A Case of Exogenous Insulin-derived Acanthosis Nigricans Caused by Insulin Injections

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A 73-year-old male with diabetes mellitus had been treated with insulin for six years. He developed a solid mass on his left lateral of the abdomen at the insulin injection site. A firm subcutaneous mass with dark-red erythema was overlaid by dark-brown keratinized plaques. On histological examination of the mass, keratin proliferation and epidermal papilloma were observed. There were four previously reported cases of acanthosis nigricans that were considered to be caused by continuous injections of insulin. Using immunohistochemistry, in our case the findings were positive in the basal epithelial and prickle cell layers when the patient's lesion was dyed with insulin-like growth factor (IGF)-1 antibody. The coexistence of dermal IGF-1 receptor and acanthosis nigricans found in our patient has not been reported previously, to our knowledge.

Key words: localized hyper insulinaemia, insulin-like growth factor (IGF)-1 receptor

INTRODUCTION

Acanthosis nigricans is characterized by symmetrical, hyperpigmented, velvety plaques that may occur in almost any location and most commonly appears on the intertriginous areas of the axilla, groin, and posterior neck [1]. It is classified into six forms, the benign form, the malignant form, falseness form, drug induced form, genetic form, and syndrome concurrence form. In particular, the benign form of acanthosis nigricans which is concerned with insulin metabolic disorder was reported [2]. In case of the benign form of acanthosis nigricans, the causal factor is probably insulin and insulin-like growth factor (IGF) that incites the epidermal cell propagation [3].

Herein, we report a case which resembles a benign form of acanthosis nigricans. The lesion was localized only one side of abdomen caused by continuously injection of insulin. This lesion which clinically and histologically resembles acanthosis nigricans, we guess that an increase in the concentration of insulin in the injected area caused the lesion.

CASE REPORT

A 73-year-old Japanese male who had been in the Department of Nephrology and Metabolism, Tokai University Hachioji Hospital with poor control type 2 diabetes mellitus visited our outpatient clinic with a skin lesion. His height was 163cm, and weight was 63kg. He had been treated with insulin therapy (Penfill ® R/Penfill® N; Novo Nordisk Inc., Princeton, NJ, USA) since 2006. The injections were to the proper depth (subcutaneous), and a sterile disposable needle was used for each injection. However, he did not follow the doctor's direction to rotate injection site, so that he had used only one site (his left lateral of the abdomen). His level of haemoglobin (Hb) A1c on admission was 11.1%. He had noticed an asymptomatic pigmented plaque on the area where he had injected insulin continually. In addition to diabetes mellitus, the patient suffered from chronic type C hepatitis, and alcoholism. He was diagnosed with chronic type C hepatitis in 2003 and as having a malignant hepatoma in 2009, while a large 7-cm tumour was observed in the right lobe of the liver on Computerized Tomography (CT).

On clinical findings, a firm, 4 × 3cm in size, subcutaneous mass with dark-red erythema was observed on his left lateral of the abdomen. The mass was overlaid by dark-brown keratinized plaques (Fig. 1). The neck, axillae, and groin were unremarkable. After initiation of insulin therapy in 2006, for six years, he had injected insulin in the same area. The clinical differential diagnosis was a benign form of acanthosis nigricans due to diabetes, a malignant form of acanthosis nigricans due to hepatoma, akatsuki disease (pomade crust), or seborrhoeic keratosis. Total extirpation biopsy was carried out. Biopsy specimen (Haematoxylin Eosin) revealed marked hyperkeratosis and papillomatosis, with mild acanthosis (Fig. 2). Using immunochemistry with IGF-1 antibodies (IGF-1 antibodies : Sc9013 SANTA CRUZ) and epidermal growth factor receptor (EGFR antibodies : Biogenex Kyowa Medics) diagnostic stain, findings were positive with IGF-1 antibodies

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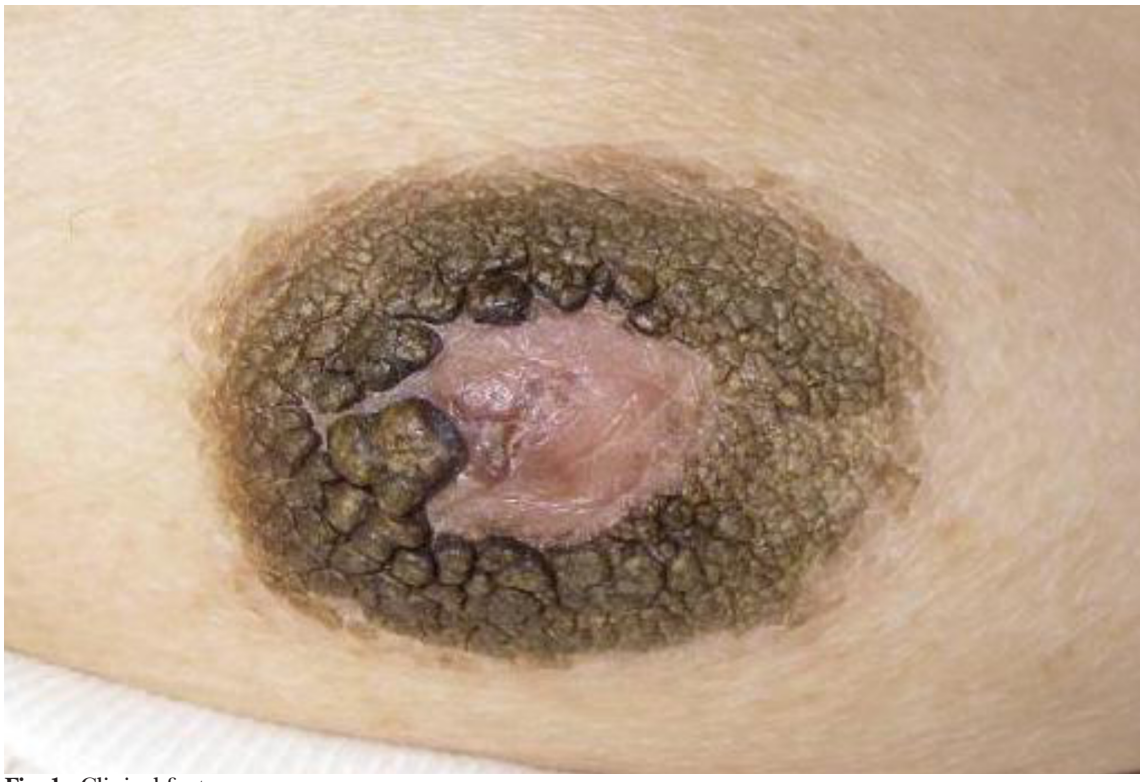

Fig. 1 Clinical features
A firm subcutaneous mass with dark-red erythema was overlaid by dark-brown keratinized plaques on the left lateral region of the abdomen. The patient had injected insulin in the center of the mass.

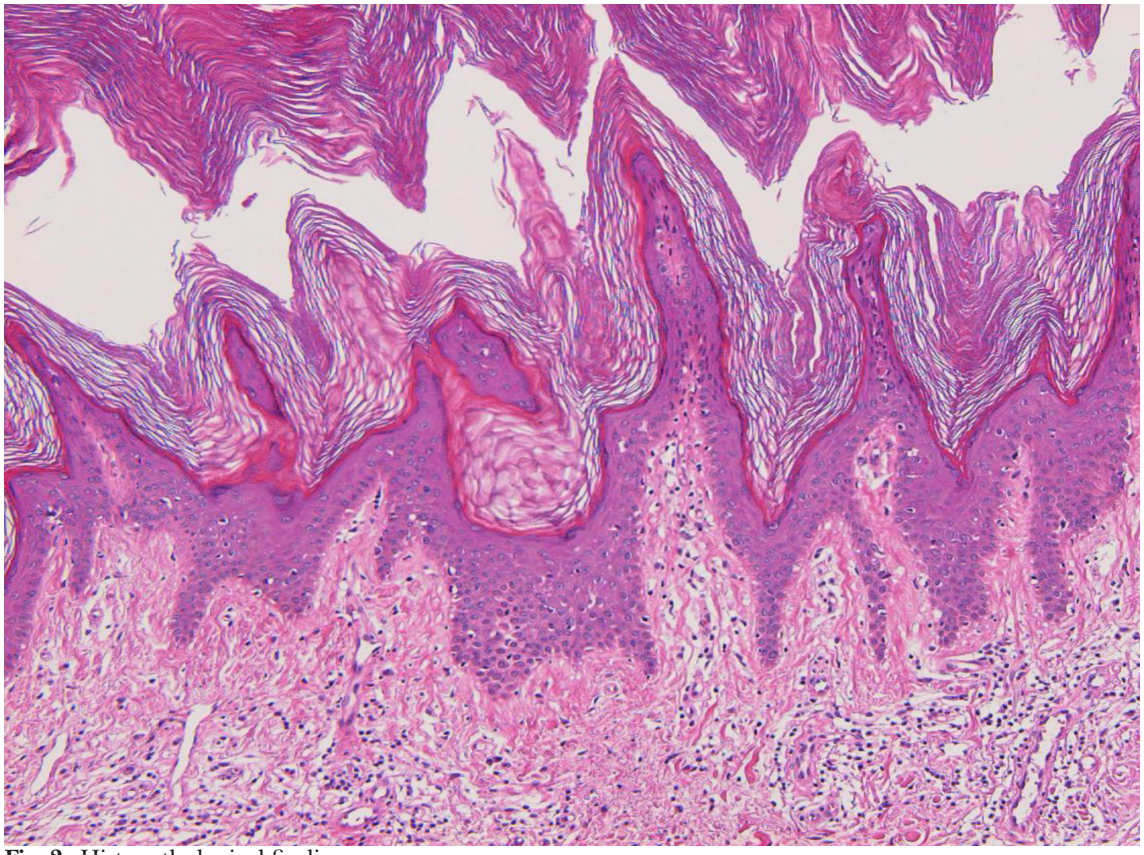

Fig. 2 Histopathological findings
Keratin proliferation and epidermal papilloma were observed. The plaque presented in a steeple shape with dermal papilla extending to the upper part of the affected area and culminating in a long and slender tip. (Haematoxylin-Eosin stain, ×10).

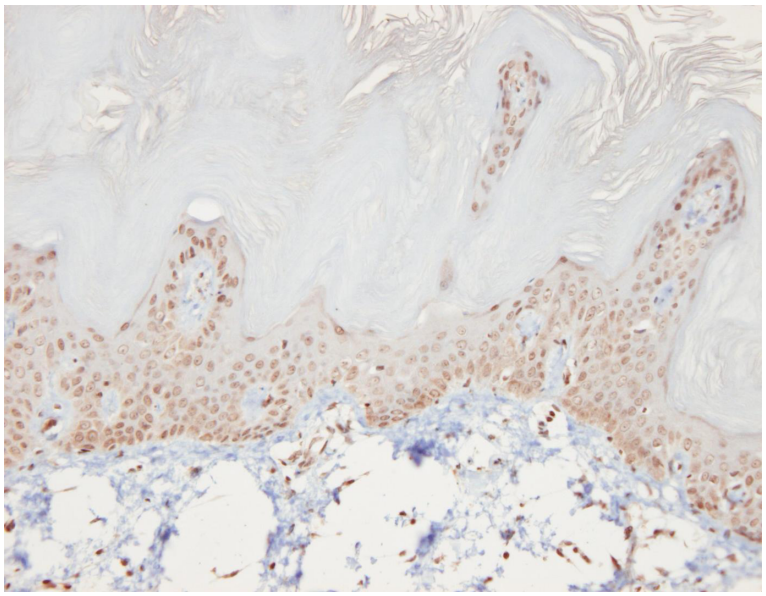

Fig. 3 Immunochemical findings
Basal epithelial and prickle cell layers were positive for IGF-1. (×20).

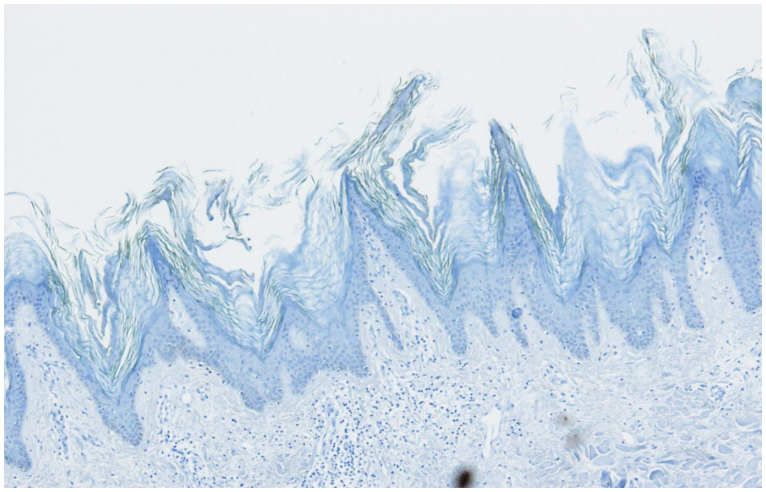

Fig. 4 Immunochemical findings
Basal epithelial and prickle cell layers were negative for EGFR. (×10).

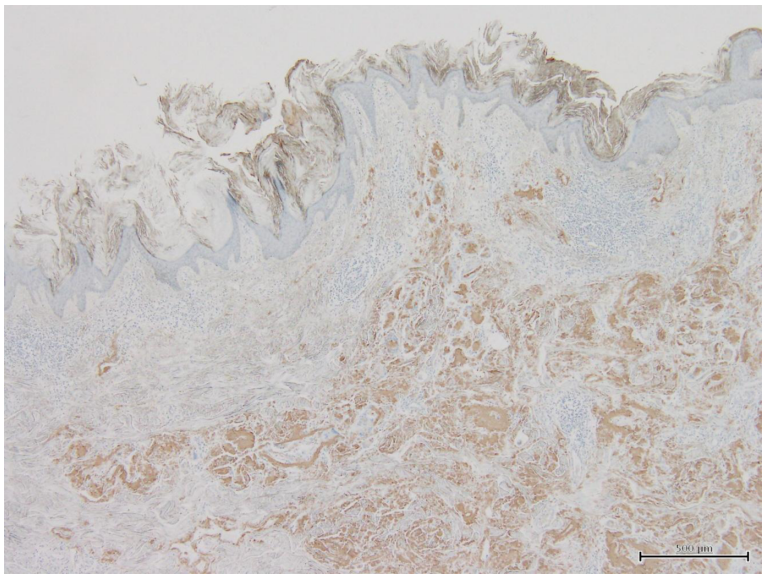

Fig. 5 Immunochemical findings
From upper dermis to lower dermis were positive for insulin. (×4).

in the basal epithelial and prickle cell layers (Fig. 3) and were negative with EGFR diagnostic stain (Fig. 4). Furthermore, we have stained using immunochemistry to confirm existence of insulin. Findings were positive with insulin from upper dermis to lower dermis (Fig. 5). However, we could not find out insulin in the

Table Previous cases of localized insulin-derived acanthosis nigricans at the site of insulin injection

Reference	Sex	Age	Site	Size (cm)	Duration of insulin injection	Immunochemical findings
Fleming MG, *et al*[4]	male	57	Both sites of anterior thighs	6.5 × 8.5	9 years	N. d.
Mailler EA, *et al*[5]	male	63	Both side of the lower abdomen	6 × 4	10 years	N. d
Kudo S, *et al*[6]	male	59	Left side of the lower abdomen	4.5 × 4.5	4 years	Guineapig antiporcine insulin
Mandeep D, *et al*[7]	male	14	Light side of the abdomen	6 × 4	4 years	N. d.
Present case	male	73	Left side of the lower abdomen	4 × 3	6 years	IGF-1 antibodies EGFR-antibodies

* N. d.=Not done

basal epithelial and prickle cell layers.

Based on these findings, the patient was diagnosed as localized insulin-derived acanthosis nigricans, but not a benign form of acanthosis nigricans. Because of the skin lesion was localized in the site where the patient had injected insulin continuously. Furthermore, we could not find any lesions in other friction areas. He was advised to stop injecting insulin into the area and started rotating his injection site regularly. Almost three weeks later, diabetic control had been improved (the level of HbA1c decreased from 11.1% to 7.9%).

DISCUSSION

There were four previously reported cases of acanthosis nigricans that were considered to be caused by continuous injections of insulin (Table). In the first case, the plaque occurred in the anterior of both thighs, the areas where the patient had injected insulin by himself. The term the patient had been receiving injections was almost 9 years [4]. In the second case, the patient had injected insulin by himself continuously for approximately 10 years in both sides of the abdomen, and the plaque occurred in these areas [5]. In the third case, the patient had injected by himself only left side of abdomen for almost 4 years [6]. In the fourth case, the patient also had injected by himself only left side of abdomen for almost 4 years. In our case, the patient had injected by himself left lateral of the abdomen for almost 6 years. These findings suggest that it takes 4–6 years to development of acanthosis-like lesion.

The histopathological findings of the previous cases included hyperkeratosis, papillomatosis and acanthosis. And it was suggested that activation of the insulin-like growth factor receptor (IGFR) might be related to classic acanthosis nigricans [3]. Insulin resistance, which contributes to development of type 2 diabetes, produces compensatory hyper-insulinemia. Insulin is homologous to IGF in structure, and at high concentration, insulin interacts with both IGFR and insulin receptor. Activation of IGFR on keratinocytes and fibroblast leads to the proliferation of these cells, resulting in the thickened and hyperkeratotic skin characteristic at acanthosis nigricans. Hence, the excessively high level of insulin at an injection site may cause acanthosis nigricans-like lesion. Furthermore, regional development of IGFR resulted in reduced therapeutic response of insulin. Thus, the level of HbA1c had been improved after the start of injections in rotation.

On the other hand, in the malignant form of acanthosis nigricans, the prevailing theory is that the malignant tumour amalgamates and the tumour cells that secrete epidermal growth factor (EGF) and transforming growth factor (TGF)-α send proliferation signals to the epidermis and fibroblast via epidermal growth factor receptors (EGFR), resulting in acanthosis and keratin proliferation [8, 9]. This case with malignant hepatoma was refuted a diagnosis of malignant forma of acanthosis nigricans by the negative finding of EGFR in immunohistochemical staining (Fig. 4).

In this our case of acanthosis nigricans-like lesion, the patient had continuously injected insulin for approximately 6 years. We guess that the continuous injection of insulin may have caused a high concentration of insulin in the injected area, which led to increased binding between the insulin and IGF-1 antibodies, which caused occurrence of the plaque. Using immunochemistry with IGF-1 antibodies have not been reported in previous cases, thus to our knowledge, this is the first case which proves coexisting of IGF with acanthosis nigricans. Our case will contribute to a better understanding of the pathogenesis of acanthosis nigricans.

This case report had been presented at the 62nd Annual Meeting of the Western Japan Division of Japanese Dermatological Association, and also won the award for best poster presentation.

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