

Recall Urticaria in Adalimumab Hypersensitivity



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A 29-year-old teacher with spondyloarthritis was referred for suspected adalimumab allergy. She responded well to subcutaneous adalimumab every 2 weeks, which was withheld because of pregnancy. After delivery, she resumed the same adalimumab formulation with satisfactory results. However, she experienced progressive painful localized injection site swelling 1 hour after each administration. Local induration persisted for 3 to 4 days and reappeared after each administration despite changing injection sites. After her seventh dose, she was admitted for a progressive 12 cm indurated and erythematous large local reaction, which began within an hour after subcutaneous injection on her right thigh (Figure 1). Infection was excluded and she was treated with systemic corticosteroids and antihistamines. Adalimumab was withheld and there was no recurrence of symptoms.

Hypersensitivity to adalimumab was suspected, and skin prick (SPT) and intradermal tests (IDT) with adalimumab (Humira; Abbott Laboratories, Lake Bluff, Illinois) were performed 1 month later on the volar surface of her left arm. SPT was negative, but IDT (5 mg/mL, nonirritant concentration tested in healthy controls) was positive with immediate wheal expansion from 7 to 20 mm (Figure 2). She was prescribed antihistamines for relief, but reported recurrence of urticaria around her skin testing and previous injection site on her right thigh 1 hour later (Figure 3). Delayed IDT readings were negative.

In this case, the presence of a large local reaction, positive immediate IDT, and recall urticaria (RU) was highly suggestive of an IgE-mediated hypersensitivity to adalimumab. She declined further allergy testing with other anti-TNF agents and was switched to subcutaneous anti-IL-17 (secukinumab) without any further reactions.

We report the first case of biologics-related RU. "Recall" reactions (local reactions at distant sites of previous injections or exposure) can either be IgE or T-cell mediated.¹ First described in 1994, IgE-mediated reactions are usually urticarial and occasionally reported to occur after skin tests with certain drugs or

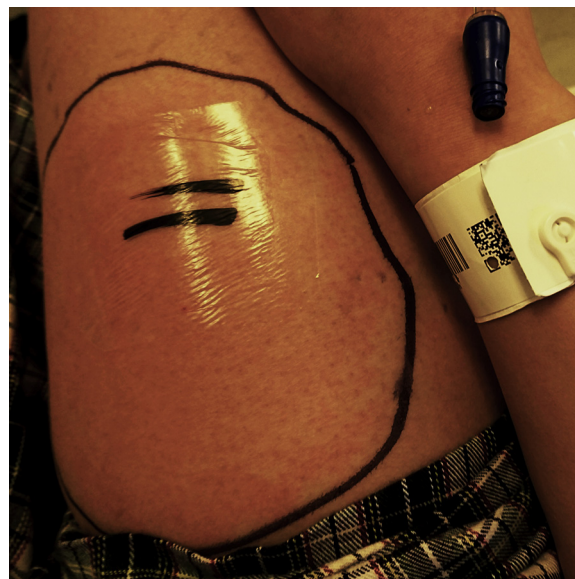


FIGURE 1. Progressive large local reaction after subcutaneous adalimumab injection on the right thigh (photograph taken 24 hours after injection).

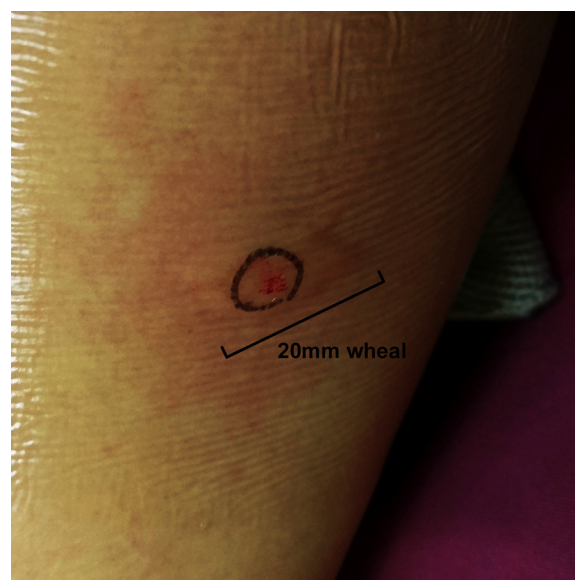


FIGURE 2. Positive intradermal test to adalimumab.

immunotherapy.² The underlying mechanisms remain to be elucidated, but long-lasting changes such as locally increased accumulation or sensitivity of mast cells have been proposed. RU

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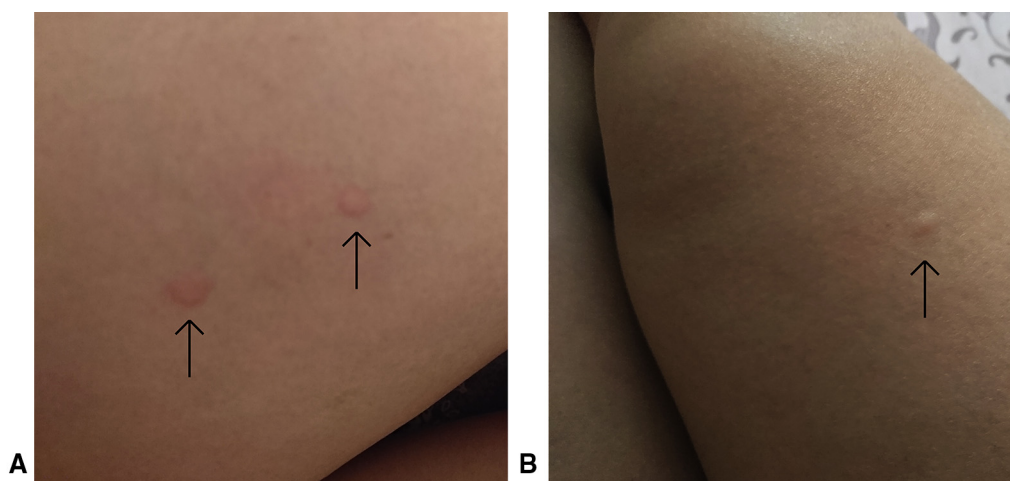


FIGURE 3. Recall urticaria at **A**, previous skin testing sites and **B**, previous injection site on the right thigh.

is likely a very specific sign and, in this case, its presence was very suggestive of both a prior (ie, at the previous reaction site) and persistent immediate-type hypersensitivity to the tested drug. Progressive large local reactions in this case were compatible with IgE-mediated late phase allergic reactions.³

Mild injection site reactions with anti-TNF agents are common and usually wane over time because of induction of tolerance.⁴ However, worsening reactions or additional IgE-mediated features (such as urticaria, angioedema, respiratory or cardiovascular involvement) warrant further investigation before additional dosing or empirical premedication. Respiratory or cardiovascular symptoms or signs would particularly raise concern for anaphylaxis.

Interestingly, a small study suggested that adalimumab may be a safe substitute for infliximab-allergic patients, although the reverse has not been studied.⁵ However, we do not recommend other anti-TNF agents without further evaluation. Anti-drug antibodies were not measured in this patient as their role in predicting immediate-type hypersensitivity reactions remains

unclear.⁶ Adalimumab desensitization could also be considered, but would only be indicated if no other alternatives were available.

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