

Cutaneous Insulin-Derived Amyloidosis Presenting as Hyperkeratotic Nodules

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PRACTICE POINTS

- Deposition of amyloid at insulin injection sites has the potential to interfere with insulin absorption, leading to poor glucose control.
- Patients with insulin-derived (AIns) amyloidosis may initially present after noticing nodular deposits.
- Insulin injection site rotation is a crucial aspect of treatment and prevention of AIns amyloidosis.

Amyloidosis consists of approximately 30 protein-folding disorders in which a specific soluble precursor protein aggregates to form the insoluble fibrils of amyloid. Insulin is the hypothesized precursor protein in localized cutaneous insulin-derived (AIns) amyloidosis. Amyloid deposition at insulin injection sites can interfere with absorption, leading to poor glucose control. Despite the increasing prevalence of diabetes mellitus and insulin use, there is a paucity of published cases of AIns amyloidosis and a lack of awareness of this condition among both dermatologists and general practitioners. We report 2 patients with insulin-dependent diabetes who developed hyperkeratotic nodules at insulin injection sites. Our cases complement the current data on iatrogenic amyloidosis and provide insight into this likely underreported phenomenon.

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Amyloidosis consists of approximately 30 protein-folding disorders sharing the common feature of abnormal extracellular amyloid deposition. In each condition, a specific soluble precursor protein aggregates to form the insoluble fibrils of amyloid, characterized by

the beta-pleated sheet structure.¹ Amyloidosis occurs as either a systemic or localized process. Insulin-derived (AIns) amyloidosis, a localized process occurring at insulin injection sites, was first reported in 1983.² There were fewer than 20 reported cases until 2014, when 57 additional cases were reported by just 2 institutions,^{3,4} indicating that AIns amyloidosis may be more common than previously thought.^{3,5}

Despite the increasing prevalence of diabetes mellitus and insulin use, there is a paucity of published cases of AIns amyloidosis. The lack of awareness of this condition among both dermatologists and general practitioners may be in part due to its variable clinical manifestations. We describe 2 patients with unique presentations of localized amyloidosis at repeated insulin injection sites.

Case Reports

Patient 1—A 39-year-old man with a history of type 1 diabetes mellitus presented with 4 asymptomatic nodules on the lateral thighs in areas of previous insulin injection. He first noticed the lesions 9 months prior to presentation and subsequently switched the injection site to the abdomen without development of new nodules. Despite being compliant with his insulin regimen, he had a long history of irregular glucose control, including frequent hypoglycemic episodes. The patient was using regular and neutral protamine hagedorn insulin.

On physical examination, 2 soft, nontender, exophytic nodules were noted on each upper thigh with surrounding hyperpigmented and hyperkeratotic collarettes (Figure 1). The nodules ranged in size from 2 to 3.5 cm in diameter.

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Remarkable laboratory data included a fasting glucose level of 207 mg/dL (reference range, 70–110 mg/dL) and a glycohemoglobin of 8.8% (reference range, <5.7%). Serum protein electrophoresis and immunofixation were normal. Histopathology of the lesions demonstrated diffuse deposition of pink amorphous material associated with prominent papillomatosis, hyperkeratosis, and acanthosis (Figure 2). Congo red staining was positive with green birefringence under polarized light, indicative of amyloid deposits (Figure 3). Liquid chromatography–tandem mass spectrometry of the specimens was consistent with deposition of AIns amyloidosis.

Due to the size and persistent nature of the lesions, the nodules were removed by tangential excision. In addition, the patient was advised to continue rotating injection sites frequently. His blood glucose levels are now well controlled, and he has not developed any new nodules.



FIGURE 1. A, Two exophytic nodules were present on each upper thigh in patient 1 with surrounding hyperpigmented and hyperkeratotic collarettes. B, A yellow-orange, semisolid material was expressed from the nodule when biopsied.

Patient 2—A 53-year-old woman with a history of type 2 diabetes mellitus presented with painful subcutaneous nodules on the lower abdomen at sites of previous insulin injections. The nodules developed approximately 1 month after she started treatment with neutral protamine hagedorn insulin and had been slowly enlarging over the past year. She tried switching injection sites after noticing the lesions, but the nodules persisted. The patient had a long history of poor glucose control with chronically elevated glycohemoglobin and blood glucose levels.

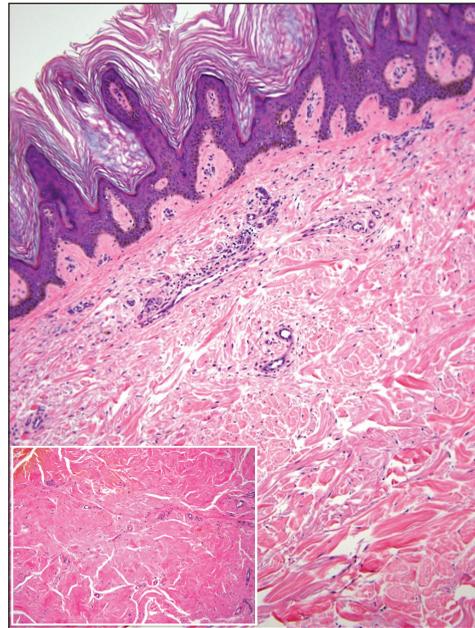


FIGURE 2. Histopathology revealed hyperkeratosis and papillomatosis in the epidermis surrounding and overlying the nodules. Diffuse amyloid deposition was noted throughout the dermis (H&E, original magnification $\times 10$ [inset, original magnification $\times 20$]).

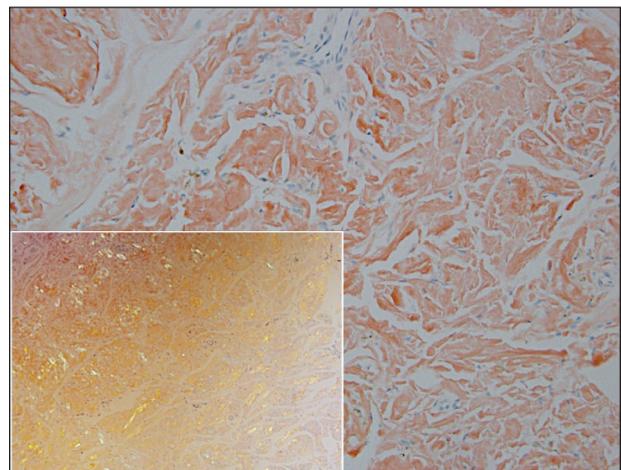


FIGURE 3. The dermal deposits were uniformly positive for Congo red (original magnification $\times 20$), showing green birefringence under polarized light (inset, original magnification $\times 10$).

On physical examination, 2 hyperpigmented, exophytic, smooth nodules were noted on the right and left lower abdomen, ranging in size from 2.5 to 5.5 cm in diameter (Figure 4).

Relevant laboratory data included a fasting glucose level of 197 mg/dL and a glycohemoglobin of 9.3%. A biopsy of the lesion on the left lower abdomen revealed eosinophilic amorphous deposits with fissuring in the dermis (Figure 5). Congo red stain was positive with green birefringence under polarized light. Liquid chromatography–tandem mass spectrometry of the specimen showed deposition of AIns amyloid. The patient began injecting away from the amyloid nodules without development of any new lesions. The original nodules have persisted, and surgical excision is planned.



FIGURE 4. A large, hyperpigmented, exophytic nodule on the left lower abdomen in patient 2.

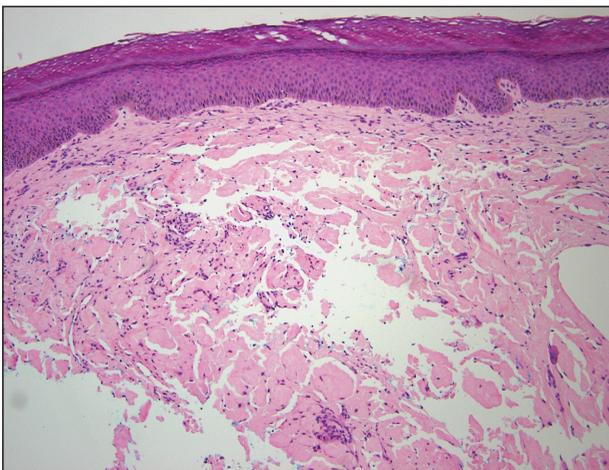


FIGURE 5. Histopathologic examination revealed eosinophilic amorphous deposits with fissuring in the dermis (H&E, original magnification $\times 10$).

Comment

Insulin is the suspected precursor protein in AIns amyloidosis, but the exact pathogenesis is unknown. The protein that is derived from insulin in these tumors is now identified as AIns amyloidosis.^{5,6} It is hypothesized that insulin accumulates locally and is converted to amyloid by an unknown mechanism.⁷ Other potential contributory factors include chronic inflammation and foreign body reactions developing around amyloid deposits, as well as repeated trauma from injections into a single site.^{4,5} It appears that lesions may derive from a wide range of insulin types and occur after variable time periods.

A majority of cases of iatrogenic amyloid have been described as single, firm, subcutaneous masses at an injection site that commonly are misdiagnosed as lipomas or lipohypertrophy.⁷⁻¹¹ To our knowledge, none of the reported cases resembled the multiple, discrete, exophytic nodules seen in our patients.^{3,4} The surrounding hyperkeratosis noted in patient 1 is another uncommon feature of AIns amyloidosis (Figures 1 and 2). Only 3 AIns amyloidosis cases described lesions with acanthosis nigricans–like changes, only 1 of which provided a clinical image.^{6,7,12} The mechanism for the acanthosis nigricans–like changes may have been due to the high levels of insulin at the injection site. It has been suggested that the activation of insulinlike growth factor receptor by insulin leads to the proliferation of keratinocytes and fibroblasts.⁶

Histologic examination of AIns amyloidosis lesions generally demonstrates deposition of homogenous eosinophilic material consistent with amyloid, as well as positive Congo red staining with green birefringence by polarization. Immunohistologic staining with insulin antibody with or without proteomic analysis of the amyloid deposits can confirm the diagnosis. In both of our patients' specimens, liquid chromatography–tandem mass spectrometry was performed for proteomic analysis, and results were consistent with AIns amyloidosis.

Reports in the literature have suggested that the deposition of amyloid at insulin injection sites has the potential to interfere with insulin absorption, leading to poor glucose control.^{4,11,13} Hence, injection site rotation is a crucial aspect of treatment and prevention of AIns amyloidosis. In their study of 4 patients, Nagase et al⁴ compared serum insulin levels after insulin injection into amyloid nodules vs insulin levels after injection into normal skin. Insulin absorption at the amyloid sites was 34% of that at normal sites. Given these results, patients should be instructed to inject away from the amyloid deposit once it is identified.⁶ Glucose levels should be monitored closely when patients first inject away from the amyloid mass, as injection of the same dosage to an area of normal skin can lead to increased insulin absorption and hypoglycemia.^{4,6} It is possible that the frequent hypoglycemic episodes noted in patient 1 were due to increased insulin sensitivity after switching to injection sites away from amyloid lesions.

Conclusion

Our patients demonstrate unique presentations of localized cutaneous amyloidosis at repeated insulin injection sites. We report these cases to complement the current data of iatrogenic amyloidosis and provide insight into this likely underreported phenomenon.

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