

MASTOCYTOSIS PRESENTING AS A SKELETAL DISORDER

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ABSTRACT

Mastocytosis is a rare disease of mast-cell proliferation with involvement of the reticuloendothelial systems including skin, bone, gastrointestinal tract, liver, lungs, spleen, and lymph nodes. Systemic mastocytosis is characterized by a combination of symptoms that relate to the mast cells' release of vasoactive substances, such as histamine. These symptoms include urticaria pigmentosa, flushing, syncope with hypotension, headaches, nausea, vomiting, diarrhea, and occasional bronchospasm. The diagnosis of mastocytosis is typically based on the presence of the characteristic extraosseous manifestations. A well recognized roentgenographic feature seen in 70-75% of patients with mastocytosis is diffuse osteolysis and osteosclerosis, affecting primarily the axial skeleton and the ends of the long bones. Rarely, the bony involvement consists of generalized osteoporosis, which may lead to pathologic fracture, or solitary lesions (mastocytomas) which may cause symptoms of localized pain. Four patients with previously undiagnosed systemic mastocytosis had unusual skeletal lesions. Clinical and laboratory evaluation of these patients eventually led to the correct diagnosis of systemic mastocytosis. We report these four cases to emphasize the need for thorough evaluation of unusual musculoskeletal findings in association with extraosseous symptoms that are characteristic of mastocytosis. Knowledge of a wide differential diagnosis of unusual skeletal lesions should include systemic mastocytosis.

INTRODUCTION

Mastocytosis is a rare disease of unknown etiology, characterized by mast cell proliferation in skin and other reticuloendothelial systems including lymph nodes, spleen,

liver, bone, bone marrow, gastrointestinal tract, and lungs²⁷. It most commonly exists in a cutaneous form, urticaria pigmentosa, characterized by a violaceous maculopapular rash over the neck and trunk. The rash demonstrates dermatographism, and urticates with stroking, a phenomenon known as Darier's sign.

Urticaria pigmentosa is more frequently seen in children and resolves spontaneously by puberty. In approximately 10-30% of cases the disease may persist into adulthood, developing into the systemic form²⁷. The disease rarely presents following adolescence.

Systemic mastocytosis is characterized by mast cell proliferation in several organs of the reticuloendothelial system and is often associated with clinical features attributable to histamine release, such as episodic flushing, hypotension, headaches, nausea, vomiting, and diarrhea. Approximately 94% of patients with systemic mastocytosis have urticaria pigmentosa²⁷. The systemic form may give rise to malignancy in the form of leukemia or mast-cell sarcoma^{9,15,17}. Patients with the adult onset form of the disease are thought to have a higher risk of developing leukemia¹⁷.

Skeletal lesions occur in 70-75% of patients with systemic mastocytosis. This association was first described by Sagher et al.²⁶ in 1952. The most common pattern of bony involvement is mixed osteosclerosis and osteolysis, affecting primarily the axial skeleton, pelvis, and proximal ends of long bones. The lesions can be mistaken for metastatic disease, Paget's disease, hyperparathyroidism, lymphoma, or myelofibrosis. Skeletal lesions in systemic mastocytosis demonstrate increased uptake in technetium-99 bone scans, particularly when the lesions involve the proximal ends of long bones^{31,34}. Although bone pain is a relatively frequent symptom, pathologic fractures are rare²³. The pattern of multiple mastocytomas occurring as discrete lytic lesions surrounded by a sclerotic halo has been described. Rarely a patient may present with a solitary mastocytoma²⁶. The diagnosis of skeletal lesions is typically a secondary finding in patients with known mastocytosis.

Due to the often nonspecific nature of the symptoms of systemic mastocytosis, patients with this disease may go undiagnosed for many years until the disease manifests itself in the form of skeletal lesions. These lesions may cause symptomatic bone pain, or may be discovered as an

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incidental finding on a routine roentgenographic exam. The evaluating orthopedist is thus faced with a diagnostic dilemma and should consider systemic mastocytosis when treating patients with unusual skeletal lesions and extraosseous symptoms characteristic of this disease.

The following four cases are examples of mastocytosis presenting as a skeletal disorder. None of the patients had known disease prior to being seen by the orthopedist. They all demonstrated unusual clinical and roentgenographic findings that with further laboratory and clinical investigation, led to the diagnosis of mastocytosis.

CASE REPORTS

Case 1:

A 52-year-old woman with a history of three prior thoracic spine compression fractures and osteoporosis was admitted for evaluation and treatment of acute back pain. Her past medical history was significant for a total abdominal hysterectomy and oophorectomy at the age of 48. She gave a 15-year history of a violaceous, maculopapular rash over the neck and trunk which was often pruritic and aggravated by sun exposure, stress, alcohol, and friction. She had been treated in the past for peptic ulcer disease and asthma.

Physical examination was remarkable for a brownish-red maculopapular rash over the neck and trunk that urticated with stroking. She had mild hepatosplenomegaly and expiratory wheezes. Her thoracolumbar spine was tender to palpation and painful with ambulation and forward bending. Roentgenographs revealed granular irregularity throughout the axial skeleton and pelvis with mixed areas of osteosclerosis and osteolysis, consistent with diffuse metastasis or metabolic bone disease (Figure 1). Laboratory studies revealed a slightly elevated alkaline phosphatase and no other abnormalities. A technetium-99 bone scan revealed increased activity throughout the axial skeleton and pelvis with some uptake in the hips and distal femora. The presumptive diagnosis at this time was widespread metastatic disease of unknown primary. A transiliac bone biopsy revealed mast-cell proliferation with fibrous changes in the bone marrow. Toluidine blue staining confirmed the presence of mast cells with their purple staining histamine-rich granules. At this time, a 24-hour urine collection was markedly positive for histamine, 70 $\mu\text{g}/24\text{h}$ (normal $< 50 \mu\text{g}/24 \text{h}$).

Six years after the diagnosis the patient suffered a minor fall, resulting in a supracondylar femur fracture. Her hospital course was complicated by a flare in her disease, resulting in marked urticaria and bronchospasm. Prior to undergoing open reduction and internal fixation of her femur fracture, the patient was treated with cimetidine and chlorpheniramine, which resulted in resolution of the bronchospasm and urticaria. The femur fracture healed

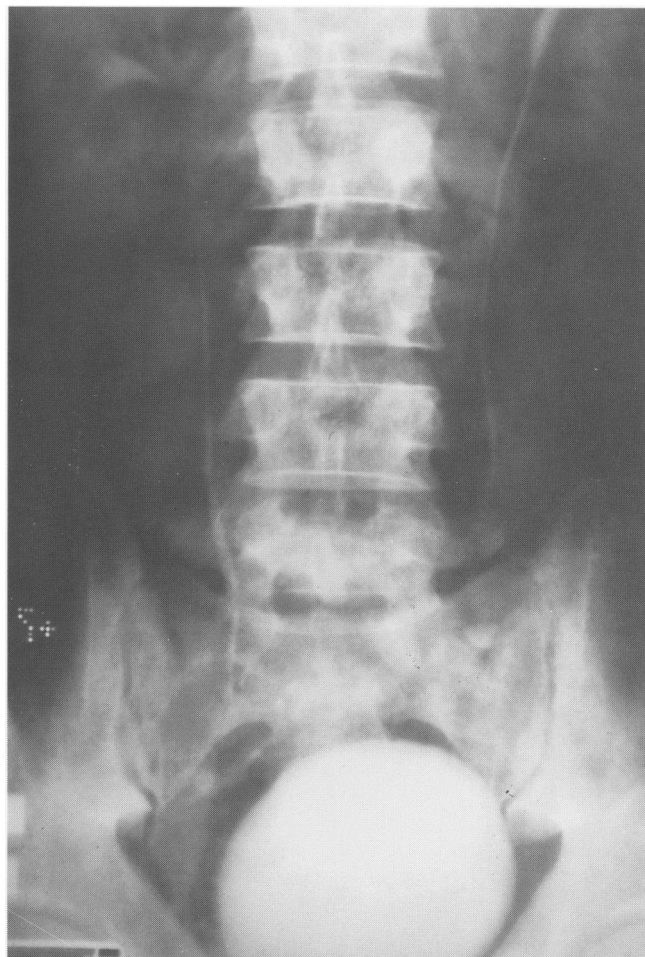


Figure 1. An anteroposterior roentgenograph of the lumbosacral spine at time of intravenous pyelogram reveals granular irregularities with mixed osteosclerosis and osteolysis.

uneventfully and two years later she was pain free and ambulating without assistance.

Case 2:

A 62-year-old woman was evaluated for complaints of low back pain. She denied any particular history of trauma and described the onset as gradual. Her past medical history was significant for occasional nausea and vomiting with crampy abdominal pain, diarrhea, and peptic ulcer disease. She was treated for this with a Bilroth II procedure. She gave a history of easy bruisability and cutaneous flushing associated with a rash over the neck and trunk present for over 20 years. She stated that the rash was exacerbated by stress, heat, extreme cold, and ingestion of alcohol.

Routine laboratory studies were all within normal limits. Roentgenographs of her spine and extremities revealed diffuse osteoblastic and lytic lesions, consistent with metastatic disease (Figures 2A-C). A chest roentgenograph was unremarkable. She underwent a transiliac bone biopsy



Figure 2A

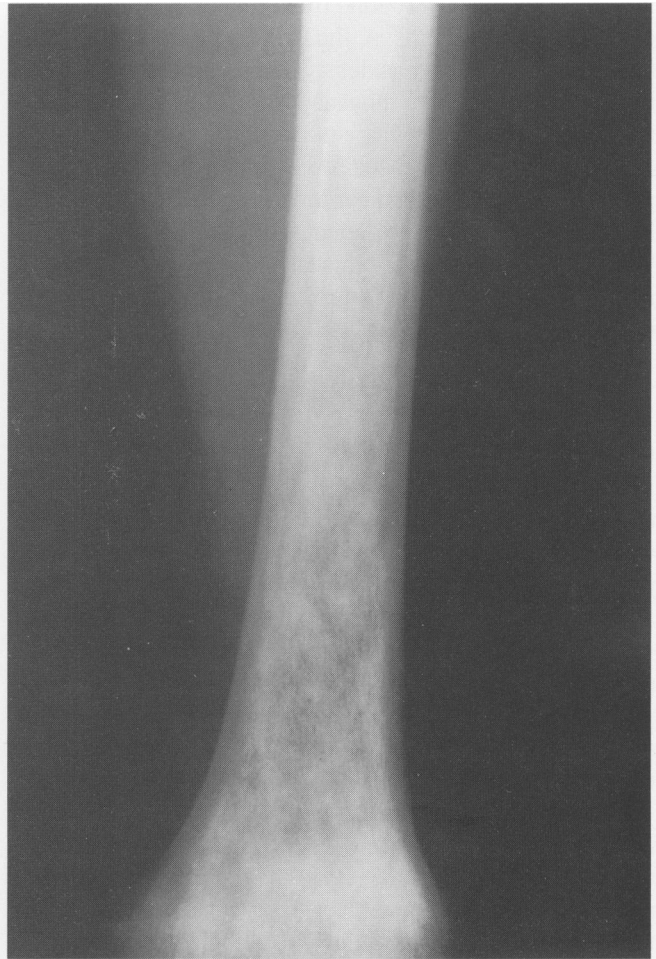


Figure 2C

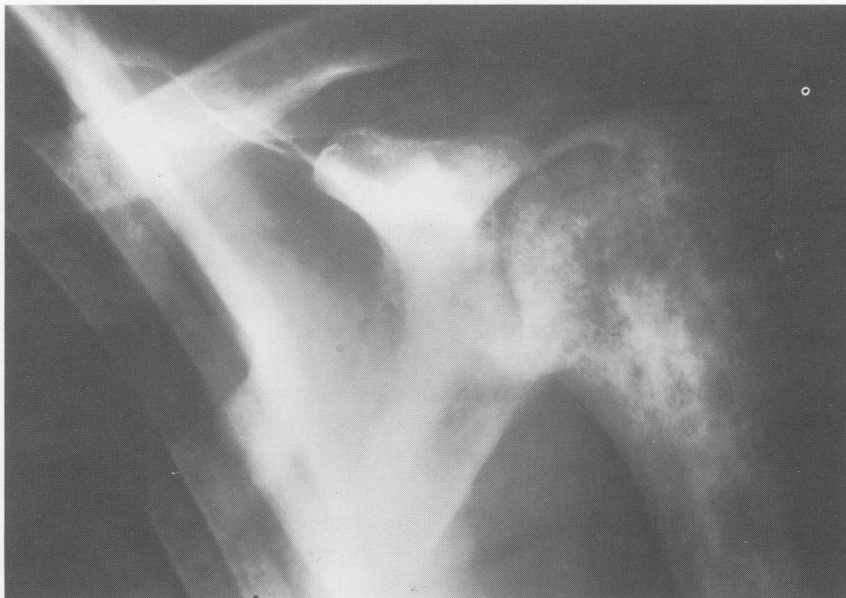


Figure 2B

Figure 2. (A) A lateral roentgenograph of the lumbar spine reveals diffuse osteoblastic and osteolytic changes. (B) Roentgenographs of the proximal humerus and scapula, and (C) distal femur exhibit a permeative pattern of patchy sclerosis and osteolysis with no evidence of cortical expansion or destruction.

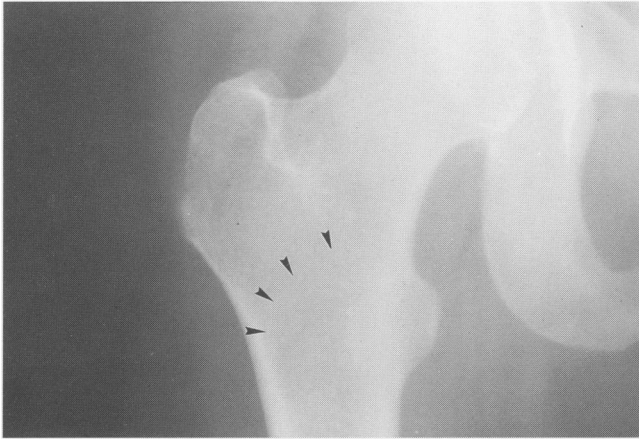


Figure 3A



Figure 3B

Figure 3. (A) Anteroposterior and (B) lateral radiographs of the proximal femur reveal a lytic lesion surrounded by a sclerotic margin, with no cortical disruption, periosteal reaction, or soft-tissue mass. Location of the lesion highlighted by arrows on both views.

which was interpreted as a spindle-cell-sarcoma. She was treated with chemotherapy for two years with no apparent clinical or roentgenographic progression of the disease. Subsequently, a repeat biopsy was interpreted as myelofibrosis with no evidence of malignancy. Chemotherapy was discontinued and the patient's back pain was treated symptomatically. She was presumptively diagnosed as having an atypical form of myelofibrosis without the usual hepatosplenomegaly, anemia, and thrombocytopenia.

During the subsequent five years, the patient required multiple admissions for back pain, nausea, vomiting, and crampy abdominal pain. In order to alleviate her symptoms of bone pain, she was treated with calcitonin with no improvement. Repeat bone scan and roentgenographs revealed no change from prior studies. The differential diagnosis at this time included Paget's disease and myelofibrosis with osteosclerosis even though the patient had normal alkaline phosphatase and urinary hydroxyproline levels.

The patient was readmitted a year later with complaints of continued back pain and an urticarial rash. The rash was diagnosed as neurodermatitis and treated with antidepressants. She was subsequently admitted to the psychiatry service for chronic anxiety, hives, depression, and back pain. Eight years after her initial presentation a repeat biopsy showed marked fibrotic replacement of the bone marrow with numerous eosinophils and histiocytes.

The patient's roentgenographs were placed in a teaching file of myeloproliferative disorders where they were reviewed by one of the authors (J.D.). On chart review, the suspicion of mastocytosis was raised based on the

patient's constellation of symptoms. The patient's original bone biopsy slides were recut and stained with toluidine blue, revealing classic mastocytosis with fibrous replacement of the marrow and early myeloid metaplasia.

Case 3:

A 35-year-old-woman was referred for evaluation of right hip pain and a lytic lesion in the proximal aspect of the right femur. The patient gave a history of the gradual onset of pain in the right inguinal area, which was exacerbated by weight bearing. She denied any history of asthma, gastrointestinal, vasomotor, or constitutional symptoms. She described the presence of an allergic rash over her neck and chest which was aggravated by exposure to sun, stress, and alcohol.

Prior to performing an incisional biopsy, routine screening laboratory tests were all unremarkable. Roentgenographs revealed a lytic lesion in the proximal femur, lateral to the lesser trochanter (Figures 3A and 3B). The lesion was surrounded by a sclerotic halo with no periosteal reaction, cortical disruption, or soft-tissue mass. A bone scan revealed an area of increased uptake that corre-



Figure 4. An anteroposterior roentgenograph of the lumbar spine and sacroiliac region of the pelvis reveals a diffuse osteoblastic pattern with focal lytic areas involving the lumbar vertebrae, sacrum, and posterior ilium bilaterally.

sponded to the lytic lesion. No other sites of abnormal uptake were noted. The lesion was further evaluated by computed tomography which confirmed the radiographic findings, showing the lesion to be lytic with sharply defined borders and no evidence of cortical destruction, periosteal reaction, or soft tissue mass extending from the lesion.

Tissue obtained from the incisional biopsy revealed a benign tumor with numerous histiocytes and eosinophils. The preliminary diagnosis was that of an eosinophilic granuloma, and the lesion was treated with curettage and bone grafting. Review of the permanent sections stained with hematoxylin and eosin showed that the cells thought to be histiocytes on frozen section were indeed mast cells. The specimen was then stained with toluidine blue and Giemsa stains which demonstrated the metachromatic purple-staining histamine granules within the mast cells, confirming the diagnosis of mastocytosis; existing in this case as a solitary mastocytoma. Following the tissue diagnosis, the patient's skin lesions were biopsied, revealing classic urticaria pigmentosa with mast-cell invasion in

the dermis. Postoperatively, the femoral lesion healed with complete incorporation of the bone graft and resolution of symptoms.

Case 4:

A 67-year-old man was admitted for elective peripheral vascular surgery. His past medical history was significant for hypertension, diabetes mellitus, peripheral vascular disease, and a 30-year history of an urticarial rash, aggravated by alcohol and stress. He admitted having symptoms of occasional flushing, without syncope.

Except for elevations in serum triglyceride and cholesterol levels, admission laboratory studies were within normal limits. His admission chest roentgenograph raised the suspicion of metastatic or metabolic disease based on a permeative granular pattern seen in the ribs and thoracic spine. Further roentgenographic investigation of the spine revealed mixed osteosclerotic and osteolytic lesions throughout the vertebral bodies and posterior elements (Figure 4). The differential diagnosis at the time included fibrous dysplasia, Paget's disease, hyperparathyroidism, myelofibrosis, or diffuse metastatic disease. A bone scan



Figure 5A

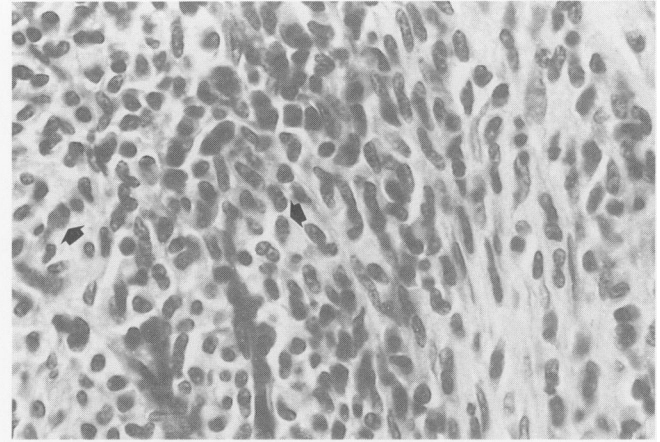


Figure 5B

revealed uneven, patchy uptake throughout the axial skeleton, ribs, and pelvis. The patient's elective surgery was postponed. He underwent bone marrow and iliac crest biopsy which demonstrated clumps of mast cells invading the bone marrow, with occasional eosinophils and fibroblasts. Subsequent biopsy of the patient's skin lesions revealed mast-cell invasion in the dermis, confirming the diagnosis of systemic mastocytosis.

DISCUSSION

Mastocytosis is characterized by mast-cell infiltration of skin and other reticuloendothelial systems. The cutaneous form of the disorder was discovered by Nettleship in 1869²¹ and later termed urticaria pigmentosa by Sangster et al. in 1878²⁹. Mastocytosis exists as variable clinical entities, from the more common cutaneous form seen in children that resolves spontaneously, to the systemic form with multiple organ involvement^{16,20,35}. The symptoms of mastocytosis, whether in the cutaneous or systemic form, are primarily attributable to the mast cell's release of histamine and other vasoactive substances²⁴. Recurrent flushing is a prominent feature of systemic mastocytosis and is occasionally associated with hypotension and syncope.

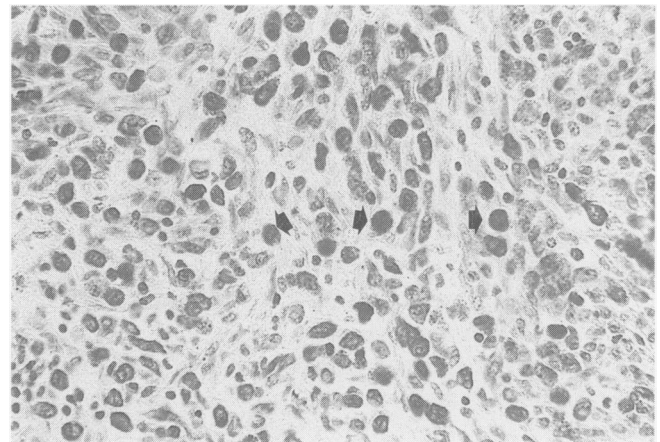


Figure 5C

Figure 5. (A) A photomicrograph of a bone marrow biopsy at low power shows mast cell proliferation, replacing marrow elements. Clumps of mast cells characteristically appear in peritrabecular and perivascular locations. (stain, Hematoxylin and eosin, original magnification = 100X.). (B) A high-power view reveals histiocytes and eosinophils replacing normal marrow elements, with occasional mast cells (arrows). (Stain, Hematoxylin and eosin, original magnification = 400X.). (C) After staining with toluidine blue, the mast cells are readily identifiable within the lesion (arrows). (original magnification = 400X).

Table 1
Mast Cell Mediators

Histamine	Platelet Activating Factor
Serotonin	Eosinophilic Chemotactic Factor
Leukotriene	Neutrophilic Chemotactic Factor
Heparin	Chondroitin 4 and 6-Sulfate
Chymase	Dermatan Sulfate
Prostaglandin D2	

The mast cell has been described as a unicellular endocrine gland since it is capable of elaborating many substances that can cause significant systemic symptoms (Table 1)¹². Mast cells are thought to originate from the monocyte lineage and can be found in virtually any tissue or organ system. They have been identified in the endosteum of bones of calcium-deficient rats by special staining with hematoxylin-eosin-azure II³⁷. The cell's prime mediator is histamine, which is stored in metachromatically staining secretory granules which are released by a host of stimulatory agents including sun, stress, alcohol, and narcotics.

Systemic mastocytosis may affect many organ systems, particularly the skin, skeleton, liver, spleen, gastrointes-

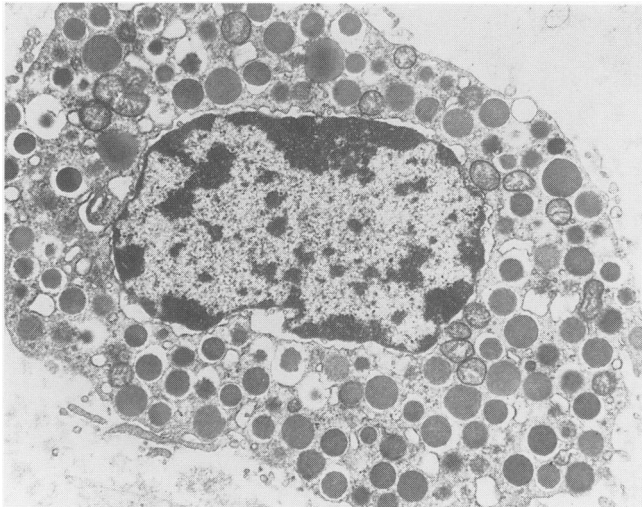


Figure 6. An electronmicrograph shows a typical mast cell with prominent secretory granules, (original magnification = 10,000X).

tinal tract, and lungs. The degree of organ involvement may be variable with the most frequent combination involving the skin, hematopoietic organs, and skeleton²⁷. The diagnosis of mastocytosis is typically based on the presence of the aforementioned clinical features and is confirmed by skin or bone marrow biopsy.

The histologic appearance of bone marrow in systemic mastocytosis characteristically reveals clumps of mast cells in peritrabecular and perivascular locations³³ (Figure 5A). The cellular infiltrates can be confused with eosinophilic granuloma, lymphoma, or myelofibrosis (Figure 5B), as identifying features of mast cells can be subtle. Mast cells contain numerous secretory granules which exhibit metachromatic properties, displaying a purple hue when stained with toluidine blue or Giemsa stains (Figure 5C). Without using these special staining techniques, the presence of mast cells may be overlooked or misdiagnosed as myelofibrosis. On electron microscopy, mast-cell granules are a prominent and readily identified feature (Figure 6). Mast cells are found throughout the marrow along with fibroblasts, eosinophils, and histiocytes, resembling histiocytosis X or eosinophilic granuloma. Some areas may be mistaken for myelofibrosis or agnogenic myeloid metaplasia^{4,36,39}. Reticulin staining of such a specimen would prove markedly positive for reticulin fibers, which may lead to an incorrect diagnosis of myelofibrosis^{17,36}. Biopsy material may be mistaken for malignant lymphoma although Reed-Sternberg cells that may be seen in Hodgkin's lymphoma are characteristically lacking. Histologic examination of the skin reveals marked mast-cell infiltration in the dermis and subcutaneous tissue.

Additional laboratory values that aid in establishing the diagnosis include elevated urinary histamine excretion, mild to moderate eosinophilia, anemia, and thrombocytopenia. Liver function studies and coagulation profiles are

normal and urine analysis for vanilylmandelic acid and catecholamines, to rule out pheochromocytoma, is negative.

Cutaneous lesions, most commonly in the form of urticaria pigmentosa, are the most overt manifestation of systemic mastocytosis, being present in greater than 90% of cases. These lesions typically flare with sun exposure, stress, and ingestion of alcohol, spicy foods, or narcotics. The presence of such lesions may lead the physician to suspect the diagnosis and search for other organ involvement. In many cases, the skin lesions are overlooked and very rarely may be absent, leading to a delay in diagnosis. Skin lesions were present in each of these cases, but were considered inconsequential, and hence overlooked.

Skeletal lesions occur in 70-75% of patients with systemic mastocytosis. This association was first described by Sagher et al in 1952 and subsequently has been documented by several authors^{1,2,3,5,6,14,19,22,23,26,28,31,33}. The pattern of bony involvement is typically that of mixed osteosclerosis and osteolysis, affecting the axial skeleton and the ends of long bones. The lesions may resemble diffuse metastatic disease², thus leading to an incorrect diagnosis and treatment as in Case 2. Other diseases that may share a similar roentgenographic appearance include Paget's disease, hyperparathyroidism, lymphoma, myelofibrosis, and agnogenic myeloid metaplasia. Rarely, osseous involvement may present as solitary or multiple lytic lesions surrounded by sclerotic halos. This type of lesion is usually seen in the vertebral bodies and near the ends of long bones. Case 3 demonstrates this rare form of osseous involvement in the proximal femur. Generalized osteoporosis has been reported in patients with systemic mastocytosis and is thought to be related to elevated levels of heparin, a known secretory product of mast cells^{13,27}. Despite elevated heparin levels, abnormal bleeding does not occur.

Skeletal lesions are frequently painful, possibly secondary to microscopic stress fractures. On occasion, the lesions may be asymptomatic as demonstrated in Case 4. Here, previously unrecognized systemic mastocytosis was diagnosed after investigation of skeletal lesions found incidentally on routine roentgenographs. Pathologic fractures are rare²³ and, as demonstrated in Case 1, heal uneventfully when treated by conventional means.

The lymphatic and hematopoietic systems are invariably involved in systemic mastocytosis. Splenic infiltration may result in mild splenomegaly with occasional anemia and thrombocytopenia, similar to but less severe than that seen in myelofibrosis. Abdominal and para-aortic nodes are invariably involved, as is bone marrow. Bone marrow is heavily involved with mast cell invasion in the majority of cases of systemic mastocytosis. Gastrointestinal involve-

ment may occur in patients with systemic mastocytosis. Some patients have symptoms of nausea, diarrhea, and crampy abdominal pain. Peptic ulcer disease is seen in 10% of patients with systemic mastocytosis¹⁸. This is thought to be due to increased gastric acid production stimulated by elevated levels of histamine. Mast-cell proliferation can be seen in the liver, with mild to moderate hepatomegaly. However, liver function studies usually remain within normal limits, and synthesis of clotting factors is rarely significantly compromised.

Pulmonary symptoms are infrequent, and range from mild rhinitis and bronchospasm to severe asthma. These symptoms are exacerbated by environmental allergens as well as the previously mentioned stimuli which cause flaring of the disease.

Determination of prognosis in mastocytosis is variable depending on the age of onset and the degree of systemic involvement. The most common form of the disease is present in childhood, involves only the skin, and resolves spontaneously by puberty. On rare occasion, the disease may persist into adulthood as the systemic form. Urticaria pigmentosa may present in young adulthood and is associated with a 15-30% risk of developing systemic disease^{10,27}. Marked enlargement of the liver and/or spleen is associated with a poor prognosis for survival with a fatal outcome in 50% of cases²⁷. Late adult onset of systemic mastocytosis can occur and is associated with the greatest risk of developing leukemia, lymphoma, or mast-cell sarcoma^{8,15,17}.

There is no known cure for systemic mastocytosis, hence therapy is directed towards symptomatic relief. This has been accomplished through the use of cromolyn sodium which stabilizes mast cell membranes^{7,11,32,38}, and the combination of the H1 and H2 antagonists, chlorpheniramine and cimetidine, which together act to block the effects of histamine by binding to histamine receptors¹¹. Medical therapy is crucial during episodes of acute exacerbation of symptoms, and may at times include intravenous epinephrine for refractory symptoms of hypotension and bronchospasm²⁵. Perioperative precautions must be taken to avoid administration of known mast-cell degranulators and to relieve emotional stress³⁰. The patient in Case 1 suffered an acute flare of her disease preoperatively which was successfully managed with cromolyn sodium, chlorpheniramine, cimetidine, and inhaled bronchodilators. These agents were used throughout the perioperative period and discontinued at the time of discharge.

Mastocytosis is a rare condition with symptoms that may be overlooked or considered inconsequential by physicians who are unfamiliar with the disease. As demonstrated by the cases in this report, the skeletal changes seen in mastocytosis may be the first recognized manifes-

tation of the disease, bringing the patient to the attention of an orthopedist. Quite frequently, the disease may be mistaken for other systemic or metastatic diseases. In treating patients with unusual roentgenographic findings, particularly in the presence of other manifestations of mastocytosis, one must be alerted to the possibility of such a systemic disease and ensure that the proper histologic techniques, such as Giemsa or toluidine blue staining, are performed to establish the correct diagnosis. A better awareness of this disease and its characteristic clinical features may aid in making the diagnosis and selecting appropriate treatment.

BIBLIOGRAPHY

1. Asboe-Hansen, G.: Urticaria pigmentosa with bone lesions. *Acta Dermat. Venereol.*, 33:471-475, 1953.
2. Barer, M.; Peterson L.F.A.; Dahlin, D.C.; Winkelman, R.K.; Stewart, J.: Mastocytosis with osseous lesions resembling metastatic malignant lesions in bone. *J. Bone and Joint Surg.*, 50-A: 142-152, 1968.
3. Bendel, W.L., Jr.; Race, G.J.: Urticaria pigmentosa with bone involvement. *J. Bone Joint Surg.*, 45-A:1043-1056, 1963.
4. Brunning, R.D.; McKenna, R.W.; Rosai, J.; Parkin, J.L.; Risdall, R.: Systemic mastocytosis-extracutaneous manifestations. *Am. J. Surg. Pathol.*, 7:425-438, 1983.
5. Clyman, S.G. and Rein, C.R.: Urticaria pigmentosa associated with bone lesions. *J. Invest. Dermat.* 18: 425-432, 1952.
6. Crisp, A.J.; Chapman, C.M.; Kirkham, S.E.; Schiller, A.L.; Krane, S.M.: Articular mastocytosis in rheumatoid arthritis. *Arth. and Rheum.* 27:845-851, 1984.
7. Dolovich, J.; Punthakee, N.D.; MacMillan, A.B.; Osbaldeston, G.J.: Systemic mastocytosis: Control of lifelong diarrhea by injected disodium cromoglycate. *J. Can. Med Assoc.*, 111(7):684-685, 1974.
8. Efrati, P.: Mast cell leukemia-malignant mastocytosis with leukemia-like manifestations. *Blood*, 12:869-888, 1957.
9. Ellis, J.M.: Urticaria pigmentosa. *Arch. Pathol.* 48: 426-435, 1949.
10. Fishman, R.S., Fleming, C.R.; Li, C-Y: Systemic mastocytosis with review of gastrointestinal manifestations. *Mayo Clin. Proc.*, 54:51-54, 1970.
11. Frieri, M.; Alling, D.W.; Metcalfe, D.D.: Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis. *Am J. Med*, 78:9-14, 1985.
12. Fulton, G.P.; Maynard, F.L.; Riley, J.F.; West, G.B.: Humoral aspects of tissue mast cells. *Physiol. Rev.*, 37:221-232, 1957.

13. Griffith, G.C.; Nichols, G.; Asher, J.D.; Flanagan, B.: Heparin osteoporosis. *JAMA*, 193: 85-88, 1965.
14. Harvard, C.W.: Urticaria pigmentosa with visceral and skeletal lesions, *Quarterly J. Med.*, 28: 459-470, 1959.
15. Klatt, E.C.; Lukes, R.J.; Meyer, P. R.: Benign and malignant mast cell proliferations. Diagnosis and separation using a pH dependent toluidine stain in tissue section. *Cancer*, 51:1119-1124, 1983.
16. Korenblatt, P.E.; Wedner, H.J.; Whyte, M.P.; Frankel, S.; Avioli, L.V.: Systemic mastocytosis. *Arch. Intern. Med.*, 144:2249-2253, 1984.
17. Lennert, K. and Parwaresch, M.R.: Mast cells and mast cell neoplasia: A review. *Histopathology*, 3:349-365, 1979.
18. Lewis, R.A.: Mastocytosis. *J. All. Clin. Immunol.*, 74:755-765, 1984.
19. Lucaya, J.; Perez-Candela, V.; Aso, C.; Calvo, J.: Mastocytosis with skeletal and gastrointestinal involvement in infancy. *Radiology*, 131:363-366, 1979.
20. Monheit, G.D.; Murad, T.; Conrad, M.: Systemic mastocytosis and the mastocytosis syndrome. *J. Cut. Pathol.*, 6:42-52, 1979.
21. Nettleship, E.: Rare forms of urticaria: chronic urticaria, leaving brown stains: Nearly two years duration. In Reports of Medical and Surgical Practice in the Hospitals of Great Britain. *British Med. J.*, 2:323-324, 1869.
22. Poppel, M.H.; Gruber, W.F.; Silber, R: The roentgen manifestations of urticaria pigmentosa (mastocytosis). *Am. J. Radiol.*, 82:239-249, 1959.
23. Rafii, M.; Firooznia, H.; Golimbu, C.; Balthazar, E.: Pathologic fracture in systemic mastocytosis-radiographic spectrum and review of the literature. *Clin. Orthop.*, 180:260-267, 1983.
24. Riley, J.F. and West, G.B.: The presence of histamine in tissue mast cells. *J. Physiol.*, 120:528-537, 1953.
25. Roberts, L.J., II.; Turk, J.W.; Oates, J.A.: Shock syndrome associated with mastocytosis: pharmacologic reversal of the acute episode and therapeutic prevention of recurrent attacks. *Adv. Shock Res.*, 8:145-152, 1982.
26. Sagher, F.; Cohen, C.; Schorr, S.: Concomitant bone changes in urticaria pigmentosa. *J. Invest. Derm.*, 18:425-432, 1952.
27. Sagher, F., Even-Paz, Z.: Mastocytosis and the Mast Cell. Year Book Medical Publishers, Chicago, 1967.
28. Sagher, F.; Liban, E.; Ungar, H.; Schorr, S.: Urticaria pigmentosa with bone involvement. *J. Invest. Derm.*, 27:355-368, 1956.
29. Sangster, A.: An anomalous mottled rash, accompanied by pruritis, factitious urticaria, and pigmentation 'urticaria pigmentosa?'. *Trans. Clin. Soc. London*, 11:161-163, 1878.
30. Scott, H.W., Jr.; Parris, W.C.; Sandige, P.C.; Oates, J.A.; Roberts, L. J. II: Hazards in operative management of patients with systemic mastocytosis. *Ann. Surg.*, 197:507-514, 1983.
31. Sostre, M. and Handler, H.: Bony lesions in systemic mastocytosis: radiographic evaluation. *Arch. Dermatol.*, 113:1245-1247, 1977.
32. Soter, N.H.; Austen, K.F.; Wasserman, S.I.: Oral disodium cromoglycate in the treatment of systemic mastocytosis. *N. Eng. J. Med.*, 301:465-469, 1979.
33. Stark, E; Van Buskin, F.W.; Daly, J.F.: Radiologic and pathologic bone changes associated with urticaria pigmentosa. *Arch. Pathol. and Lab. Med.*, 62:143-148, 1956.
34. Sy, W.M.; Bonventre, M.V.; Camera, A.: Bone scan in mastocytosis: case report. *J. Nucl. Med*, 17:699-701, 1976.
35. Szweda, J.A.; Abraham, J.P.; Fine, G.; Nixon, R.K.; Rupe, C.E.: Systemic mast cell disease. A review and report of three cases. *Am. J. Med.*, 32:227-239, 1962.
36. Udoj, W.E. and Razavi, S.A.: Mast cells and myelofibrosis. *Am. J. Pathol.*, 63:203-209, 1978.
37. Urist, M.R. and McLean, F.C.: Accumulation of mast cells in endosteum of bones of calcium-deficient rats. *Arch. Pathol.*, 63:239, 1957.
38. Volkel, N. and Kruse, H-P.: Disodium cromoglycate (Intal) for the symptomatic treatment of generalized mastocytosis. *Int. Med.*, 4:325-330, 1977.
39. Webb, T.A.; Li, C.Y.; Yam, L.T.: Systemic mast cell disease: A clinical and hematopathologic study of 26 cases. *Cancer*, 40:927-938, 1982.