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CASE REPORT

Insulin-derived amyloidosis without a palpable mass at the insulin injection site: A report of two cases

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ABSTRACT

To date, almost all case reports of insulin-derived amyloidosis described the presence of a subcutaneous mass that was observable on physical examination. This report presents two cases of insulin-derived amyloidosis without palpable masses at insulin injection sites. In both cases, blood glucose concentrations improved, and the insulin dose could be reduced by an average of 45% after changing the insulin injection sites. The insulin absorption at the site was reduced to at most 40% of that at a normal site in one case. Magnetic resonance imaging and ultrasonography were useful to screen and differentiate insulin-derived amyloidosis without a palpable mass. This report showed that insulin-derived amyloidosis without a palpable mass can be present at the insulin injection site, and has similar clinical effects to insulin-derived amyloidosis with palpable masses.

INTRODUCTION

Insulin-derived amyloidosis is a skin-related complication of insulin therapy. The amyloid fibril protein is derived from the injected insulin and forms an amyloid deposit at the injection site[1–4]. Insulin-derived amyloidosis causes poor glycemic control and increased insulin dose requirements because of impaired insulin absorption[2,3]. Additionally, it might have toxicity[5]. A clue to recognizing insulin-derived amyloidosis has up to now been palpable masses, well-marginated amyloid deposits felt on palpation, at insulin injection sites. A recent review of insulin-derived amyloidosis showed that the majority of case reports (96.5%, $n = 86$) described the presence of a localized, subcutaneous mass that was observable on physical examination[4]. In this report, two cases of insulin-derived amyloidosis without palpable masses are presented.

CASE 1

An 81-year-old Japanese man with a 29-year history of type 2 diabetes was admitted because of poor glycemic control. He had been taking insulin for 26 years, with a multiple daily insulin injection regimen using insulin lispro and insulin glargine. On admission, the insulin dose was 46 units/day, and glycated hemoglobin was 9.1%. Physical examination showed lipohypertrophy bilaterally on the lower abdomen, but no mass was palpable. After changing the insulin injection sites, blood glucose concentrations improved, and the insulin dose could be reduced to 24 units/day.

To clarify the differences in insulin absorption, 6 units of insulin lispro were injected into a previously used site (previous site injection) or a normal abdominal site (normal site injection) before breakfast on different days. The previously used site could be identified, because the patient remembered the area of each insulin injection, while the normal site was located by avoiding bilateral lipohypertrophy. Serum insulin and C-peptide and plasma glucose concentrations were measured sequentially. Serum insulin concentrations after previous site injection were markedly lower than those after normal site injection (Figure 1). The areas under the curve (AUC) of the serum insulin values were 320 pmol/L·h (previous site) and 798 pmol/L·h (normal site), and the ratio of AUCs was 0.40.

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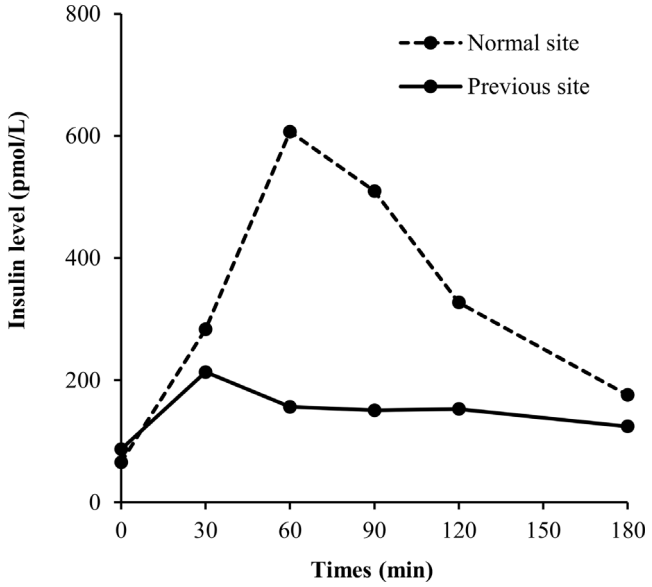

Figure 1 | Serum insulin levels after 6 units of insulin lispro injection into a previously used site (previous site; straight line) or a normal abdominal site (normal site; broken line) before breakfast on different days. The areas under the curve of the serum insulin values from 0 to 120 min are 320 pmol/L·h (previous site) and 798 pmol/L·h (normal site), and the ratio of areas under the curve is 0.40.

Serum C-peptide concentrations after previous site injection resembled or were even higher than those after normal site injection (Figure S1). Taken together, the insulin absorption at the previous site was reduced to at most 40% of that at the normal site, resulting in increased plasma glucose concentrations (Figure S2).

Magnetic resonance imaging (MRI) of insulin injection sites showed heterogeneous hypointense streaks or spots bilaterally in the hypertrophic subcutaneous fat tissue (Figure 2).

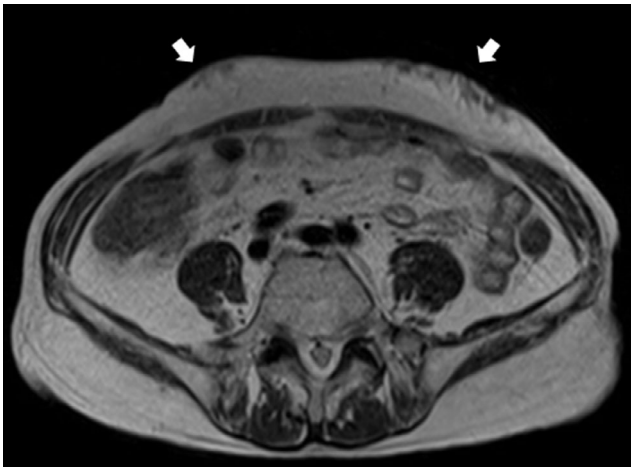

Figure 2 | Magnetic resonance imaging of insulin injection sites (arrows) on the lower abdomen in case 1.

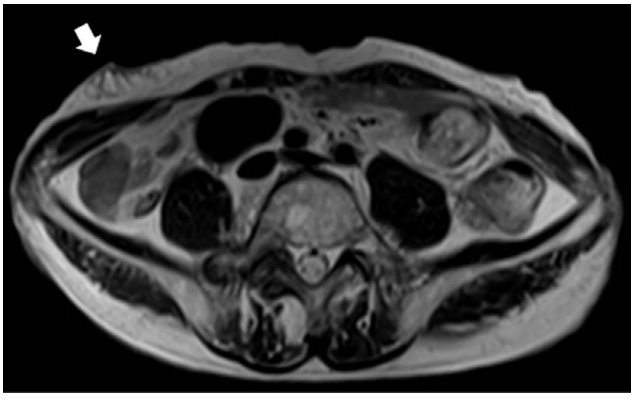

Figure 3 | Magnetic resonance imaging of insulin injection sites (arrow) on the right lower abdomen in case 2.

Histological examination after skin incision biopsy showed deposition of amyloid material that was stained positively by monoclonal anti-insulin antibody[3,5].

CASE 2

An 87-year-old Japanese man with a 16-year history of type 2 diabetes was admitted because of hypoglycemic coma. He had been taking insulin for 16 years, with a multiple daily insulin injection regimen using insulin aspart and insulin detemir. The insulin dose was 36 units/day, and glycated hemoglobin was 8.3%. Physical examination showed a soft swelling on the right lower abdomen, but no masses were palpable. After changing the insulin injection sites, the insulin dose could be reduced to 21 units/day with good glycemic control.

MRI of the insulin injection sites showed heterogeneous hypointense streaks in the subcutaneous fat tissue (Figure 3). Ultrasonography showed hyperechoic streaks with loss of the normal layer structure of the subcutaneous fat tissue (Figure 4). Histological examination after fine-needle aspiration biopsies showed insulin-derived amyloidosis[3,5].

Both patients gave their written, informed consent for this report.

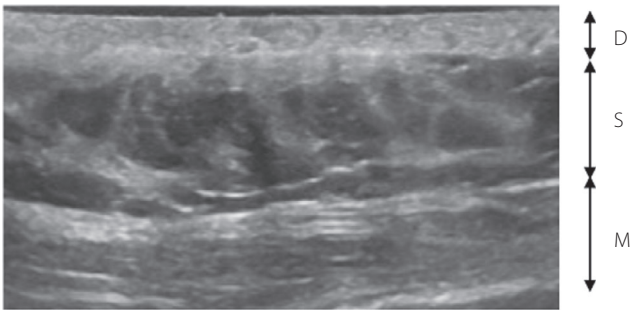

Figure 4 | Ultrasonography of insulin injection sites on the right lower abdomen in case 2. D, dermis; M, muscle; S, subcutaneous tissue.

DISCUSSION

This report showed that insulin-derived amyloidosis can be present at insulin injection sites without a palpable mass. Before having seen these two patients, we had treated 14 patients with insulin-derived amyloidosis[6], all of whom had the amyloid deposits as palpable masses at insulin injection sites. Only one report presented three cases with insulin-derived amyloidosis who did not have local masses[7], in whom abdominal fat aspiration was carried out for the diagnosis of suspected systemic amyloidosis, and mass spectrometry analyses unexpectedly showed insulin within the amyloid deposits. We believe that there are many more such cases among insulin-treated patients.

This report also showed that insulin-derived amyloidosis without a palpable mass causes poor glycemic control and increased insulin dose requirements, because blood glucose concentrations improved, and the insulin dose could be reduced by an average of 45% after changing the injection sites. Additionally, severe hypoglycemia occurred in case 2, probably because an increased dose of insulin was injected into a normal site instead of amyloidosis sites. Thus, insulin-derived amyloidosis without a palpable mass has similar clinical effects to insulin-derived amyloidosis with palpable masses[3]. The insulin absorption study showed that the ratio of AUCs in case 1 was comparable to the mean ratio of AUCs in patients with insulin-derived amyloidosis with palpable masses[3], and it was much lower than the ratio of mean AUCs in patients with lipohypertrophy[8]. Therefore, insulin-derived amyloidosis with and without palpable masses might have similar clinical effects.

As screening for insulin-derived amyloidosis without a palpable mass by physical examination alone is difficult, MRI was carried out. The MRI findings were heterogeneous hypointense streaks or spots, differing from the MRI findings of insulin-derived amyloidosis with palpable masses, namely, hypointense masses[3]. Recently, ultrasonography has been shown to be useful to screen for transthyretin amyloidosis in abdominal fat tissue[9]. Furthermore, ultrasonography is useful for detecting insulin-derived amyloidosis[10]. In case 2, ultrasonography of abdominal insulin injection sites showed hyperechoic streaks comparable to the MRI findings of the sites.

The mechanism resulting in the difference between insulin-derived amyloidosis with and without palpable masses is unknown. The clinical features of the two present patients were compared with those of 14 patients with insulin-derived amyloidosis with palpable masses[6]. The features including the durations of diabetes and insulin therapy, glycated hemoglobin, and total daily insulin dose were not significantly different between the two groups, although age was slightly higher than in the present cases ($P = 0.089$). These findings might suggest that insulin-derived amyloidosis without a palpable mass is not a lesion at an earlier stage. Additionally, the past medical histories of the two patients were not unusual. In contrast, although the histological findings of the biopsy materials in a patient with insulin-derived amyloidosis with palpable masses[2] showed dense amorphous deposits with slight inflammatory cells, those in case 1 showed sparse amorphous deposits surrounded by striking inflammatory cells (Figure S3). However, further studies are clearly necessary.

In conclusion, insulin-derived amyloidosis without a palpable mass can be present at the insulin injection site and has similar clinical effects to insulin-derived amyloidosis with palpable masses.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Serum C-peptide levels after 6 units of insulin lispro injection into a previously used site or a normal abdominal site.

Figure S2 | Plasma glucose levels after 6 units of insulin lispro injection into a previously used site or a normal abdominal site.

Figure S3 | Histological findings of the biopsy materials on hematoxylin–eosin staining in patients with insulin-derived amyloidosis with and without palpable masses.