Pathology and Classification of Urticaria

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KEYWORDS

• Chronic urticaria • Physical urticaria • Autoimmune urticaria • Acute urticaria

KEY POINTS

- Chronic urticaria is normally defined as daily or almost daily urticaria for more than 6 weeks. Chronic urticaria has been traditionally subdivided into physical urticaria (wheals evoked by a physical stimulus, such as pressure, friction, cold contact, or sun exposure) and spontaneous urticaria.
- A patient with a length of history less than 6 weeks is designated as having acute urticaria, although most patients with acute urticaria have a much shorter duration.
- Depletion of the peripheral blood basophil leukocyte count occurs in some patients with chronic spontaneous urticaria.
- Patients with chronic urticaria have an increased frequency of HLA-DR and HLA-DQ alleles that are characteristically associated with autoimmune diseases. Some of these patients have functional anti-FceR1 and/or anti-IgE autoantibodies which are considered to be the cause of the urticaria.

WHAT IS URTICARIA?

In 1480, King Richard III of England, whose mortal remains have recently been discovered under a public car park in Leicester, developed an itchy red rash after consuming strawberries procured by a courtier. Accused by the king of witchcraft, the courtier was put to death.[1] Fortunately, even when accompanied by angioedema, urticaria is rarely fatal. The term, urticaria, was first used by Johann P Frank in 1792 in his classic *De curandis hominum morbus epitome praelectionibus dicata*. Aided by Thomas Bateman, Robert Willan, in his *A Practical Synopsis of Cutaneous Diseases* (1813), attempted classification of subtypes of urticaria.[2] He recognized *urticaria febrilis* (urticaria associated with fever), *urticaria evanida* (corresponding with spontaneous chronic urticaria), and *urticaria perstans*, in which individual wheals last several days, consistent with urticarial vasculitis or possibly delayed pressure urticaria.

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The role of mast cells and histamine in the pathogenesis of urticaria was not revealed for many decades. In 1879, Paul Ehrlich,[3] a medical student, using recently discovered basic dyes as histochemical stains, proposed the name, *mastzellen* (well-fed cells), for these cells whose granules exhibited metachromatic properties and water solubility. More than 30 years later, Dale[4] identified histamine as an important pharmacologic mediator of vasodilation and vascular permeability, and in the 1920s, Lewis,[5] in his description of the actions of histamine in the skin, drew attention to its potential role as a mediator of urticaria.

Urticarial wheals are clinically characterized by central swelling due to local increased permeability of cutaneous capillaries and postcapillary venules. The redness of the urticarial wheal is due to vasodilation, the more central component of which is caused by a direct action of histamine on postcapillary venules, but the surrounding bright red, often patchily distributed, flare is a result of an axon reflex, these (wheal, central redness, axon flare) being components of Lewis' famous triple response.[5] Increased blood flow causes the affected skin to be warm and also often causes a visible halo of pallor surrounding the wheal, which is due to a steal effect. Curiously, in his otherwise comprehensive treatise on actions of histamine in human skin, Lewis omits mention of itch. It was not until the 1950s that Riley and West[6] firmly confirmed the localization of histamine in tissue mast cells of the skin and other organs, thereby establishing the dermal mast cell as the target cell in urticaria.

Angioedema is frequently associated with most subtypes of urticaria, although it occurs alone without urticaria in hereditary forms, and angioedema evoked as an adverse reaction to ACE inhibitors. Credit for clear descriptions of the clinical features of angioedema should be shared jointly by John Milton of Edinburgh[7] and Heinrich Quincke,[8] although the latter frankly acknowledges that he was essentially describing the work entitled, "Uber akutes Odem," of one of his graduate students, Eugen Dinkellacker. Unlike urticaria, angioedema affects mucous membranes as well as skin, with a predilection for mucocutaneous junctions, including eyelids and lips. Increased vascular permeability is abrupt and massive and located deep in the dermis, subcutaneous tissue, and submucosa. Vasodilation is variable and often angiedema swellings are the color of normal skin and painful rather than itchy.

The histopathology and immunopathology of urticaria have been insufficiently studied and vary depending on the subtype of urticaria studied. The histopathologic findings in a physical urticaria, such as symptomatic dermographism, in which the wheal lasts only a few minutes before fading without leaving a trace, are different from the findings in chronic spontaneous urticaria, in which the duration of each individual wheal is usually 12 to 18 hours. There are certain common features, however. Dermal edema, vasodilation, and a perivascular cellular infiltrate are microscopically evident with variations in all subtpypes of urticaria. Although prominent in urticarial vasculitis, endothelial cell damage is not seen in any form of nonvasculitic urticaria. Available data on the histopathology of the wheal in urticaria are mainly derived from studies in chronic spontaneous urticaria.

THE DERMAL MAST CELL IN URTICARIA

Despite their central role in the pathogenesis of urticaria, histologic studies have not convincingly demonstrated quantitative or qualitative abnormalities in dermal mast cells in any subtype of urticaria. Using a double-labeling immunohistochemical technique, no significant difference in mast cell numbers in lesional, nonlesional, or control (healthy) skin were observed.[9] Human mast cells are of 2 types, based on the protease content of the granules. Mast cells of the Tc type (MC Tc) contain tryptase and