

Autoimmune chronic urticaria associated with type 1 diabetes and Graves' disease

To the Editor:

It is now widely accepted that in many cases chronic urticaria (CU) should be regarded as an autoimmune disorder caused by circulating and functionally active IgG autoantibodies specific for FcεRI present on mast cells and basophils or for IgE.^{1,2} The well-known association of CU with Hashimoto's thyroiditis or with thyroid autoimmunity represents further indirect evidence of its autoimmune origin.² In recent years, some studies have suggested that CU might be associated also with other autoimmune conditions. In 1981, one study reported an association between hyperthyroidism and CU,³ an association observed also by Irani et al.⁴ Recently, we reported some cases of autoimmune CU associated with thyroid autoimmunity and Raynaud's phenomenon with anti-centromere antibodies.⁵ In the present study we report an unusual association between autoimmune disorders characterized by autoantibodies showing 4 distinct specificities.

A 33-year-old woman was recently seen at our allergy outpatient clinic. She had been experiencing type 1 diabetes mellitus for 8 years and Graves' disease for 7 years. During the last 6 months, she had noted the recurrence of pruritus and erythema at different sites, with typical wheals after scratching sometimes associated with angioedema of the lips. Symptoms were not associated with cold exposure, pressure, or increase in body temperature. The intradermal injection of 0.05 mL of fresh autologous serum (autologous serum skin test)¹ induced a large wheal (mean diameter, 10 mm) with a flare ring, whereas no skin reaction was noted at the site at which an equivalent volume of saline was injected. Strong skin reactions to autologous serum have been associated with autoimmune CU.⁶

Circulating anti-insulin antibodies were determined by means of quantitative radioimmunoprecipitation assay (DLD Diagnostika, Hamburg, Germany) by using iodine 125-labeled monoiodinated insulin and anti-human IgG. On the basis of the levels found in 30 normal sera, values of greater than 0.5 U/mL were considered positive. The level of anti-insulin antibodies in the patient's serum was 4.37 U/mL.

Autoantibodies to glutamic acid decarboxylase (GAD) were detected by using an RIA (GAD Ab-RSR, Cardiff, United Kingdom) with iodine 125-labeled human recombinant GAD 65. Values of greater than 1.0 U/mL were considered positive. Our patient's serum level was 12.64 U/mL.

Thyroid-stimulating hormone (TSH) receptor antibodies were measured by using a second-generation radioreceptor assay (Dynotest TRAK Human; B.R.A.M.S., Henningsdorf, Germany) with human recombinant TSH receptor. The assay was calibrated according to World Health Organization standard 90/672. Values of greater

than 1.0 U/L were considered positive. Our patient's serum level was 1.44 U/L.

Finally, an *in vitro* histamine release assay was carried out by using basophils from healthy donors as substrate, as previously described.⁷ Results were expressed as the net percentage of histamine release over total histamine content. A 5% histamine release was used as the cutoff point. Our patient's serum induced 6.5% histamine release.

In this patient we detected autoantibodies specific for FcεRI, GAD, insulin, and TSH receptor. GAD autoantibodies are a rather specific marker of type 1 diabetes and are found in up to 90% of patients at diagnosis.⁸ It is well known that genetic factors underlie many autoimmune disorders, and an association with specific antigens of the MHC (often of class II) has been frequently found. For CU, an association with HLA-DR4 has been reported.¹

A strong association of Graves' disease with HLA-DR3 has been observed in white subjects,⁹ and more recent studies indicate that HLA-DR3 is in strong linkage disequilibrium with DQB1*0201 and DQA1*0501, both of which are strongly associated with Graves' disease.¹⁰ The association between type 1 diabetes and Graves' disease has been observed for a long time.¹¹ HLA-DR3 and HLA-DR4 convey a high risk for type 1 diabetes, and individuals with the highest risk express both DQA1*0501 and DQB1*0201.¹² Furthermore, these haplotypes have been identified as a risk factor for thyroid autoimmunity in patients with type 1 diabetes.¹³

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COX-2-selective inhibitor valdecoxib induces severe allergic skin reactions

To the Editor:

Since the 1960s, when the nonsteroidal anti-inflammatory drugs (NSAIDs) were launched into the market, several adverse events have been reported,¹ including skin eruptions mostly caused by nonimmunological rather than allergic mechanisms.^{2,3} NSAIDs exert their analgesic, antipyretic, anti-inflammatory, and antithrombotic effects by inhibiting both COX-1 and COX-2 activities.⁴⁻⁶ However, the primary responsibility for the synthesis of prostanoids involved in acute and chronic inflammatory states has been credited to COX-2, whereas the gastrointestinal adverse effects have been attributed to COX-1 activity.^{1,6} The consequent hypothesis that specific inhibition of this enzyme could have therapeutic effects similar to those of other NSAIDs but without causing gastrointestinal side effects led to the development of COX-2-selective antagonists. Valdecoxib (Bextra, Pfizer, Buckinghamshire, United Kingdom) is one of these new drugs. In the last few years, it has been increasingly prescribed for the treatment of osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, and moderate to severe postoperative pain.⁷

COX-2-specific inhibitors have an alleged safer profile compared with other nonselective NSAIDs.⁴⁻⁶ However, several adverse events caused by selective COX-2 inhibitors have been described.^{8,9} We report here a case of severe hypersensitivity skin reaction caused by valdecoxib.

A 58-year-old man presented with a 2-day history of exanthem, malaise, and fever. For the treatment of arthralgia, the patient had been taking a daily dose of 20 mg valdecoxib for 6 days before the onset of skin lesions. No previous history of skin reactions to other NSAIDs or sulfonamides was reported. On admission, physical examination showed a generalized confluent maculopapular exanthem without mucous membrane involvement (Fig 1, A).

Routine blood examination revealed leukocytosis and increased values of creatinine, lactate dehydrogenase, total bilirubin, C-reactive protein, and eosinophil cationic

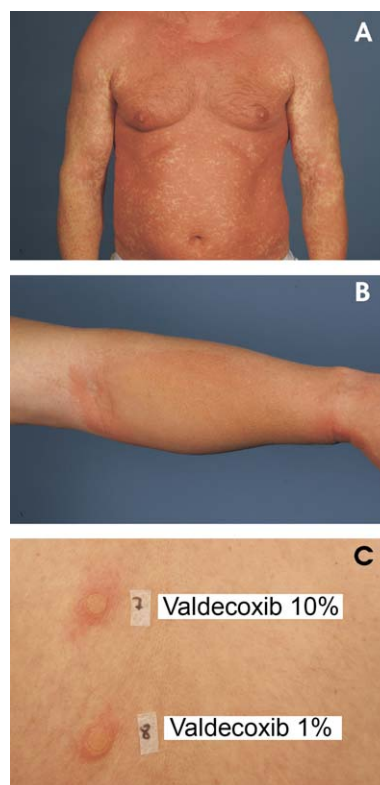


FIG 1. Severe allergic skin reactions to valdecoxib. **A**, A 58-year-old patient with a generalized maculopapular exanthem induced by valdecoxib. **B**, Severe and spreading skin reaction 48 hours after scratch testing with valdecoxib. **C**, Skin reaction (++++) day 2 after epicutaneous patch testing with valdecoxib (at a concentration of 10% in the upper reaction and 1% in the reaction below).

protein. Serological tests for adenovirus, echovirus, coxsackie, measles, and hepatitis virus were negative, and antibodies to rubella and Epstein-Barr virus showed signs of previous infection. Ultrasonography revealed enlargement of lymph nodes caused by local inflammation. After discontinuation of valdecoxib and treatment with systemic glucocorticosteroids, antihistamines, and local glucocorticosteroids, the exanthem disappeared.

Histopathological examination of a skin biopsy revealed slight spongiosis of the epidermis and a perivascular inflammatory infiltrate consisting mostly of lymphocytes, neutrophils, and few eosinophils.

Skin prick tests with seasonal and perennial airborne allergens as well as standard food allergens were uniformly negative. Scratch tests performed with nonspecific NSAIDs (acetylsalicylic acid, metamizol, paracetamol, diclofenac, indometacin, ibuprofen) as well as the COX-2-selective inhibitors celecoxib and valdecoxib showed no skin reactions after 20 minutes. However, 24 hours later, a severe erythematous and edematous skin lesion occurred, spreading over the forearm where scratch tests had been performed (Fig 1, B). Notably, subsequent scratch tests with acetylsalicylic acid, metamizol, paracetamol, diclofenac, indometacin, ibuprofen, and celecoxib, but without valdecoxib, were uniformly negative at 20