An underlying systemic disease is common among patients with chronic, treatment resistant urticaria, referred to a tertiary referral centre for autoimmune diseases

Sirs,

Chronic urticaria (CU) is urticaria (hives) lasting longer than six weeks (1, 2). An exogenous etiology (foods, parasitic infections, medication, topical allergens) is identified in only 10–20% of the cases (3). IgG autoantibodies against IgE or IgE-receptor are present in 35–50% of the cases, implying a possible autoimmune etiology of the disease (4). Moreover, various autoimmune diseases include urticarial or urticaria-like lesions in their manifestations. Autoimmune thyroid disease – predominantly thyroiditis Hashimoto – is the most common, occurring in up to 27% of the cases (4-6). Urticarial vasculitis (UV) is encountered in 5–20% of the cases (7, 8) and other autoimmune diseases are much less frequent (9).

We investigated the prevalence of connective tissue diseases among patients with CU, and we examined whether clinical or laboratory characteristics could predict this association. We studied all consecutive patients with CU referred to the Rheumatology Department of the University Hospital in Heraklion (Greece), over a 2-year period (2004-2006). Urticaria related to physical factors, malignancies, and infections were excluded. Most patients had treatment-resistant urticaria, defined as persistence of symptoms in spite of standard therapy (maximum dose of anti-histamine with or without glucocorticoids). Patients were followed for a median of 18 (range 12–36) months and had complete physical examinations, routine blood and urine tests, immunological studies, and virology studies for hepatitis B and C virus. Skin biopsies were performed when indicated. Nineteen patients (14 women, 74%) with a median age of 43 (range 13–80) years and a recent diagnosis of CU were studied (Table I). An underlying systemic disease was diagnosed in 12 patients (63%). Six of them (32%) had urticarial vasculitis (UV) documented by skin biopsy. Five additional patients were diagnosed with systemic lupus erythematosus (SLE), and another patient with undifferentiated connective tissue disease (UCTD). The remaining 7 patients (37%) had chronic idiopathic urticaria (CIU). Five patients (26%) had concurrent thyroid disease (n=2 with SLE, n=1 with UV, n=2 with CIU). Five patients (26%) had at least one episode of angioedema (n=1 with SLE, n=2 with UV, n=2 with CIU).

Systemic manifestations (fatigue, fever, arthritis/arthralgias) were present in all patients with underlying systemic disease as compared to only one patient with CIU (100% *vs*. 14%, $p<0.001$, sensitivity 100%, specificity 86%, positive predictive value 92%). Most patients with underlying systemic disease had elevated inflammatory markers (ESR or CRP), compared to one patient with CIU (92% *vs*. 14%, $p=0.002$). Anaemia and/or elevated inflammatory markers had a sensitivity value of 92%, a specificity value of 86%, and a positive predictive value of 92% for a systemic autoimmune disease.

Urticarial vasculitis was normo-complementemic and clinically mild in all but one patient, who also had features of glomerulonephritis. Of note, patients in this group were older (median age 58 years) and 67% of them were males. Patients with CU and SLE were all female, with a median age of 31 years and also had mild disease.

We found a high prevalence (63%) of a systemic autoimmune disease, which may be attributed to referral bias, since our department is a referral centre for autoimmune diseases. Systemic symptoms (fatigue, fever, arthritis) were strong predictors of a systemic autoimmune disease. Other signs such as weight loss or lymphadenopathy were not evident. No differences were found between SLE-associated urticarial lesions and lesions of CIU. Nonetheless, in most patients with vasculitis, lesions lasted longer and caused pain and pruritus. Neither angioedema nor thyroid disease were associated with underlying systemic autoimmune disease.

In conclusion, systemic signs and symptoms should raise suspicion for underlying systemic disease in CU patients. In these patients, further work up is recommended as well as skin biopsy in cases of long lasting, painful rather than pruritic-only skin lesions, or lesions that heal with residual pigmentation.

Table I. Clinical and laboratory parameters of 19 patients with chronic urticaria[§].

	SLE/UCTD (n=6)	UV (n=6)	CIU (n=7)	*p*-value [†]
Age (years) (median, range)	31 (13–45)	58 (28–80)	41 (27–49)	0.028
Female sex (n, %)	6 (100)	2 (33)	6 (86)	0.021
Fever (n, %)	1 (17)	4 (67)	0 (0)	0.020
Fatigue (n, %)	5 (83)	4 (67)	1 (14)	0.032[*]
Arthritis (n, %)	5 (83)	5 (83)	0 (0)	0.002[*]
Angioedema (n, %)	1 (17)	2 (33)	2 (29)	–
High ESR (n, %)	6 (100)	4 (67)	1 (14)	0.008[*]
High CRP (n, %)	4 (67)	5 (83)	0 (0)	0.032[*]
Anaemia (n, %)	2 (33)	3 (50)	0 (0)	–
ANA/ENA (n, %)	5 (83)	1 (17)	1 (14)	0.082[**]
ANCA (n, %)	0 (0)	0 (0)	0 (0)	–
Low C3 or C4 (n, %)	1 (17)	0 (0)	0 (0)	–
Cryoglobulins (n, %)	0 (0)	1 (17)	0 (0)	–
RF (n, %)	0 (0)	2 (33)	0 (0)	0.089

[§]SLE: systemic lupus erythematosus; UCTD: undifferentiated connective tissue disease; UV: urticarial vasculitis; CIU: chronic idiopathic urticaria. [†]Kruskal-Wallis test for statistically significant variations among the three groups (SLE/UCTD, UV, CIU). Only *p*-values <0.100 are shown. [*] $p<0.05$, comparison between SLE/UCTD + UV and CIU groups (Fisher's exact test). [**] $p=0.01$, comparison between SLE/UCTD and UV + CIU groups (Fisher's exact test).

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References

1. POONAWALLA T, KELLY B: Urticaria: a review. *Am J Clin Dermatol* 2009; 10: 9-21.
2. KAPLAN AP: Clinical Practice. Chronic urticaria and angioedema. *N Engl J Med* 2002; 346: 175-9.
3. NAJIB U, SHEIKH J: The spectrum of chronic urticária. *Allergy Asthma Proc* 2009; 30: 1-10.
4. KAPLAN AP, GREAVES M: Pathogenesis of chronic urticaria. *Clin Exp Allergy* 2009; 39: 777-87.
5. BOGUNIEWICZ M: The autoimmune nature of chronic urticaria. *Allergy Asthma Proc* 2008; 29: 433-8.
6. GREGORIOU S, RIGOPOULOS D, KATSAMBAS A: Etiologic aspects and prognostic factors of patients with chronic urticaria: nonrandomized, prospective, descriptive study. *Cutan Med Surg* 2009; 13: 198-203.
7. BROWN NA, CARTER JD: Urticarial vasculitis. *Curr Rheumatol Rep* 2007; 9: 312-9
8. KHAN AD: Chronic urticaria: Diagnosis and management. *Allergy Asthma Proc* 2008; 29: 439-46.
9. SONTHEIMER RD, GILLIAM JN: Systemic lupus erythematosus and the skin. *In*: LAHITA, RG (Ed.): *Systemic Lupus Erythematosus*. New York: Churchill Livingstone, 1992.