

# Urticaria pigmentosa associated with acute stress and lesional skin mast-cell expression of CRF-R1

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doi:10.1111/j.1365-2230.2008.03043.x

## Summary

A 38-year-old woman presented with a pronounced increase in symptoms and proliferation of urticaria pigmentosa (UP) after acute psychological stress, which was quantified using the Spielberger's State-Trait Anxiety Inventory. Immunohistochemical examination of a skin biopsy from a new UP lesion showed a large number of activated mast cells expressing corticotrophin-releasing factor receptor-1 (CRF-R1) and there was high serum CRF. This is the first documented report to our knowledge of UP worsening associated with acute stress, possibly through activation of skin mast-cell CRF-R1.

Mastocytosis represents a wide spectrum of proliferative disorders of mast cells,<sup>1</sup> the most common feature of which is urticaria pigmentosa (UP), characterized by small brown-red maculopapules on the skin.<sup>2</sup> Psychological factors may increase symptoms of allergic and skin diseases, possibly through activation of mast cells, which are located close to a rich supply of sensory nerve endings in the skin. The skin also contains the main components of a functional equivalent of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>3</sup> Corticotrophin-releasing factor (CRF) regulates the HPA axis through specific receptors, but CRF is also found outside the brain where it could have pro-inflammatory actions through mast cell activation.<sup>4</sup> CRF can be synthesized by a variety of immune cells, but human mast cells are also particularly rich in CRF; they

also express CRF receptor 1 (CRF-R1), activation of which leads to release of vascular endothelial growth factor (VEGF),<sup>5</sup> suggesting autocrine actions.

We present here a unique case in which acute stress appears to have caused UP to spread, and lesional mast cells of which expressed CRF-R1.

## Report

A 38-year-old white Greek woman had been diagnosed with UP primarily on her waist (Fig. 1a) and breasts, confirmed by a skin biopsy taken in 2003. Symptoms included intense itching, headaches, diarrhoea and flushing of the upper chest and neck. Autoimmune diseases or malignancies were excluded.

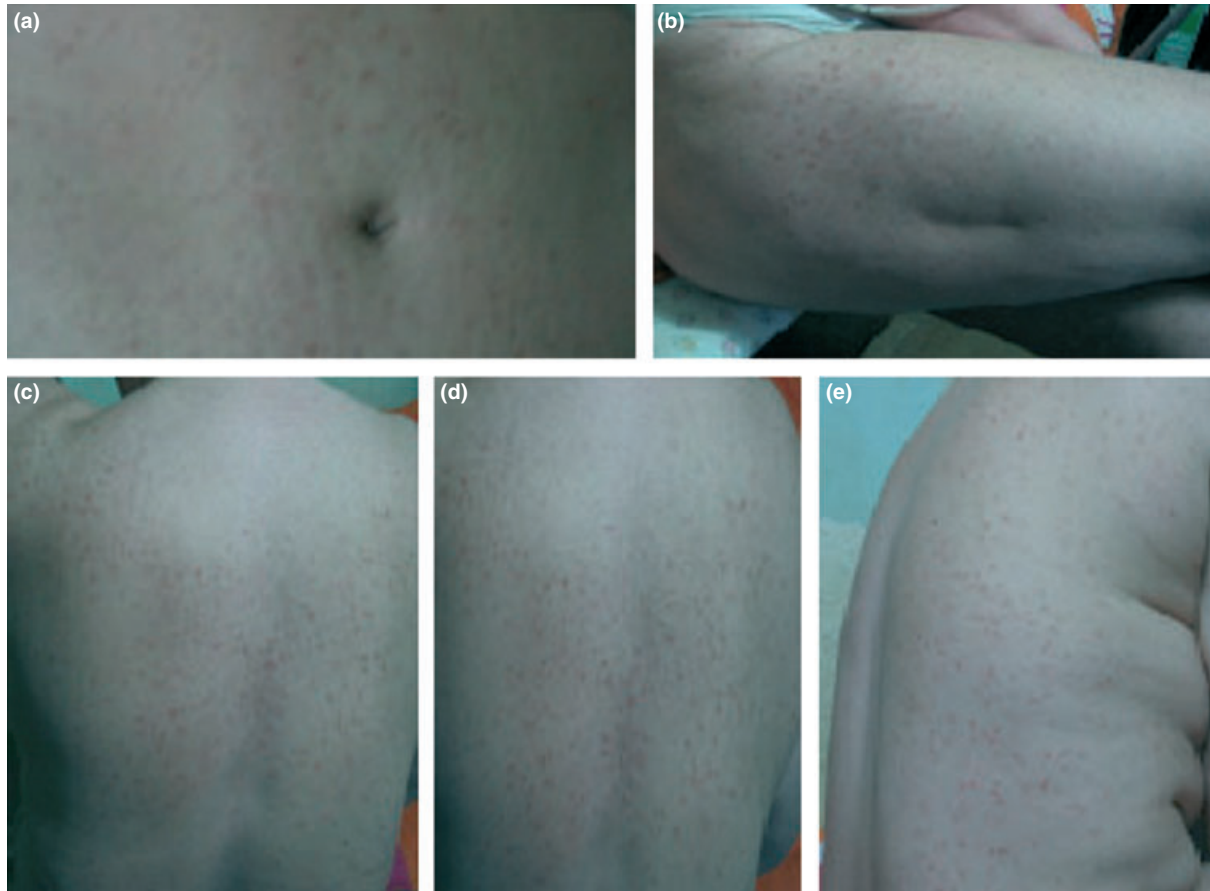
Laboratory investigations showed that serum tryptase was 10.3 µg/L (normal range < 10 µg/L), serum IgE was 38.5 IU/L (0–100), and 24-h urine N-methyl histamine level was 242 µg/g creatinine (50–230). All other tests were normal except for anti-TPO of >750 IU/mL (normal range < 2) and cholesterol of 398 mg/dL (normal range 140–220) for which she was treated with thyroxine 175 µg/day and atorvastatin 0 40 mg/day. The patient had worked as a bank administrator for 18 years and retired because of mastocytosis-related disability in 2004.

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Conflict of interest: none declared.

Accepted for publication 16 May 2008



**Figure 1** Sites of urticaria pigmentosa lesions (a) before and (b–e) after stress.

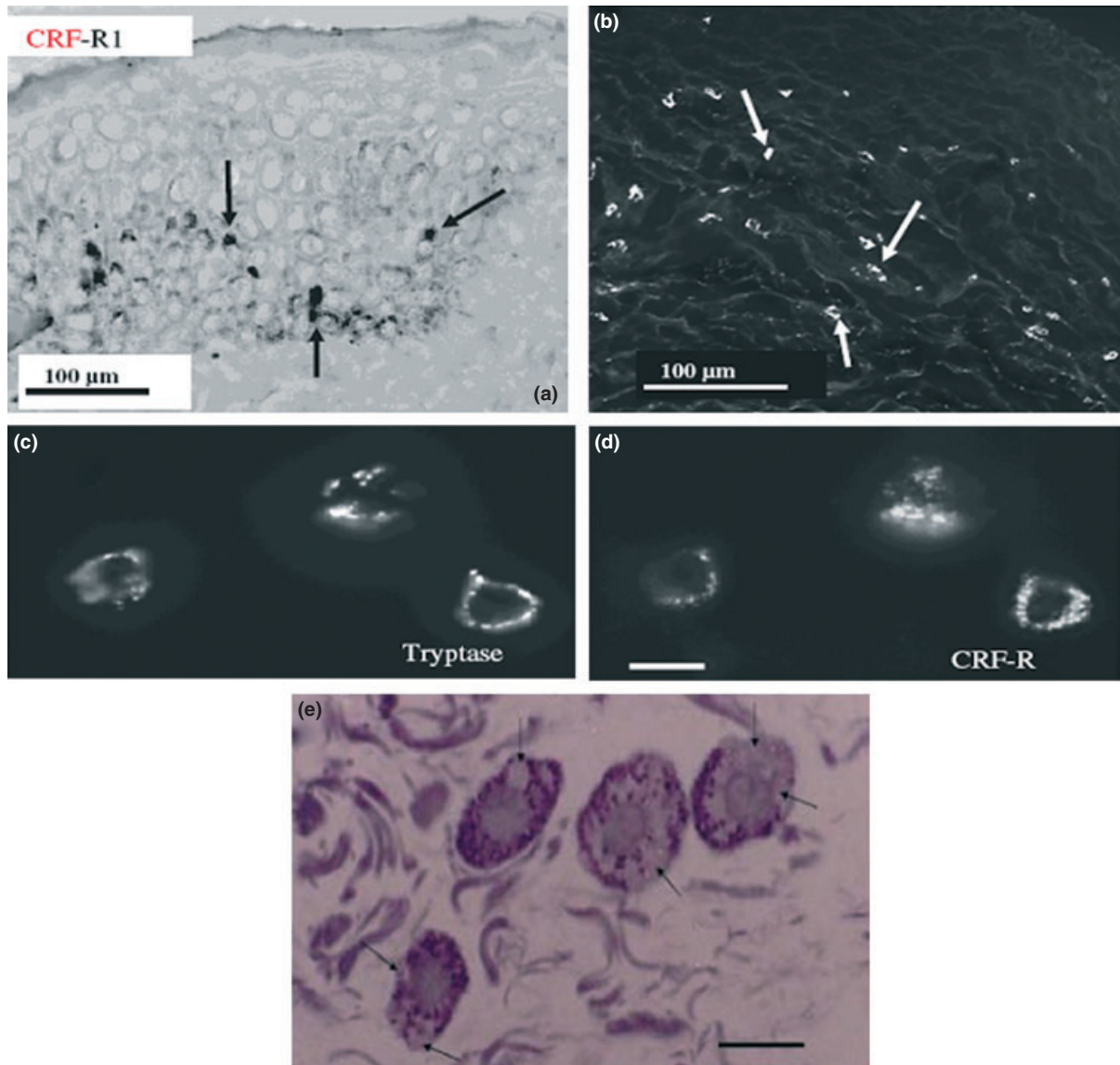
In late November 2005, she reported a pronounced increase in symptoms and extensive UP proliferation on her back (Fig. 1c–e) a couple of days after severe psychological stress, triggered by her husband suddenly leaving her and their two children after 22 years of marriage. Spielberger's State–Trait Anxiety Inventory (STAI) indicated severe state-associated anxiety. The patient's serum tryptase was now 36.8 µg/L and plasma corticotrophin-releasing factor (CRF) was 16.5 pg/mL (normally undetectable).

A bone-marrow biopsy was taken, which showed the patient was negative for BCR-ABL protein and the c-Kit D816V mutation. Flow cytometry of the bone-marrow aspirate using a panel of 18 antibodies, including antibodies for CD2 and CD25, did not show any abnormal cell population. There were occasional mast cells that stained with CD117 and tryptase antibodies. A skin biopsy taken from a new UP lesion showed a population of cells expressing CRF-R1 that could be mast cells (Fig. 2a). Staining of adjacent sections with tryptase confirmed that some of the cells were indeed

mast cells (Fig. 2b). Double immunostaining for CRF-R1 and tryptase showed that most mast cells expressed the CRF-R1 protein (Fig. 2c,d). Mast cells stained with Giemsa contained extensive areas of degranulation (Fig. 2e).

The patient's symptoms were initially managed with doxepin (25 mg at bedtime), hydroxyzine (75 mg at bedtime), methylprednisolone (16 mg four times daily for 2 weeks), and bromazepam (3 mg once daily) to reduce anxiety, and a quercetin-containing dietary supplement (two capsules twice daily; Algonot Plus<sup>®</sup>; Algonot, Sarasota, FL, USA), after which serum tryptase levels dropped to 3.5 µg/L and CRF was undetectable. Because the new UP lesions were widespread and persisted, the patient was started on imatinib mesylate (300 mg orally once daily for 3 months), even though it is not recommended for cutaneous mastocytosis, and this led to considerable reduction in lesions.

UP is the most common and benign expression of mastocytosis,<sup>1</sup> the pathogenesis of which is still



**Figure 2** Skin sections from an urticaria pigmentosa lesion showing (a) cells staining positive for CRF receptor 1 (CRF-R1) immunoreactivity using a goat polyclonal antibody (1 : 200 dilution; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). Arrows indicate possible mast cells, as shown by (b) tryptase staining. (c, d) Mast cell double-label immunofluorescence using (c) mouse antihuman mast cell tryptase monoclonal antibody labelled with fluorescein isothiocyanate (Chemicon International Inc. Temecula, CA, USA) and (d) CRF-R1 antibody labelled with cyanine-3; (e) Giemsa staining of the same lesion showing four mast cells with obvious areas of degranulation (arrows). (c–e) Bar = 10 µm.

unknown. Patients report flushing when they are stressed, as well as other symptoms such as diarrhoea and headaches, but typically have normal serum IgE and have negative results on skin testing for common allergens.<sup>1,2</sup> Systemic mastocytosis (SM) can be diagnosed using flow cytometry of bone-marrow aspirates containing mast cells expressing surface antigen 117.<sup>2</sup> Mutations of the c-Kit tyrosine kinase, the receptor for

stem-cell factor (SCF), have been identified; the most common is the c-Kit D816V mutation, which typically resists treatment with the tyrosine kinase inhibitor imatinib mesylate. Successful management of patients with SM with imatinib mesylate 400 mg/day for 3–6 months was reported.<sup>6</sup> Our patient responded to this treatment, even though imatinib is not recommended for indolent or cutaneous mastocytosis, probably

because of the extensive proliferation of the UP lesions. Nevertheless, the apparent 'fading' of the lesions may also be due to the drug's inhibitory effect on melanocyte c-Kit action.

Acute stress in this patient was shown by the raised plasma CRF and high score on the STAI, an anxiety index validated in the Greek population. The STAI has previously been used to show that atopic dermatitis and allergic urticaria are highly correlated with stress.<sup>7</sup> Moreover, the level of anxiety has been correlated with the severity of atopic dermatitis and its response to psychotherapy.

Stress activates mouse skin mast cells, 25% of which express CRF-R1 and lead to increased vascular permeability. This process could be mimicked by intradermal administration of CRF,<sup>4</sup> which is released in the skin under stress and may involve other neuropeptides secreted from dorsal root ganglia.<sup>8</sup> Local CRF administration was also shown to cause mast cell-dependent skin vasodilation in humans.<sup>9</sup> CRF-R1 has previously been found in human skin and could be involved in producing the colour of UP lesions, as it has been shown to have melanogenic effects.<sup>10</sup> Human cultured mast cells express functional CRF-R1 activation, which leads to release of vascular endothelial growth factor (VEGF), an isoform of which is very vasodilatory.<sup>5</sup> Cutaneous mast-cell CRF-R1 activation serves as the link in a 'brain-skin connection'.<sup>11</sup>

In conclusion, CRF-R1 expression is seen on lesional UP mast cells and acute stress may have been the contributing factor in UP proliferation up in this patient through CRF activation of mast cells.

## Acknowledgements

We thank Professor C. D. Spielberger, University of South Florida, for useful discussions about the STAI. This study was funded in part by the Mastocytosis Society (USA), the William James Foundation (Sarasota, FL, USA) and Theta Biomedical Consulting and Development, Co., Inc., Brookline, MA, USA.

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