Insulin injection-site acanthosis nigricans and other local cutaneous reactions may occur from repeated same-site insulin injections. The purpose of this article is to describe a case of acanthosis nigricans resulting as a localized reaction to insulin injections, review medical literature describing injection-site acanthosis nigricans resulting from same-site insulin injections, describe other injection-site cutaneous reactions related to insulin administration, and discuss clinical implications and lessons learned from the literature.

Case Presentation:
A 75-year-old patient with a history of type 2 diabetes mellitus presented with 2 discrete hyperpigmented plaques on the anterior abdominal wall, suggestive of acanthosis nigricans and confirmed on histopathology. These lesions were localized to the site of insulin injection and improved after the patient started rotating insulin injection sites.

Conclusions:
Rotation of insulin injection sites is an effective way to prevent and reduce cutaneous complications of insulin therapy. In addition to improving education regarding insulin injection technique, diabetes health care professionals should inspect injection sites at each patient encounter. Most cutaneous complications are asymptomatic but may impact glycated hemoglobin (HbA1c), cosmetic appearance, insulin absorption, and required dose of insulin.

CASE IN POINT
Insulin Injection-Site Acanthosis Nigricans: Skin Reactions and Clinical Implications
Megan Hower, MS, RD; Harrison Shawab; Apra Sood, MD; Joshua Schulman, MD; Mary Julius, RD; and Ajay Sood, MD

Background: Insulin injection-site acanthosis nigricans and other local cutaneous reactions may occur from repeated same-site insulin injections. The purpose of this article is to describe a case of acanthosis nigricans resulting as a localized reaction to insulin injections, review medical literature describing injection-site acanthosis nigricans resulting from same-site insulin injections, describe other injection-site cutaneous reactions related to insulin administration, and discuss clinical implications and lessons learned from the literature.

Conclusions: Rotation of insulin injection sites is an effective way to prevent and reduce cutaneous complications of insulin therapy. In addition to improving education regarding insulin injection technique, diabetes health care professionals should inspect injection sites at each patient encounter. Most cutaneous complications are asymptomatic but may impact glycated hemoglobin (HbA1c), cosmetic appearance, insulin absorption, and required dose of insulin.

CASE PRESENTATION
A 75-year-old patient with an 8-year history of T2DM, as well as stable coronary artery disease, atrial fibrillation, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and stage 3 chronic kidney disease, presented with 2 discrete abdominal hyperpigmented plaques. At the time of the initial clinic visit, the patient was taking metformin...
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1000 mg twice daily and insulin glargine 40 units once daily. When insulin was initiated 7 years prior, the patient received neutral protamine Hagedorn (NPH) insulin for the first year and transitioned to insulin glargine. After 4 years of insulin therapy, insulin aspart was added and discontinued after 2 years. The patient’s hemoglobin A1c (HbA1c) was 6.8%, suggesting good glycemic control.

The patient reported 5 years of progressive, asymptomatic hyperpigmentation of the skin surrounding his insulin glargine injection sites and injecting in these same sites daily without rotation. He reported no additional skin changes or symptoms. He had noticed no skin changes while using NPH insulin during his first year of insulin therapy. On examination, the abdominal wall skin demonstrated 2 well-demarcated, nearly black, soft, velvety plaques, measuring 9 × 8 cm on the left side and 4 × 3.5 cm on the right, suggesting acanthosis nigricans (Figure 1A). The remainder of the skin examination, including the flexures, was normal. Of note, the patient received biweekly intramuscular testosterone injections in the gluteal region for secondary hypogonadism with no adverse dermatologic effects. A skin punch biopsy was performed and revealed epidermal papillomatosis and hyperkeratosis, confirming the clinical diagnosis of acanthosis nigricans (Figure 2).

After a review of insulin-injection technique at his clinic visit, the patient started rotating insulin injection sites over his entire abdomen, and the acanthosis nigricans partially improved. A few months later, the patient stopped rotating the insulin injection site, and the acanthosis nigricans worsened again. Because of worsening glycemic control, the patient was then started on insulin aspart. He did not develop any skin changes at the insulin aspart injection site, although he was not rotating its site of injection.

Subsequently, with reeducation and proper injection-site rotation, the patient had resolution of his acanthosis nigricans (Figure 1B).

DISCUSSION

A review of the literature revealed 18 reported cases of acanthosis nigricans at sites of repeated insulin injection (Table). Acanthosis nigricans at the site of insulin injection afflicts patients of any age, with cases observed in patients aged 14 to 75 years. Sixteen (84%) of 19 cases were male. Fourteen cases (73%) had T2DM; the rest of the patients had T1DM. The duration of insulin injection therapy prior to onset ranged from immediate to 13 years (median 4 years). Fourteen cases (73%) were reported on the abdomen; however, other sites, such as thighs and upper arm, also were reported. Lesions size varied from 12 to 360 cm². Two cases had associated amyloidosis. The average HbA1c reported at presentation was 10%. Following insulin injection-site rotation, most of the cases reported improvement of both glycemic control and acanthosis nigricans appearance.

In the case described by Kudo and colleagues, a 59-year-old male patient with T2DM had been injecting insulin into the same spot on his abdomen for 10 years. He developed acanthosis nigricans and an amyloidoma so large and firm that it bent the needle when he injected insulin.11
Most of the cases we found in the literature were after 2005 and associated with the use of human or analog insulin. These cases may be related to a bias, as cases may be easier to find in digital archives in the later years, when human or analog insulins have been in common use. Also noteworthy, in cases that reported dosage, most were not very high, and the highest daily dose was 240 IU/d. Ten reports of injection-site acanthosis nigricans were in dermatology journals; only 5 reports were in endocrinology journals and 3 in general medical journals, indicating possible less awareness of this phenomenon in other HCPs who care for patients with DM.

Complications of Same-Site Injections

Acanthosis nigricans. Commonly found in the armpits, neck folds, and groin, acanthosis nigricans is known as one of the calling cards for insulin resistance, obesity, and hyperinsulinemia. Acanthosis nigricans can be seen in people with or without DM and is not limited to those on insulin therapy. However, same-site insulin injections for 4 to 6 years also may result in injection-site acanthosis nigricans-like lesions because of factors such as insulin exposure at the local tissue level.

Acanthosis nigricans development is characterized by hyperpigmented, hyperkeratotic, velvety, and sometimes verrucous plaques. Acanthosis nigricans surrounding repeated injection sites is hypothesized to develop as a result of localized hyperinsulinemia secondary to insulin resistance, which increases the stimulation of IGF, thereby causing epidermal hypertrophy. If insulin injection therapy continues to be administered through the acanthosis nigricans lesion, it results in decreased insulin absorption, leading to poor glycemic control.

Acanthosis nigricans associated with insulin injection is reversible. After rotation of injection sites, lesions either decrease in size or severity of appearance. Also, by avoiding injection into the hyperkeratotic plaques and using normal subcutaneous tissue for injection, patients' response to insulin improves, as measured by HbA1c, and by decreased daily insulin requirement.

Lipoatrophy. This is characterized by an increase in localized adipose tissue and is the most common cutaneous complication of insulin therapy. Lipohypertrophy presents as a firm, rubbery mass in the location of same-site insulin injections. Development of lipohypertrophy is suspected to be the result of either (1) anabolic effect of insulin on local adipocytes, promoting fat and protein synthesis; (2) an autoimmune response by immunoglobulin (Ig) G or IgE antibodies to insulin, immune response to insulin of different species, or to insulin injection techniques; or (3) repeated trauma to the injection site from repeated needle usage.

In a study assessing the prevalence of lipohypertrophy and its relation to insulin technique, 49.1% of participants with lipohypertrophy had glycemic variability compared with 6.5% of participants without lipohypertrophy. Johansson and colleagues described an impairment of insulin absorption in lipohypertrophic tissues, causing a 25% lower plasma insulin concentration compared with that of normal tissues. These findings suggest a significant effect of lipohypertrophy on insulin absorption—unnecessarily increasing insulin consumption and worsening glycemic control.

Primary prevention measures include injection site inspection and patient education about rotation and abstaining from needle reuse. If a patient already has signs of lipohypertrophy, data supports education and insulin injection technique practice as simple and effective means to reduce insulin action variability and increase glycemic control.
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Pathophysiology of Localized Insulin Resistance

Insulin regulates glucose homeostasis in skeletal muscle and adipose tissue, increases hepatic and adipocyte lipid synthesis, and decreases adipocyte fatty acid release. Generalized insulin resistance occurs when target tissues have decreased glucose uptake in response to circulating insulin. Insulin resistance increases the amount of free insulin in surrounding tissues. At high concentrations, insulin fosters tissue growth by binding to IGF-1 receptors, stimulating hypertrophy and reproduction of keratinocytes and fibroblasts. This pathophysiology helps explain the origin of localized acanthosis nigricans at same-site insulin injections.

CONCLUSIONS

Cutaneous complications are a local adverse effect of long-term failure to rotate insulin injection sites. Our case serves as a call to action for HCPs to improve education regarding insulin injection-site rotation, conduct routine injection-site inspection, and actively document cases as they occur to increase public awareness of these important complications.

If a patient with DM presents with unexplained poor glycemic control, consider questioning the patient about injection-site location and how often they are rotating the insulin injection site. Inspect the site for cutaneous complications. Of note, if a patient has a cutaneous complication due to insulin injection, adjust or decrease the insulin dosage when rotating sites to mitigate the risk of hypoglycemic episodes.

Improvement of glycemic control, cosmetic appearance of injection site, and insulin use all begin with skin inspection, injection technique education, and periodic review by a HCP.

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Author disclosures

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References

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<table>
<thead>
<tr>
<th>Source</th>
<th>Type</th>
<th>Age, y/sex</th>
<th>HbA1c, %</th>
<th>Size, cm</th>
<th>Duration of Injection Before Onset, y</th>
<th>Insulin Type</th>
<th>Results of Injection Site Rotation</th>
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</thead>
<tbody>
<tr>
<td>Erickson et al, 1969</td>
<td>2</td>
<td>25f</td>
<td>No data</td>
<td>Bilateral anterior thighs 4 × 5</td>
<td>No data</td>
<td>Human, NPH</td>
<td>Decrease in plaque size 2 mo later No data N/A</td>
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<tr>
<td>Fleming et al, 1986</td>
<td>2</td>
<td>57m</td>
<td>No data</td>
<td>Bilateral anterior thighs 6.5 × 8.5</td>
<td>No data</td>
<td>Beef-pork, NPH</td>
<td>No data 25% reduction in lesions 2 mo later</td>
</tr>
<tr>
<td>Gannon et al, 2005</td>
<td>1</td>
<td>25f</td>
<td>No data</td>
<td>Left abdomen 4 × 6</td>
<td>No data</td>
<td>Human, NPH</td>
<td>Area was nearly normal after 4 mo; no recurrence with rechallenge</td>
</tr>
<tr>
<td>Mailler et al, 2008</td>
<td>2</td>
<td>63m</td>
<td>No data</td>
<td>Abdomen 6 × 6.5</td>
<td>No data</td>
<td>Human, NPH, regular</td>
<td>Reduction in HbA1c to 7.8% and reduced pigmentation after 1 y</td>
</tr>
<tr>
<td>Burgos et al, 2008</td>
<td>2</td>
<td>46f</td>
<td>No data</td>
<td>Left abdomen 4.5 × 4.5</td>
<td>No data</td>
<td>Human, NPH</td>
<td>Reduction in acanthosis nigricans size 3 wk later</td>
</tr>
<tr>
<td>Buzasi et al, 2011</td>
<td>2</td>
<td>70m</td>
<td>No data</td>
<td>Abdomen 9 × 36</td>
<td>No data</td>
<td>Human, NPH, regular</td>
<td>Reduction in HbA1c to 7.9% after 3 mo</td>
</tr>
<tr>
<td>Kudo et al, 2011</td>
<td>2</td>
<td>59m</td>
<td>No data</td>
<td>Left abdomen 4.5 × 4.5</td>
<td>No data</td>
<td>Human, NPH</td>
<td>No data No data</td>
</tr>
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<td>Brodeli et al, 2012</td>
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<td>No data</td>
<td>Abdomen 11 × 15</td>
<td>No data</td>
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<td>Reduction in HbA1c to 7.9% after 3 mo</td>
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<td>Kanwar et al, 2013</td>
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<td>21f</td>
<td>No data</td>
<td>Abdomen 6 × 4.5</td>
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<td>No data</td>
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<td>Regression over 1 y</td>
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<td>Regression over 1 y</td>
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<td>Yahagi et al, 2016</td>
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<td>Regression over 1 y</td>
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<td>Regression over 1 y</td>
</tr>
<tr>
<td>Pal et al, 2018</td>
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<td>21f</td>
<td>No data</td>
<td>Abdomen 6 × 4.5</td>
<td>No data</td>
<td>Human, NPH, regular</td>
<td>Regression over 1 y</td>
</tr>
<tr>
<td>Bomar et al, 2019</td>
<td>2</td>
<td>64/m</td>
<td>No data</td>
<td>Lower abdomen 4 × 3.5</td>
<td>No data</td>
<td>Human, NPH, regular</td>
<td>Regression over 1 y</td>
</tr>
<tr>
<td><strong>Current case</strong></td>
<td>2</td>
<td>75/m</td>
<td>No data</td>
<td>Abdomen (2 sites) 9 × 8</td>
<td>No data</td>
<td>Analog insulin, glargine</td>
<td>Resolution of acanthosis nigricans 3-4 mo later</td>
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</table>

**Abbreviations:** HbA1c, hemoglobin A1c; NPH, neutral protamine Hagedorn.