

Simultaneous occurrence of insulin-derived amyloidosis and acanthosis nigricans at the abdominal site of insulin injection



Chloe Vuillamy, MD, Jean-Philippe Arnault, MD, Christophe Attencourt, MD, Ali Dadban, MD, Camille Joachim, MD, Guillaume Chaby, MD, and Catherine Lok, PhD
Amiens, France

Key words: acanthosis nigricans; amyloidosis; diabetes; insulin.

INTRODUCTION

The most common complications of subcutaneous insulin injection are lipoatrophy, lipohypertrophy, and localized allergic reactions. More rarely, skin abscesses, insulin edema, insulin allergy, acanthosis nigricans (AN), and insulin-derived amyloidosis have been reported at insulin injection sites.¹ We report a patient with concomitant insulin-derived amyloidosis and AN at the abdominal site of insulin injection.

CASE REPORT

A 68-year-old woman with a history of hypertension, liver transplant for nonalcoholic steatohepatitis cirrhosis, and a 30-year history of type 2 diabetes presented with growing asymptomatic plaques on the abdomen. Her antirejection treatment consisted of mycophenolate mofetil and tacrolimus. Insulin glargine and insulin lispro had been started 10 years before the visit. Abdominal plaques appeared at the injection sites, but treatment was continued until 1.5 years prior to presentation, when treatment was changed to insulin glargine and insulin aspart due to worsening blood glucose control.

Physical examination showed 2 large hyperkeratotic, hyperpigmented, and indurated plaques symmetrically located on either side of the umbilicus. No masses were palpable. Along the superior edge, the plaques were confined by the liver transplantation scar (Fig 1). Examination of the back of the neck and armpits revealed AN.

Histologic examination of the abdomen showed hyperkeratosis and papillomatosis with mild acanthosis, confirming AN (Fig 2, A). Examination of the

Abbreviation used:

AN: acanthosis nigricans



Fig 1. Hyperkeratotic plaques located on either side of the umbilicus.

dermis revealed masses of eosinophilic and amorphous material. The deposit stained orange-red with Congo red (Fig 2, B) and showed green birefringence under polarized light (Fig 2, C), which is diagnostic for amyloidosis. The amyloid deposit showed positive staining with anti-insulin and antiserum amyloid A antibodies.

Based on these findings, a diagnosis was made of insulin-derived amyloidosis associated with AN at the site of insulin injection.

Surgical excision was considered, but not considered feasible in view of the absence of a palpable mass. Clobetasol propionate cream applied once daily resulted in no clinical change. Topical adapalene 0.1% resulted in significant reduction in the appearance of clinical plaques. Induration, however, persisted (Fig 3).

From the Centre Hospitalier Universitaire Amiens-Picardie.
Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Chloe Vuillamy, MD, Centre Hospitalier Universitaire Amiens-Picardie, Place Victor Pauchet, 80080 Amiens, France. E-mail: vuillamy.chloe@chu-amiens.fr.

JAAD Case Reports 2022;19:94-6.

2352-5126

© 2021 Published by Elsevier on behalf of the American Academy of Dermatology, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jdc.2021.11.003>

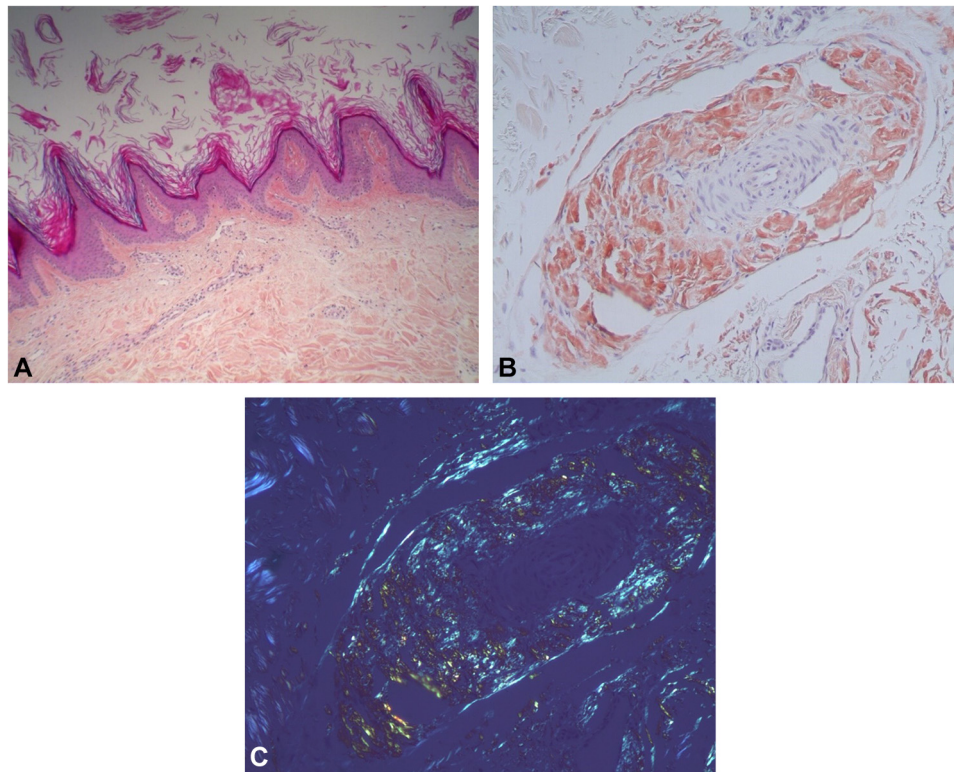


Fig 2. **A**, Hyperkeratosis and papillomatosis. (Hematoxylin-eosin stain, original magnification: $\times 6.5$.) **B**, Cutaneous amyloidosis: Amyloid deposits staining Congo red—positive. (Original magnification: $\times 15$.) **C**, Cutaneous amyloidosis: apple-green birefringence in polarized light. (Original magnification: $\times 15$.)



Fig 3. Improvement after 4 months of topical retinoid treatment.

DISCUSSION

Amyloid deposition at the injection site of porcine insulin was described for the first time in 1988 by Dische et al.² Since then, at least 86 cases of insulin-derived amyloidosis have been reported.³ Any type of insulin can cause insulin amyloidosis.³

The usual clinical presentation is a rigid subcutaneous mass at the site of insulin injection. Nagase et al⁴ reported 2 cases of insulin-derived amyloidosis without a palpable mass, suggesting that its incidence may be underestimated.

Patients often exhibit poor glycemic control because of local degradation of insulin in amyloid or trapping of insulin in amyloid fibrils after injection.⁵ Patients may also present with severe hypoglycemia due to erratic absorption from the affected site.

Diagnosis is confirmed by histopathology with the presence of amyloid positively stained by an antibody against insulin.⁶

Lipohypertrophy is the most common differential diagnosis.⁶ This localized reaction site is less firm and solid than an amyloid tumor and regresses after cessation of insulin injections.

The treatment for insulin-derived amyloidosis is to avoid the injections at the sites of amyloidosis or surgery.⁶ Surgical excision can result in improved glycemic control in cases of localized amyloid tumors.

AN at the site of insulin injection is another rare complication of insulin injection, with a dozen cases reported.⁷ The patients are mostly men. The abdomen is the most commonly affected site. For 2 patients, plaques disappeared after rotating injection sites. The pathophysiology remains unknown, but may be the same as in benign AN. High concentrations of insulin

in the epidermis may bind to insulin-like growth factor 1 receptors on keratinocytes, stimulating proliferation and inducing hyperkeratosis.⁸

To our knowledge, this is the third reported case of a simultaneous occurrence of insulin-derived amyloidosis and AN at the site of insulin injection. The first case reported was a 59-year-old man, whose dermatosis was located on the abdomen and was secondary to the use of human insulin.⁹ The second case, published in 2014, reported on a 54-year-old man, whose dermatosis was also located on the abdomen. The insulin used was recombinant human insulin with no further details.¹⁰ The clinical presentation was similar to the one observed in our patient.

Because our patient was seen many years after the occurrence of AN and insulin-derived amyloidosis, it is difficult to know which pathology occurred first. We offer 2 hypotheses as to why these 2 conditions might co-occur. Firstly, it is possible that the presence of induration from amyloid led to more superficial insulin injection, with higher concentrations of insulin in the epidermis resulting in AN. Another possibility is that amyloid hindered the absorption of insulin and poorer glycemic control, requiring increased doses of insulin and development of AN.

CONCLUSION

Although insulin-derived amyloidosis and AN are uncommon complications of insulin injection, dermatologists should be aware of them. Prevention of these complications can be achieved by rotating insulin injection sites, self-monitoring, and the use of fine needles.

Conflicts of interest

None disclosed.

REFERENCES

- Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. *Am J Clin Dermatol*. 2003;4(10):661-667. <https://doi.org/10.2165/00128071-200304100-00001>
- Dische FE, Wernstedt C, Westermark GT, et al. Insulin as an amyloid-fibril protein at sites of repeated insulin injections in a diabetic patient. *Diabetologia*. 1988;31(3):158-161. <https://doi.org/10.1007/BF00276849>
- Nilsson MR. Insulin amyloid at injection sites of patients with diabetes. *Amyloid*. 2016;23(3):139-147. <https://doi.org/10.1080/13506129.2016.1179183>
- Nagase T, Iwaya K, Kogure K, et al. Insulin-derived amyloidosis without a palpable mass at the insulin injection site: a report of two cases. *J Diabetes Investig*. 2020;11(4):1002-1005. <https://doi.org/10.1111/jdi.13199>
- Nagase T, Iwaya K, Iwaki Y, et al. Insulin-derived amyloidosis and poor glycemic control: a case series. *Am J Med*. 2014;127(5):450-454. <https://doi.org/10.1016/j.amjmed.2013.10.029>
- Gupta Y, Singla G, Singla R. Insulin-derived amyloidosis. *Indian J Endocrinol Metab*. 2015;19(1):174-177. <https://doi.org/10.4103/2230-8210.146879>
- Bomar L, Lewallen R, Jorizzo J. Localized acanthosis nigricans at the site of repetitive insulin injections. *Cutis*. 2020;105(2):E20-E22.
- Pal R, Bhattacharjee R, Chatterjee D, Bhadada SK, Bhansali A, Dutta P. Exogenous insulin-induced localized acanthosis nigricans: a rare injection site complication. *Can J Diabetes*. 2020;44(3):219-221. <https://doi.org/10.1016/j.jcjd.2019.08.010>
- Kudo-Watanuki S, Kurihara E, Yamamoto K, Mukai K, Chen KR. Coexistence of insulin-derived amyloidosis and an overlying acanthosis nigricans-like lesion at the site of insulin injection. *Clin Exp Dermatol*. 2013;38(1):25-29. <https://doi.org/10.1111/j.1365-2230.2012.04373.x>
- Nandeesh BN, Rajalakshmi T, Shubha B. Cutaneous amyloidosis at the site of insulin injection with coexistence of acanthosis nigricans. *Indian J Pathol Microbiol*. 2014;57(1):127-129. <https://doi.org/10.4103/0377-4929.130920>