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Case Report

High Grade Chondrosarcoma of the Pelvis with Intense Sclerosis and Delayed Development: Can Biphosphonates be Responsible?

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Abstract

High grade chondrosarcoma (CS) is a surgical disease despite its aggressive behavior of recurring locally and spreading to the lungs; conventional chemo- and radiotherapy are ineffective. Pelvis is frequently involved: calcified mass invading the pelvis and bone lytic area with amorphous snow flake calcification are typical. To obtain adequate margins, surgery is highly demanding with severe residual disability. Some preliminary *in vitro* studies showed that Nitrogen-containing Bi Phosphonates (N-BPs) may play a role in the treatment of CS; *in vivo* only sporadic cases are reported. We report on a 83-year-old man patient affected by high grade CS of the left pelvis, characterized by radiographic abundant preminent unusual sclerotic bone, and the typical large calcified mass spreading into the pelvis. The tumour developed at least 10 years before, when a typical sclerotic and lytic lesion at the left pelvis, hypercaptant at whole body bone scintigraphy, was documented and misdiagnosed. During these last 10 years the patient was treated with N-BPs weekly for fragility vertebral fractures and primary hyperparathyroidism. We hypothesize that N-BPs inhibited the bone resorption, induced bone sclerosing and controlled pain for many years. This case suggests that N-BPs may play a role in controlling the development of CS and pain, confirming the *in vitro* results.

Further research is needed, but, especially when surgery is highly demanding with disabling results such as in primary CS of the pelvis in old patient, N-BPs therapy could be considered as a palliative therapy able to delay symptoms, allowing a good quality of life.

ABBREVIATIONS

CS: Chondrosarcoma; N-BPs: Nitrogen-containing BiPhosphonates; BPs: Biphosphonates; CT: Computer Tomography; MRI: Magnetic Resonance Images; US: Ultrasound; CEUS: Contrast-Enhanced Ultrasound; LIV and LV: Fourth and Fifth Lumbar Vertebra; MGUS: Monoclonal Gammapathy of Un determinated Significance; pHPT: primary Hyperparathyroidism; IL6: Interleukine 6; TNFalfa: Tumour Necrosis Factor alfa

INTRODUCTION

Chondrosarcoma (CS) is the second most frequent malignant bone tumour in adults. The intramedullary or central CS is the most frequent type and most commonly involves the long bones or pelvis in up to 65% of cases [1]. It is characterized by the production of malignant cartilaginous tissues with lobular type architecture; hyaline cartilage nodules have a high water content and peripheral enchondral ossification. Imaging is typical [2-4]: at X-rays CS appear translucent, at Computed Tomography (CT) hypodense, at Magnetic Resonance Imaging (MRI) hypointense at T1-weighted and hyperintense at T2-weighted and fat suppressed sequences. The lobular endosteal scalloping and the distinctive ring-and-arc calcification with progressive cortical destruction and extension in contiguous soft tissue are typical. The cortex responds leading to cortical remodelling and thickening, less frequently to periosteal reaction, but not to a diffuse reactive bone sclerosis. Although high grade CS is considered to be at high risk for metastases, usually CS is treated only by *en bloc* surgical resection with wide margins because it does not respond to conventional chemotherapy or to conventional radiotherapy

[1,5], whereas proton beam radiotherapy could be considered a referent therapy for un respectable sarcomas [6,7].

Surgical adequate margins are difficult to be obtained when CS develops in the pelvic girdle because often the CS has a large size and connections with articular, nervous, vascular and visceral structures; severe disability is often the final result [8,9]. Nitrogen-containing BiPhosphonates (N-BPs) are currently approved for the treatment of bone metastases independently of the primary tumor type: they are able to change the bone and tumor microenvironment, delaying (or reducing) the ability of malignancy to emerge [10-13]. Some preliminary studies *in vitro* and *in vivo* suggest that N-BPs might be able to inhibit growth of primary bone tumours [14-18]. As far as concern CS, it was demonstrated that BPs inhibit *in vitro* CS cell invasion and preclinical experiments carried out in animal models confirmed these results [19-23]. In human patients, only one case was reported [24]: a 63-year-old man, suffering for bone metastatic chondrosarcoma, had good pain control with N-BPs.

We report on an 83-year-old male patient with high grade CS of the left pelvis diagnosed after three months of moderate pain at left hip. Imaging is characterized by abundant preminent unusual sclerotic bone with small well delimited lytic areas (not typical of high grade CS) and the typical large calcified mass spreading into the pelvis.

At history, the patient referred recurrent left sciatic pain ten years before, when he started treatment with N-BPs weekly for fragility vertebral fractures and primary hyperparathyroidism. Contemporary, ten years before, the progressive pelvic bone radiographic lesions, typical of CS, were documented and misdiagnosed.

We hypothesize that N-BPs influenced the development *in vivo* of the CS inhibiting the bone resorption, inducing bone sclerosis and controlling pain for ten years, allowing a high quality of life until the last three months.

CASE PRESENTATION

In June 2012 an 83-year-old Caucasian male, with persisting pain from three months at the left side of the groin and thigh, was sent for diagnosis and staging to our Regional Referral Centre for Bone and Soft Tissue Sarcomas. X-Rays (Figure 1a) and CT scan (Figure 1b, 1c) showed an extensive lesion in the left pubic ramus, acetabulum and iliac bone (area 1, 2 and 3 according to Musculoskeletal Tumors Society): abundant sclerotic bone with few small translucent areas, partial cortical destruction and a large soft tissue mass with arc-and-ring calcifications arising from the pubic ramus protruding into the pelvis. MRI (Figure 1d, 1e, 1f, 1g) demonstrated the typical lobular lesion extending into contiguous soft tissue. At general staging, absence of metastatic lesions. After gray scale ultrasound (US) and color power Doppler, contrast-enhanced ultrasound (CEUS) study of the intra pelvic mass showed numerous vessels with an important, rapid and inhomogeneous enhancement and avascular areas, confirming the hypothesis of malignant tumour [25]. The US guided core needle biopsy was focused on the more inhomogeneous vascularised area at CEUS, as a potential source of a representative pathological tissue (Figure 1h) [26]. The histological diagnosis was of high grade chondrosarcoma (GIII), in accordance with clinical symptoms and imaging. The patient refused any surgical treatment and a palliative therapy started.

At history, in 1990, when the patient was 61 years- old, he referred recurrent chronic aspecific low back pain irradiating to the left lower limb; the X-ray of the pelvis demonstrated two small spot calcifications in the left pubic bone, not considered (Figure 2). Twelve years after, in July 2002, for an acute low back pain and left sciatic pain, X-ray of the lumbar spine and of the pelvis were performed: a fragility fracture of LIV and LV and an irregular sclerotic and lytic lesion in the left pubis and acetabulum, with endostal scalloping and a lobular pattern of translucency were documented (Figure 3). Whereas this pelvic bone lesion, ypercaptant at whole body bone scintigraphy, was not considered, diagnosis of primary hyperparathyroidism (pHPT) and lumbar fragility fractures was advanced. Therapy with alendronate 10mg/die (replaced in 2007 with risedronate 75 mg/ a week), calcium and vitamin D3 was started (alfacalcidol, replaced in 2004 until 2007 with colecalciferol 20 mg, equivalent to 800 IU/die and calcium phosphate 3100 mg, equivalent to 1200mg/ die). Periodical clinical and blood controls were performed in the following years. In 2003, epidural corticosteroids injection solved an acute left sciatic pain, which was related with a lumbar discal protrusion in a narrow canal documented at MRI. In 2003 the X-ray of the pelvis showed a progression of the active-aggressive bone lesion: in comparison with the X-ray of one year before, the endosteal scalloping at pubic ramus was more evident and the lesion appeared more sclerotic in the acetabulum, but once more the lesion was not considered (Figure 4). In 2003 also diagnosis of: acute myocardic infarction, monoclonal gammapathy of indeterminate significance (MGUS), one episode of deep venous thrombosis at left lower limb, hyperuricemia.

In the following years, in absence of any symptoms, no further imaging was performed. In March 2012 a mild-moderate pain at the left hip occurred and was treated with paracetamol and antinflammatory therapy. Three months later, for worsening of the left hip pain, imaging of the pelvis was performed and the diagnosis of malignancy was advanced, as reported at the beginning of this text. At the time of diagnosis the patient was in good clinical conditions and was in treatment with acetylsalicylic acid and allopurinol.

DISCUSSION

Usually, high grade CS in the pelvis is extra compartmental: X-ray and CT scan show largely calcified extraosseous masses protruding from underlying areas of cortical and spongious bone destruction. The bone cortex appears destroyed from within; reactive bone is minimal to absent with vaguely defined edges, according to the aggressiveness of the lesion [1-3]. MRI is typical with hypo intensity at T1 sequences and hyper intensity at T2 weighted and fat suppressed MR sequences [4].

In this reported case, whereas the large extra osseous mass protruded into the pelvis was typical of high grade CS; pelvic bone radiological characteristics were quite different from the usual: sclerotic bone was the prominent aspect with numerous dense irregular sclerotic trabeculae instead of cartilage lobules, particularly at the acetabular roof. The edge between the soft tissue portion of the tumour and the bone was well marked by

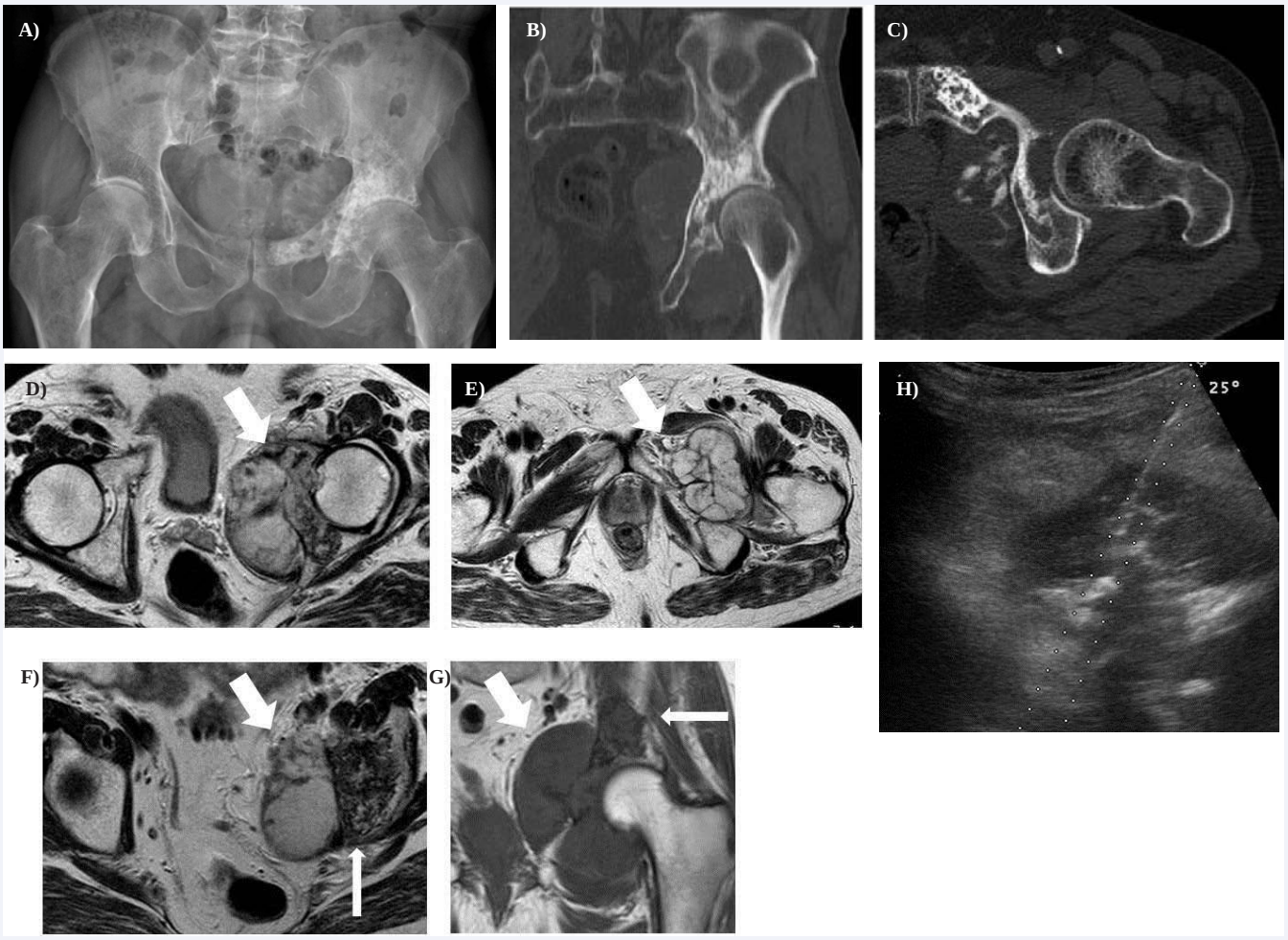

Figure 1a: Imaging of the 83-year-old man in 2012, when diagnosis of high grade chondrosarcoma of the left pelvis was made. The patient suffered of persisting pain at the left hip from three months (1a: X-Ray, 1b-1c: CT; 1d-1e-1f-1g: MRI; 1h: US guided core needle biopsy; X-ray antero-posterior view of the pelvis: sclerosis is preeminent with small translucent areas in pubic ramus and whole acetabulum. The cortex is destroyed. A soft tissue mass is protruding into the pelvis and obturator areas with typical arc-and-ring calcifications. All left pelvic zones (zone 1,2,3 according to Musculoskeletal Society) are severely involved.

1b and 1c: CT coronal (1b) and axial (1c) views: the bone sclerosis is preeminent, particularly at the pubic ramus and at the acetabular roof; the large pelvic soft tissue mass shows typical arc-and-ring calcifications.

1d, 1e, 1f, 1g: At axial T2 weighted sequence (figure 1d-1e-1f) and at coronal T1 weighted sequence (figure 1g) in the extra skeletal component *(large white arrows)* of the chondrosarcoma the typical lobulated pattern with chondral matrix rich in water and arc-and-ring calcifications are evident. Conversely in the ileum *(narrow white arrows)* unusual reactive sclerosis of the bone is pre eminent and markedly hypointense in both sequences.

1h: Core needle ultrasound-guided biopsy was focused in the vascularized area of the intrapelvic mass, depicted by contrast-enhanced ultrasound (CEUS).

sclerotic bone and only mottled cortical destruction was present, always well delimited. Furthermore, the 83-year-old patient had a good quality of life until three months before the diagnosis, in particular without pain, while an active-aggressive pelvic bone lesion was evident (and misdiagnosed) at least from ten years before. During the last ten years, the patient was continuously treated with N-BPs for fragility lumbar vertebral fractures and pHPT, and from 2003 until 2007 with vitamin D3 and calcium. We hypothesized that N-BPS played a role in controlling the CS development and pain.

In fact, malignant bone tumour development is related to the induction of bone resorption by osteoclast activation. Bone resorption contributes to tumour growth into bone by the release of cytokines (IL6, TNFalfa) and other complex microenvironment changes. N-BPs has antiosteoclast functions and indirect anti-tumour effects: they interfere with bone microenvironment and target endothelial and immune cells (tumour-associated macrophages, gamma9 delta 2 T cells) and osteoclasts [10-18]. *In vitro* and in animal models N-BPs induce chondrosarcoma cell death [19-23]; *in vivo* only one case report on metastatic CS treated with N-BP was reported [24].

In our reported case, we cannot demonstrate when the pelvic CS started, but while the radiological diagnosis of the two small spot calcification in the pubic ramous in 1990 (Figure 2)

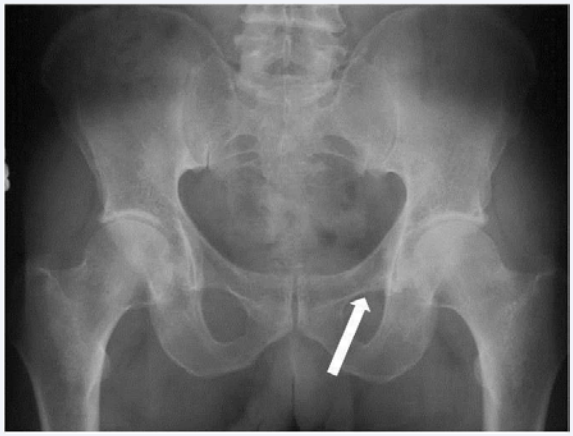

Figure 2 X-ray antero-posterior view in 1990. Two punctated calcifications were evident in the left pubic ramus; no osteolysis neither endosteal scalloping was evident. The X-ray was performed because the patient suffered of recurrent left sciatic pain.

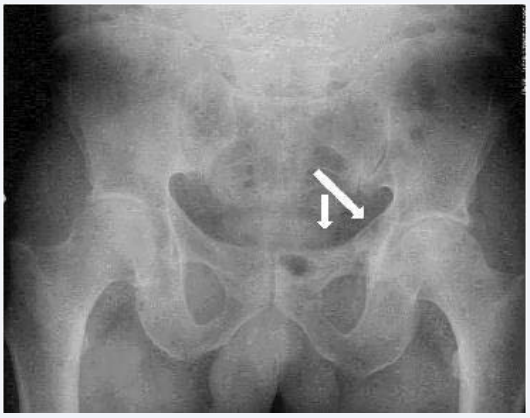

Figure 3 X-ray antero-posterior view in 2002. Osteolysis with endosteal scalloping in the left pubic ramus, and cortical bulging and sclerosis of acetabulum were evident. The bone lesion was not considered, the patient started a therapy with bisphosphonates for fragility lumbar vertebral fractures and primary hyperparathyroidism.

could be of an undetermined non active lesion, the pelvic X-ray in 2002 (Figure 3) and in 2003 (Figure 4) were quite suggestive of an active-aggressive low grade bone lesion, confirmed by the clinical and radiological development ten years after (Figure 1). It is possible that the uninterrupted therapy with N-BPs for the last ten years was responsible for pain control, bone remodeling and, possibly, inhibition or slowing down of CS growth. It is possible that also the supplementation of calcium and vitamin D positively influenced the bone turnover in terms of density, but the doses were lower than that recommended and the supplementation was administered for only four years (2003 – 2007) [27,28].

Our hypothesis has the following limits. First of all, CS of the pelvis can remain asymptomatic for long periods, and this is why the development of large tumoral masses are allowed [1,2]; furthermore, it is possible that the bone lesion at diagnosis was a dedifferentiated CS, characterized sometimes by more sclerotic areas than usually, but the sequential imaging is quite suggestive and US-guided core needle biopsy after CEUS study is quite sensitive and specific [26]. Unfortunately we cannot know when the CS Probably of low grade in 2002-2003, evolved to high grade CS, and therefore we can only hypothesize that N-BPs was able to control the development of a CS, without specifying the histological grade. Last consideration: we cannot demonstrate histological the preeminent bone sclerosing (evident at imaging) because the core needle biopsy was focused in the inhomogeneous hyper vascularized area of the pelvic soft tissue mass, avoiding any ossified tissue in order to obtain representative diagnostic samples.

As far as concern the topographical characteristics and the standard surgical therapy, we can hypothesize that at the beginning (in 2002-2003) the lesion was a low grade CS, limited at the left pubic area and acetabulum (zone 3 and 2 according to the Musculoskeletal Society). At that time, the surgical *en bloc* excision with adequate margins followed by reconstruction could be possible with acceptable disability and low risk for recurrence and metastases. Ten years later, in 2012, the high grade tumour is involving the three areas of the pelvic bone and a large mass is invading the pelvis; surgery is highly demanding (interilioabdominal disarticulation or limb salvage with resection

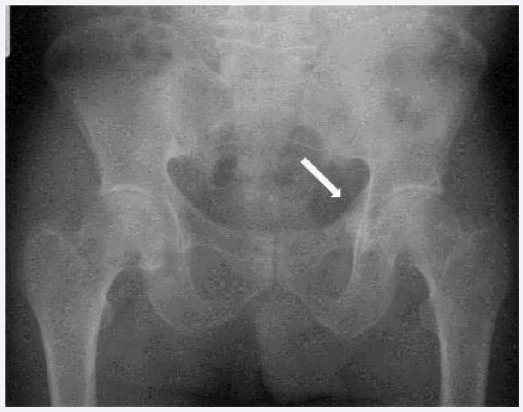

Figure 4 X-ray antero-posterior view in 2003. Sclerosis is more evident, particularly at the acetabular roof. Once more the lesion was not considered.

of the three areas with or without reconstruction), with a high risk of perioperative complications and severe residual disability. However, the 83-year-old patient had a good quality of life until the last three months before the diagnosis: we wonder if standard surgical resection in 2002-2003 could have had similar results.

In conclusion, this case may suggest that N-BPs may play a role *in vivo* in controlling the development of CS and pain. The role of a supplementation of vitamin D and calcium must be clarified. Further research is needed but, especially when surgery is highly demanding with disabling results such as in primary CS of the pelvis in old patient, N-BPs therapy could be considered as a palliative therapy able to delay symptoms, allowing a good quality of life, in particular when the limb cannot be saved or the patient refuses surgery. In absence of any clinical trial, this case could be the point to start a prospective study.

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To the General Practitioner who treated and followed the Patient for many year.

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