

Successful treatment of osteolytic epithelioid hemangioendothelioma with pamidronate

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ABSTRACT

We describe the case of a 70-year-old man with unicentric grade 1 epithelioid hemangioendothelioma (EH) of the bone that favourably responded to intravenous pamidronate as a single agent. After 6 years of follow-up, the patient was in complete remission. We suggest that use of bisphosphonates should be considered in the treatment of osteolytic EH.

Introduction

Epithelioid hemangioendothelioma (EH) of bone is a rare tumor of vascular origin, the treatment of which usually requires surgery associated with adjuvant radiotherapy and/or chemotherapy. We report here on a patient who presented with a unicentric upper limb EH that was successfully treated with pamidronate as a single agent.

Case report

A 70-year old male was admitted for a severe pain of the right wrist following a trauma. He had a past history of pulmonary tuberculosis at 18, and a myocardial infarction 2 years prior the present hospitalization. At admission, the patient had a painful and inflammatory swelling of the right radio-cubital joint and proximal inter-phalangeal of the fourth finger.

Standard radiography revealed a distal cubitus osteolysis with blurred and irregular outlines (Fig.1a), associated with lysis and destruction of the cortex of the first phalanx of the fourth finger (Fig. 1b). Magnetic resonance imagery and computerized scanography confirmed the bone destruction process. Complete skeletal radiography ruled out any other localization. Both chest radiography and total body bone scintigraphy were normal. Main laboratory findings were: erythrocyte sedimentation rate 15 mm at first hour, C reactive protein 18 mg/l ($N < 5$), and white blood cell count $10 \times 10^9/L$ with $6 \times 10^9/L$ neutrophils. A surgical biopsy of the lytic cubital and phalanx lesion was performed which revealed an erosion of cortical bone associated with synovial infiltration by a hemorrhagic vascular tissue.

Bacteriological investigations includ-

ing a search for *Mycobacterium tuberculosis* were negative. Histopathological examination revealed a proliferation of large epithelioid cells with no mitotic activity, and mild cytologic atypia. Nuclei showed slight variations in size and shape. Immunohistochemical staining disclosed a diffuse and intense staining with antibodies to vimentin, consistent with the diagnosis of grade I EH. In an attempt to control severe post-operative pain, the patient received pamidronate 90 mg intravenously. Soon after the first infusion, the pain completely and durably resolved. At 3 months, treatment resulted in resolution of bone lysis accompanied by bone reconstruction (Fig. 2). Pamidronate was thus pursued twice a month for 6 additional months. There was no clinical nor radiological relapse after 6 years of follow-up.

Discussion

Bone epithelioid hemangioendothelioma (HE) is a rare tumor of endothelial origin that occurs preferentially in males at any age. It is a low-grade malignancy with a clinical course between that of a hemangioma and a conventional angiosarcoma. Bone EH can be multicentric, and may affect any portion of the skeleton, though it tends to involve more frequently the lower limbs. Less frequently, the tumor affects the upper limbs. Multicentric lesions within the same bone are seen in 25% of cases (1,2). In some patients parenchymal organs are involved (2). Histology is required to confirm the diagnosis, and to grade the lesion from 1 to 3, with 3 being the most anaplastic. Treatment consists of surgical resection associated in some cases with adjuvant radiotherapy and/or chemotherapy (2). Long-term survival is 89% for patients with unicentric EH and 50% for those with multifocal disease (2). Visceral involvement seems to be the most important criterion in predicting the prognosis of bone EH (2).

Bisphosphonates have been largely used to control severe hypercalcemia, and to reduce the incidence of bone events in metastatic breast cancer (3) and in multiple myeloma (4). Pamidronate is a second generation aminobis-



Fig. 1. Standard radiographic analysis of first phalanx of fourth finger (a) and right wrist (b) revealed osteolysis with cortical destruction.



Fig. 2. Standard radiograph following pamidronate treatment. X-rays of the wrist (a) and phalanx (b) after 3 months of treatment with i.v. pamidronate revealed bone mineralisation as well as resolution of the cortical destruction.

phosphonate that can inhibit osteoclast activity, control bone pain and improve the quality of life in cancer patients (5). We have reported a patient with unicentric grade I EH that favorably responded to intravenous pamidronate as a single agent. This treatment resulted in complete resolution of bone pain and allowed bone reconstruction, presumably by inhibiting osteoclastic activity. After 6 years follow-up the patient was in complete remission, although the

total disappearance of the lesions was not assessed on biopsies and thus we cannot exclude the possibility that some tumoral cells were still present. However, such a hypothesis is very unlikely given the long follow-up in the absence of any treatment. Spontaneous EH regression is unlikely, since it has never been reported so far. One possibility is that pamidronate exerted a direct anti-tumor effect in our patient. Interestingly, in some animal models bis-

phosphonates were shown to inhibit tumor cell adhesion and to reduce invasion through the extracellular matrix (6). In addition, pamidronate has been recently shown to induce apoptosis of neoplastic plasma cells and acts directly on monocytes/macrophages in multicentric reticulohistiocytosis cells (7). This effect has been attributed to an inhibition of the mevalonate pathways and to a loss of prenylated small GTPases (8).

We suggest that use of bisphosphonates should be considered in the treatment of osteolytic EH. Further studies will be required to evaluate the efficacy of this treatment in patients with multifocal disease or visceral involvement.

References

1. BOUTIN RD, SPAETH HJ, MANGALIK A, SELL JJ: Epithelioid hemangioendothelioma of bone. *Skeletal Radiol* 1996; 25: 391-5.
2. KLEER CG, UNNI KK, MCLEOD RA: Epithelioid hemangioendothelioma of bone. *Am J Surg Pathol* 1996; 20: 1301-11.
3. LIPTON A: Aredia: the once-monthly infusion for the treatment of bone metastases. *Curr Opin Oncol* 1998; 10 (Suppl. 1): S1-S5.
4. KANIS JA, MCCLOSKEY EV: Bisphosphonates in multiple myeloma. *Cancer* 2000; 88 (Suppl. 12): 3022-32.
5. ARZOO K, SADEGHI S, PULLARKAT V: Pamidronate for bone pain from osteolytic lesions in Langerhans'-cell histiocytosis. *N Engl J Med* 2001; 345: 225.
6. GREEN JR: Antitumor effects of biphosphonates. *Cancer* 2003; 97 (3 Suppl.): 840-7.
7. GOTO H, INABA M, KOBAYASHI K *et al.*: Successful treatment of multicentric reticulohistiocytosis with alendronate. *Arthritis Rheum* 2003; 48: 3538-41.
8. DENOYELLE C, HONG L, VANNIER JP, SORIAIAJ, SORIA C: New insights into the actions of biphosphonate zoledronic acid in breast cancer cells by dual RhoA-dependent and -independent effects. *Br J Cancer* 2003; 88: 1631-40.