

Immediate local and systemic hypersensitivity due to etanercept and adalimumab

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Clinical Implications

- TNF antagonists are first-line treatment for inflammatory and autoimmune diseases and can cause several adverse drug reactions. We present a case with immediate local and systemic hypersensitivity reaction due to both etanercept and adalimumab, TNF blockers with different molecular features, which have never been previously reported.

TO THE EDITOR:

Dysregulation of production, processing, and signaling of TNF- α and its receptors is associated with the pathogenesis of several immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriasis, and psoriatic arthritis.¹ Neutralization of TNF- α activity with TNF antagonists is effective in the treatment of these disorders. TNF- α antagonists (mAbs and soluble receptor fusion protein) can cause several adverse drug reactions (ADRs)²; however, urticaria and angioedema are rarely reported.²⁻⁴

A 57-year-old nonatopic woman with a 10-year history of RA had been successfully treated with methotrexate (MTX) (15 mg/wk subcutaneous [SC]), folic acid (5 mg/wk), and prednisone (12.5 mg/d, cyclically). After 8 years, MTX was discontinued because of MTX-related hepatitis with nausea, vomiting, and increased liver enzymes, and etanercept (ET) (50 mg/wk SC) was started. An itchy erythematous and edematous reaction involving the injection site appeared 30 minutes after the first injection of ET; the reaction spontaneously resolved in less than 24 hours. The patient had no problems with the subsequent 2 administrations of ET, but a few minutes after the fourth injection, she developed a similar reaction involving almost the entire abdominal area (Figure 1, A). ET was discontinued, and during the following 4 months the patient's RA worsened. For this reason, adalimumab (AD) (40 mg/2 wk SC) was started. During ET and AD therapy, prednisone was continued at the same dose. Ten minutes after the first AD injection, erythema, edema, and pruritus developed at the injection site, with spontaneous resolution in 24 hours. Subsequent 5 injections of AD were well tolerated, but a few minutes after the seventh injection, the patient developed a severe urticarial reaction involving her trunk, limbs, and axillary, inguinal, and submammary folds along with angioedema of the eyelids and lips (Figure 1, B). The patient was hospitalized and treated with chlorfenamine maleate (10 mg

intravenous [IV]) and methylprednisolone (40 mg IV) with complete resolution in 48 hours.

Two months later, skin tests with ET and AD were performed. Abatacept (AB) as alternative treatment (a fusion protein composed of IgG₁ fused to the extracellular domain of CTLA-4), and mannitol, an inactive ingredient found in both AD and ET, were also tested (Table 1). Prick test with AD (full-strength) and intradermal test with ET diluted 1:10 in saline solution showed an immediate positive reaction (++) (Figure 1, C and D). The latter test results in 20 healthy subjects were negative. Basophil activation test results for both AD and ET were positive, whereas assay for anti-AD and anti-ET IgG antibodies by ELISA (Promonitor manufactures; Progenika Biopharma, Derio, Spain) were negative. In view of the results of the skin tests, AB was started with clinical efficacy and without ADRs at 1-year follow-up.

The use of TNF- α blockers is generally well tolerated. However, they can cause side effects, such as infections, neoplasms, neurological and hematological diseases, heart failure, and autoimmune disorders.⁵ TNF- α blockers, as well as the other biological agents, are able to induce an immune response by the production of antidrug antibodies, which can impair drug efficacy and can cause hypersensitivity reactions.⁶ Several case reports and case series described cutaneous ADRs induced by anti-TNF agents, including immediate (infusions and injection-site reactions, urticaria, anaphylaxis) and delayed (psoriasis, psoriasiform eruptions, lupus-like syndrome, eczematous and lichenoid dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, granulomatous reactions, cutaneous vasculitis) reactions.²⁻⁷ Immediate hypersensitivity reactions are particularly important.

In our patient, the negativity of the skin test result with mannitol excluded the possibility of a hypersensitivity reaction due to the additive of commercial preparations. The widespread erythematous and edematous reaction involving the entire abdominal surface after the fourth injection of ET and the severe urticaria and angioedema after the seventh injection of AD are indicative of immediate hypersensitivity reactions, as confirmed by *in vivo* and *in vitro* tests, probably induced by an IgE-mediated mechanism. Prick and intradermal tests are useful for identifying immediate hypersensitivity to TNF- α blockers.⁴

Surprisingly, our patient presented immediate reactions caused by 2 biologic agents with different molecular features. This could be interpreted as a possible cosensitization between drugs with different chemical structure and different immunogenic properties. However, a cross-reaction could not be excluded, suggesting the presence of metabolites or structural motifs common to both molecules. The "late" onset of urticaria and angioedema during AD therapy could be explained by the continuous therapy with prednisone.

Winfield et al⁸ previously described a case of pruritic, erythematous, and edematous dermatitis involving the injection sites of both AD and ET. The authors speculated that the injection-site reaction caused by the 2 TNF- α blockers were probably induced by the link between rheumatoid factor autoantibody and FcIgG component of the 2 TNF- α blockers. This speculation seems not to fit in our patient because she did not

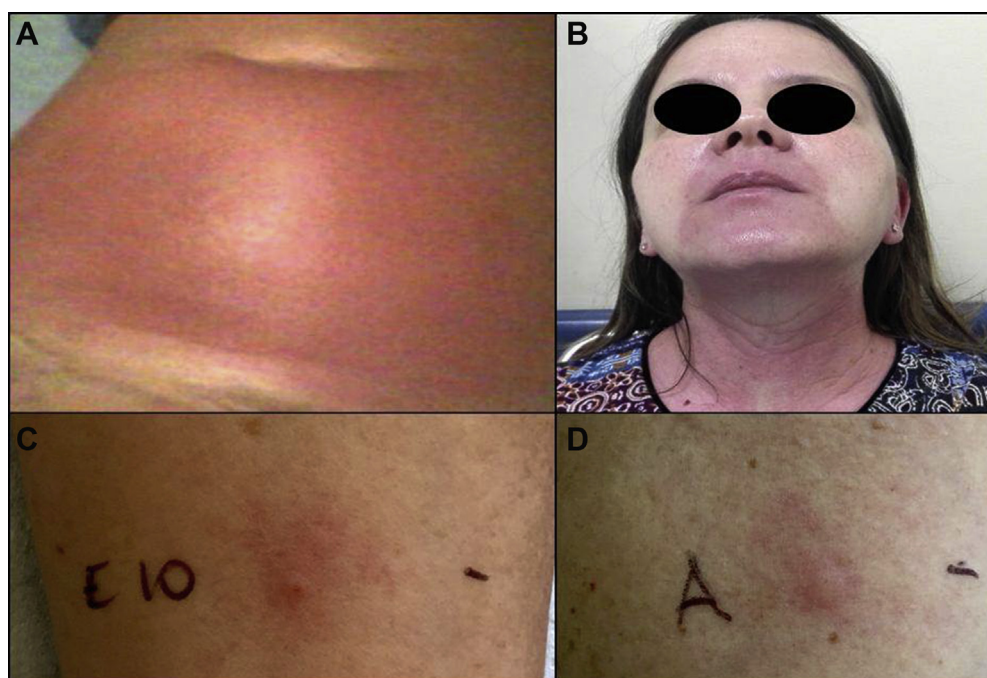


FIGURE 1. Erythematous and edematous reaction involving almost the entire abdominal surface after the fourth injection of etanercept (A) and urticaria and angioedema after the seventh injection of adalimumab (B). Positive intradermal test result with etanercept (1:10 in saline solution) (C) and positive prick test result with adalimumab (as is) (D).

TABLE I. Skin test results

Substance tested	Patch test (as is)			Prick test (as is)		ID test (aq)	
	20'	D2	D4	20'	D1	20'	D1
Etanercept	—	—	—	—	—	— (1:1000)	—
						— (1:100)	—
						++ (1:10)	—
Adalimumab	—	—	—	++	—	NP	
Abatacept	—	—	—	—	—	— (1:1000)	—
						— (1:100)	—
						— (1:10)	—
						— (as is)	—
Mannitol	—	—	—	—	—	— (1:10)	—

aq, In saline solution; NP, not performed.

have constant reactions when the 2 anti-TNF- α blockers were administered. Moreover, the immediate positivity of skin test results suggests an IgE-mediated activation of mast cells. Although we cannot exclude the possibility that the simultaneous hypersensitivity to ET and AD is a simple coincidence, it remains an open question whether either cosensitization or cross-reactivity occurred in this patient.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 6, 2018; revised May 31, 2018; accepted for publication June 20, 2018.

Available online July 10, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.06.020>

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