A clinical case of familial Paget's disease of bone complicated by early osteogenic sarcoma

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Case presentation

A 65 years-old Italian woman came to our attention at the Medicina-Malattie Metaboliche dell'Osso Department. She came as an outpatient and the reason of the visit was persistent bone pain.
Through family history of the patient, it was possible to ascertain a familial form of Paget's disease of bone (PDB), because the father, two uncles and 4 cousins (3 males and 2 females) were affected by the disease, suggesting that the disease segregates in an autosomal dominant pattern (Figure 1). She was diagnosed with Paget's disease of bone when she was 62 years-old because of the occasional finding of an elevated alkaline phosphatase and subsequent bone scintigraphy. Bone scintigraphy showed signs of disease at right pelvis, right proximal femur and IV and VIII left ribs.
After the diagnosis of PDB she was followed-up at our Department with clinical evaluation and dosage of alkaline phosphatase every 4 months, and she was treated with clodronate infusion whenever bone pain was reported or alkaline phosphatase level was more than twice the laboratory upper limit.

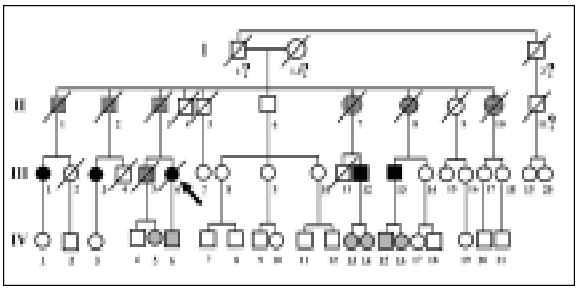

Figure 1- Genealogic tree of the patient discussed. Patient case corresponds to subject III-6. With kind permission of Alberto Falchetti, M.D.

During the period from the diagnosis of Paget's disease when she was 62 years old until the age of 65, a total of 3 clodronate infusion (each consisting in five days courses with clodronate 300 mg daily) were employed, without significant side effects and with a good response in term of clinical and biochemical parameters.
Three years after the diagnosis of PDB, bone pain at right pelvis markedly increased.
On physical examination she had normal motility of her hips, and tenderness of the right inguinal region was observed.
Alkaline phosphatase was 2259 U/L (upper normal limit 145 U/L), with serum calcium levels into the normal range.
In the hypothesis of a reactivation of pagetic symptoms, a new clodronate infusion (consisting in five infusions with clodronate 300 mg daily) was employed.
After one month the patient described persistent and increased bone pain at the right hip.
A new dosage of bone turnover markers was done along with blood count and basic chemistry: alkaline phosphatase level was 2160 U/L, markers of inflammation were elevated and mild anemia was found.
An x-ray evaluation of the right hip was performed, showing an ill-defined destructive radiolucent lesion in the neck of the femur, with multifocal cortical disruption.
Therefore, the patient was admitted to the Hospital and a bone biopsy was performed at the right hip on the site of involvement.
The histologic examination of the biopsy showed "osteoid matrix in which there is a proliferation of spindle cells with atypia, with irregular nuclei. Cells with the same characteristics diffusely infiltrate the muscle present in the specimen". It was diagnostic of an osteogenic sarcoma with muscle fibers involvement.
A chest X-ray was also performed: it showed bilateral pulmonary nodules, subsequently confirmed as secondary dissemination by CT.
To further stage the osteosarcoma, an MRI of the hip was performed, confirming the involvement of the right femoral neck.
According with the Oncologist consultant, the lesion was considered not treatable with surgery because of the metastatic lesions, and it was decided to start a treatment with ifosfamide (3 g/m^2 in 48 hours), adriamicine (60 mg/m^2 for 24 hours) and cisplatinum (100 mg/m^2 for 48 hours) with a palliative intent. Pamidronate 90 mg e.v. was also administered in order to reduce local pain.
In the subsequent days, a partial reduction of local pain was observed.
Unfortunately, patient died 3 months after the diagnosis of osteosarcoma.

Discussion

Familial Paget's disease accounts for about 20% of PDB cases, and it is often found to segregate in an autosomal dominant pattern. Mutations of p62/sequestosome 1 gene (*SQSTM1/p62*) account for familial forms of PDB (1).
It is well known that the presentation of familial PDB is most frequently poliostotic than in sporadic cases, and that levels of alkaline phosphatase are frequently higher.

From PDB diagnosis, patient was treated with antireabsorptive therapy. There are four general indications for treatment of Paget's disease: symptoms due to metabolically active Paget's disease such as bone pain or neurological syndromes; patient planning to undergo elective surgery on a pagetic site; the management of hypercalcemia, a rare occurrence following prolonged immobilization; finally, some investigators believe that treatment is indicated as an attempt to decrease local progression and reduce the risk of future complications.
Nowadays pharmacological treatment is based upon the use of bisphosphonates.
Bisphosphonates approved by the US Food and Drug Administration for the treatment of Paget's disease include pamidronate, which is given intravenously, and etidronate, tiludronate, alendronate and risedronate, all of which are taken orally. Clodronate, though not approved for treatment of Paget's disease in many countries, has been successfully used. Daily infusions of clodronate 300 mg for 5 days have showed the ability to significantly reduce disease activity (2, 3).
Our patient was repeatedly treated with clodronate infusions with a satisfying clinical and biochemical response during the past years.
Investigators have recognized that secondary resistance to individual bisphosphonates can occur. Therefore, it may be necessary for a patient to use more than one bisphosphonate in long-term management of the disease (4).
In this patient, after the diagnosis of osteosarcoma was made, we used pamidronate to obtain both an antiresorptive effect and a reduction of pain.
It is important to search and diagnose all familial cases of Paget's disease of bone in order to treat them and to avoid the occurrence of future severe complications in these subjects.
In fact, a number of complications may result from Paget's disease. Of these, the most devastating is a transformation of the bone that becomes cancerous. Osteosarcoma or other types of sarcoma occurs in less than 1 percent of patients with Paget's disease, with a significantly higher rate than in non-PDB individuals. Malignant complication is mostly described over 70 years of age, after a large number of years from PDB diagnosis, and it is often rapidly progressive with early metastasis and death.
Osteosarcoma is the most common type of Paget's sarcoma. Skeletal distribution of these tumors mirrors that of Paget's disease. A patient presents with the sudden onset of a mass and/or severe pain at the site of previously-asymptomatic Paget's disease. Frequently, this presents as a pathologic fracture. Pain is the most reliable indicator of malignant transformation in Paget's disease.
In the case of our patient, the symptom of presentation was bone pain, at first misdiagnosed as a possible reactivation of the pagetic lesion, but subsequently suspected as a malignant evolution.
On radiograph, there is development of a radiolucent, destructive process within a well-established area of pagetic bone. The early, destructive phase of Paget's can be confusing. Multiple, small radiolucencies are less suggestive than a single, large area. The lucencies must be clearly destructive and progressive to reliably indicate malignant transformation.
On isotope scan, it is often difficult to distinguish between the increased uptake in the lesion and that seen in Paget's disease. This study is not helpful unless there is a dramatic change.
Preoperative evaluation of the extent of local disease was performed with MRI (5).
Diagnosis is based and confirmed on biopsy (Figure 2).
Microscopic features are strikingly varied within a single lesion. Areas of high-grade, classic osteosarcoma can usually be found but are often overshadowed by other areas of undifferentiated spindle cells, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, and even giant cell tumor. For this reason, some prefer to call the lesion "Paget's sarcoma" rather than osteosarcoma. The lesional cells often infiltrate the adjacent, Pagetic bone, and plugs of tumor are frequently seen within the large, vascular channels peculiar to Pagetic bone.

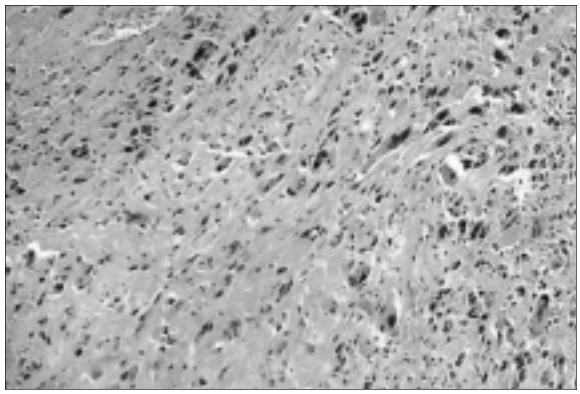

Figure 2 - Histologic features of bone biopsy: osteoid matrix in which there is a proliferation of spindle cells with atypia, with irregular nuclei.

After the diagnosis of sarcoma has been made, a thorough search for evidence of intrathoracic disease should be performed because pulmonary nodules are the most common site of metastatic disease for both soft tissue and bone sarcomas. If chest radiographic findings are normal, chest computed tomography should be performed. The discovery of metastatic disease clearly influences decisions about the need to subject the patient to aggressive local therapy to achieve long-term local control.
Surgical treatment, when possible, is indicated. Radical margins, usually amputation, are required for reliable, local control. The prognosis, even with local control, is dismal.
In our patient the site of the lesion would have required a destructive operation, furthermore, the presence of pulmonary metastasis contraindicated surgical excision.
Chemotherapy is currently used, but when dealing with osteosarcoma in Paget's disease, response to chemotherapy is generally much less positive than with classic osteosarcoma. It seldom provides meaningful alteration in the rapid, downhill course and is often devastating to the remaining lifestyle in this age group. Two randomized clinical studies have documented significant benefit using adjuvant chemotherapy in patients presenting with osteogenic sarcoma (6,7).
In conclusion, at the moment prognosis of bone sarcoma in PDB remains generally poor due to late and difficult diagnosis, high grade of malignancy of the tumors, difficulties at their surgical removal and the old age of patients.
The particularity of the case presented above was the early occurrence of bone sarcoma in a case of polyostotic Paget's disease with a family history segregating in an autosomal dominant pattern.

References

1. Falchetti A, Di Stefano M, Marini F et al. Two novel mutations at exon 8 of Sequestosome 1 gene (SQSTM1) in an Italian serie of patients affected by Paget's disease of bone (PDB). JBMR. 2004;19: 1013-1017.
2. Plosker GL, Goa KL. Clodronate. A review of its pharmacological

properties and therapeutic efficacy in resorptive bone disease. Drugs. 1994;47:945-982.
3. Yates AJP, Percival RC, Gray RES et al. Intravenous clodronate in the treatment and retreatment of Paget's disease of bone. Lancet. 1985;1:1474-1477.
4. Gutteridge DH, Ward LC, Stewart GO et al. Paget's disease: acquired resistance to one aminobisphosphonate with retained response to another. JBMR. 1999;14(suppl 2):79-84.
5. Manaster B, Ensign M. Imaging of musculoskeletal tumors. Semin Oncol. 1991;18:140-149.
6. Eilber F, Guiliano A, Eckardt J et al. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol. 1987; 5:21-26.
7. Link M, Goorin A, Miser A, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med. 1986;314:1600-1606.