Skeletal mastocytosis

S M Andrew, A J Freemont

Abstract

***Aims*—To characterise the condition of skeletal mastocytosis, an uncommon cause of apparently "idiopathic" osteoporosis.**

***Methods*—Transiliac crest biopsy specimens submitted over a period of five years were examined for nodular accumulation of mast cells. The cases were reviewed histologically and clinical follow up was obtained from hospital notes.**

***Results*—Six cases of mastocytosis occurring in bone biopsy specimens submitted to our department were identified. Four patients presented initially with vertebral collapse and the other two were known to have extraskeletal mast cell disease at presentation. On clinical review of the four patients with vertebral collapse, one was found to have urticaria pigmentosa. This patient died from his mastocytosis, whereas the three patients without evidence of extraskeletal disease remain alive and well. Histological examination showed that patients with the poorer clinical outcome had severe peritrabecular fibrosis as well as mast cell nodules; those with prolonged disease-free survival had nodules without peritrabecular fibrosis.**

***Conclusion*—There is a form of mastocytosis which presents clinically as "idiopathic" osteoporosis. Clinically it does not have the same prognostic implications as skeletal disease in "malignant mastocytosis", running a much more benign course.**

(*J Clin Pathol* 1993;46:1033–1035)

Systemic mastocytosis has been defined as an abnormal increase in mast cells in tissues other than skin, and the term "malignant mastocytosis" is used when a patient has overwhelming disease such that mast cells are present in the blood.[1] Organs particularly affected by systemic mastocytosis are liver, gastrointestinal tract, and bone.[2 3] In the bone lytic lesions are typical and back pain secondary to vertebral compression fracture may be the major presenting symptom of systemic mastocytosis in some cases, and the sole presenting symptom in others.[4–7]

In this study we reviewed the occurrence of nodular mast cell accumulation in diagnostic transiliac bone biopsy specimens submitted to our department and related this finding to the clinical presentation and progress of the patients. The prognosis of systemic mastocytosis is variable and indicators of those patients likely to do badly would be a useful adjunct to clinical management.

Department of Pathological Sciences, Stopford Building, Manchester University, Manchester M13 9PT
S M Andrew
A J Freemont

Correspondence to:
Dr S M Andrew

Accepted for publication
1 June 1993

Methods

Biopsy specimens coded as having excess mast cells were obtained from the files of the Department of Osteoarticular Pathology, Manchester University. The tissue sections were reviewed, as were the patients' notes, for clinical history and follow up information. The follow up times recorded were the time from initial onset of symptoms specific to the presenting condition and that of most recent clinic visit or death.

Transiliac crest bone biopsy specimens taken with a 6 mm trephine were fixed in alcohol and then divided longitudinally before processing. One half was embedded in LR White Resin (The London Resin Co., PO Box 34, Basingstoke, Hampshire, RG21 2NW) for undecalcified sectioning and the other half was decalcified before embedding in paraffin wax. Undecalcified sections were cut at 5 μm on an LKB 2260 macrotome (Brommer) and stained with toluidine blue (pH 4·2), Jenner giemsa, and Von Kossa stains, according to standard techniques. Decalcified sections were cut at 5 μm and then stained with haematoxylin and eosin. Further details of staining and quantitative analysis of sections in our laboratory have been reported before.[8]

The abnormal accumulation of large numbers of mast cells was recognised by the presence of characteristic intertrabecular nodules of mast cells which were atypical in that many were spindle-shaped, had prominent nucleoli, and fewer cytoplasmic granules than are usual in dermal mast cells.

Results

Six biopsy specimens contained excess mast cells in the intertrabecular spaces (table 1). Four of the specimens were submitted fixed in alcohol for undecalcified sectioning and quantitative analysis was performed (table 2). Trephine biopsy specimens fixed in formol-saline were submitted for confirmation of marrow disease in cases 5 and 6. It was possible to get a subjective impression of osteopenia with increased resorptive surfaces from the decalcified section, but quantitation was not possible. It was, however, possible to count the number of osteoclasts in the section.

Two postmenopausal women and one man in whom osteoporosis was the only manifestation of disease at presentation (cases 1, 2, and 3) remained alive and well after 72, 37, and 31 months, respectively, following their initial presentation. The three cases with extraskeletal disease were all men. They died of their disease five, nine, and 26 months after their investigation for skeletal disease.

Histological features are summarised in

Table 1 Details of patients found to have nodular accumulations of mast cells in their bone marrow

No/age/sex	Presenting condition	Skin disease	Outcome
1/53/F	Vertebral collapse	None	Osteoporosis treated with calcium and oestrogen after 6 years
2/56/M	Vertebral collapse	None	Osteoporosis treated with Etidronate after 31 months
3/72/F	Vertebral collapse	None	Osteoporosis treated with Etidronate after 37 months
4/52/M	Vertebral collapse	Urticaria pigmentosa for 10 years	Bone pain improved with APD but died from malignant mastocytosis 26 months after presentation
5/60/M	Splenomegaly and hepatomegaly	None	Died from malignant mastocytosis 5 months after presentation
6/50/M	Night sweats and portal hypertension	Urticaria pigmentosa for 6 years	Died from malignant mastocytosis 9 months after presentation

APD = 3-aminohydroxypropylidin-1-1-bisphosphamate.

Table 2 Histomorphometric and histological data

Case No	TBV	ES	OC cells/mm²	NF	DF
1	14·9 (20 (4·1))	17 (4·0 (1·5))	2·14 (0·05 (0·01))	Yes	No
2	11·8 (20·6 (5·2))	7·2 (3·6 (1·0))	0·3 (0·05 (0·01))	Yes	No
3	14·3 (19·6 (5·2))	4·1 (3·8 (1·3))	0·02 (0·05 (0·01)) on APD	Yes	No
4	10·6 (14·6 (4·3))	11·7 (4·8 (2·0))	0·69 (0·05 (0·01))	Yes	Yes
5	ND	ND	0·76 (0·05 (0·01))	Yes	Yes
6	ND	ND	0·94 (0·05 (0·01))	Yes	Yes

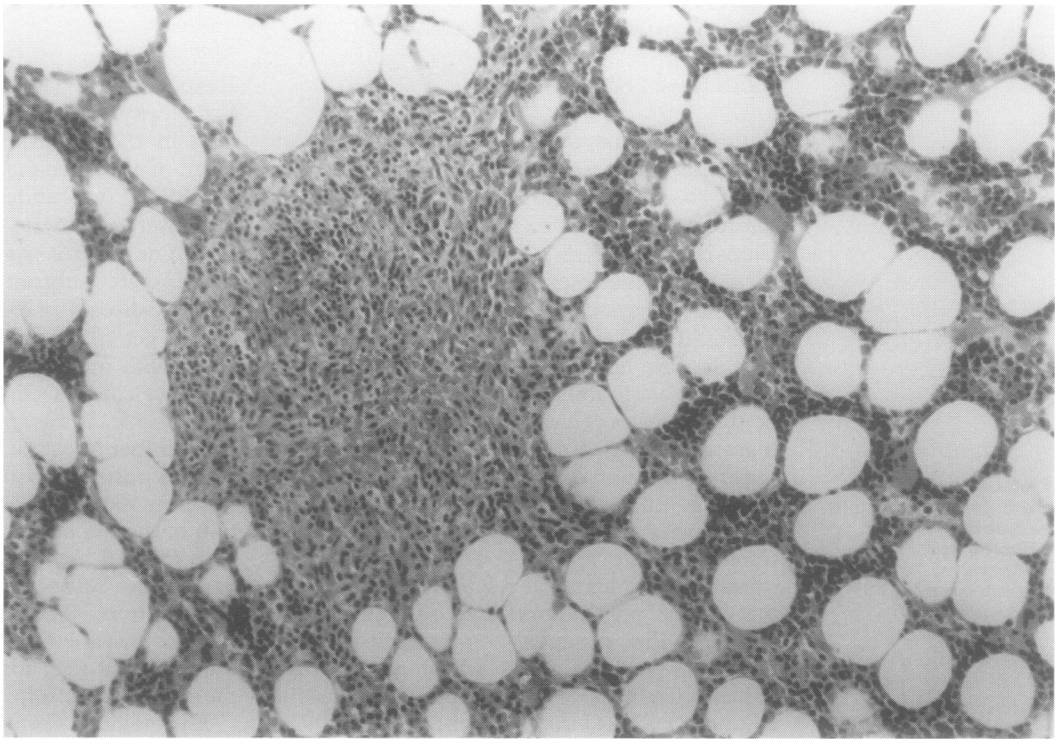
TBV = trabecular bone volume as a percentage of total bone volume
ES = eroded surfaces as a percentage of total bone surfaces
(figures in parentheses are normal values of means (2) standard deviations of age/sex matched individuals)
OC = osteoclast numbers per mm² of section.
NF = intertrabecular fibrous nodules
DF = diffuse fibrosis
ND = not done

table 2. All patients had decreased cortical bone with enlargement of Haversian canals. All had increased resorptive surfaces and five had increased numbers of osteoclasts. The only patient without an increase in osteoclast numbers was case 4 who was receiving APD (3-aminohydroxypropylidin-1-1-bisphosphonate) which decreases osteoclast numbers. All biopsy specimens showed nodular intertrabecular fibrous nodules containing mast cells away from the trabeculae (fig). Cases 4 to 6 also had dense peritrabecular fibrosis reminiscent of that seen in severe osteitis fibrosa.

Discussion

All six patients reported here had mastocytosis affecting the skeleton as demonstrated by trephine bone biopsy. All the patients had intertrabecular fibrous nodules containing mast cells: eosinophils and lymphocytes were few so that these lesions did not resemble the eosinophilic fibrohistiocytic lesions described by Rywlin *et al*,[9] which are thought to be due to drug sensitivity, and are not particularly associated with systemic mastocytosis or osteoporosis.

There were three patients with nodular lesions and osteoporosis who have as yet developed no other signs of systemic mastocytosis despite follow up periods of six, three, and two and a half years. The association of osteoporosis and mastocytosis is well described.[10 11] The occurrence of nodular mast cell infiltrates associated with osteoporosis, but in the absence of any other clinical evidence of spread beyond the marrow, in these patients seems so far to have had a benign course in that all the patients are completely disease free after treatment of their osteoporosis. These patients presented with vertebral osteoporosis. The diagnostic biopsy specimens were taken from iliac crests, indicating that they had diffuse marrow disease.



Intertrabecular nodular accumulation of spindle-shaped mast cells without severe diffuse fibrosis: this appearance was typical of skeletal mastocytosis without evidence of extra-skeletal disease.

The development of osteoporosis many years before the onset of urticaria pigmentosa has already been reported in a young man,[6] two middle aged men, and five middle aged women.[4 5] The mast cell population of the marrow is thought to be diffusely increased in postmenopausal osteoporosis,[12] but trends in mast cell numbers in older men have not, to our knowledge, been described, but nodular mast cell infiltrates do not seem to be common in the general population.

The three patients who had clinical evidence of systemic mastocytosis (disease outwith the bone marrow) had much denser peritrabecular fibrosis than the other patients. Peritrabecular fibrosis may occur as a direct result of the action of mast cell mediators on peritrabecular fibroblasts, as in other fibrosing diseases,[13] or it may occur as a result of the increased osteoclastic activity. Mast cells secrete various substances which may promote osteolysis. Heparin,[14] prostaglandins,[15] and cytokines are all released when mast cells degranulate.[16] Among the cytokines produced by mast cells is interleukin-6 which is thought to be important in promoting bone resorption and fibrosis.[17]

The pronounced peritrabecular fibrosis observed in the marrow of the patients who succumbed rapidly to their disease might have been due to the different functional characteristics of their mast cells compared with the mast cell infiltrates occurring in the patients whose disease followed a benign course.

Mast cell disease in the skeleton may be analagous to urticaria pigmentosa in the skin—that is, the disease is confined in most cases to the one organ but may occasionally be associated with systemic disease. In view of the graver prognosis of patients with systemic mastocytosis we suggest that patients who have nodular mast cell infiltrates in their marrow without evidence of mast cell disease outside the skeleton should be given the diagnostic label of skeletal mastocytosis in recognition of the benign course of this form of the disease. The presence of dense peritrabecular fibrosis in addition to nodules in bone biopsy specimens may be a useful diagnostic aid in the prediction of progression to malignant mastocytosis. Osteoporosis due to marrow mastocytosis is caused by increased osteoclasis. It can be treated by anti-osteoclastic agents, notable among which are the bisphosphonates.

We thank Professor PH Adams of Manchester Royal Infirmary and Professor DC Anderson of Hope Hospital, Salford, for allowing their clinical information to be used.

1 Greaves MW. The Mastocytoses. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH, Burton JL, eds. *Textbook of Dermatology*. 4th edn. Oxford: Blackwell Scientific Publications, 1986:1724.
2 Korenblat PE, Wedner J, Whyte MP, Frankel S, Avioli LV. Systemic mastocytosis. *Arch Intern Med* 1984; **144**:2249–53.
3 Brunning RD, Parkin JL, McKenna RW, Risdall R, Rosai J. Systemic mastocytosis: extracutaneous manifestations. *Am J Surg Pathol* 1983;7:425–38.
4 Fallon MD, Whyte MP, Teitelbaum SL. Systemic mastocytosis associated with generalised osteopenia. *Hum Pathol* 1981;**12**:813–20.
5 Chines A, Pacifici R, Avioli LV, Teitelbaum SL, Korenblat PE. Systemic mastocytosis presenting as osteoporosis: a clinical and histomorphometric study. *J Clin Endocrinol Metab* 1991;**72**:140–4.
6 Harvey JA, Anderson HC, Borek D, Morris D, Lukert BP. Osteoporosis associated with mastocytosis confined to bone: report of two cases. *Bone* 1989;**10**:237–41.
7 Colver GB, Dawber RPR, Smith R, Ryan TJ, Wojnarowska F. Osteoporosis and mastocytosis with late appearance of urticaria pigmentosa. *J R Soc Med* 1985;**78**:866–7.
8 Hutchinson AJ, Freemont AJ, Lumb GA, Gokal R. Renal osteodystrophy in CAPD. *Adv Peritoneal Dial* 1991; 7:237–9.
9 Sagher F, Cohen C, Schorr S. Concomitant bone changes in urticaria pigmentosa. *J Invest Dermatol* 1952;**18**: 425–32.
10 Stark E, Van Buskirk FW, Daly JF. Radiologic and pathologic bone changes associated with urticaria pigmentosa. *Arch Pathol Lab Med* 1956;**62**:143–8.
11 Rywlin AM, Hoffman EP, Ortega RS. Eosinophilic fibrohistiocytic lesion of bone marrow: a distinctive new morphologic finding, probably related to drug hypersensitivity. *Blood* 1972;**40**:464–72.
12 Fallon MD, Whyte MP, Craig RB, Teitelbaum SL. Mast-cell proliferation in postmenopausal osteoporosis. *Calcif Tissue Int* 1983;**35**:29–31.
13 Hawkins RA, Claman HN, Clark RAF, Steigerwald JC. Increased dermal mast cell populations in progressive systemic sclerosis: a link in chronic fibrosis. *Ann Int Med* 1985;**102**:182–8.
14 Avioli LV. Heparin-induced osteopenia: an appraisal. *Adv Exp Med Biol* 1975;**52**:375–91.
15 Raisz LG, Martin TJ. Prostaglandin in bone and mineral metabolism. In: Peck WA, ed. *Bone and mineral research annual*. 2nd edn. Amsterdam: Elsevier Science Publishers, 1983:286–310.
16 Stevens RL, Austen KF. Recent advances in the cellular and molecular biology of mast cells. *Immunol Today* 1989;**10**:381–6.
17 Linkhart TA, Linkhart SG, MacCharles DC, Long DL, Strong DD. Interleukin-6 messenger RNA expression and interleukin-6 protein secretion in cells isolated from normal human bone: regulation by interleukin-1. *J Bone Min Res* 1991;6:1285–94.