Hamman's syndrome. Recently, he has injected a total of 68 units of lispro and 50 units of degludec. Although he didn't notice at all, there was a huge subcutaneous induration on the left abdomen. We diagnosed this as an insulin ball. It is noted here that insulin injection site had been fixed for 19 years. After resuming insulin injection while avoiding the insulin ball, good glycemic control was obtained only with 31 units of aspart and 17 units of degludec. doi：10.11482/KMJ-E202450069 *(Accepted on October 23, 2024)*
Key words：Diabetic ketoacidosis, Habitual action, Hamman's syndrome, Insulin ball, Type 1 diabetes

INTRODUCTION

While lipohypertrophy, one of skin symptoms at the insulin injection site, is recognized as a bulge of subcutaneous fat, insulin-derived amyloid deposits under the skin have been recently named insulin ball[1]. Differential diagnosis of these two diseases is important because insulin ball much more significantly impairs insulin absorption compared to lipohypertrophy. In addition, insulin ball is usually harder than lipohyoertrophy and takes longer time to disappear[2]. It is often difficult to distinguish them with clinical findings alone. Injecting insulin into an insulin ball causes insulin malabsorption instead of relieving pain, leading to unexpected hyperglycemia.

CASE REPORT

A 41-year-old man with type 1 diabetes mellitus diagnosed at 22 years old was referred to our hospital because of general fatigue, nausea, and frequent vomiting. Recently, he has had subcutaneous insulin injection with 26, 20, 22 units of lispro before each meal and 50 units of degludec before dinner (total insulin dose, 118 units; 1.9 units/kg). At that time, his blood glucose level was 438 mg/dL. Ketoacidosis was observed as follows:

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pH, 7.145; base excess -22.9 mEq/L; lactate, 1.6 mEq/L. Total ketone bodies were 14,360 μmol/L (acetoacetic acid, 4,670 μmol/L; 3-hydoxybutyric acid, 9,690 μmol/L). Thereby, we diagnosed him with diabetic ketoacidosis (DKA) and hospitalized him. On admission, his height and body weight were 167 cm and 62.2 kg, respectively. Blood pressure, heart rate and body temperature were 125/77 mmHg, 117/min and 37.5℃, respectively. Severe dry mouth and peripheral limb dryness were observed. HbA1c value was 10.2%. Anti-GAD antibody was 7.8 U/mL and anti-IA-2 antibody was negative. Serum C-peptide was below the measurement sensitivity. The concentration of insulin antibodies was below the sensitivity threshold (< 125 nU/ml), and the insulin binding rate was also below the sensitivity threshold (< 0.4%). There was a huge subcutaneous induration on the left abdomen (9.5 × 6.5 cm) (Fig. 1A), which was observed in abdominal computed tomography (CT) (Fig. 1B). We thought that this was an insulin ball. In addition, in chest CT, pneumomediastinum was observed around the trachea (Fig. 1C). Thereby, we diagnosed him as Hamman's syndrome together with DKA. It is noted here that Hamman's syndrome could be induced by severe DKA due to increase of air pressure and vulnerability of alveolar walls after repeated vomiting. During the two-week treatment period for the pneumomediastinum, nutritional management with total parenteral nutrition and continuous insulin administration were performed. After resuming subcutaneous insulin injection while avoiding the insulin ball, good glycemic control was obtained only with 31 units of aspart and 17

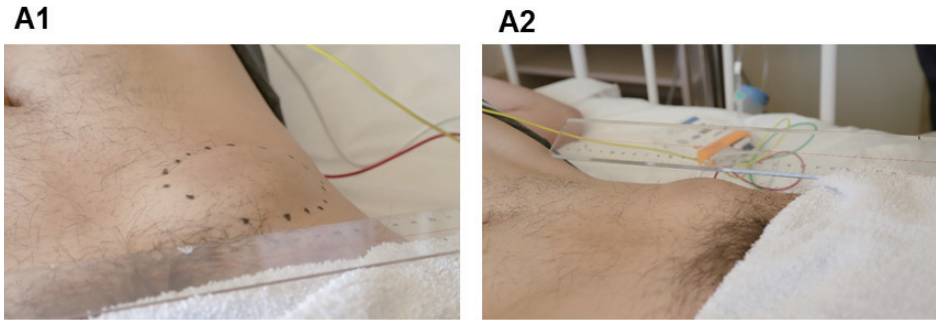

Fig. 1. Marked insulin ball on the left abdomen in a subject with type 1 diabetes mellitus.

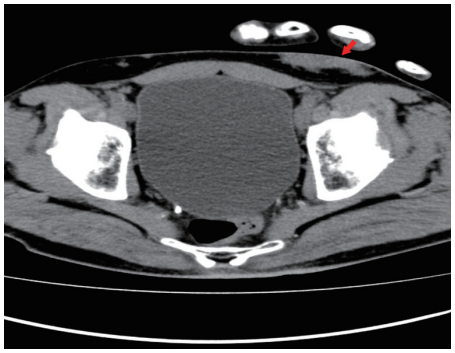

Fig. 2. Insulin ball shown in abdominal computerized tomography (red arrow).

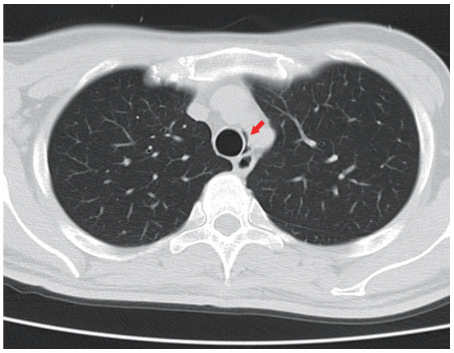

Fig. 3. Pneumomediastinum around the trachea shown in chest computerized tomography (red arrow).

units of degludec. The total insulin dose (48 units, 0.75 units/kg) was much smaller compared to the previous one (118 units, 1.9 units/kg). One and a half months later, HbA1c value was reduced to 8.7%.

He had started insulin treatment shortly after being diagnosed with diabetes mellitus. Initially he used a total of 21 units of insulin but gradually increased up to 90 units within 10 years. Five years before, although the daily dose of insulin was already as high as 120 units, HbA1c value hovered around 10 to 12%. Insulin injection site had consistently been fixed on his left abdomen from the beginning, and surprisingly, he was not aware of the presence of induration until this hospitalization.

DISCUSSION

While lipohypertrophy, one of skin symptoms at the insulin injection site, is recognized as a bulge of subcutaneous fat, insulin-derived amyloid deposits under the skin have been recently named insulin ball[1]. Differential diagnosis of these two diseases is important because insulin ball much more significantly impairs insulin absorption compared to lipohypertrophy. However, the exact prevalence of insulin-derived amyloidosis among insulin-treated patients remains unclear. This uncertainty is partly due to the frequent confusion with lipohypertrophy caused by fat deposition, as well as the insufficient thorough clinical examinations conducted in practice.

In addition, insulin ball is usually harder than lipohyoertrophy and takes longer time to disappear[2]. It is often difficult to distinguish them with clinical findings alone. It has been shown, however, that CT and magnetic resonance imaging (MRI) examinations are useful for this diagnosis. In CT examination, the insulin ball is recognized as a mass showing a higher signal than the surrounding adipose tissue[3], which point is different from lipohypertrophy showing an equal signal. MRI findings typically show that on T1-weighted images, the lesion appears as a low signal compared to surrounding adipose tissue. In T2-weighted images with fat suppression, it exhibits a slightly higher signal than the surrounding fat, and it does not demonstrate high signal intensity on diffusion-weighted imaging. Ultrasound examination often reveals a low-echo area with deep attenuation corresponding to the lesion, and Doppler imaging typically shows poor blood flow. However, a variety of appearances have been reported[3]. In this case, a mass showing a clearly higher signal was observed on CT imaging, which led to diagnosis of an insulin ball. D'Souza *et al*. pointed out that amyloid deposit at frequently injected site of insulin is composed of insulin derived from insulin preparations, but not insulin synthesized in the body[4]. The detailed mechanism by which insulin is converted to amyloid is still unknown, but it has been pointed out that insulin-degrading enzymes in the phagocytic cells may be involved in the process[5]. Pathological findings reveal the deposition of eosinophilic amorphous material in proximity to collagen fibers on hematoxylin and eosin (HE) staining. This material exhibits orange coloration with Congo red staining and demonstrates green birefringence under polarized light microscopy. Additionally, insulin immunostaining is positive, and foreign body-type giant cells cluster around the amyloid deposits, with phagocytic activity of the amyloid also observed[6]. Although this subject received an explanation about insulin injection procedure only once 20 years before, the medical staffs failed to re-confirm such procedure for a long time. This was the biggest reason in this subject for delaying the detection of lesions.

The frequency of subcutaneous nodules in patients using insulin has been reported to vary widely, ranging from 3.6% to 50%[7-9]. Common factors associated with insulin nodules include a high frequency of injections, prolonged treatment

duration, injections in localized areas, and a low awareness of subcutaneous nodules. Additionally, a higher prevalence of nodules has been reported in obese patients, suggesting that increased subcutaneous fat may impede the detection of these nodules. All of these factors were found to be relevant to the present case. For patients initiating insulin therapy, it is essential to conduct an assessment of injection techniques and an abdominal examination during the subsequent two follow-up visits. Currently, there are no established guidelines regarding the frequency of abdominal examinations thereafter, which is left to the discretion of the attending physician. In our institution, it is generally recommended to conduct abdominal examinations once every six months to one year.

Taken together, we should bear in mind that just a simple and habitual action of repeated insulin administration to an insulin ball can lead to life-threatening conditions such as severe diabetic ketoacidosis accompanied by Hamman's syndrome especially in subjects with type 1 diabetes mellitus. In addition, for the above reasons, in cases where an unconventionally high dose of insulin is required, it is important to check the injection site taking the possibility of the presence of insulin ball into account.

DISCLOSURE

The authors declare no conflict of interest.

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