Reminder of important clinical lesson

MRI for the detection of prostate cancer origin vertebral metastases in the preosteoblastic phase

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Summary

This report describes the case of a gentleman aged 59 years presenting with low-back pain, who had undergone radical prostatectomy for prostate cancer 8 years ago. On evaluation, a slightly elevated serum alkaline-phosphatase level prompted a search for bone metastases. Although x-ray radiography and a bone scan were apparently normal, an MRI scan revealed the presence of metastatic marrow infiltration in the lumbar vertebrae. The patient subsequently was initiated on therapy with androgen-deprivation therapy and bisphosphonates, and currently enjoys symptom-free and progression-free survival. The images in this paper intend to impress upon the limitations of bone scan and x-ray radiography with regard to the detection of vertebral marrow infiltration in the absence of cortical bone invasion. In addition, a brief review of the pathophysiology of vertebral metastases arising from prostate cancer is included.

BACKGROUND

The x-ray radiography is the most commonly procured radiological investigation in the evaluation of bone metastases from prostate carcinoma, owing to its simplicity and vast availability. Bone scan with technetium-99m methyl-diphosphonate (^{99m}Tc-MDP) is the most common scintigraphic investigation used for a quick 'whole-body' evaluation of suspected bone metastases in prostate cancer. Vertebral metastases must involve the cortical bone in order to become visible on x-ray-based investigations (such as conventional x-radiography or CT), or must be associated with an osteoblastic response in order to be visualised on a bone scan.^{1 2} Vertebral metastases are bloodborne metastases, which are very common in prostate cancer because of unique bone-trophic properties of prostate cancer cells. Invasion of the marrow, via the blood stream is the first step in the order of sequences leading to the development of an osteoblastic lesion which would ultimately be visualised on x-ray-based imaging modalities as well as on bone scans.^{3 4} However, in the time window between marrow invasion by prostate cancer cells, to the development of osteoblastic lesions, imaging of the marrow with the help of MRI could lead to the diagnosis of 'preosteoblastic' vertebral metastases.

CASE PRESENTATION

This description pertains to an adult male patient aged 59 years who presented with a history of episodes of intense 'burning pain' abruptly arising in the lower back, often disturbing night-time sleep. His history was significant for having undergone extracorporeal shock-wave lithotripsy (ESWL) at the age of 56 years for ureteric calculus, and more significantly, had undergone a radical prostatectomy for T_{2b}N₀M₀-staged prostate carcinoma at his age of 51 years.⁵

The patient had ignored the pain for about 4 months since the intensity was not too high. However, since the intensity of the pain increased subsequently, the patient visited his urologist, concerned that his pain could be related to what he presumed as 'a complication of the ESWL which was performed 3 years ago'. The urologist procured an ultrasonological examination of the abdomen and pelvis which was not suggestive of any abnormality. A routine blood investigation, however, revealed an elevated serum alkaline-phosphatase level (248 IU/l against the normal upper limit of 140 IU/l), while the other parameters were within normal limit. Given his previous history of prostate cancer the patient was referred for further oncological evaluation. Since the prostate-specific antigen (PSA) levels were elevated 36 ng/ml (normal upper limit for his age being 5 ng/ml) we further procured an x-ray radiograph of the lumbar spine, along with a whole-body ^{99m}Tc-MDP scintigraph ('bone scan'). However, the radiograph (figure 1) and the scintigraph (figure 2) appeared to be negative for bony pathology. Then, an MRI scan was obtained (with the intention to evaluate the marrow component as well as to rule out soft-tissue pathology), which showed stark signal changes in the T1-weighted turbo spin-echo (TSE) sequences, affecting the first, second, fourth and fifth lumbar vertebrae (figure 3).

The patient was then assigned the diagnosis of metastatic prostate cancer, with metastases to the marrow of the lumbar vertebrae (L1–2 and L4–5). Subsequently, the patient was initiated on androgen-deprivation therapy (ADT) with leuprolide luteinizing hormone releasing hormone (LHRH) analogue and bicalutamide (antiandrogen). Zoledronic acid (4 mg, intravenous monthly) was initiated to prevent further progression and also in view of its potential to provide a survival benefit.⁶ Radiotherapy, though was contemplated to the lumbar

Figure 1 x-Ray film radiograph (lateral-view) of the lumbar spine showing no obvious abnormalities.

area, was deferred in view of very good symptom relief after the initiation of ADT and zoledronic acid.

OUTCOME AND FOLLOW-UP

The patient has currently completed 5 months of ADT and bisphosphonate therapy and remains asymptomatic, with his disease status being non-progressive with regard to PSA measurements as well as clinical symptomatology.

DISCUSSION

Bone is a preferential site for metastases from prostate cancer. Skeletal metastasis is preceded by a series of processes—the escape of metastatic cells from the primary prostate cancer into the blood stream, the establishment of marrow metastasis, proliferation within the marrow, promotion of osteoclastic and osteoblastic activity leading to cortical bone invasion and overproduction of disorganised bone, which manifests radiologically/pathologically as the well-known ‘osteoblastic metastasis’.^{4 7}

The escape of prostate cancer cells from the primary site (prostate) requires the degradation of extracellular matrix, which is facilitated by a group of zinc-dependent enzymes known as ‘matrix metalloproteinases’.⁸ Once within the blood stream, prostate cancer cells exhibit a unique affinity to bone (bone-trophism), especially to the marrow-rich axial skeleton and the pelvis. Erstwhile hypothesis tried to explain this ‘unique bone-trophism’ to the increased rate of blood flow in the bone marrow, but

Figure 2 Bone scan showing an unremarkable tracer distribution.

such a hypothesis would ignore the fact that other sites, such as the pulmonary circulation is 30 times higher in magnitude compared with the bone marrow flow.⁹ Later it was suggested that the ‘slow flow’ that occurs in the bone marrow, along with the frequent change in direction in the vertebral Batson’s valveless venous plexuses (the direction of flow dependent on the intrathoracic and intra-abdominal pressures) is a more feasible explanation for the ‘bone-trophism’ from prostate cancer.^{4 7}

Recently, it has been discovered that there are molecular factors which cause the unique bone-trophism. It has been discovered that prostate cancer cells express the chemokine receptor CXCR4 on their surface. This causes an affinity towards the bone microenvironment, which is rich in the chemokine named stromal-derived factor-1 (SDF-1).^{4 7 10 11}

Thus, once the prostate cancer cells enter the marrow of the bone, their ‘engraftment’ in the marrow is facilitated by factors which promote cell-to-cell adhesion (integrins and annexins) and also via factors enhancing cell adhesion to extracellular matrix (osteopontin).^{7 12 13}

Figure 3 T1-weighted turbo spin-echo MRI of the spine showing altered signal intensities in the first, second, fourth and fifth lumbar vertebral bodies.

Subsequently, the engrafted malignant cells proliferate within the rich marrow environment. They also secrete factors that promote osteoclast activity (proposed mechanisms include increased levels of interleukin 7, tumour necrosis factor- α and an increased receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio), which facilitates subsequent bone cortical involvement. Osteoblastic activity too is enhanced since the prostate cancer cells express factors such as platelet-derived growth factor, insulin-like growth factor, transforming growth factor- β and fibroblast growth factors. In addition, prostate cancer cells express factors that are mitogenic for osteoblasts, namely the bone morphogenic proteins, kallikrein-3 (more commonly known as the PSA) and urokinase-type plasminogen activator. Very recent research has hinted towards a multitude of molecules and pathways which too play a role, however, a discussion on such factors would require a dedicated systematic review on the topic. Overall, it can be said that the 'osteoblastic' metastases which are manifested in patients of prostate cancer are not a 'direct deposition of malignant cells over the bone', but indeed are preceded by marrow invasion, marrow engraftment, enhancement of osteoclast and osteoblast activity, bone cortex erosion, and lastly the generation of disorganised bone which are indeed the classically described 'osteoblastic metastases'.^{3 4 7 10 11 14 15}

In clinical practice, the bone scan and x-ray radiography (including CT scans) are the most commonly utilised modalities for the evaluation of patients with prostate cancer for bone metastases. However, various studies have shown poor sensitivities with both the bone scan and CT scan, and in addition, these modalities also suffer from poor specificity owing to the frequent presence of bone-

degenerative diseases in the age-bracket into which majority of patients with prostate cancer belong to.¹⁶

Considering a hypothetical scenario of enhanced 'sensitivity' of a hypothetical modality 'specialised' in detecting osteoblastic metastases, it can still be said that this (hypothetical) modality which excels in the detection of osteoblastic metastases would fail to detect a patient with malignant marrow invasion which is yet to generate detectable osteoblastic activity.

This 'window period' from the invasion and engraftment of prostate cancer cells into the marrow, prior to the generation of detectable osteoblastic lesions can be compared with the situation with multiple myeloma, wherein patients frequently have marrow involvement, but will be detected on conventional x-ray radiography/CT scans only after considerable erosions of the cortex. Hence, in the case of myeloma, research is progressing briskly in the utilisation of MRI and FDG-PET (¹⁸F-fluoro-deoxyglucose positron-emission tomography) for marrow assessment. In addition, there seems to be good promise with regard to the assessment of marrow infiltration with the newer radiopharmaceuticals which depend on different mechanisms of uptake; such as ¹⁸F-FLT-PET (¹⁸F-tagged thymidine which is an indicator for increased DNA synthesis), ^{99m}Tc-MIBI is considered a rapid alternative to ¹⁸F-FDG-PET scan, especially when PET facility is unavailable.¹⁷⁻¹⁹

It would not be unreasonable to state that the MRI scan should be given due preference in the case of patients with prostate cancer who are being suspected of harbouring bone metastases. In the current scenario, where we encountered a patient with biochemical relapse (elevated PSA levels after the completion of therapy with curative intent), we were unable to visualise any evidence of osteoblastic activity on two of the most commonly used imaging modalities—namely the x-ray radiograph and the bone scan. We were, however, able to observe involvement of the lumbar vertebral marrow on MRI. In short, the utilisation of T1-weighted imaging (fast-spin echo or TSE sequences) and short inversion time inversion recovery can detect the replacement of the 'red marrow' which is the usual occupant of lumbar vertebral marrow.²⁰⁻²²

In fact, the patient was diagnosed of relapse 8 years after radical prostatectomy for low-risk, early-stage prostate cancer. The complaint of 'back-pain of burning character' was the trigger for presentation, evaluation and ultimate diagnosis of tumour relapse. It could be speculated that the pain was likely due to malignancy-related osteoclast-mediated osteolysis, tumour cells themselves or associated cytokines receptors.^{3 4 23-25}

Although a bone marrow aspiration would have been confirmatory for 'malignant marrow invasion', it was avoided with a view to prevent discomfort to the patient. Subsequent to the initiation of zoledronic acid, the patient had total relief from pain (which was not achieved earlier by non-steroidal anti-inflammatory drugs). This in our opinion could be confirmatory of two important facts—first that the patient's marrow signal changes were indeed due to malignancy and second that osteoclastic activity indeed has a role in the generation of ultimately osteoblastic lesions.¹⁴

In the future, it is likely that MRI, ¹⁸F-FDG-PET and hybrid PET/CT imaging will have an increasing role in the evaluation of patients suspected of harbouring bone marrow involvement from prostate and other malignancies.

Learning points

- ▶ Patients with prostate cancer have a high incidence of bone metastases which are classically osteoblastic.
- ▶ Bone marrow invasion and engraftment of malignant cells must occur prior to the manifestation of frank osteoblastic lesions.
- ▶ Commonly used imaging methods (radiographs, CT and bone scans) will not be able to detect marrow invasion which occurs prior to development of osteoblastic lesions.
- ▶ The future may witness the emergence of the roles of MRI and ¹⁸F-fluoro-deoxyglucose positron-emission tomography/CT for the evaluation of marrow routinely (to complement the currently utilised methods which assess the bone cortex) in patients with cancer suspected to be harbouring bone metastases.

Competing interests None.

Patient consent Obtained.

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