Urticaria and Angioedema*

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Urticaria and angioedema are usually discussed together because they often coexist in the patient, have a similar pathology and common causes. In this article I shall refer only to urticaria (U), but most of the discussion is also relevant to angioedema (A). Most aspects of this subject are well covered in recent textbooks[1] and reviews.[2] However, the past decade has seen more understanding of the possible cause of this disease and of the varied pathogenic mechanisms. I will attempt to review the subject in general but to stress this more recent experience.

CLINICAL SIGNS

Clinically, urticaria is characterised by multiple itchy skin or mucus membrane lesions each consisting of an erythematous flare which is slightly elevated because of local oedema. When this oedema is more marked it results in a pale wheal. The lesions vary in size from a few millimetres to many centimetres in diameter and the shape may be circular or irregular. Lesions may spread and coalesce. The erythema fades on pressure. Each lesion lasts from a few minutes to less than 24 hours and fades without a trace. The lesions of angioedema are similar but larger, deeper and more oedematous. In their early pahse, they are well demarkated but later the margins become more diffuse. Angioedema may last longer than an urticarial lesion but it too disappears with no residua.

HISTOPATHOLOGY

The histopathology of urticaria was reexamined by Natbony *et al.*[3] They point out the vasodilatation and oedema of the upper dermis and the characteristic sparse perivascular round cell infiltration. Monocyte numbers average four times normal and mast cell numbers are ten times normal. Involvement of venule walls with inflammatory cells is infrequent and immunoglobulin and complement deposition uncommon. Mekori *et al*[4] demonstrated that the mononuclear cells in the infiltrate are mainly activated T inducer cells with Ia markers on the cell surface. They question whether the presence of T cells is secondary to chemotaxis from mast cell degranulation or, in contradistinction, whether the mast cell accumulation is a consequence of the action of the T inducer cells.

PATHOPHYSIOLOGY

Most episodes of acute urticaria and angioedema are due to allergic responses to polyvalent antigens which reach mast cells via the blood. The antigen links two or more specific immunoglobulin E (IgE) molecules on the mast cell surface, causing distortion pressure on the IgE receptors in the cell membrane. The earliest biochemical reaction subsequent to this (within seconds) is the activation of a series of membrane bound enzymes. Methyltransferases result in the generation of new phospholipids including phosphatidyl choline, with a resultant change in the polarity of the membrane necessary for calcium (Ca^{++}) influx into the cells. Phospholipase A2 and other enzymes convert this compound into arachidonic acid for the subsequent synthesis of prostaglandins and leucotrienes.[5] Other phospholipases result in the generation of the fusogenic compounds monoacylglycerol and diacylglycerol and free fatty acids which facilitate fusion of granule and cell membranes preparatory to granule secretion.[6] Platelet activating factor is also derived by enzymatic action on membrane phospholipids.[7] Several seconds later the mast cells begin to degranulate with secretion of preformed mediators, including histamine, heparin, serotonin and eosinophil and neutrophil chemotactic factors.[8] These products and the newly synthesised derivatives of arachidonic acid cause the observed inflammatory reaction.[5] Where mast cell degranulation is intense, a late phase IgE reaction may occur resulting in the persistence of local inflammation up to 48 hours.[9]

Immunoglobulin G (IgG) mediated reactions, as in serum sickness, can cause urticaria via complement activation, with the generation of anaphylatoxins C4a, C3a and C5a which cause local vasodilatation and mast cell degranulation. However, in such cases the concurrent

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activation of other complement components (C3b, C5b, C5, 6,7 and the alternate pathway) usually causes a picture more consistent with vasculitis rather than simple U.

It should not be surprising that such a potent inflammatory system induced by mast cell activating mechanisms requires a regulatory process. This has been described by Hirata *et al*[10] and Blackwell *et al.*[11] The activation of phospholipases at the cell membrane is suppressed by the presence of a membrane bound protein called lipomodulin (also called macrocortin in Europe), which is synthesised by the cell in response to the action of hydrocortisone. This mechanism, which applies to membranes of most cells, explains many of the antiinflammatory actions of glucocorticoids. Intracytoplasmic factors regulating mast cell stability such as levels of cyclic adenosine monophosphate are discussed by Plaut and Lichtenstein.[12]

There are other mechanisms which cause urticaria. Histamine releasing drugs such as codeine, polymyxin or some muscle relaxants used in anaesthesia can cause direct release of histamine from mast cells. Mast cell granule secretion due to physical stimuli is a normal phenomenon, but some patients release vastly increased quantities due to specific stimuli such as cold, heat or exercise. Cell mediated immunity may also play a role in some urticarial reactions as is suggested by the nature of the lymphocytic infiltrate seen in histological sections. Van Loveren *et al* have identified an antigen binding T cell factor with activity analogous to IgE.[13]

Chemically induced complement, bradykinin and platelet activation, as well as histamine release occurs in anaphylactoid reactions to radiographic contrast media.[14,15] The concept that there is a specific C2, C4 kinin activity has been disproved. Cyclooxygenase inhibition may be the cause of urticaria in patients sensitive to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAID).[16] It is postulated that this inhibition channels arachidonic acid into the production of the extremely potent vasoactive leucotrienes via lipoxygenase, which is not inhibited by these drugs.[17,18] However, in one study the use of a drug which blocks lipoxygenase did not inhibit aspirin induced asthma,[19] casting some doubt on the validity of this hypothesis.

CAUSES OF URTICARIA

The great challenge in any patient with urticaria is to identify its cause, since this offers the best chance for cure or prevention. Despite investigation, the aetiology is identified in acute urticaria in fewer than 50 per cent of cases and in chronic urticaria in fewer than 20 per cent of cases.[1] A classification of causes of urticaria is listed in Table 1. A careful history and physical examination is the most important way to achieve a diagnosis. Selected allergy skin tests or RAST tests may be useful in some cases, but random testing with a battery of antigens is rarely of value. Similarly wasteful is a routine protocol of other laboratory investigations.

In adults the most commonly diagnosed cause of acute urticaria is drug sensitivity due to allergic or nonallergic mechanisms. Allergic reactions can be caused by almost any drug and the reaction may occur immediately if there is circulating specific IgG or mast cell bound specific IgE; in about 48 hours if the patient has been previously sensitised, but the level of antibody has subsequently fallen to zero; or in seven to 21 days, if there is primary sensitisation from the drug. The diagnosis of drug allergy is usually made on clinical grounds alone, except in the case of penicillin or biologic products like serum derivatives, protein hormones or enzymes, where accurate skin testing procedures are available. Recent studies suggest that skin testing may be of value in patients with allergy to local anaesthetics,[20] muscle relaxants used during anaesthesia[21,22] and other compounds.[23] Consequently the physician should not be reluctant to do skin tests with a dilute solution of a suspect drug providing adequate controls are performed. A positive reaction may be meaningful, although a negative skin test would not rule out an allergic reaction, since the drug acts (in most instances) as a hapten.

Table 1 Causes of urticaria and angioedema

Allergic reactions:	Hereditary diseases
Drugs and biologicals	C1 inhibitor deficiency
Foods and additives	Familial cold urticaria
Inhalants	Amyloidosis, deafness and urticaria
Contactants	Others.
Insect stings or bites	Idiopathic
Non-allergic reactions:	*Physical urticarias:*
Drugs	Cold
Diagnostic agents	Heat
Foods and additives	Cholinergic
Scombroid fish poisoning	Dermographism
	Water
Infections	Exercise
Autoimmune diseases	Vibration
Malignancy	Pressure
Urticaria pigmentosa	Solar

Non immunologically mediated urticarial reactions to aspirin and NSAID occur within minutes to a few hours after the administration of the drug, but even though these may be severe they usually last less than 24 hours. More persistent reactions with vasculitis, as have occurred following administration of phenylbutazone or zomepirac probably have an immunological basis. For the common reactions to aspirin, the only useful testing procedure is a carefully graded provocative challenge. Since a sub – threshold dose may desensitise a patient to the next dose,[24] incremental challenge doses should be given several days apart. For aspirin challenge, a schedule of 5 mg, 20 mg, 40 mg, 75 mg, 150 mg, 300 mg and 600 mg at 5 days intervals is used with careful observation of the patient. The principle that a patient may be desensitised to NSAID has been used to maintain such patients in a continuously desensitised state in the hope of reducing their underlying disease. That this approach may be successful in patients with asthma has been reported,[25] but there is no evidence that it is effective in the treatment of urticaria caused by these agents.

Asthma and urticaria due to NSAID sensitivity occasionally coexist in a patient but most patients react with one disease pattern or other. Although most authors postulate that both conditions are due to the same previously described mechanisms, this may not be true. Double blind challenge testing has shown that cross sensitivity with tartrazine, azo-dyes and benzoates is uncommon in asthmatics,[26] but such cross sensitivity is often observed in patients with urticaria. Since tartrazine does not inhibit prostaglandin systhesis,[27] the urticarial reaction to it may be due to a different mechanism. Conclusions from the study of one group of patients should not be extrapolated uncritically to patients with the other disease.

Acute anaphylactoid reactions to radioopaque contrast media cannot be predicted by skin tests or even by small intravenous challenge doses. However, they usually can be prevented or diminished in a patient who previously suffered such a reaction, by pre-treatment with prednisone, 50 mg, 24 hours, 12 hours and 6 hours prior to the radiological study.

When considering drug allergy, the physician is reminded of the many drugs inadvertently taken by a patient in such products as lozenges, confections (phenophthalein) or in other ingestants such as quinine in tonic water. Several recent reports document urticaria plus anaphylaxis caused by an IgE reaction to albumin ethylene oxide conjugate produced in renal dialysis equipment.[28]

Other drugs may play a permissive role in facilitating urticarial reactions, even though they are not the primary cause of it. Histamine releasers such as codeine or narcotics potentiate urticaria, beta blockers reduce the threshold for mast cell degranulation and vasodilators increase leakage through skin capillaries.

Food allergy is a more common cause of urticaria in children than in adults but is likely to persist if it is still present after the age of 3.[29] The diagnosis may be obvious in some acute cases, but the pitfalls of relying on a seemingly convincing history or even on an open challenge have been stressed. Skin testing or RAST testing may yield false positive results and the ultimate proof may require a double blind challenge protocol.[30] Food additives or contaminants (i.e. vegetable gums, enzymes, fungal derivatives or preservatives) cause an increasing number of allergic or non-allergic urticarial reactions. The role of benzoates and food dyes has been stressed by Juhlin.[31] A recent discovery of acute urticaria following ingestion of sulfiting agents explains some hitherto puzzling reactions.[32] Only a few patients react to these common preservatives but the reaction may be severe with anaphylaxis. Sulfiting agents such as metabisulfite are commonly used in restuarants to keep salads fresh or potatoes and apples from turning brown, or as preservatives in many other prepared foods.

Acute urticaria due to Scombroid (tuna family) fish poisoning can mimic an acute allergic reaction.[33] Bacterial contamination of these fish produces histidine decarboxylase which converts muscle histidine to histamine, which accumulates in toxic quantities. The histamine is not destroyed by cooking and there is no rotten smell to warn the victim. Since this is not an immunological reaction such patients can eat fish again.

Acute urticaria due to insect stings or bites may be allergic or toxic. The more common allergic reactions such as those following hymenoptera stings has been reviewed by Valentine.[34] However, almost any insect sting or bite can induce urticaria in a sensitive individual.

Any systemic disease in which there is exogenous antigen or autoantigen release into the circulation can theoretically cause urticaria if the immune response to it can trigger mast cell mediator release. The association of urticaria with infection has been noted anecdotally for many years. Recently more credible reports have appeared of urticaria during the prodrome of hepatitis B infection[35] or during or after E-B virus infection.[36] In the latter case, cold urticaria was also noted.[37] In children, acute urticaria associated with virus infection is occasionally observed but an aetiologic relationship is difficult to prove. The concept that chronic urticaria is often due to an elusive hidden focus of bacterial infection is mentioned in many texts. However, very few such cases have been proven.[2] Systemic fungal infection with histoplasmosis or coccidioidomycosis is accompanied, during a focal epidemic, by erythema multiforme which may be misdiagnosed as urti-

caria.[38] Parasitic infestations such as ascariasis or schistosomiasis may occasionally cause urticaria, especially during the haematogenous phase.[39] In chronic urticaria, in the absence of clinical evidence of systemic infection, routine microbiological or immunological investigations for infection are rarely rewarding.

Neoplasms frequently release antigen into the circulation, which may react with specific antibody to produce immunologically mediated disease including urticaria. This may occur after the use of chemotherapy or radiotherapy. Angioedema may occur in lymphoproliferative diseases,[40] which in some cases is due to acquired C1 esterase inhibitor deficiency.[41]

Physical allergy encompasses cholinergic urticaria dermographism, and urticaria due to cold, pressure, heat, vibration, sunlight, water and exercise. In most cases the final pathogenic mechanism is mast cell degranulation as evidenced by increased levels of histamine and neutrophil chemotatic factor in the draining blood.[42] Delayed pressure urticaria may relate to complement activation[43] and other delayed types of urticaria may involve late phase IgE reactions.[9] Several cases of delayed pressure urticaria due to food allergy have been reported.[44] There are three types of exercise urticaria or anaphylaxis. This syndrome can be distinguished from cholinergic urticaria as such patients do not react to heat, to sweating or to emotional stress.[45] The urticarial lesions are usually large, angioedema is not uncommon and anaphylactic shock may occasionally develop. Such patients react whenever they exercise above a certain threshold, which is relatively constant for each patient. Others react only if they exercise within a few hours after eating any food,[46] and the third variety will react if they exercise only after eating specific foods.[47] These patients do not develop urticaria if they eat the foods and do not exercise or *vice versa*. They may have a positive skin test reaction to the specific food or to inhalant allergens of the same botanical family (i.e. a patient with food-exercise urticaria related to celery has ragweed allergic rhinitis).

Chronic urticaria has been associated with autoimmune disease. It may be a feature of systemic lupus erythematosus or may precede it for several years.[48] Low titres of antinuclear antibody are not uncommon in patients with chronic urticaria. Urticaria has been reported in patients with thyrotoxicosis,[49] and we have identified a group of patients with idiopathic chronic urticaria and angioedema associated with thyroid autoimmunity.[50] Their features are detailed in Table 2. In most of these patients the thyroid disease was discovered because of the investigation of chronic urticaria. Most patients were female with severe prolonged urticaria and with frequent angioedema. In some cases urticaria disappeared after treatment with L-thyroxin. Since Satoh *et al* have shown, using monoclonal antibody methodology, that individual antibodies in poly endocrine autoimmune disease may react with multiple organs or cells,[51] we speculate that in these patients with chronic urticaria and thyroiditis, autoimmunity may be responsible for both diseases. We recommend studies for thyroid antibodies in all females with idiopathic chronic urticaria.

Though angioedema due to deficiency of the inhibitor of the first component of complement (C1 INH) is usually discussed in reviews of urticaria, it is clearly a different and specific disease.[52] The patients do not have urticaria, the angioedema is extensive, pale and has a burning quality. Involvement of mucus membranes is common and potentially dangerous. Uncontrolled activation of the early complement sequence with unregulated bradykinin generation is responsible for the swelling. C1 INH regulates several levels of the Hageman factor – Kallikrein-Kinin system.[53] Since patients consume the early complement components, they have a reduction in the level of serum C4 which can be detected in a simple screening test before ordering the more difficult assay for C1 INH. This disease can be successfully treated using the impeded androgens danazol or stanozolol which induce the liver to synthesise C1 INH. These agents cause some virilism in females.[54]

Other hereditary urticaria syndromes include hereditary forms of cold urticaria, heat urticaria and vibratory urticaria, complement component deficiency syndromes, familial urticaria with amyloidosis, and one case with a deficiency of the anaphylatoxin inactivator car-

Table 2 Chronic idiopathic urticaria with thyroid autoimmunity.

Number and sex	28 F, 6 M
Age range (years)	8 – 76.
Duration of urticaria (years)	0.5 – 20.
Number with recurring angioedema	27.
Follow up (years)	0.5 – 5
Number with physical allergy*	0
Number with vasculitis	0
Titre of T.M.A. † (range)	1:1600 – 1:25,600
Number with clinical thyroid disease‡	10.

* excluding dermographism.
† thyroid microsomal antibodies – minimal titre for diagnosis of thyroid autoimmunity = 1:1600.
‡ goitre, hypothyroidism, hyperthyroidism.

boxypeptidase N.[2,55]

Other uncommon causes of urticaria include contact with antigens such as henna, or animal saliva or fur. Inhalation of fumes or dust such as chromates can occasionally produce urticaria. Surgically implanted metals or sutures or accidentally ingested metal products can also cause urticaria. A recent report documented an urticarial reaction associated with pulmonary infiltrates and eosinophilia following the accidental swallowing of a nickel coin.[56]

Some patients with cutaneous vasculitis present with skin lesions that look like urticaria and angioedema. These patients usually feel sick with other symptoms of systemic disease. They often have a violacious discolouration over articular surfaces and the urticaria-like lesions last longer than 24 hours, leaving a palpable bluish coloured residual lesion (palpable purpura). There may be laboratory evidence of complement consumption.[57] Skin biopsy confirms vasculitis with extensive cellular infiltration in the walls of the venules or other small vessels rather than the sparse perivascular lymphocytosis of urticaria. Immunoglobulin and complement may be detected in the vessel walls. Since vasculitis may be a life threatening disease, a correct diagnosis is urgent and biopsy should be done quickly. If there is evidence of systemic involvement, aggressive therapy with prednisone and cyclophosphamide may be indicated.[58]

DRUG TREATMENT OF URTICARIA

The most important factor in the management of urticaria is to identify the cause and to eliminate it. Mild urticaria may be partially or completely suppressed by antihistamines. Hydroxyzine is the most commonly used H1 blocker for this purpose but it often causes drowsiness. The newer antihistamines such as astemizole which do not cross the blood brain barrier rarely produce drowsiness but are not any more effective than the older agents.[59] The addition of an H2 blocker such as cimetidine has given relief in some cases where H1 blockers alone were unsuccessful.[60] The use of broader mediator inhibitors such as Ketotifen has been used with mixed success. In theory, the addition of beta stimulators or theophylline should raise the threshold for mast cell degranulation, and in some cases they have been useful in controlling urticaria. Calcium channel blockers such as verapamil reduce basophil degranulation but have lesser effects on mast cells.[61] Where the urticaria is very severe and self limited (because the cause is temporary or can be removed) prednisone may be administered if there are no contraindications. However, in chronic urticaria glucocorticoids should be avoided to prevent the complications of prolonged steroid administration unless the disease is very incapacitating. Alternate day prednisone is often useful in such cases. Life threatening anaphylaxis, angioedema or shock must be treated with adrenalin and other life supporting measures. The use of prophylactic oral cromolyn 200 mg 15 minutes before meals to prevent the urticaria of food allergy has been reported.[62] We have also used this drug successfully in a few patients to block exercise induced urticaria, whether or not it was related to food and to treat other types of physical urticaria. It should be noted that in most cases of urticaria this drug is not successful.

Conclusion

Urticaria remains a distressing disease for the patient and a perplexing problem for the doctor. Increasing scientific study of this problem will help the physician to diagnose the cause in a greater number of cases. Newer therapeutic agents may be useful even where no diagnosis can be achieved. The rapid expansion of knowledge about the specific enzymatic steps in the inflammatory process and mast cell degranulation should lead to the rapid development of specific pharmaceutical agents capable of blocking critical stages in the urticarial reaction. In all cases the physician should use his clinical judgement as a guide for appropriate laboratory investigation. It is rarely helpful to blame a puzzling case of urticaria on emotional causes. The physician should know that he or she is in good company when admitting an inability to diagnose the cause of this illness.

Summary

Urticaria and angioedema may be caused by immunological or other mechanisms. In most cases mast cell degranulation is the central phenomenon. The final common pathway is local capillary dilatation and leakage which is usually due to mast cell mediators, but may be caused by other vasodilator systems or by vascular inflammation. The diagnosis of the aetiology of this disease in a given patient requires disciplined analysis of the factors affecting these processes. Treatment involves avoidance of the cause, if possible, and the use of appropriate drugs to raise the threshold for mast cell degranulation, to reduce vasodilatation and to inhibit specific stages in the inflammatory process.

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