Hormone-refractory prostate cancer and the skeleton

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Chapter 7

Clear osteolytic metastases and hypercalcaemia: an unusual presentation of hormone refractory prostate cancer.

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Submitted

Introduction

Prostate cancer frequently metastasizes to the skeleton and osseous metastases are characteristically osteoblastic, although increased bone resorption is consistently demonstrated biochemically and histologically[1-4]. Seldom described in the literature, osteolytic metastases probably coexist with osteoblastic metastases in most cases. Hypercalcaemia is frequently encountered in the late stages of malignant diseases, but is rarely observed in patients with prostate cancer[5-19]. In this malignancy, patients have indeed the tendency to develop hypocalcaemia rather than hypercalcaemia once metastases spread to the skeleton, largely due to increased calcium utilization by the predominantly osteoblastic process[19-24].

Case Report

We report the case of a 47 year old man who presented with a hydrocoele and a fear of possible prostate cancer as he had lost his father and an older brother to this malignancy. The prostate gland felt normal on digital rectal examination, but a serum PSA, checked on the basis of the patient's strongly positive family history was grossly elevated (600 μg/l). Despite multiple prostate biopsies, a tissue diagnosis of prostate cancer could not be confirmed at that stage, but multiple areas of increased radioactive isotope uptake were seen on skeletal scintigraphy. A computerized tomography (CT-scan) of the abdomen further demonstrated partial obstruction of the right ureter due to enlarged retroperitoneal lymph nodes. Serum biochemistry was not evaluated beyond assessing serum creatinine concentration, which was within the normal laboratory reference range, and serum alkaline phosphatase activity which was elevated at 190 IU/l (upper limit of normal 120 U/l).

Treatment with the LH-RH analogue goserelin was instituted. Initial response was adequate with achievement of castrate testosterone concentrations and significant decrease

in serum PSA levels to 9.4 μ/l, although these did not normalize three months into therapy. The patient unfortunately developed increasingly troublesome hot flushes and treatment with goserelin had to be discontinued at his express request after seven months, at which time there was already evidence for hormone-refractoriness with rising PSA levels despite adequate androgen deprivation. An emergency admission was required shortly after discontinuing hormonal treatment because of acute diplopia because of right abducens nerve palsy. This was found to be caused by a skeletal metastasis at the base of the skull leading to entrapment of the sixth cranial nerve. Local irradiation was applied with adequate relief of the patient's visual symptoms. The patient however, developed progressively worsening generalized bony pains, despite maximum analgesia which prompted his referral to our unit for palliative treatment with bisphosphonates.

At presentation, there were no significant abnormalities on physical examination. Laboratory investigations showed the patient to be severely hypercalcaemic with a serum calcium of 3.01 mmol/l (normal range 2.25-2.55 mmol/l) corrected for albumin with a normal serum phosphate concentration of 1.07 mmol/l. Renal function was impaired with a serum creatinine of 145 μmol/l (upper limit of normal 120 μmol/l). Serum alkaline phosphatase activity was more than 3-fold increased at 627 U/l (normal up to 120 IU/l) but liver transaminases were also elevated (ASAT 113 U/l, ALAT 109 U/l, gamma-glutamyl transferase 204 U/l and LDH 3148 IU/l), suggesting possible liver metastases. Serum PTH and 1,25(OH)2D3 concentrations were appropriately suppressed for the degree of hypercalcaemia (<1.0 pmol/l and <10 pmol/l respectively) and serum PTHrP was undetectable. Serum PSA had significantly risen to 873 μg/l.

There was scintigraphic evidence for widespread skeletal metastases with heavy involvement of the spine. In addition to the expected osteoblastic metastases, unequivocal osteolytic metastases were also clearly demonstrable on close examination of the lateral X-rays of the spine (Figure 1) and of the computerized tomography scan (Figure 2).

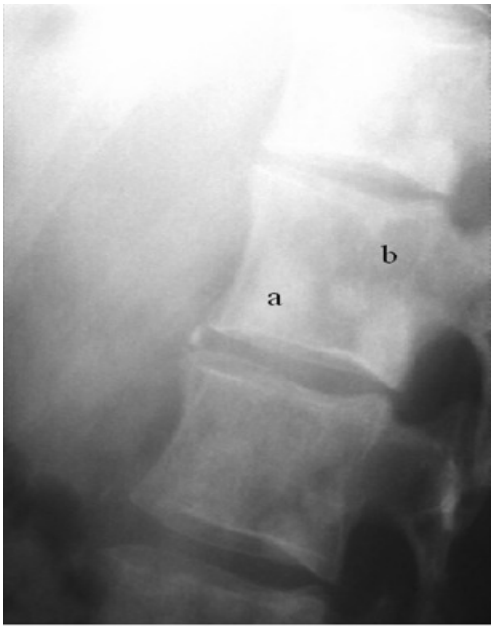

Figure 1. Plain radiography of the lumbar spine (lateral view) demonstrating mixed osteoblastic (a) and osteolytic (b) metastases.

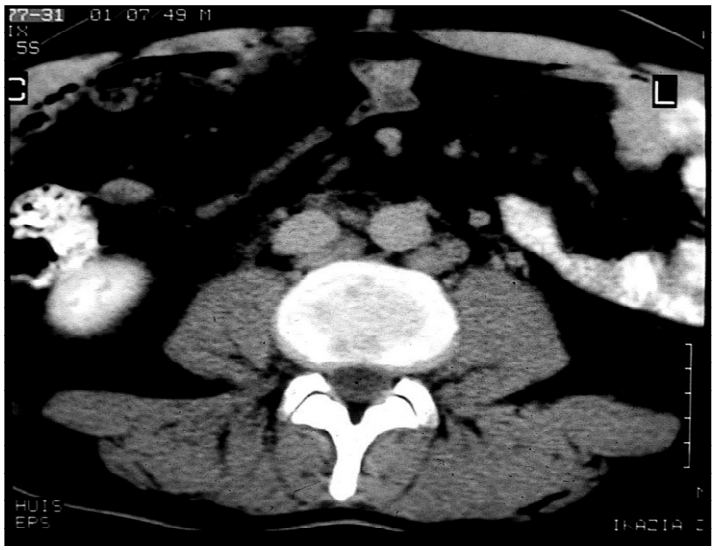

Figure 2. Computerised tomography scan of the first lumbar spine vertebra demonstrating clear osteolytic metastases.

Repeat needle prostate biopsies were undertaken and these now demonstrated a highly undifferentiated adenocarcinoma (Gleason score 10). Primary tumour tissue did not

express PTH on immunocytochemistry, and a validated polyclonal antibody directed against amino acids 34-53 of the mid-region of PTHrP[25] demonstrated only patchy expression of PTHrP.

Palliative treatment in the form of the nitrogen-containing bisphosphonate olpadronate was administered as an intravenous infusion at a dose of 20 mg diluted in 500 ml 0.9% saline over four hours. This resulted in complete normalization of serum calcium and a significant improvement in skeletal symptoms within days. The patient received maintenance oral olpadronate at a dose of 200 mg/day and over the following 6 weeks the beneficial palliative effects of olpadronate were maintained. Although hypercalcemia did not recur and skeletal pains remained controlled, clinical deterioration was rapid with extraskeletal spread of metastases. A malignant pleural effusion developed within two months of presentation with a rapidly fatal course. Consent was not granted for an autopsy examination.

Discussion

We report the case of a relatively young patient with hormone-refractory aggressive, undifferentiated prostate cancer, in whom widespread osteolytic metastases were associated with severe hypercalcaemia. Whereas hypercalcaemia is a relatively common complication of solid tumours due to mobilization of calcium from skeletal sites because of locally-induced bone destruction or as a result of the systemic effects of humoral factors such as PTHrP[27,28], this metabolic complication has been described in only up to 9% of patients with prostate cancer at some stage during their malignancy. Two of the some 20 cases reported in the English literature[5-19], were due to concomitant disease: hyperparathyroidism[9] and multiple myeloma[7]. Hypercalcaemia directly related to prostate cancer has otherwise most commonly been described in highly undifferentiated tumour types or in the presence of unusual histologic features which may be associated with ectopic endocrine function or unexpected systemic syndromes[11]. Hypercalcaemia is also reported to be often but not exclusively associated with widespread skeletal metastases[6], to revert in a number of cases following orchiectomy[8,10,14] but to follow a rapidly fatal course in most, with a mean duration of survival of 3.9 months from the time of detection of hypercalcaemia[8].

Biochemical and histological data suggest that bone resorption is an important component of the skeletal manifestations of prostate cancer[5-19]. In prostate cancer, osteolytic metastases probably often coexist with osteoblastic metastases but the latter clearly dominate the clinical picture in the majority of patients with this malignancy. In prostate cancer, a significant coupling is reported between biochemical parameters of bone formation and resorption[2-26]. Disturbances in calcium homeostasis are thus only seldom observed and these are mainly in the form of hypocalcaemia likely to be due to increased utilization of calcium in the osteoblastic process although other mechanisms may also play a role[19-24].

Whereas the exact mechanism of hypercalcaemia in prostate cancer is not known, osteoclast-mediated bone resorption certainly plays a central role in its pathophysiology. It is of note, however, that an osteolytic lesion has to destroy some 50% of cancellous bone in a vertebral body before it can be detected on plain radiology of the spine. Pathologic fractures are less common in prostate cancer than in tumours associated with osteolytic metastases so that their occurrence should raise suspicion of the nature of the metastatic process. In malignant disease, mediators of osteolysis include factors such as cytokines and prostaglandins released either by metastatic tumour cells or by host cells in response to the invading tumour. PTHrP is a primary factor responsible for humoral hypercalcaemia of malignancy. PTHrP is also thought to be an early response gene that may be involved in the cellular proliferation and differentiation of malignant cells. An increased production of PTHrP by a primary tumour which would act humorally, or a local increase in the production of PTHrP by metastatic cells acting as a local osteolytic factor have been implicated in enhancing the metastatic process in breast carcinoma[27,29]. Common to other solid tumours, prostate cancer is among the malignant cell types shown to overproduce PTHrP[30]. Large amounts of PTHrP are thus found in conditioned media of undifferentiated prostate cancer cells and enhanced expression of PTHrP has been demonstrated by immunocytochemistry in poorly differentiated and metastatic tumours[31], with the intensity of staining correlating with high grade tumours[32]. In the patient reported here, PTHrP was undetectable in peripheral blood and PTHrP staining was only patchy in the primary tumour despite its highly undifferentiated grade. It is possible, however, that PTHrP production may have been increased at the site of skeletal metastases, locally contributing to the osteolytic process[33] or that expression of cytokines by the tumour may have been responsible for the enhancement of osteoclast activity[34]. A possible explanation for the predominant osteoclastic activity may also be the previously described potential

alteration in the hormonal bioactivity of PTHrP due to defective cleavage of the molecule by prostate specific antigen accounting for a residual intact PTH domain and enhanced PTH-like activity[35].

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption which have been used with variable success in the palliation of metastatic bone pain in prostate cancer[36-38]. In this respect, our group has reported the beneficial effect of the amino-bisphosphonate olpadronate in the palliation of metastatic bone pain in up to 75% of patients with metastatic prostate cancer. The beneficial clinical response was shown to parallel changes in biochemical parameters of bone resorption[26]. Whereas the rationale for the use of bisphosphonates in a malignancy with predominant osteoblastic metastases, is not immediately obvious, their beneficial effects in prostate cancer rest on a number of observations. There is thus ample evidence that prostate cancer metastases are associated with increased bone resorption as determined by bone histomorphometry as well as by markers of bone resorption[1-4]. In the presence of widespread osteoblastic metastases, such as these observed in prostate cancer, profound hypocalcaemia may follow the administration of these agents, probably due to the expected suppression of bone resorption in the face of continuing calcium utilization. It is our experience that most patients with hormone refractory prostate cancer metastatic to the skeleton require supplementation with calcium and vitamin D to maintain calcium homeostasis when palliatively treated with bisphosphonates. The unusual presentation of hypercalcaemia associated with clear osteolytic metastases and its favourable response to bisphosphonate therapy suggests that under certain as yet unknown circumstances, the resorptive component of the metastatic proces may become predominant. Most isolated case reports describe the association of hypercalcaemia with severely undifferentiated histological features. In prostate cancer, similar to other cancers, the skeletal morbidity attached to the metastatic process, particularly if lytic, is high. The favourable clinical as well as biochemical response to olpadronate indeed suggests that in addition to their clear role in the palliation of metastatic bone pain, bisphosphonates are also valuable in controlling hypercalcaemia by successfully suppressing excessive bone resorption. Our findings from this case and that of others under our care as well as a review of the available literature suggest that metabolic abnormalities are far from rare in patients with hormone refractory prostate cancer and are associated with significant morbidity. Routine measurement of serum calcium should be advocated in the management of these patients, to allow the timely institution of treatment.

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