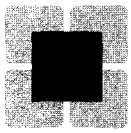

Newer aspects of urticaria pigmentosa

IN THIS ISSUE of the *Journal*, Andreano and associates describe eight patients with adult-onset urticaria pigmentosa, two of whom had prominent systemic symptoms—particularly hematologic. The authors review the manifestations, prognosis, and clinical implications of systemic mast cell disease.

■ *See Andreano and associates (pp 259-265)*

Three issues are pertinent to our understanding of this disease: (1) what we know about the mast cells in mastocytosis; (2) the prevalence of mast cell disease without cutaneous lesions; and (3) the state of the art of mastocytosis treatment.

THE MAST CELL IN MASTOCYTOSIS

The exact nosology of the mast cell has not been established, but it is clear that these cells are bone-marrow derived. Recent studies of mast cells from the skin and spleen of mastocytosis patients have shown that, upon stimulation, these cells release mediators, similar to the activity of mast cells extracted from normal tissues.[1,2] Cutaneous mast cells from patients with urticaria pigmentosa, for example, have been shown to release histamine when stimulated by secretagogues such as anti-IgE, C3a, morphine, and calcium ionophore. The histamine content of these cells also appears to be similar to that of normal skin mast cells.[2]

Despite their biological similarities to normal mast cells, cutaneous mastocytosis cells appear morphologically larger and have indented or bilobed nuclei. Furthermore, they have numerous elongated cytoplasmic projections.[2] These morphologic differences are important; a recent study showed that in patients with systemic mast cell disease, the cutaneous mast cells had larger mean cytoplasmic area, nuclear size, and granular diameter compared with the mast cells of patients with urticaria pigmentosa without systemic involvement.[3] The number of granules within the cell did not vary between these two groups.[3] One can, therefore, conclude that in patients with mastocytosis, the mast cells retain their biologic function, which enables them to produce the symptoms of this condition. Whether the cells in the subgroup of patients who develop systemic mast cell disease differ from those with nonsystemic urticaria pigmentosa remains to be determined.

MASTOCYTOSIS WITHOUT CUTANEOUS LESIONS

The literature suggests that 99% of patients with mastocytosis present with skin lesions. Various types are recognized, including urticaria pigmentosa, cutaneous solitary mastocytoma, diffuse cutaneous mastocytosis (with or without blisters), telangiectasia macularis eruptiva perstans (TMEP), and erythroderma.

The assumption that cutaneous involvement is a sine qua non for this condition has recently been challenged. An increasing number of patients have been reported to present with a variety of vague symptoms and are subsequently diagnosed as having systemic mastocytosis.[4,5] Some authors believe that this entity is not uncommon and is greatly underdiagnosed.[5] If this is true, then the incidence of mastocytosis is probably much greater than previously recognized.

Diagnosis is far from easy, since patients usually have episodic symptoms and the severity varies with the episode and among individuals. Nevertheless, the symptoms can be severe and the disease occasionally life-threatening, so correct diagnosis is important. The common symptoms are recurrent flushing and episodes of hypotension; a variety of other symptoms have been described, including palpitations, dyspnea, dizziness, syncope, chest pain, headaches, pruritus, diarrhea, nausea and vomiting, fatigue, vertigo, emotional liability, memory loss, and difficulty concentrating.[5] Several

biochemical assays have been proposed to aid in the diagnosis, including plasma and urine histamine, urinary histamine metabolite, urinary prostaglandin D_2 metabolites, and plasma tryptase levels, but most of these are available only in research settings.[6] Because tissue diagnosis remains the gold standard, a high index of suspicion is required.

The diagnosis is further complicated by the possibility that some patients who present with the same symptoms (eg, episodic flushing and hypotension) and biochemically detectable increased mast cell products may actually represent a subset with increased mast cell *activity* rather than increased mast cell *numbers*.[5]

TREATMENT OF MASTOCYTOSIS

The treatment of mastocytosis is far from satisfactory. Various options are available, but they are aimed at the symptoms rather than the pathogenesis. The use of psoralen and ultraviolet light-A (PUVA) has gained popularity for the treatment of cutaneous lesions;[7–9] various investigators have found that PUVA results in fading of the lesions[8,9] with relief of itching.[7–9] Additionally, Darier's Sign (whealing upon stroking of a lesion) has also been shown to decrease.[7] Unfortunately, relapses are common upon discontinuation of treatment.

The mechanism of action of PUVA is unknown. It was originally thought that this modality decreased the number of mast cells in the skin,[8] but subsequent studies have shown that this is not the case.[9] Some investigators have found that the levels of major urinary histamine metabolites, which correlate with disease activity, decrease after PUVA therapy.[8] Antihistamines, particularly H_1 and H_2 antihistamines in combination, effectively relieve the pruritus and whealing associated with mastocytosis.[10] This combination also may help in the treatment of bullous mastocytosis in children.[11] The use of H_2 antihistamines is clearly indicated for the treatment of mastocytosis-associated gastrointestinal symptoms such as gastric hypersecretion, diarrhea, abdominal pain, and malabsorption.[12,13]

Low-dose aspirin in combination with H_1 and H_2 antihistamines has been proposed for patients with severe systemic mast cell disease who present with episodic attacks of flushing and hypotension.[14] The rationale is that this treatment inhibits the synthesis of prostaglandin D_2, whose metabolites have been found in high levels in the urine of patients with mastocytosis and could be responsible for some of the symptoms. This therapy has good theoretical basis for success, but it should be started in a hospital setting. Adverse reactions to aspirin are not uncommon among mastocytosis patients, and severe hypotension with shock can occur.

Cromolyn has also been used in the treatment of mastocytosis. Even though only 1% of this compound is absorbed through the gastrointestinal tract, it decreases pruritus, whealing, and flushing.[15,16] Moreover, some patients have experienced increased attention span, increased work performance, and decreased diarrhea with cromolyn therapy.[15] This compound also may be useful in the treatment of bullous mastocytosis.[17] Although in a recent trial, cromolyn was no better than the combination of H_1 and H_2 antihistamines in the treatment of mastocytosis, it was somewhat more effective in the treatment of gastrointestinal symptoms.[10]

Ketotifen, which inhibits mast cell degranulation and has H_1 receptor antagonist properties, has recently been used in the treatment of this disease.[18] This compound has the advantage over cromolyn of being well absorbed from the gastrointestinal tract. In patients with cutaneous mastocytosis, ketotifen has decreased pruritus and whealing.[18] Except for tiredness, few side effects have been noted with the use of this drug.

The use of nifedipine or other calcium channel blockers for the treatment of mastocytosis also has a good theoretical basis since calcium influx into the mast cell occurs early in the degranulation process. In a single case report, nifedipine resulted in decreased whealing and flushing.[19]

Intralesional as well as potent topical steroids in the treatment of mastocytosis has received attention recently. Both intralesional and potent topical steroids under occlusion have resulted in decreased pruritus, loss of Darier's sign, and a decrease in the number of cutaneous mast cells in the lesions where the compounds were used.[20] One prominent side effect was noted—the development of cutaneous atrophy—but this treatment had long-lasting beneficial effects. The possibility of narrowing the clinical effects of these compounds in order to avoid atrophy and obtain maximum therapeutic efficacy warrants further study.

Surgical treatment of large mastocytomas is a recognized therapeutic option,[21] but it needs careful consideration; these lesions can bleed profusely,[21] probably because of the large amounts of heparin contained in the cells.

Patients with mastocytosis should be advised to avoid spicy foods, alcohol, and metabisulfites since these substances can trigger attacks. Similarly, substances known to degranulate mast cells, such as dextran, opiates, and radiocontrast media, should be used only when absolutely necessary.

Patients also should take precautions during hymenoptera season to avoid being stung which, in some instances, has proved fatal. They should be warned, for example, not to wear brightly colored or flowered patterned clothing and not to use strongly scented toiletries.

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