CLINICAL REPORT

Infectious Urticaria with Purpura: A Mild Subtype of Urticarial Vasculitis?

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Urticaria is characterized by transient wheals. We report here five cases with long-lasting urticarial lesions persisting for more than 24 hours. Each lesion left purpura after fading. There was no systemic involvement. C-reactive protein and serum levels of complement were elevated or normal. Histologically, marked infiltration by eosinophils and neutrophils with karyorrhexis in the perivascular and intercollagenous spaces was observed, but there was no evidence of vasculitis (venulitis). Skin symptoms were resistant to systemic corticosteroids. In contrast, treatment of underlying bacterial infections resulted in marked improvement of skin lesions. E-selectin, VCAM-1 and ICAM-1 were expressed on endothelial cells. Marked deposition of C3a, C5a, neutrophil elastase and major basic protein in the dermis was observed. These urticarial lesions provoked by bacterial infections seem to lie on the continuum between urticaria and urticarial vasculitis. Key words: cell adhesion molecule; focal infection; purpura; urticaria; urticarial vasculitis.

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Table I. Clinical and laboratory profiles of purpuric urticaria (abnormal values in bold typeface)

| Case no. | Sex/age (years) | Disease duration | White blood cell count | Complement components | Presumed causative factor |
|----------|-----------------|------------------|------------------------|-----------------------|--------------------------|
|          |                 |                  | Total (3600–9300) Neutrophils (41.7–74.1) Eosinophils (0.6–8.0) CRP (<0.6) mg/dl | C3 (74–130) mg/dl | C4 (11–30) mg/dl | CH50 (26–49) U/ml |
| 1        | F/26            | 2 days           | 10,800                 91.0 0 | 7.3 79 23 | ND | Acute tonsillitis |
| 2        | F/60            | 3 days           | 8700                   87.8 0.5 | 24.8 107 37 | ND | Acute cholecystitis |
| 3        | F/81            | 2 months         | 10,300                 72.5 0.4 | 4.8 130 27 | 50 | Maxillary sinusitis |
| 4        | M/49            | 6 days           | 7800                   86.0 0 | 17.2 87 46 | ND | Cellulitis |
| 5        | M/50            | 3 years          | 7600                   63.0 4.0 | 0.2 143 44 | 54 | Dental caries |

ND, not determined; CH50, total activity of serum complements in the classical pathway (C1–C9) as determined by haemolytic assay of sensitized SRBC (Mayer’s method).
With systemic administration of antibiotics, after which appearance of new wheals ceased.

**Case 2**

A 60-year-old woman had a 2-week history of right abdominal pain. Three days before admission, wheals appeared on her face and extremities. Oral corticosteroids produced no clinical improvement. On admission, erythema and wheals of various sizes with bruising were observed (Fig. 2a). Laboratory findings revealed elevated levels of CRP and C4 as well as AST (66 IU/l), ALT (59 IU/l) and GTP (178 IU/l). The patient had a moderate fever (38.5°C). Ultrasonography revealed that she suffered from acute cholecystitis. She underwent urgent cholecystectomy followed by administration of antibiotics. Skin symptoms improved within a few days after the operation.

**Case 3**

An 81-year-old woman had a 2-month history of recurrent wheals and erythema on her trunk and thighs. She had been taking antihistamines and systemic corticosteroids, but the skin symptoms worsened. Each lesion lasted for >1 day and resolved with irregularly shaped purpuric macules (Fig. 2b and c). ANA was negative. The patient had nasal obstruction, and roentgenography revealed the presence of acute sinusitis, as indicated by decreased permeability of the maxillary sinus. She underwent nebulization and was given oral antibiotics. Her skin symptoms gradually improved after the treatment of her sinusitis.

**Special investigations**

To further analyse the pathomechanisms of the urticarial lesions in the present cases, immunohistochemical analysis was performed. E-selectin (anti-E-selectin Ab, DAKO, Glostrup, Denmark), VCAM-1 (anti-VCAM-1 Ab, DAKO) and ICAM-1 (anti-ICAM-1 Ab, DAKO)
were expressed on endothelial cells (Fig. 3a, b and c). Vascular walls and perivascular spaces were positive for C3a (anti-C3a Ab, Quidel, San Diego, CA, USA) and C5a (anti-C5a Ab, CN Bioscience Inc., La Jolla, CA, USA) (data not shown). Moreover, there was extensive extracellular deposition of MBP (anti-eosinophil major basic protein Ab, Chemicon Industrial, Inc., CA, USA) (Fig. 3d) and neutrophil elastase (anti-neutrophil elastase Ab, DAKO).

DISCUSSION

Clinical manifestations of the present cases were characterized by recurrent pruritic wheal or oedematous erythema. Individual lesions lasted longer than ordinary urticaria, and faded to leave purpura or brownish pigmentation. We have experienced five similar cases to date (see Table I). All patients had slight or moderate fever, but no symptoms or signs suggestive of arthritis or renal involvement. Laboratory tests revealed elevated WBC counts with neutrophilia and elevated CRP and/or complement components.

Skin biopsy specimens revealed extensive neutrophil and eosinophil infiltration with karyorrhexis throughout the entire dermis. There was no evidence of vasculitis or venulitis, and this was confirmed by the evaluation of serial tissue sections. The patients had various bacterial infections that seemed to trigger urticarial eruptions. The skin lesions became responsive to antihistamines only after antibiotics (cases 1, 3 and 4), cholecystectomy (case 2) and tooth extraction (case 5), respectively.

Endothelial expression of E-selectin, VCAM-1 and ICAM-1 is crucial in promoting recruitment of neutrophils, eosinophils and/or lymphocytes. Neutrophils express E-selectin ligands, whereas eosinophils do not (3). VLA-4, a ligand for VCAM-1, is expressed on eosinophils (4) but not on neutrophils. Deposition of complement-split products, such as C5a, may contribute to chemotaxis and activation of neutrophils and eosinophils (5). In addition, prominent extracellular deposition of MBP probably contributed to the pathogenesis of wheals by stimulating histamine release from mast cells and basophils (6). Extensive release of neutrophil elastase and MBP may cause damage to dermal tissues and the walls of venules.

It seems likely that bacterial infection was a precipitating factor of the present skin lesions, because skin symptoms appeared in association with infectious symptoms, and because treatment of the bacterial infection completely inhibited the appearance of new wheals and purpura. Bacterial infections, such as tonsillitis, tooth infection, maxillary sinusitis and other upper respiratory tract infections have been implicated as precipitating factors of acute infectious urticaria (7–11).

![Fig. 3. Immunohistochemical staining of skin lesions in case 1. Black arrowheads indicate dermal endothelial cells positive for (a) E-selectin (× 200), (b) VCAM-1 (× 200) and (c) ICAM-1 (× 200). Dermal eosinophils were positive for major basic protein (MBP) (d). The MBP was also deposited in the extracellular spaces (arrowhead) (× 100).]
Tsunoda et al. (12) described 13 cases characterized by urticarial skin rash with leukocytosis and/or neutrophilia, elevated levels of CRP, resistance to antihistamines and corticosteroids. The precise mechanisms involved in urticarial reactions provoked by bacterial infections are unknown. Complement-dependent activation of mast cells or eosinophils may be involved in the pathogenesis. Histamine release from mast cells can be induced by bacterial antigens via a toll-like receptor (13). In some patients with long-lasting urticarial rash caused by bacterial infection, the percentage of circulating T cells bearing T-cell receptor V\textsubscript{b}3i is decreased during the active stage, suggesting alterations in T cells triggered by bacterial superantigens (14). In conclusion, there appears to be a subtype of urticaria with purpura that is caused by bacterial infection.

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