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Visual Diagnosis Pearl

Delayed Cutaneous Insulin Hypersensitivity Reactions

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A 39-year-old patient with Type I diabetes developed recurrent, pruritic nodules at subcutaneous injection sites with multiple insulin formulations, including lispro and glulisine. These lesions appeared 24–72 hours after insulin administration, progressing from localized erythema to firm, indurated erythematous nodules with a surrounding pink halo (Figure 1). On palpation, the lesions were mildly tender and pruritic without systemic symptoms such as urticaria, diffuse angioedema, or signs of anaphylaxis. Findings recurred at multiple injection sites despite appropriate rotation. This presentation is consistent with a delayed hypersensitivity reaction to insulin or its excipients, which may reflect either a Type III (immune complex–mediated) or Type IV (T cell–mediated) mechanisms. Delayed insulin hypersensitivity reactions are clinically important and require recognition to guide appropriate management.[1] A definitive diagnosis requires a broad differential. In addition to delayed allergic reactions, the differential includes injection technique issues, contact dermatitis from adhesive or insulin delivery devices, cellulitis, and thickening or swelling of subcutaneous fatty tissue known as lipohypertrophy. The morphology is key to recognize this reaction. Lesions typically present as pruritic indurated erythematous nodules or eczematous patches at multiple injection sites. These findings may be mistaken for cellulitis which usually presents as a diffuse contiguous area of erythema and is frequently more painful than pruritic and may be accompanied by a fever. Rarely, it may resemble lipohypertrophy which is non-erythematous, has a rubbery or adipose-like texture, is rarely pruritic, and develops gradually over weeks to months.

Type III hypersensitivity reactions result from anti-insulin IgG antibodies forming immune complexes, leading to localized inflammation and Arthus-type nodules. Type IV reactions typically present as localized indurated or eczematous lesions.[1] Differentiating these types may include skin biopsy or skin patch testing. In the correct clinical context, the etiology involves insulin or its excipients. Reactions may be directed against insulin or its additives such as latex, metacresol, zinc, or protamine.[1]

Figure 1. Erythematous indurated nodules with surrounding halos at a prior insulin injection site, consistent with delayed hypersensitivity reactions.

It is worth noting that our case is a delayed hypersensitivity reaction which is less common than the immediate or Type I (IgE mediated) reaction, the most frequent form of insulin hypersensitivity. It presents with localized erythema, pruritis, urticaria and swelling at the injection site within minutes of injection. This type can progress to generalized urticaria, angioedema, or anaphylaxis. Symptoms do usually resolve quickly (<1 hour). Reactions usually develop one week after initiation of insulin therapy or when restarting insulin after a prolonged pause in regular use.[2]

Management of all types include rotating injection sites, trialing alternative insulin formulations, using topical corticosteroids and oral antihistamines, single use needles, and referring to dermatology and/or allergy and immunology for evaluation if a biopsy, patch testing, or if discussions about formal desensitization is required.[3]

Recognition of delayed insulin hypersensitivity helps avoid misdiagnosis and unnecessary antibiotic use for cellulitis. Early identification enables targeted management and supports continued adherence to insulin therapy.

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