



Letter

Expanding the spectrum: chronic urticaria and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

Chronic urticaria (CU) affects approximately 1% of the general population and occurs most frequently in adult women, usually presenting in the third to fifth decade of life.¹ Current research suggests a link between CU and autoimmune disease supported in part by the detection of anti-FCεRI autoantibodies and positive autologous serum skin test reactions in many patients with CU.^{2–5} Despite the numerous autoimmune features of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), this rare primary immunodeficiency disorder has not been linked with CU.

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy occurs as a result of a mutation in the AIRE gene that regulates central tolerance in the thymus through medullary thymic epithelial cells and thymic dendritic cells.⁶ Clinical manifestations identified to date include hypoparathyroidism, adrenal failure, diabetes mellitus, parietal cell atrophy, hypothyroidism, ovarian failure, testicular failure, candidiasis, alopecia, vitiligo, keratopathy, hepatitis, intestinal malabsorption, enamel hypoplasia, tympanic membrane calcification, and nail dystrophy. An acute urticarial-like rash also has been reported in 9% of patients in a Finnish cohort and appeared in association with recurrent fevers up to 4 to 5 times monthly.^{5,7} Given the suspected autoimmune etiology of up to 25% to 60% of patients with CU and the strong autoimmune character of APECED, a high incidence of CU in this population might be predicted.^{2–5} An extensive review of the literature yielded only 1 incompletely characterized case report of CU in an 18-month-old male patient with APECED in Northern Ireland.⁸ We present 2 cases of APECED that developed refractory CU in early adolescence and were successfully treated with omalizumab.

In case 1, APECED was diagnosed when the patient was 3 years old after she presented with blepharospasm, keratoconjunctivitis, and severe hypocalcemia in the setting of intermittent chronic diarrhea. Subsequent genetic testing showed a 13-bp deletion in exon 8 of AIRE, the most common mutation among those of white British ancestry.⁹ Other clinical features included alopecia, vitiligo, tooth enamel hypoplasia, hypothyroidism, and premature ovarian failure. At 12 years of age, she developed CU unassociated with fever and refractory to 180 mg of fexofenadine and 10 mg cetirizine twice daily, 150 mg ranitidine twice daily, 10 mg of montelukast daily, and up to 100 mg of doxepin nightly. Serology demonstrated the presence of anti-FCεRI autoantibodies and positive histamine release assay results (Table 1). Notably, there were no flares or significant changes in the autoimmune processes previously noted

and no associated fevers. Treatment with 150 mg of omalizumab administered subcutaneously every 4 weeks and later extended to every 12 weeks resulted in resolution of her symptoms. Omalizumab was discontinued; however, this resulted in a relapse that required continued treatment with omalizumab every 6 weeks to maintain control of the patient's symptoms.

In case 2, APECED was diagnosed at 9 years of age after the patient presented acutely with severe tetany and hypocalcemia in the setting of recurrent candidiasis and chronic intermittent diarrhea. Genetic testing showed that the patient was compound heterozygous with AIRE mutations R257X and c.967_979del13. Additional clinical manifestations included adrenal insufficiency, gonadal failure, vitiligo, tooth enamel hypoplasia, and dystrophic nails. At 13 years of age, she developed CU without fever that was refractory to 180 mg fexofenadine and 10 mg cetirizine twice daily, 150 mg of ranitidine twice daily, and 10 mg of montelukast daily. The patient was found to have positive anti-FCεRI autoantibodies (Table 1). No flares or significant changes in her autoimmune status were noted, and there were no associated fevers. The patient was treated with 150 mg of omalizumab administered subcutaneously every 4 weeks, resulting in the resolution of her symptoms. The patient has been able to transition to treatments every 6 weeks without recurrence of symptoms.

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is a rare disorder intimately associated with autoimmunity but uncommonly linked with CU. Although the recent literature has highlighted a possible association of CU with autoimmune polyendocrine syndrome type II, this syndrome differs from APECED in its endocrine manifestations and underlying genetic basis.¹⁰ Only 1 other case of APECED and CU appears in the literature, but details surrounding the features of the patient's urticaria and response to treatment are sparse.⁸ Omalizumab appears to be an effective therapy for CU in patients with APECED, but its role in relation to its underlying mechanism and impact on immune dysregulation in this population is unclear. The significance of anti-FCεRI

Table 1
Summary of pertinent laboratory findings

Laboratory testing ^a	Case 1	Case 2	Reference range
IgE (IU/mL)	60.47	21	2.06–195.2
TSH (μIU/mL)	2.06	0.71	0.27–4.2
Thyroglobulin antibody (IU/mL)	129	<20	0–80
TPO antibody (IU/mL)	>1,000	<1	0–29
FCεRI antibody (IU/mL)	5.6	33.9	0–5
Histamine release assay (%)	22	indeterminate	<16

Abbreviations: FCεRI, high-affinity IgE receptor; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

^aQuest Diagnostics, Baltimore, Maryland.

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autoantibodies and CU in this patient population requires further study, especially given the current thought that links CU with an autoimmune basis. Further review of patients with APECED could show additional cases of CU, raising the possibility that CU is part of the APECED spectrum of disease. If established, such a link could open new avenues for inquiry regarding the nature of CU's autoimmune character and potential relation with mechanisms of central and peripheral tolerance.

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