

Clinical features of urticaria pigmentosa

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■ A 1-year experience with adult-onset urticaria pigmentosa, including two patients with systemic mast cell disease, demonstrates the clinical and pathologic manifestations of the disease and leads to recommendations for patient evaluation.

□ INDEX TERM: MASTOCYTOSIS, URTICARIA PIGMENTOSA □ CLEVE CLIN J MED 1990; 57:259-265

MASTOCYTOSIS refers to a diverse group of conditions that may include cutaneous, systemic, and malignant forms. Systemic involvement is a common feature in patients with adult-onset disease.

We report a 1-year experience with adult-onset urticaria pigmentosa. The cases of eight adults, including two illustrative cases of systemic mast cell disease, are presented.

PATIENTS AND METHODS

Eight adult patients seen in the Department of Dermatology in 1988 were included in the study. Children under age 18 were not included because of the better prognosis and lower incidence of systemic disease in this age group. The diagnosis of urticaria pigmentosa in the eight patients was based on careful histories and physical examinations and was confirmed by skin biopsies. All patients had skin lesions that were generally symmetrical with varying density and were most abundant on the trunk. The lesions usually appeared as small, scattered, red-brown macules and papules. Patients with evidence

of systemic involvement based on symptoms, complete blood count, and urine histamine levels underwent a number of tests, including bone marrow biopsy, gastrointestinal (GI) evaluation, and radiographic studies.

■ See related editorial by Kerdel (pp 242-244)

The data on the eight patients described in this study are presented in *Table 1*. Of the eight patients, three were men and five were women, ranging in age from 32 to 74 years (mean, 54 years). The mean duration of symptoms preceding diagnosis was 7 years.

Six of the eight (75%) patients had pruritus as a symptom; the other two were asymptomatic. A positive Darier's sign (urtication upon stroking a lesion) was elicited in two of seven patients (28%) where it was recorded. Three of eight patients had skin biopsies read as telangiectasia macularis eruptiva perstans (TMEP).

To date, two of the eight patients (25%) have systemic involvement. Both patients had diarrhea in addition to pruritus as symptoms.

ILLUSTRATIVE CASES

Case 1

A 33-year-old woman with a diagnosis of systemic mastocytosis presented to the Department of Dermatology in June 1988 for further evaluation of a 6-year his-

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TABLE 1
SUMMARY OF CLINICAL FEATURES

Case no.	Age/sex	Duration of disease (yr)	Symptoms	Skin biopsy results	Bone marrow biopsy results	Complete blood count			Histamine in urine ($\mu\text{g}/24\text{ h}$)	Bone scan results	Treatment
						Hb (g/L)	WBC/ mm^3	% eos*			
1	33/F	2	Diarrhea, pruritus	TMEP†	Foci of mast cell aggregates	125	9,100	4	167	ND	Ranitidine Terfenadine
2	68/F	6	Diarrhea, pruritus, back pain, fatigue, weight loss	Mastocytosis	Myelodysplasia with clusters of mast cells	84	7,100	0	Not recorded	Uptake L5-S ₁ and T12	Cimetidine Cromolyn
3	52/M	25	Pruritus	TMEP	ND‡	148	2,900		63	ND	None
4	32/M	12	Pruritus	Urticaria pigmentosa	ND	153	6,300	0	Not recorded	ND	PUVA
5	45/F	1	Asymptomatic	Urticaria pigmentosa	ND	132	7,900	0	Not recorded	ND	None
6	72/M	1	Pruritus	Urticaria pigmentosa	Increased iron stores, focal increased eosinophils	156	7,300	14	Not recorded	Normal	Hydroxyzine
7	74/F	2	Pruritus, burning skin	Urticaria pigmentosa, plaque type	Normal	139	8,910	0.8	39	ND	Hydroxyzine Pramosone lotion
8	53/F	7	Pruritus	TMEP	ND	153	5,800	6	58	ND	None

*eos = eosinophils

†TMEP = telangiectasia macularis eruptiva perstans

‡ND = not done

tory of freckle-like skin lesions that were gradually spreading. A skin biopsy performed 3 years earlier showed proliferating dilated small capillaries in the upper dermis that were surrounded by mast cells and mixed with scattered eosinophils and mononuclear cells. Toluidine blue stain showed intracytoplasmic metachromatic granules, confirming the histologic impression of telangiectasia macularis eruptiva perstans.

The patient also complained of watery, intermittent diarrhea. An upper gastrointestinal series performed 3 years earlier was reportedly normal except for a rapid transit time, and a D-xylose absorption test was normal. Her medical history included anemia that had been unresponsive to treatment with iron supplementation. Itching and occasional diarrhea were her main symptoms. Current medications included ranitidine as needed for the diarrhea and terfenadine to relieve itching.

Physical examination revealed brown macules on the chest, back, legs, and arms (Figure 1). Lymphadenopathy, splenomegaly and hepatomegaly were absent.

A complete blood count revealed a mild normochromic anemia with a hemoglobin of 118 g/L and a hematocrit of 35.5%. The leukocyte differential was

normal. A 24-hour urine collection for histamine demonstrated elevated histamine to 167 $\mu\text{g}/24\text{ hours}$ (normal 17 μg to 68 μg per 24 hours). In view of the abnormal laboratory results, a bone marrow aspirate and biopsy from the iliac crest was performed. The slightly hypocellular marrow content showed a normal myeloid-erythroid ratio with good maturation of the elements. Occasional aggregates of mast cells were identified embedded in a reticulin matrix, with scattered eosinophils, lymphocytes, and plasma cells. The marrow aspirate was unremarkable. The findings were those of eosinophilic fibrohistiocytic lesion, or mastocellular lesion, of the bone marrow and were consistent with systemic mastocytosis (Figures 2 and 3).

Case 2

A 68-year-old woman was admitted to the Cleveland Clinic Hospital in April 1988 for further evaluation of a 1-year history of a 30-pound weight loss, diarrhea, fatigue, and hepatosplenomegaly. A skin biopsy 2 years earlier had resulted in a diagnosis of urticaria pigmentosa. Sideroblastic anemia had been diagnosed in 1982 by a sternal bone marrow aspiration and was unresponsive to treatment with vitamin B₁₂ and folate. Her diar-



FIGURE 1. Numerous discrete hyperpigmented macules distributed over the thigh are seen in this patient with TMEP (case 1).

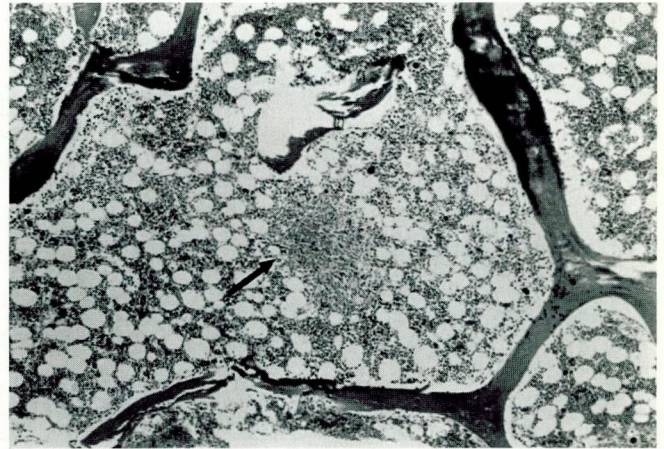


FIGURE 2. Low-power view of the bone marrow core biopsy specimen showing slightly hypocellular bone marrow with a focal fibrohistiocytic mastocellular lesion (arrow). (Hematoxylin-eosin stain. Original magnification $\times 100$)

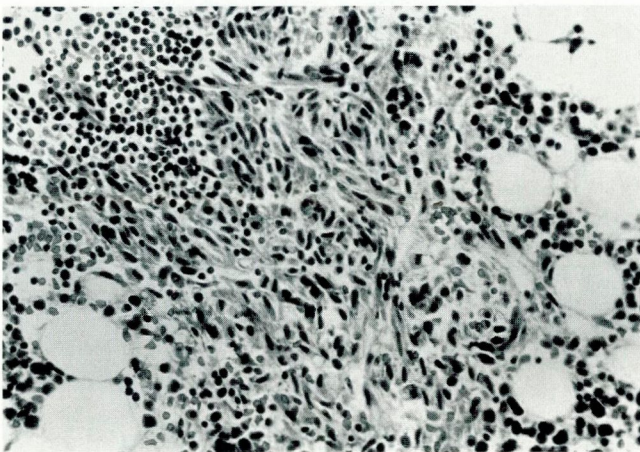


FIGURE 3. High-power view of the eosinophilic fibrohistiocytic lesion of the bone marrow core biopsy showing the mast cell infiltrate with scattered mononuclear cells, plasma cells, and eosinophils. (Hematoxylin-eosin stain. Original magnification $\times 200$)

rhea was characterized by four to five bowel movements daily with mucus and incontinence. A previous evaluation included an upper GI series, barium enema, and stool for culture and occult blood, all of which were normal or negative. Treatment with cimetidine alleviated the patient's symptoms.

A physical examination 5 months prior to admission revealed hepatosplenomegaly. Liver and bone marrow

biopsy at that time reportedly suggested hairy cell leukemia, but a myelodysplastic process could not be ruled out, and a definitive diagnosis was not made. A recent computed tomogram (CT) of the abdomen revealed splenomegaly. A bone scan showed increased radioactivity of L5 and S1 vertebral interspaces and mildly increased radioactivity involving T12, which suggested osteoarthritis. Her current medications included cyclobenzaprine, 10 mg tid, for chronic low back pain and cimetidine, 300 mg qid, for diarrhea.

Physical examination at the time of admission showed hyperpigmented, reddish-brown macules and papules on the arms, thighs, legs, and trunk. Darier's sign was positive. Marked hepatosplenomegaly with tenderness to palpation was noted, and a stool specimen was negative for occult blood.

Pertinent initial laboratory studies disclosed a white blood cell count of $7,100/\text{mm}^3$ with 37% neutrophils, 40% lymphocytes, 6% monocytes, 5% bands, and 12% atypical immature myelomonocytic cells. She was anemic with a hemoglobin of 84 g/L, a hematocrit of 27.5%, a reticulocyte count of 1.5%, and a platelet count of $277 \times 10^3/\mu\text{L}$. Liver function testing revealed an elevated alkaline phosphatase of 129 U/L (normal 20 U/L to 110 U/L), an elevated total bilirubin of 32.49 $\mu\text{mol/L}$ (normal 5.13 $\mu\text{mol/L}$ to 25.65 $\mu\text{mol/L}$), and a normal LDH and SGOT.

Two skin biopsies taken from the left arm and left back demonstrated a dense, upper dermal, predominantly perivascular infiltrate composed of mast cells

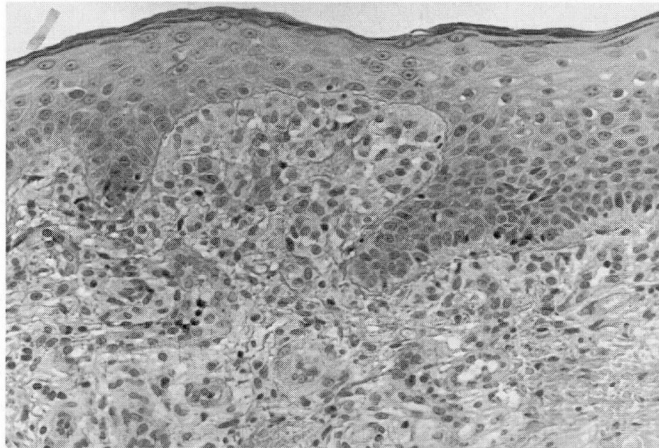


FIGURE 4. The papillary dermis shows a dense, diffuse, and perivascular infiltrate composed predominantly of mast cells. (Hematoxylin-eosin stain. Original magnification $\times 200$)

(Figures 4 and 5). Cutaneous mastocytosis, papular or plaque type, was diagnosed. A bone marrow biopsy from the iliac crest was hypercellular with an increased number of immature myeloid precursors and ringed sideroblasts consistent with a myelodysplastic syndrome. Occasional clusters of monocytoid cells with clear cytoplasm were suspicious for a mast cell infiltrate; however, metachromatic stains were noncontributory. A review of the needle biopsy of the liver showed a diffuse infiltrate of mast cells in both portal tracts and parenchyma consistent with systemic mastocytosis. A flexible sigmoidoscopy showed only a small polyp in the sigmoid colon.

The clinical picture and histologic confirmation pointed to the diagnosis of systemic mastocytosis. The patient received a transfusion of two units of packed red blood cells and was discharged on a regimen of oral disodium cromoglycate at an initial daily dosage of 10 mg to 20 mg to be gradually increased to 800 mg/day in three divided doses.

DISCUSSION

Mastocytosis is characterized by increased mast cell population, most frequently in the skin. Urticaria pigmentosa (UP) refers to cutaneous mastocytosis, which has several clinicopathological variants.¹ UP lesions are well defined, reddish-brown macules and papules that may occur in an isolated or a generalized distribution. The formation of an urticarial wheal at the lesion site upon stroking, called Darier's sign, indicates an ab-

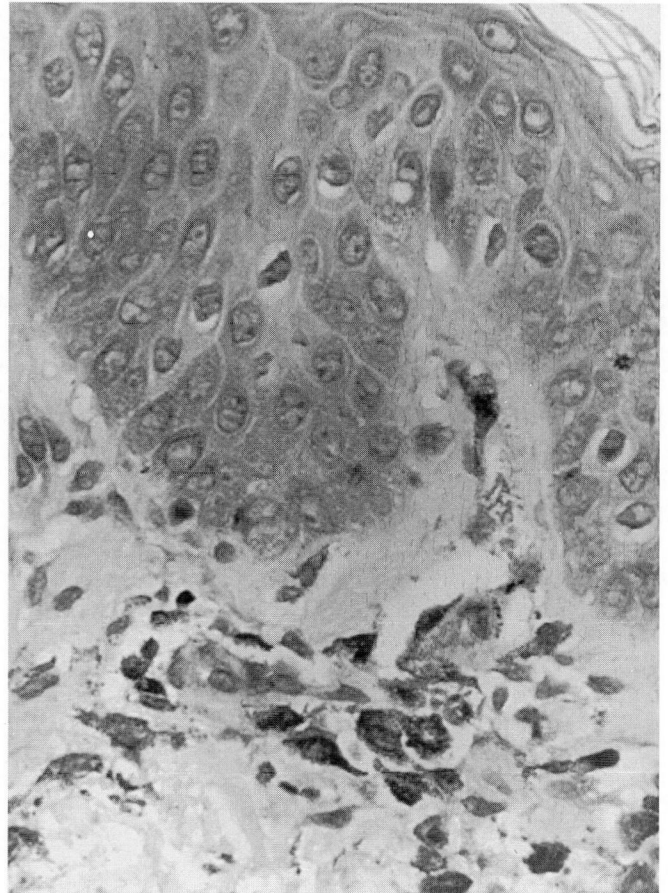


FIGURE 5. Mast cell infiltrate within the papillary dermis. Small granules within the cytoplasm can be seen. (Giemsa stain. Original magnification $\times 400$)

normal accumulation of cutaneous mast cells and the release of their vasoactive mediators.² The low incidence of Darier's sign observed in this series demonstrates that a skin biopsy of a characteristic lesion must be performed to confirm the diagnosis of cutaneous mastocytosis.

A solitary hyperpigmented nodule or mastocytoma may be present at birth or early infancy; it characteristically involves a distal extremity, with a predilection for the wrist area.^{1,2}

Diffuse cutaneous mastocytosis, or the erythrodermic form, is characterized by diffuse mast cell infiltration of the skin, giving it a red, thickened, and lichenified appearance with a doughy consistency. Patients with diffuse cutaneous mastocytosis have the highest frequency of concurrent systemic mast cell disease.³

Telangiectasia macularis eruptiva perstans is a rare variant that accounts for only about 1% of all cases and

occurs primarily in adults.⁴ This appears as numerous, discrete, hyperpigmented macules with overlying telangiectasias distributed symmetrically over the trunk and proximal extremities.³ Three of our eight patients were diagnosed as having TMEP based on clinical findings and biopsies that showed increased numbers of mast cells about the superficial capillary plexus and absence of eosinophils.

Systemic disease

Systemic mastocytosis or systemic mast cell disease (SMCD) implies an aberrant accumulation of mast cells in several organs, usually including the skin.² Sagher and Even-Paz estimated that among adults with mastocytosis, the incidence of systemic involvement is eight times higher than in children.⁵ SMCD constitutes approximately 10% of all mast cell disease, but it has been suggested that up to 50% of adults with urticaria pigmentosa may have SMCD. Systemic mastocytosis is, therefore, probably more common than the number of reported cases would lead one to suspect.⁶ Systemic involvement without cutaneous lesions, although rare, has also been reported.⁷

Besides the skin, the most commonly involved organs are the bone marrow, skeletal system, gastrointestinal tract, liver, lymph nodes, and spleen. Symptoms associated with SMCD include fever, malaise, weight loss, bone pain, epigastric pain, fatigue, episodic flushing, tachycardia, hypotension, dizziness, and syncope.^{2,3} Symptoms of mastocytosis are mostly attributed to the products of mast cell degranulation, including histamine, eosinophil chemotactic factor, neutrophil chemotactic factor, heparin, prostaglandin D₂, exoglycosidases, proteases, and leukotrienes.³

Rarely, a malignant form of SMCD develops, often associated with leukemia or a related malignant condition affecting the lymphoreticular tissues.⁸ According to Lennert and Parwaresch, malignant mast cell disease can be differentiated from a benign SMCD process by cytologic and cytochemical criteria, in addition to the patient's clinical course. Larger nuclei, mitotic activity, and decreased numbers of metachromatic granules are commonly observed in a malignant process.⁸

A variety of forms may manifest bone involvement. Sagher and Even-Paz reported that approximately 90% of their systemic mastocytosis patients had abnormal accumulations of bone marrow mast cells.⁵ Mast cells infiltrating the marrow are frequently localized to the paratrabecular or perivascular areas and may resemble fibrohistiocytic granulomas.⁷ An eosinophilic infiltrate and myelofibrosis may accompany the mast cells.^{2,9} Be-

cause these cellular accumulations are composed primarily of mast cells, eosinophilic myeloid cells and lymphocytes, Olafsson⁶ termed them MEL lesions. Bone marrow lesions, similar to MEL lesions, in patients without UP are called eosinophilic fibrohistiocytic or mastocellular lesions of the bone marrow.⁷ MEL lesions may be a sign of mast cell accumulation in the bone marrow and thereby indicate progression to SMCD.^{6,10} This possibility is further supported by the correlation between the duration of the disease and the number of mast cells in the bone marrow.^{6,10} According to Czarnet-ski and associates,⁹ a more intense infiltration of the bone marrow was seen in patients who also had massive cutaneous involvement and symptoms related to other organ involvement.

In a recent study of 45 patients to determine the predictive value of histologic changes in bone marrow, patients with fibrosis, osteosclerosis with decreased fat cell content, and increased granulocytogenesis were categorized as having malignant mastocytosis.¹¹ The bone marrow mast cell infiltrate can simulate bone marrow involvement by tricholeukemia or hairy cell leukemia. Both show clusters of fairly uniform, oval-shaped cells with abundant clear cytoplasm within a reticulin-rich matrix.¹² A mixed cellular infiltrate may be present in some cases. Mast cell disease can be differentiated from hairy cell leukemia by histochemistry, immunohistology, and electron microscopy, with histochemistry showing cytoplasmic granules and electron microscopy showing elongated cytoplasmic processes.¹³

Hematologic abnormalities

The challenge in diagnosing SMCD lies in differentiating it correctly from various reticuloendothelial disorders and malignancies, thus avoiding the morbidity associated with their respective treatments.⁷ For example, case 2 was referred with the tentative diagnosis of UP and hairy cell leukemia. Appropriate testing revealed that the patient had systemic mast cell disease with associated myelodysplastic syndrome.

Nearly half of patients with SMCD have a demonstrable hematologic abnormality in the peripheral blood.^{2,4} The anemia associated with SMCD is usually mild, normochromic, and normocytic.¹⁴ The development of anemia is thought to be multifactorial, with infiltration of the bone marrow, splenomegaly, and enhanced effects of heparin on erythrophagocytosis.¹⁴ Both patients described above (cases 1 and 2) had SMCD with anemia. Thrombocytopenia, eosinophilia, leukopenia, and lymphocytosis have been reported less frequently.¹ Eosinophilia, found in about 15% of cases, is

believed to be mediated by the release of eosinophilic chemotactic factor of anaphylaxis (ECF-A).¹⁴

Only rarely does mast cell leukemia occur in patients with systemic mastocytosis, but monocytic and myelocytic leukemia, as well as Hodgkin's disease, myelofibrosis, polycythemia vera, and large cell or immunoblastic lymphoma have been recorded.¹ Patients with SMCD and associated hematologic disorders are generally older and more commonly present with anemia, leukocytosis, constitutional symptoms, and pathologic fractures than other SMCD patients.¹⁵ According to Cryer and Kissane,¹⁴ leukemia develops in 4% to 5% of patients with systemic mastocytosis. However, it has been estimated that a malignant process will develop in as many as one third of adult patients with benign systemic mastocytosis.^{2,5}

Lennert and Parwaresch⁸ noted the development of a leukemic phase of either mast cell, myeloid, or monocytic leukemia in 16 of 43 patients with malignant mastocytosis, supporting the view that mast cells are derived from monocytes. Lymphocytosis, especially when accompanied by circulating mast cells and eosinophilia, may be an early indicator of this monocytic leukemia, which is often refractory to treatment and has a poor prognosis.^{5,7,8} Travis et al¹⁶ state that mast cell leukemia is characterized by increased atypical mast cells in the peripheral blood, diffuse infiltration with atypical mast cells in the bone marrow, a strong association with peptic ulcer disease, constitutional symptoms, and hepatosplenomegaly.

Skeletal involvement

Skeletal involvement, with a reported incidence of 65% to 70%, may be manifested clinically as pain, tenderness, and deformity following fracture.¹⁷ Radiographic abnormalities are common and occur in approximately 70% of these patients.⁵ Findings are heterogeneous and include either diffuse or well-circumscribed osteolytic or osteoblastic lesions. The most common abnormalities are diffuse, poorly demarcated areas of osteosclerosis and radiolucency involving the axial skeleton. Radiographic findings may not be indicative of systemic disease and may be absent despite extensive accumulation of mast cells in bone tissue.¹⁷ Generalized osteopenia may be a more common radiographic manifestation of systemic mastocytosis than is generally appreciated.¹⁷ Heparin, a mast cell product, is known to be associated with the enhancement and stimulation of bone resorption, possibly leading to osteoporosis.¹⁴ Skeletal scintigrams are believed to be more sensitive and useful than radiographs in assessing bone pathology.¹⁸

Approximately 50% to 70% of patients with SMCD have hepatomegaly at the time of diagnosis, despite usually normal liver function tests. Splenomegaly is observed in approximately 50% of patients with systemic mastocytosis, and lymphadenopathy occurs in 28% to 40%, mast cell infiltration of the abdominal chain occurring most commonly.^{5,7,8} Mast cells and eosinophils are found predominantly in the perifollicular and paracortical areas, effacing the normal lymph node architecture.⁷

Gastrointestinal symptoms

Gastrointestinal manifestations of mastocytosis occur in approximately 23% of patients.⁵ Lesions may occur at all levels of the GI tract and radiographs with the use of contrast material may show nodular irregularities, particularly in the small bowel.⁴ The many gastrointestinal symptoms of this disease, including nausea, vomiting, diarrhea, epigastric pain, and mild malabsorption, are believed to be due to an increased tissue level of histamine and increased prostaglandin D₂ production.^{19,20} Both of our patients with SMCD had diarrhea as a chief complaint.

Laboratory evaluation

The only irrefutable criterion of mast cell hyperplasia is its histological demonstration.¹ Preoperative cleansing of the biopsy site and administration of local anesthesia should be done with minimal trauma to avoid degranulation of mast cells. Most commonly, there is infiltration of mast cells in the upper third of the dermis with occasional perivascular aggregates. Eosinophils are scattered within the infiltrate except in TMEP, where eosinophils are generally absent because of the small numbers of mast cells within the lesions.²¹ The cytoplasmic granules of mast cells stain metachromatically with Giemsa's stain or toluidine blue.¹ According to Travis and associates,¹² when dense infiltrates of mast cells are seen on skin biopsy specimens associated with increased mast cell atypia, systemic mast cell disease should be considered.

The evaluation of a patient for evidence of SMCD should include a complete blood count with differential and 24-hour urine specimen for histamine metabolites. Twenty-four hour quantitative urine determinations of histamine metabolites N-methylhistamine and N-methylimidazoleacetic acid are more sensitive than measurement of histamine itself;²² however, these assays are currently not widely available. Urinary methylimidazoleacetic acid excretion correlates well with the number of mast cells in sections of bone marrow biopsies

and appears to be a good indicator of the extent of disease.⁶ Increased excretion of histamine metabolites also may be found in other settings, such as anaphylactic reactions to drugs or wasp stings, cold-induced urticaria, and chronic myelocytic leukemia.²² If anemia, lymphocytosis, or eosinophilia is present, or the results of urine studies are abnormal, we recommend a bone marrow biopsy to evaluate the possibility of systemic involvement or a myelodysplastic syndrome. Since the involvement may be focal, a normal bone marrow biopsy does not necessarily rule out bone involvement.¹² The use of radionuclide bone scans also may be useful for screening patients suspected of having extracutaneous disease.¹⁸

Prognosis and treatment

The prognosis of patients with childhood mastocytosis is good; many become disease-free or markedly im-

proved by early adulthood.³ However, in adult-onset disease, the skin lesions often persist throughout life and, as mentioned, the risk of developing SMCD may be eight times greater.⁵ Those whose systemic disease begins in late middle age or old age are at the highest risk for lymphoma, leukemia, and mast cell neoplasia.¹⁹ Long-term clinical follow-up of patients with SMCD is necessary to detect the possible development of more aggressive mast cell disease or other reticuloendothelial malignancies.

An important aspect of therapy for mast cell disease is the avoidance of triggering factors such as temperature changes, friction, physical exertion, emotional stress, and ingestion of certain substances such as ethanol and opiates.⁴ Specific treatment is directed toward symptoms and includes various combinations of H₁ and H₂ receptor blockers. Recently, oral disodium cromoglycate was reported to be useful for mitigating the cutaneous and gastrointestinal symptoms of SMCD.²³

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