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LETTER

Osteopontin in chronic urticaria: Elevated plasma levels and significantly increased osteopontin expression in patients' skin samples compared to controls

Dear Editor,

The pathogenesis of chronic urticaria (CU) is characterized by a multiplicity of mechanisms, including autoimmunity, autoallergy, and coagulation each of interlinked rather than independent events.[1] Osteopontin (OPN) is a multifunctional protein produced by many immune system cells. Although the distribution of OPN within normal tissue is limited, its expression increases in inflammatory and allergic conditions.[2] It was shown in murine fetal skin that OPN is produced by mast cells, indicating that OPN is a mast cell mediator, and it enhances mast cell responses to antigens. Therefore, OPN might influence mast cell-related pathological conditions such as CU.[3] There is emerging evidence to support an active role for OPN in Th2-linked inflammation and allergic disease. OPN is expressed and functional in peripheral blood eosinophils of atopic human subjects.[4] Samitas et al found OPN levels in bronchoalveolar lavage fluid and serum samples to be higher in asthma patients compared to controls.[5] Elevated levels of OPN were also detected in other allergic conditions.[6-8]

Our case-control study included 34 patients and 34 age and sex-matched healthy controls (Table 1). Patients having a coexisting systemic disease, infection, malignancy, and receiving immunosuppressive, systemic steroid and/or systemic antihistaminic or ketotifen therapies within the last 2 months, the last 4 weeks and last week, respectively, were excluded. The diagnosis of physical urticaria was based on clinical examination and anamnesis. Urticarial activity was estimated according to the number of wheals scored as follows: 0 = no wheals; 1 = 1 to 10 small (<3 cm in diameter) wheals; 2 = 10 to 50 small wheals or 1 to 10 large wheals; 3 = more than 50 small wheals or 10 to 50 large wheals; and 4 = totally covered with wheals. Pruritus severity was scored as no pruritus (0), mild (1), moderate (2), and severe (3).[9]

Plasma OPN levels were studied by enzyme immunometric assay method. Nonlesional and urticarial plaque skin samples were obtained from 20 patients who consented to a biopsy. Five healthy donors who had undergone abdominoplasty were used as controls. OPN expression was investigated by immunohistochemical analysis. One patient's skin samples were excluded because of technical reasons.

The mean ± SD plasma OPN levels of patients were higher than controls (61.03 ± 17.99 vs 45.94 ± 15.81 ng/mL, $P < .001$) (Figure 1) and showed a negative correlation with patient age and a positive correlation with disease duration, disease severity and pruritus severity (Table 2).

While intercellular epidermal and/or dermal OPN expression was identified in 18 nonlesional (94.7%) and in 18 urticarial (94.7%) lesions of patients, none of five control skin samples showed OPN expression ($P < .001$). Intracellular OPN expression was identified for

TABLE 1 Clinical features of patients

Clinical features		n = 34
Female/male (n)		27/7
Age (mean ± SD year)		41.0 ± 14.0
Disease duration, median ± SD (min. month – max. year)		60.14 ± 16.50 (2-17)
Disease severity, n (%)	(0) No wheals	6 (16.62)
	(1) 1-10 small wheals	14 (40.99)
	(2) 10-50 small or 1-10 large wheals	12 (36.50)
	(3) More than 50 small or 10-50 large wheals	2 (5.89)
	(4) Virtually covered with wheals	0 (0)
Pruritus severity, n (%)	(0) No pruritus	3 (8.84)
	(1) Mild	15 (44.11)
	(2) Moderate	9 (26.48)
	(3) Severe	7 (20.57)
ASST, n (%)	–	10 (29.41)
	+	24 (70.59)
Angioedema, n (%)	–	14 (41.18)
	+	20 (58.82)
Physical urticaria, n (%)	Vibratuar urticaria	5 (14.70)
	Cholinergic urticaria	5 (14.70)
	Aquagenic urticaria	2 (5.89)
	Solar urticaria	1 (3.10)
	Urticarial dermographism	9 (26.48)
Coexisting disease, n (%[a])	–	24 (70.6)
	+	10 (29.4)

Hypertension in five patients, hypercholesterolemia in two patients, type 2 diabetes in one patient, peptic ulcus in one patient, and osteoporosis in one patient.

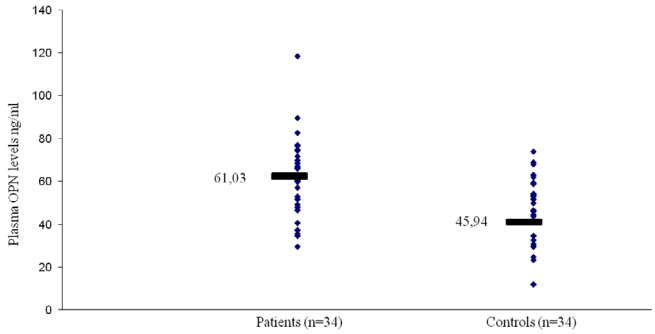

FIGURE 1 Plasma osteopontin (OPN) levels of patients and controls

TABLE 2 The correlation of plasma osteopontin levels with patients' age, disease duration, disease severity, and pruritus severity

	r	*P*
Patients' age	−.143	>.05
Disease duration	.280	>.05
Disease severity	.870	>.05
Pruritus severity	.158	>.05

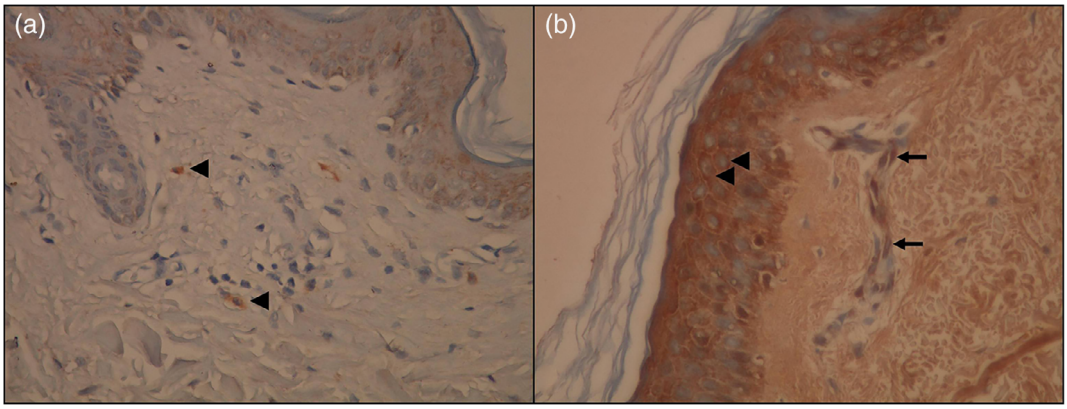

FIGURE 2 A, Osteopontin (OPN)-positive mast cells in control skin sample (arrowheads, original magnification ×40) B, Intercellular epidermal and/or dermal OPN expression and intracellular OPN expression on keratinocytes (arrowheads) and endothelial cells (arrows) in a patient's urticarial plaque skin sample (original magnification ×40)

keratinocytes, immune cells, mast cells, and/or endothelial cells in patient skin samples; OPN staining was also seen in mast cells of control skin samples (Figure 2).

Our findings indicate the possibility that OPN takes part in multiple steps in the pathogenesis of CU. Not only mast cell degranulation but also Th2-mediated cytokine effects are influenced by OPN. The presence of OPN expression in nonlesional skin samples might indicate a predisposition to develop the disease in those areas. Mast cell staining in control skin samples indicates that mast cells produce OPN in adult human skin as well.

Our results suggest a role of OPN in the multistep pathogenesis of CU, showing for the first time the possibility of using this inflammatory cytokine as a novel target in the treatment of CU. The mechanisms by which OPN acts in CU pathogenesis should be further studied.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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