A case of mastocytosis involving bone

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A case of mastocytosis of the bone associated with urticaria pigmentosa was first suspected of being a generalized metastatic malignancy, for the radiographic manifestations were not connected by us with the patient's skin disease. The histologic diagnosis of systemic mastocytosis was also missed primarily, because mast cells are not visualized in the conventional hematoxylin and eosin staining of the histologic sections. Special stainings revealed mastocytosis. Irregular remodeling of the bone was also seen, which was consistent with the radiographically irregular bone structure.

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We describe a patient with urticaria pigmentosa where the skeletal findings suggesting skeletal metastases were not immediately considered to be related to the patient's chronic skin manifestations.

Case report

A 59-year-old woman underwent a mammographic examination in October 1989. A benign-appearing density was found. Simultaneously, she had back pain after a minor twisting incident, and a radiographic examination of the thoracolumbar spine in January 1990 showed irregular sclerosis. The possibility of breast carcinoma with generalized metastases was entertained. A mamma biopsy, taken in February 1990, showed, however, fibroadenomatosis; and other explanations for the manifestations in the spine and pelvis had to be sought. Her ESR (Westergren) was 12 mm/hr, Hb 13.3 g/100 mL, leukocytes 7.0 × 10^9/L, platelets 354 × 10^9/L, s-(serum) Ca 2.31 mmol/L, s-urea 5.4 mmol/L, s-creatinine 59 µmol/L, s-ASAT 17 U/L, s-ALAT 17 U/L, s-LD 190 U/L, s-GT 36 U/L, s-alkaline phosphatase 601 U/L (elevated). Repeated studies of s-Ca showed normal values with continuously increased levels of s-alkaline phosphatase. The study of isoenzymes showed increased bone alkaline phosphatase, with a normal liver alkaline phosphatase level. Her s-PTH was 1.9 pikomol/L (reference values 1.1–6.8) and s-osteocalcin 6.7 µg/L (1.8–6.6). A generalized malignancy was still suspected; and in April, two bone biopsies were taken from the trochanteric area. The findings were initially interpreted as necrotic bone, with fibrosis in the bone marrow (Figure 1). This evaluation was made without information about the patient's skin disease.

For 20 years, the patient had had irregular, faintly pigmented, macular and papular skin lesions up to 1 cm in diameter that were spread over her entire body. These skin manifestations could swell and itch. In 1989, urticaria pigmentosa was diagnosed, and she was told that there was little to do other than to use antihistamines to counteract the itching. The same year, she had had spells of unexplained dizziness and vertigo with accompanying facial flushing.

A pelvic radiograph showed diffuse sclerosis with patchy, less dense areas (Figure 2). The medullary canals of the femora were of normal width. In May of 1989, attention was drawn to the connection between skeletal manifestations in urticaria pigmentosa, which have been reported to occur in approximately 10 percent of the cases (Murray and Jacobsen 1977).

With the new information on urticaria pigmentosa, the bone biopsies were reexamined. Because hematoxylin and eosin fail to visualize mast cells, other staining methods were now included. In the review, the bone marrow was seen with fibrosis, unevenly populated with cells originally read as hematopoietic elements. In pinocyanol-erythrocyanate-stained sections, groups of mast cells were identified on the basis of the typical metachromasia of their granules (Figure 3). The granules also had a high affinity for basic dyes, e.g., toluidine blue. Large infiltrates of mast cells were not seen, only small, patchy, usually perivascular clusters of granulated cells in addition to peritrabecular fibrous areas with cytoplasm-rich, spindle-shaped, granulated mast cells mimicking histiocytic cells in ordinary staining. Neither mitoses nor cellular atypia were seen. The infiltrates had a patchy focal distribu-

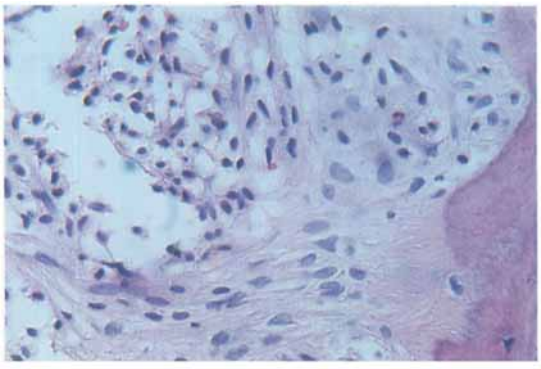

Figure 1. Bone marrow with fibrosis, mostly peritrabecular. Note the ill-defined border between bone and marrow fibrosis. H&E, objective 40 ×.

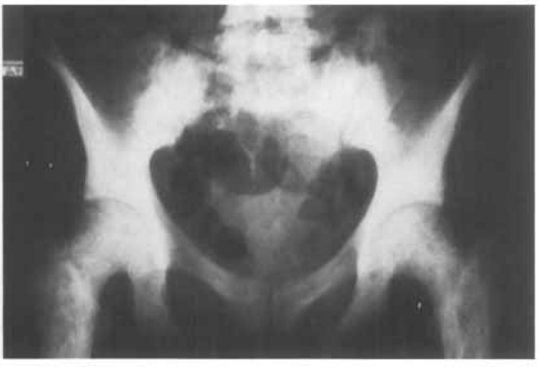

Figure 2. AP radiograph of the pelvis showing areas of osteosclerosis with stippled areas of less dense bone.

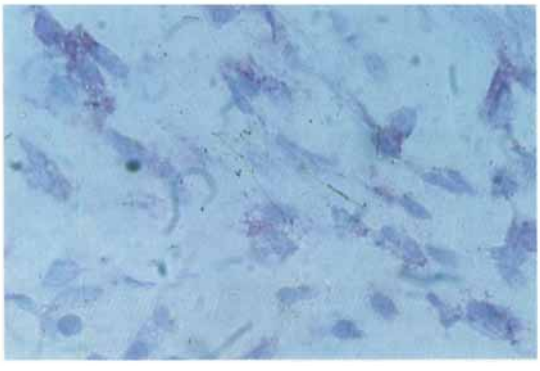

Figure 3. Spindle-shaped, cytoplasm-rich mast cells with red granules. Pinocyanol erythrocyanate stain, objective 100 ×.

Figure 4. Bone trabeculae in polarized light: partly old, parallel fibered, and partly newly formed with a woven appearance. Objective 25 ×.

tion. The bone trabeculae were partly sclerotic. In areas with marked peritrabecular fibrosis, the border towards the bone was often ill-defined (Figure 1). In polarized light, a highly pleomorphic picture was seen, with bone trabeculae that were partly sclerotic with parallel fibers and trabeculae that were partly newly formed and woven (Figure 4). However, no extensive osteoblastic activity was observed.

Although the radiographs taken in November 1990 did not show pathologic fractures of the spine, the patient had continuous back pain, making it impossible for her to continue her standing work, which required much lifting. However, her back pain may be due to microfractures, which would be consistent with the microscopically confirmed areas of necrotic bone.

Discussion

Mast cells are distributed diffusely throughout the connective tissue, but normally their numbers are small. Reactive mastocytosis is associated with parasitic disease and soft tissue tumors. Mast cells can also be seen in connection with carcinomas. Mast cell degranulation, resulting in the release of heparin-type glycosaminoglycan and histamine, is primed by IgE and complement activation (Lennert and Parwaresch 1979). The systemic effects, such as bronchospasm, diarrhea, flushing, and headache, are believed to be due to the release of vasoactive amines from the mast cells.

Mast cell neoplasms are usually benign. Diffuse cutaneous mastocytosis, usually urticaria pigmentosa, is the most common type. Originally described by Nettleship (1869), the disease most often makes its debut in childhood or adolescence without clinical evidence of systemic disease (Fraser and Richter 1928, Travis et al. 1985). The most common type of urticaria pigmentosa is a generalized skin disease with pigmented macules and papules. The areas of predilection are the trunk, upper arms, and thighs. When the lesions are rubbed, a urticaria-like reddish elevation may be produced. The association between urticaria pigmen-

tosa and systemic mastocytosis has been well recognized since Ellis (1949) reported the first autopsy case. In the systemic mast cell disease, infiltrates can be found, besides in the skin, in bone marrow, in the spleen, in lymph nodes, and in the liver.

The most prominent systemic involvement is the accumulation of mast cells in the bone marrow. This may be focal or diffuse, and may result in fibrosis of the marrow. Sclerotic thickening of the bone trabeculae occurs, but also marked osteopenia may be seen (Lennert and Parwaresch 1979), resulting in the variable radiologic changes. Focal marrow involvement has been reported to occur mainly in perivascular and paratrabecular locations (Brunning et al. 1983). It is not clear why fibrosis develops in areas with mast cell infiltrations; further, the mechanism behind the bone changes is not known.

Cases of benign systemic mastocytosis must be distinguished cytologically from the very rare malignant forms. Large irregular nuclei and mitotic activity are signs of malignancy (Lennert and Parwaresch 1979).

In our case, the bone changes were stippled, whereas the bone manifestations in the case of Hills et al. (1981) were predominantly sclerotic. They suggested that the osteosclerosis is a response to the presence of abnormal cells—the same phenomenon as is encountered in metastases of carcinoma, in myelofibrosis, and in Gaucher's disease. The rarefaction of bone may, on the other hand, be attributed to the fibrotic tissue in the bone marrow. The varying bone density is a sign of imbalance between the osteoblastic and osteoclastic activity. In our case, irregular areas of woven bone were seen. These areas were not, however, associated with appreciable osteoblastic activity, which was probably due to a slow turnover of bone.

It is well known that the histologic diagnosis of mastocytosis can be missed when using only conventional staining methods in the histologic study (Berlin 1955). We recommend that clinically diffuse cases, and especially those with marrow fibrosis, be studied using mast cell stains.

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