Coexistence of insulin induced acanthosis and lipoatrophy in a patient with type 1 DM

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ABSTRACT
Localized acanthosis nigricans at the insulin injection site is a rare skin disorder in patients with diabetes mellitus. We report co-existence of acanthosis nigricans and lipoatrophy at injection sites in the same patient with type 1 DM. A 23 year old male patient with a history type 1 DM for 11 years was admitted to hospital due to recurrent diabetic ketoacidosis attacks. There were two lesions over the abdominal skin which occurred due to repeated insulin injection at the same sites. Despite structured and continuous education even in developed countries, poor injection technique still remains a challenging factor in uncontrolled diabetes mellitus. Injection sites should be checked for localized acanthosis nigricans in addition to lipodystrophy.

There is no other report in the literature regarding coexistence of both lipoatrophy and localized acanthosis nigricans in the same patient with type 1 diabetes mellitus.

Introduction
There is a variety of cutaneous reactions induced by insulin administration at the injection site including hyperemia, pruritus, lipoatrophy, lipohypertrophy, infection, folliculitis, cheloid, and acanthosis nigricans (AN) [1]. Lipoatrophy and lipohypertrophy are collected under the name of local lipodystrophy. Lipodystrophy is thickening of subcutaneous tissue giving a feeling for rubbery mass. Lipoatrophy is characterized with depressed paper like skin due to loss of subcutaneous tissue. Lipodystrophy is a common manifestation (up to 50% in different series) even in developed countries despite purity of insulin preparations and burden of knowledge regarding good injection technique [2,3]. Lipoatrophy is more common in type 1 DM and lipohypertrophy in type 2 [2]. Lipodystrophy may occur with both human and analogue insulins. Number of daily injection, duration of diabetes, duration of insulin therapy, reuse of needles, and needle size are contributors of lipodystrophy probably due to intensity of trauma to subcutaneous tissue [2]. AN is rarely encountered at the site of injection. AN is a dermatosis commonly observed in diseases associated with insulin resistance including type 2 DM, obesity, and polycystic ovary syndrome and rarely accompany malignancies [4,5]. AN is characterized by velvety texture, commonly hyperpigmented and brownish in colour, and verrucous structure which gave an impression of dirty appearance [4]. It may involve skin of intertriginous areas (armpits, antecubital fossae, folds of the neck, between digits, beneath the breasts, and groin) and less commonly mucosa, palms and soles [4]. A few cases of localized AN associated with insulin usage have been reported in the literature [6]. There is no report in English written language regarding coexistence of lipodystrophy and AN in a patient with type 1 DM.

Case Report
A 23 year old male patient, who had type 1 DM for 11 years, was admitted to the endocrinology ward because of nausea and vomiting. He was
Diagnosed with diabetic ketoacidosis (DKA). He denied any other chronic illness. He was suffering from frequent hospitalizations due to ketoacidosis. He was on 14 U glargine once a day and 10 U aspart insulin thrice a day before meals therapy and not using other medications or herbal products. He was a current smoker. He was using prefilled pens and 32 G needles. On physical examination a brown-coloured verrucous lesion measuring approximately 4 cm in diameter over the upper left quadrant of abdomen (FIGURE 1) and a 10 x 3 cm area of thinned paper-like skin over the right quadrant of upper abdomen were noted (FIGURE 2). He weighed 44.7 kg and was 170 cm tall. Neither lipoatrophy nor AN were present elsewhere in the body except the aforementioned site. The site of AN was atypical for that observed in insulin resistance disorders including malignancy. He used to rotate only upper quadrants of abdomen interchangeably for insulin injection. Therefore localized AN and lipoatrophy due to incorrect insulin injection pattern were diagnosed.

He refused excisional biopsy of the lesion. Renal and liver function tests were normal; hemoglobin A1C was 57 mmol/mol (7.4%); antibodies against TPO, endomysium, and gliadin were negative, microalbuminuria was absent, TSH and vitamin B12 levels were normal. Fundus examination was normal. He suffered from frequent DKA attacks probably due to poor absorption of insulin. Therefore to decrease the

**KEYWORDS**
- acanthosis nigricans
- lipoatrophy
- primary care
- insulin
- type 1 diabetes mellitus
number of injections, avoid metal needle trauma,
and fine tune insulin dosage, we switched
multiple day injection therapy to continuous
subcutaneous aspart insulin infusion using soft
silicone infusion set. The lesions were persisting
at the 5th month of follow-up. One year after
follow-up by two medical centers (Yunus Emre
State hospital and Osmangazi University), he
was doing well and had hemoglobin A1C level
of 43 mmol/mol (6.1%). Localized acanthosis
nigricans disappeared with slight brownish
colour at the site of the lesion (FIGURE 3).
However right-sided lipoatrophy persisted
despite improvement (FIGURE 4). He has still
avoids abdomen as injection site for CSII.

Discussion

We present the first case of co-existence of two
dermatoses (AN and lipoatrophy) due to
repeated injection of insulin to the same sites in
a patient with type 1 DM.

Local lipodystrophy (lipoatrophy and
lipohypertrophy) at the sites of insulin injection
mostly occurs with porcine or bovine derived
insulin, but it may also be due to human or
analogue insulins administered by needle or
subcutaneous infusion systems [7]. It takes 4
weeks to 2 years for lipodystrophy to develop.
Neglecting rotation of sites for insulin injection
is a frequent cause. Degenerative changes in
adipose tissue and IgM, complement, and
fibrin-fibrinogen deposition in dermal vessels
of neighbouring tissue suggest an immune
mediated inflammatory reaction [7]. Injected
insulin and antibody developed against
exogenous insulin forms a complex which
in turn activates complement formation and
resultant infiltration with inflammatory cells [7].
Cytokines secreted from mastocytes may inhibit
adipocyte differentiation [7]. Lipoatrophy has
immunologic basis and impurity of insulins may
contribute lipolytic reaction [2]. On the other
hand lipohypertrophy is due to lipogenic activity
of insulin and hypertrophy of subcutaneous
adipocytes replace mid derm collagen leading
to thickened skin [2]. Poor injection technique
due to avoiding rotation and injecting repeatedly
at the same site is the most common cause
[2]. Both atrophy and hypertrophy may cause
erratic glucose levels due to impaired insulin
reabsorption [2].

Figure 3. Brown coloured skin at the site of localized
acanthosis nigricans one year after improved
injection technique.

Figure 4. Close-up of lipoatrophic lesion one year
after improved injection technique.
The diagnosis of AN can be made easily on clinical grounds and histopathological examination confirms the diagnosis. Our patient refused the biopsy of lesions. Therefore we are unable to show structural changes in dermis and subcutaneous tissue. However the microscopic features of localized AN have already been defined in the literature. The diagnosis of AN can be made easily on clinical grounds and histopathological examination confirms the diagnosis. Our patient refused the biopsy of lesions. Therefore we are unable to show structural changes in dermis and subcutaneous tissue. However the microscopic features of localized AN have already been defined in the literature. Pathophysiologic data regarding AN are derived from studies executed in genetically determined insulin resistance syndromes and fibroblast growth factor (FGF) defects [4]. Normal epidermal cells especially the actively proliferating cells of the basal layer present epidermal growth factor receptor (EGFR) [8]. Basal layer is involved in growth and differentiation of normal keratinocytes [8]. Keratinocytes comprise 95% of epidermal cells and arise from the basal layer of epidermis. Keratinocytes migrate into the upper epidermal layers. Aside from their structural role, keratinocytes also exert immunological activity via release of cytokines. There is marked hyperkeratosis and papillary hypertrophy of the basal layer of epidermis in haematoxylin eosin stained skin tissue. Antibodies directed against IGF receptor and EGFR expressed by fibroblasts and keratinocytes might play a role in the pathogenesis of AN [4]. Amyloid deposits may accompany other characteristic histological findings of AN [9]. Transforming growth factor (TGF-α acting via (epidermal growth factor receptor (EGFR)), insulin-like growth factor (IGF)-1, fibroblast growth factor (FGF), and melanocyte stimulating hormone-α (MSH-α) play a role in melanocyte pigmentation and growth of keratinocytes, which in turn may lead to AN [8,10].

A large survey done in 500 patients with type 1 DM revealed exogenous insulin related localized AN only in 2 patients [1]. In the literature all reported cases are male patients with either type 1 or type 2 DM, aged between 14-73 years [6,9-12]. Duration of insulin administration varies between 4 to 10 years. Malrotation is the major cause in all. The first case in the literature was due to beef pork insulin usage. Other cases are due to human recombinant regular and NPH insulin, except one with glargin and aspart insulin. In many health facilities diabetes nurses and doctors provide structured education about insulin therapy. Despite all efforts, the patients may not adhere to the instructions. This case represents a good example of different skin reactions occurring in the same patient due to exogenous insulin.

Conclusion

The patients with poor glycaemic control, erratic course, and frequent hospitalizations should be sought for proper injection and related cutaneous pathologies including localized AN and lipodystrophy.

References