Skeletal mastocytosis

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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”8, running a much more benign course.

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 clinical 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 (Brommer) and 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 formosaline 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

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

APD = 3-amino hydroxypropylidin-1-1-bisphosphamate.

Table 2  Histomorphometric and histological data

<table>
<thead>
<tr>
<th>Case No</th>
<th>TBV</th>
<th>ES</th>
<th>OC cells/mm²</th>
<th>NF</th>
<th>DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.9 (20.45)</td>
<td>17 (9.0 (1.5))</td>
<td>2-14 (0.05 (0.01))</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>11.6 (26.0 (5.2))</td>
<td>7.2 (3.6 (1.0))</td>
<td>0.3 (0.05 (0.01))</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>14.8 (19.6 (5.2))</td>
<td>4.1 (3.8 (1.5))</td>
<td>0.02 (0.05 (0.01))</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>10.6 (14.6 (4.3))</td>
<td>11.7 (4.8 (2.0))</td>
<td>0.69 (0.05 (0.01))</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>0.76 (0.05 (0.01))</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>ND</td>
<td>ND</td>
<td>0.94 (0.05 (0.01))</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TBV = trabecular bone volume as a percentage of total bone volume
ES = eroded surfaces as a percentage of total bone surfaces
OC = osteoclast numbers per mm² of section.
NF = nodular intertrabecular fibrous nodules
DF = diffuse fibrosis
ND = not done

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 Rywin 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.

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-amino hydroxypropylidin-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.

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

The development of osteoporosis many years before the onset of urticaria pigmentosa has already been reported in a young man,2 two middle aged men, and five middle aged women.45 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 out-with 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 grave 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 osteoclasti. 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.