CASE REPORT

Dual pathology at the injection site: Insulin-derived amyloidosis with superimposed acanthosis nigricans in a patient with type 1 diabetes

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ABSTRACT

Insulin-derived amyloidosis (IDA) and acanthosis nigricans (AN) are conditions that may develop at injection sites, though their co-occurrence is exceptionally rare. This case report highlights the rare coexistence of insulin-derived amyloidosis and acanthosis nigricans by presenting the clinical features, histopathological findings, and underlying pathophysiological mechanisms. It emphasizes the importance of recognizing atypical injection-site dermatoses and their impact on glycemic control and patient care. We report the case of a 51-year-old woman with long-standing T1DM who presented with progressively thickened, hyperpigmented plaques at her abdominal and thigh injection sites. Histological evaluation of punch biopsies confirmed the presence of amyloid deposits consistent with IDA, with overlying epidermal changes of AN. These findings highlight a rare dual pathology at insulin injection sites. This case underscores the importance of recognizing unusual skin changes at insulin injection sites, particularly in patients with poorly controlled diabetes. Early recognition, supported by biopsy and histopathology, is crucial for accurate diagnosis and effective management. (www.actabiomedica.it)

Key words: insulin-derived amyloidosis, acanthosis nigricans, injection site dermatoses, diabetes-related skin manifestations, hyperkeratotic plaques, localized skin reaction

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Introduction

Insulin therapy is a life-saving treatment for patients with Type 1 diabetes mellitus (T1DM). However, it may rarely cause localized cutaneous complications. Two such conditions—insulin-derived amyloidosis (IDA) and acanthosis nigricans (AN)—have been documented at insulin injection sites (1). IDA results from the deposition of amyloid protein from injected insulin, while AN manifests as hyperpigmented, hyperkeratotic, thickened skin, often associated with hyperinsulinemia. The coexistence of these two phenomena at injection sites is exceedingly rare, with only a handful of cases reported in the literature (1). This report presents a rare case of coexisting IDA and AN in a patient with T1DM and reviews current knowledge on their pathophysiology, clinical presentation, potential mechanisms of coexistence, and diagnostic and therapeutic challenges.

Case presentation

A 51-year-old female with T1DM, diagnosed in 1988 with a 36-year-long history of insulin-dependent T1DM was admitted under the department of Internal medicine as case of hypertensive emergency with flush pulmonary oedema and Acute Kidney Injury and uncontrolled T1DM with no evidence of diabetic ketoacidosis Hyperosmolar Hyperglycemic state, presented with progressive skin lesions on the abdomen and left thigh evolving over two years. Her medical history includes class III obesity (body mass index: 40.9), poorly controlled diabetes (HbA1c: 12.3%), hypertension, dyslipidemia, and obstructive sleep apnea. Surgical history included left great-toe amputation due to gangrene, cesarean section, and ocular surgery for left eye cataract that resulted in blindness in the left eye. The patient reported that her skin lesions initially appeared as areas of hyperpigmentation at insulin injection sites, especially on the abdomen, which gradually thickened and became firm. She also experienced mild pruritus and localized swelling, but denied any recent episodes of hypoglycemia or hyperglycemia. Her diabetes regimen consisted of insulin glargine 80 IU at bedtime, insulin aspart 65 IU before meals, semaglutide 1 mg once weekly, and empagliflozin 10 mg daily. She is taking nifedipine 30 mg for hypertension, rosuvastatin 20 mg for dyslipidemia, and additional medications including furosemide, hydralazine, amlodipine, pantoprazole, and aspirin. On examination, her blood pressure was elevated at 187/71 mmHg, while other vital signs were stable. Patient height: 154 cm and weight: 97 kg BMI: 40.9 A local examination revealed two hyperpigmented plaques on the anterior abdomen with a rough, thickened surfaces measuring 5 x 4 cm and 10 x 6 cm (Figure 1). The lesions were firm, and the skin overlying them could not be pinched. A similar hyperpigmented patch, with a central crusted plaque, was noted on the left thigh.

Laboratory investigations showed poor glycemic control with HbA1c of 12.3%. Complete blood count revealed macrocytic anemia (mean corpuscular volume 105 fL) and (hemoglobin 8.5 gm/dL) with normal leukocyte and platelet counts. Renal profile demonstrated elevated serum creatinine (4.13 mg/dL) and blood urea nitrogen (81 mg/dL). Liver enzymes showed elevated lactate dehydrogenase (225 U/L) and elevated Gamma glutamyltransferase (60 U/L) and bilirubin was unremarkable. Urinalysis revealed elevated proteinuria, glucosuria, hematuria, and pyuria without ketonuria, and a 24-hour urine collection confirmed elevated proteinuria (825.5 mg/dL) and 24 hour urine protein (11557 mg/24h). To investigate further, two 6-mm punch biopsies were obtained from the abdominal lesions. Histopathology revealed insulin-derived amyloidosis with features of acanthosis nigricans. Both trichrome and Congo red stains were positive, confirming the diagnosis (Figure 2).

Discussion

This case highlights, the rare coexistence of insulin-derived amyloidosis (IDA) and acanthosis nigricans (AN) at insulin injection sites, a dual pathology with important clinical implications. The exact mechanism behind insulin amyloidogenesis remains unclear. IDA develops when repeated injections at the same site lead to high local insulin concentrations that favor protein misfolding and amyloid fibril formation. Dissociation of insulin into its monomeric form promotes

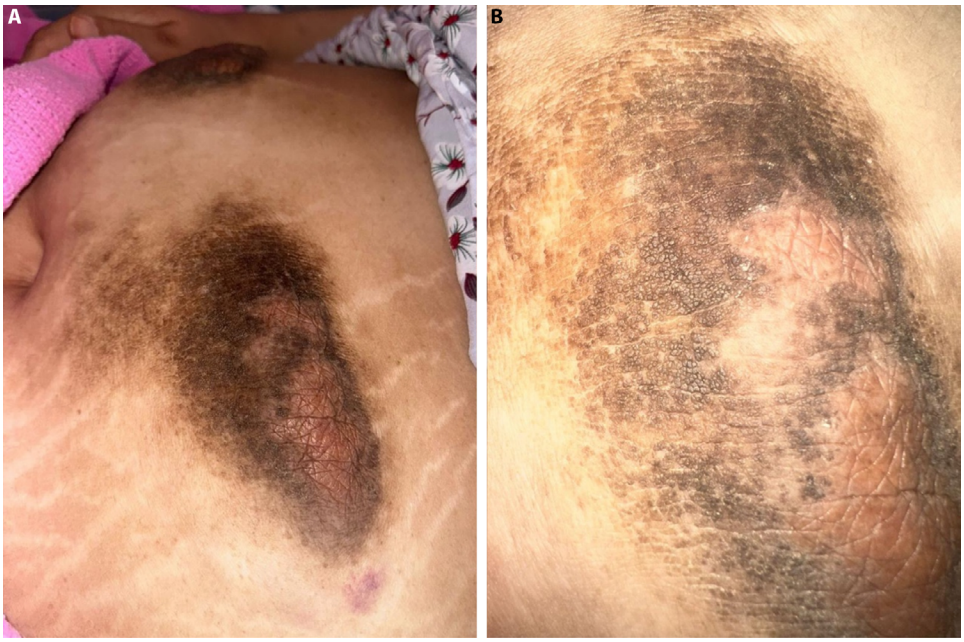

Figure 1. (A) Clinical image of the abdomen showing multiple hyperpigmented plaques with a rough, thickened surface at insulin injection sites. (B) Close-up view of one plaque revealing a velvety, hyperpigmented texture consistent with acanthosis nigricans overlying a firm, indurated base suggestive of insulin-derived amyloidosis.

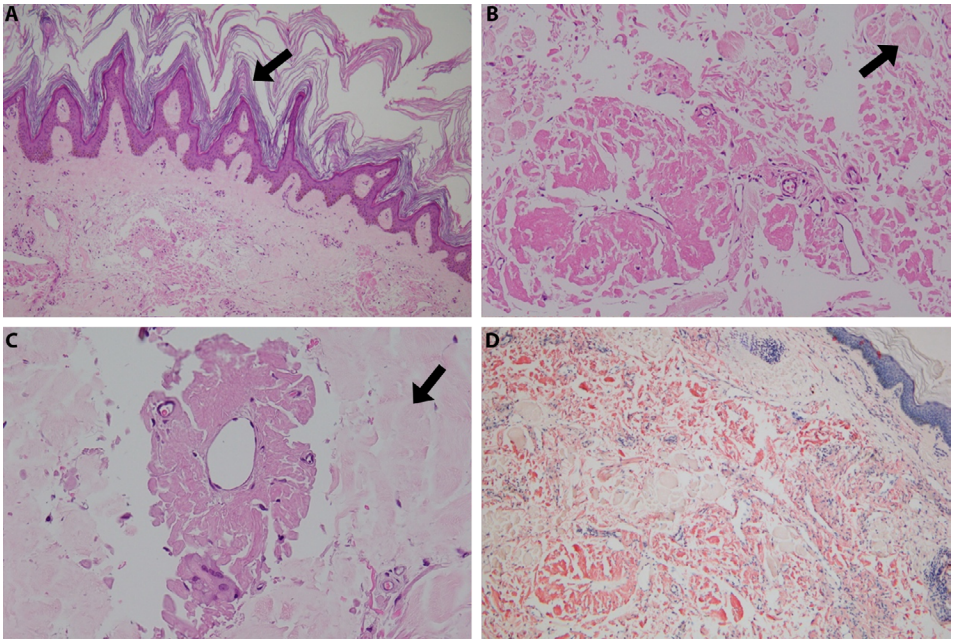

Figure 2. Histopathological analysis of the biopsy. (A) The epidermis shows features of acanthosis nigricans (hematoxylin–eosin stain ×10 HPF magnification). (B & C) Perivascular and dermal scattered deposition of amorphous eosinophilic material with cracking artefact (hematoxylin–eosin stain ×20 HPF magnification and ×40 HPF magnification, respectively). (D) Amyloid deposition exhibits a salmon color, (Congo red stain ×10 HPF magnification).

aggregation, while chronic mechanical trauma further facilitates disposition (2,3) Over time, previously injected insulin can act as a "seed," for new fibrils, and immunostaining with anti-insulin antibodies confirms their insulin origin (1,2). Clinically, IDA typically presents as firm, painless subcutaneous nodule or plaques at long-standing injection sites, most commonly on the abdomen (1). These lesions are often misdiagnosed as lipohypertrophy, but unlike lipohypertrophy, amyloid nodules feel firmer and persist despite site rotation (2). Glycemic control often becomes erratic because insulin absorption from amyloid-laden sites has reduced bioavailability; in one study found that only about one-third of the dose is absorbed. Consequently, patients compensate by increasing their insulin dose, which in turn predisposes them to hypoglycemia once injections are shifted to unaffected areas (1,2). Histologically, IDA is confirmed by the presence of amorphous eosinophilic material in the dermis or subcutis, exhibiting classic apple-green birefringence under polarized light after Congo red staining (1). Acanthosis nigricans is characterized by velvety, hyperpigmented, and hyperkeratotic plaques, most commonly in intertriginous areas but occasionally at insulin injection sites in patients with T1DM (4). In this context, repeated injections deliver supraphysiologic insulin concentrations to the skin, where excess insulin binds to insulin-like growth factor-1 (IGF-1) receptors on keratinocytes, promoting epidermal proliferation and melanogenesis (1). Histopathology demonstrates hyperkeratosis, papillomatosis, mild epidermal acanthosis, and increased basal layer pigmentation (1). The coexistence of IDA and AN is exceptionally rare, with only a few cases reported (1). Two hypotheses are thought to contribute: first, amyloid nodules may cause patients to inject insulin more superficially, exposing the epidermis to higher insulin concentrations; second, sequestration of insulin within amyloid deposits can lead to poor absorption, promoting dose escalation and systemic hyperinsulinemia, provoking AN lesions locally and potentially in typical AN sites (1). Repeated trauma from injections may also contribute, mimicking a frictional AN-like response. In fact, some lesions have been misdiagnosed as keloids initially (5). The coexistence of these two conditions poses important diagnostic and therapeutic challenges. Indurated or hyperpigmented injection-site lesions in long-standing diabetes should not be assumed to represent lipohypertrophy or scarring. A biopsy, with Congo red staining and immunolabeling confirming IDA (1). Imaging such as ultrasound or MRI may provide additional information, distinguishing amyloid masses from fat hypertrophy (2). Management primarily relies on strict avoidance of affected sites, which often improves glycemic control and reduces daily insulin requirements (2). In selected cases, surgical excision of localized amyloid deposits can be beneficial, although it is not always feasible (1). AN overlying IDA may respond partially to topical therapies such as retinoid, keratolytics, or high-potency corticosteroids, although cosmetic improvement does not resolve the underlying amyloid. In one case, a potent steroid cream had no effect, but topical retinoid (adapalene 0.1%) improved hyperkeratosis and pigmentation over months (1). Patient education remains critical. Many individuals continue to inject into abnormal sites because they are less painful or more accessible, yet this practice perpetuates disease progression and worsens glycemic variability (2). Regular inspection of injection sites, reinforcement of rotation techniques, and collaboration between dermatologists and endocrinologists are essential for early recognition and prevention. Ultimately, this case emphasizes that awareness of rare injection-site complications can improve both dermatological outcomes and diabetes management (5).

Conclusion

This case underscores the importance of recognizing the rare coexistence of IDA and AN at insulin injection sites. Physicians should maintain a high index of suspicion in long-standing diabetic patients with indurated or hyperpigmented plaques and erratic glycemic control. Early identification, patient education on proper injection techniques, and avoidance of affected sites are key to improving both cutaneous outcomes and metabolic stability.

Ethic Approval: Ethical approval was obtained on June 16, 2025, from the Institutional Review Board of Imam Abdulrahman Bin Faisal University (IRB Number: IRB-2025-01-0413)

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interests, patent/licensing, arrangement etc-) that might pose a conflict of interest in connection with the submitted article.

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