Localized Acanthosis Nigricans at the Site of Repetitive Insulin Injections

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PRACTICE **POINTS**

- Benign acanthosis nigricans (AN) is most often related to insulin resistance and presents as asymptomatic, hyperpigmented, velvety plaques on the neck, axillae, groin, and other body folds.
- Benign AN related to insulin resistance occurs when insulin binds to insulinlike growth factor 1 on keratinocytes and stimulates proliferations.
- Although insulin injections have been associated with several cutaneous side effects, including lipoatrophy, lipohypertrophy, and postinflammatory hyperpigmentation, localized AN is an uncommonly reported cutaneous adverse effect.

FIGURE 1. Localized acanthosis nigricans presenting as a lichenified, hyperpigmented, hyperkeratotic plaque at a recurring insulin injection site on the lower abdomen in a 64-year-old man with type 2 diabetes mellitus.

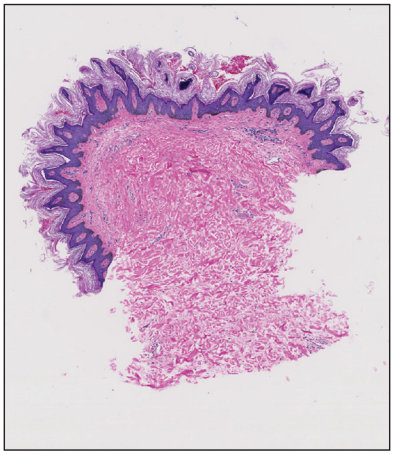

FIGURE 2. Histopathology demonstrated hyperkeratosis, papillomatosis, acanthosis, and hyperpigmentation (H&E, original magnification ×10).

To the Editor:

Acanthosis nigricans (AN) is characterized by asymptomatic, hyperpigmented, velvety plaques that can occur anywhere on the body but most often present on the skin of the neck, axillae, groin, and other body folds.[1-12] Although there are 5 subtypes, benign AN is the most common and is related to insulin resistance.[1-4] Insulin can bind to insulinlike growth factor 1 (IGF-1) on keratinocytes, stimulating their proliferation. In type 2 diabetes mellitus, endogenous insulin levels are high enough to bind IGF-1 and activate keratinocytes, leading to the development of AN. Insulin injections have been associated with cutaneous side effects including lipoatrophy, lipohypertrophy, and postinflammatory hyperpigmentation.[3] Acanthosis nigricans at insulin injection sites is a rare clinical condition.

A 64-year-old man presented for evaluation of a growing asymptomatic lesion on the abdomen of 6 years' duration. He had a 17-year history of type 2 diabetes mellitus treated with insulin injections for 14 years after failing oral hypoglycemic agents. The patient reported

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injecting at the same site on the abdomen for the last 14 years. Physical examination revealed a lichenified, hyperpigmented, verrucous plaque on the lower abdomen under the umbilicus (Figure 1). No similar skin lesions were observed elsewhere on the body. A punch biopsy of the plaque showed hyperkeratosis, papillomatosis, acanthosis, and hyperpigmentation, which was consistent with AN (Figure 2). The patient was instructed to rotate injection sites and avoid the affected area. Over-the-counter ammonium lactate cream applied twice daily to the affected site also was recommended. After 2 months of treatment with this regimen, the patient reported softening and lightening of the lesion on the abdomen.

A PubMed search of articles indexed for MEDLINE for all English-language studies with human participants using the terms *acanthosis nigricans* and *insulin injections* yielded 20 results. Of them, 13 discussed localized AN at insulin injection sites: 12 case reports (Table)[1-12] and 1 observational study in a group of diabetic patients.[13]

In the observational study, 500 diabetic patients were examined for insulin injection-site dermatoses and only 2 had localized injection-site AN. No other information was provided for these 2 patients.[13] In the 12 published case reports,[1-12] all patients did not rotate sites for their insulin injections and repeatedly injected into the affected area. The abdomen was the most commonly affected site, seen in 83% (10/12) of cases, while 25% (3/12) involved

Reports of Acanthosis Nigricans at Insulin Injection Sites

Reference (Year)	Patient Age, y/ Sex	DM Type	Site	Lesion Size, cm	Duration of Insulin Injections, y	Other Findings
Erickson et al[8] (1969)	51/M	Type 2	Bilateral anterior thighs	NA	2	
Fleming and Simon[9] (1986)	57/M	Type 2	Bilateral anterior thighs	6.5×8.5 (2 lesions)	9	
Mailler-Savage and Adams[4] (2008)	63/M	Type 2	Across lower abdomen	4×6 (2 lesions)	10	
Pachón Burgos and Chan Aguilar[10] (2008)	46/F	Type 2	Across lower abdomen	NA	0.04	
Buzási et al[3] (2011)	70/M	Type 2	Across lower abdomen	10×36	10	Resolved 12 mo after rotating injection sites
Brodell et al[7] (2012)	63/M	Type 2	Right abdomen	6×6.5	0.5	Acanthosis nigricans resolved after rotating injection sites, then restarted injections at prior site and acanthosis returned
Dhingra et al[2] (2013)	14/M	Type 1	Right abdomen just above umbilicus	6×4.5	4	
Kudo-Watanuki et al[6] (2013)	59/M	Type 2	Left abdomen	4.5	4	Amyloid plaque with overlying acanthosis nigricans
Nandeesh et al[5] (2014)	54/M	Type 2	Periumbilical region	5×4	5	Cutaneous amyloid plaque with overlying acanthosis nigricans
Yahagi et al[1] (2014)	73/M	Type 2	Left lateral abdomen	4×3	6	IGF-1 stain positive
Chapman and Bandino[11] (2017)	58/M	Type 2	Abdomen	5×6	1	
Huang and Hessami-Booshehri[12] (2018)	60/M	Type 2	Abdomen, right thigh	NA	15	

Abbreviations: DM, diabetes mellitus; M, male; NA, not available; F, female; IGF-1, insulinlike growth factor receptor 1.

the thighs. All but 1 patient had type 2 diabetes mellitus. In 2 patients, "amyloid" was noted on the biopsy report in addition to changes consistent with AN. At least 2 patients had clearance after rotating injection sites.[3,12]

It has been suggested that localized AN at insulin injection sites develops through similar mechanisms as benign AN. Contributing factors to the development of benign AN may be IGF-1, fibroblast growth factor, and epidermal growth factor.[1-3] Insulin is similar in structure to IGF-1 and can bind to IGF-1 receptors at high enough concentrations. Insulinlike growth factor 1 receptors are present on keratinocytes and fibroblasts, which proliferate upon activation, leading to the development of AN.[1-3] Localized AN is thought to occur when repetitive insulin at the injection site saturates IGF-1 receptors on local keratinocytes.

Based on our patient and prior reports in the literature, localized AN is an uncommon cutaneous complication of insulin injections. Physicians should ask about repetitive insulin injections in the same site when localized AN occurs in patients with diabetes mellitus on insulin therapy. They also should discuss the importance of rotating sites for insulin adminstration to prevent the development of cutaneous complications including AN.

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