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Should prostate cancer be considered as a differential diagnosis in patients with osteolytic bone lesions?

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Abstract. – OBJECTIVE: Prostate cancer is the most frequently diagnosed cancer in men, as well as the second leading cause of death among cancers after lung cancer. In the United States, it is more prevalent in African-American men than in Caucasian men. Prostate cancer frequently metastasizes to the bone, with most of the reported lesions appearing to be osteoblastic on radiographs. Here, we describe an unusual presentation of metastatic prostate cancer with diffuse osteolytic bone lesions.

CASE PRESENTATION: An 80-year-old previously healthy Hispanic man presented with worsening back pain, difficulty with ambulation, and bladder outlet obstruction. Physical examination was significant for spinal tenderness in the thoracic and lumbar region. Digital rectal examination was remarkable for asymmetric enlargement of the prostate with nodularity and firmness. Imaging studies revealed diffuse osteolytic lesions. His prostate-specific antigen was 562.8 ng/mL (normal 0-4). Prostate biopsy and imaging studies confirmed a diagnosis of metastatic prostate cancer.

CONCLUSIONS: This case demonstrates that bone metastases of prostate cancer are not purely osteoblastic although most of the reported bone metastases in prostate cancer have been osteoblastic in nature. Therefore, clinicians are to consider metastatic prostate cancer as a differential diagnosis for patients with osteolytic bone lesions.

Key Words:
Metastatic prostate cancer, Bone metastases, Osteolytic, Osteoblastic.

Introduction

Prostate cancer is the most frequently diagnosed non-skin cancer of men, the second leading cause of death after lung cancer and the fifth most common cancer worldwide[1]. It is more common in African-American men over the age of 65 than Caucasian men[2,3]. African-American and Hispanic populations are at a higher risk of being diagnosed with an advanced disease in the United States[4]. Prostate cancer frequently metastasizes to bones in up to 90% of patients with advanced diseases, and lungs (46%) and the liver (25%) follow[3,5,6]. Bone metastases contribute significantly to morbidity and mortality, causing severe pain, pathogenic fracture, or spinal cord compression[7,8].

Although most of reported bone metastases in prostate cancer are osteoblastic in nature, they are not purely osteoblastic. This is supported by an increased bone-metastasis-free survival in patients treated with denosumab[9,10], and a few cases of disseminated osteolytic metastases have also been reported[11,12]. Nevertheless, the diagnosis and treatment of prostate cancer with osteolytic lesions could be delayed if clinicians are not aware of this unusual occurrence of osteolytic bone metastases. Here we present a patient with prostate cancer with disseminated osteolytic bone metastases and discuss the pathophysiology of both osteolytic and osteoblastic lesions in prostate cancer.

Case Presentation

An 80-year-old previously healthy Hispanic man presented with complaints of lower back pain. The patient was in his usual state of health until four days ago when he noticed back pain while lifting up garbage bags. The pain radiated to lower limbs. It was initially mild but progressively

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worsened, which prompted the patient to seek immediate medical attention. There was no reported trauma to the back or a mechanical fall. He denied weight loss, cough, breathing difficulty, fatigue, or gastrointestinal symptoms. He complained of increased straining while passing urine along with frequency, nocturia, and intermittent dysuria. Family history was significant for prostate cancer in his nephew who died in his 50's.

Physical examination was remarkable for moderate pallor and tenderness to percussion over thoracic and lumbar spines with no swelling or deformity. No skin lesions were found. Digital rectal examination revealed asymmetric enlargement of the prostate with nodularity and diffuse firmness.

Complete blood count, basic metabolic panel, liver function panel, and renal function panel were within normal limits. Serum calcium was 10.4 mg/dL. Serum and urine protein electrophoresis did not reveal M-protein band or Bence-Jones protein. Immunofixation was not remarkable. Prostate-specific antigen (PSA) was 562.85 ng/mL (normal 0-4) and parathyroid hormone was 62.2 pg/mL (normal 12-88). Peripheral blood smears did not reveal anisocytosis, nucleated red cells, polychromasia, or rouleaux formation.

Imaging studies revealed multiple osteolytic lesions in bones: bone survey and computerized tomography (CT) of the lumbar spine revealed osteolytic lesions at L5 and S2, multiple ribs, and C7 transverse process, as well as a pathologic fracture secondary to a large lytic lesion at T5 (Figure 1A). CT of abdomen and pelvis showed extensive retroperitoneal and pelvic lymphadenopathies along with heterogeneous enlargement of the prostate (Figure 1B). No evidence of lung nodules or masses was noticed from imaging studies. Transrectal biopsy of the prostate confirmed adenocarcinoma of the prostate with a Gleason score of 8. Prostate cancer (stage IV, T3N1M1, poorly differentiated with marked anaplasia) was diagnosed, based on imaging studies and prostate biopsy. Bone biopsy was not considered due to low suspicion of primary bone tumors or multiple myeloma.

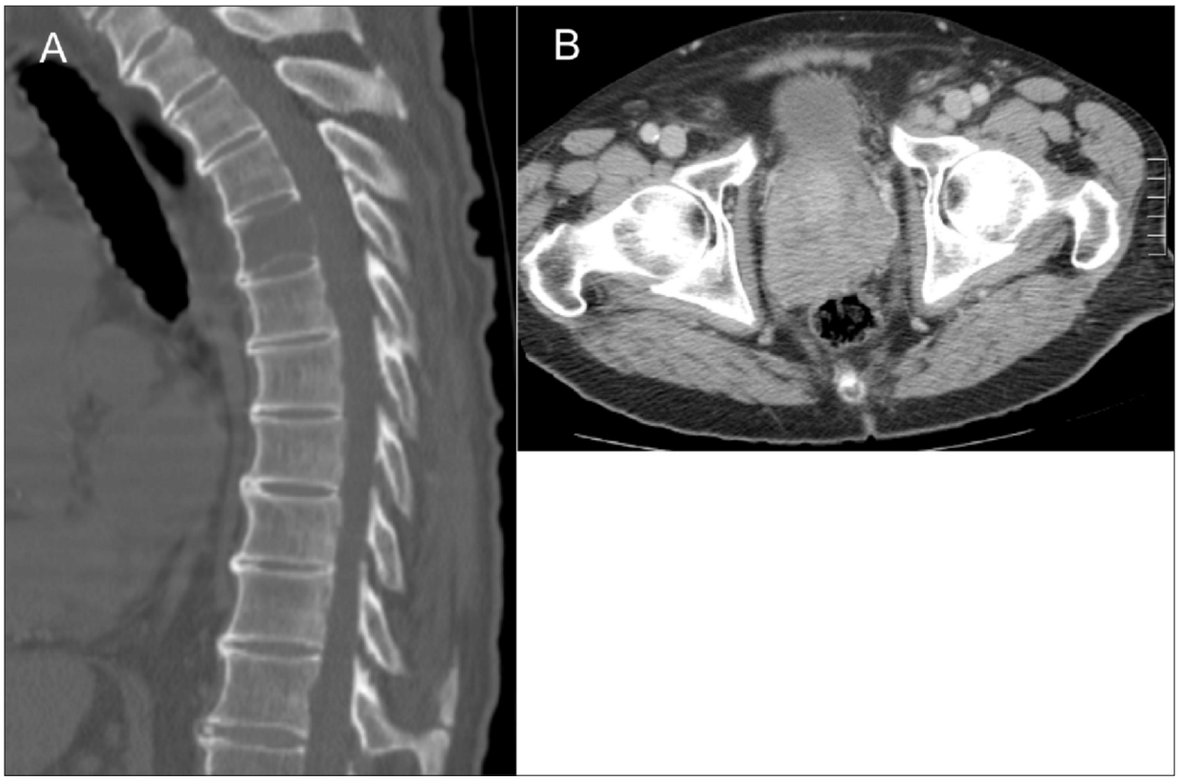

Figure 1. Metastatic prostate cancer of this patient. ***A,*** Reveals a pathological fracture at T5, caused by a large osteolytic bone lesion. Other vertebral bodies do not show osteoblastic or osteoclastic lesions. ***B,*** Shows heterogeneous enlargement of the prostate with extensive pelvic lymphadenopathies.

The patient was started on androgen suppression therapy with bicalutamide 50 mg oral daily, leuprolide 45 mg intramuscular injection once every 6 months, and denosumab 120 mg subcutaneous once every 6 months. He continued to follow up with radiation oncology for palliative radiation.

Discussion

Although the diagnosis of this patient is most likely metastatic prostate cancer, given the biopsy results and clinical presentations showing multiple, asymmetric bone lesions, other metastatic cancers should also be considered as differential diagnoses. Primary bone cancers in particular can present as osteolytic lesions. However, bone cancers usually have characteristic radiographic features and do not involve multiple asymmetric lesions as presented in this patient[13,14]. Metastatic bone lesions from renal cell cancer, melanoma, multiple myeloma, lung cancer, thyroid cancer, and lymphoma are predominantly osteolytic in nature[15]. However, computerized tomography and physical examination did not show evidence of these cancers. Multiple myeloma was ruled out by no evidence of anemia or renal injury, negative protein electrophoresis, and skeletal survey showing no osteolytic lesions in the skull.

Metastatic lesions of prostate cancer are predominantly osteoblastic in nature, though only a few osteolytic lesions have been reported in the literature[10,11]. However, there has been emerging evidence that metastases of prostate cancer not only require osteoblastic, but also osteoclastic activities. Prostate-specific antigen produced by tumor cells is known to block bone resorption via modifying parathyroid hormone-related peptide and activate pro-osteoblastic growth factors including insulin-like growth factors and transforming growth factor-β[9,16]. Endothelin-1, bone morphogenic proteins (BMP)-2 and BMP-6 also contribute to osteoblastic metastases[17,18]. Although the pathophysiology of osteoclastic activities of metastatic prostate cancer is not fully understood, the interaction of receptor activator of nuclear factor kappa B ligand (RANKL) and RANK is suggestive as an underlying mechanism of osteolytic lesions in prostate cancer. The RANKL-RANK interaction induces osteoclastogenesis and promotes osteoclastic activities as demonstrated in other cancers producing osteolytic bone lesions including breast cancer or multiple myeloma[19]. As demonstrated by Corey et al[20], osteoprotegerin (OPG), which binds to RANKL and therefore inhibits tumor-induced osteolysis, is also responsible for osteoblastic lesions in prostate bone metastases. OPG and RANKL are identified as regulators of the bone remodeling and bone resorption, and the ratio of RANKL to OPG is an important factor of determining skeletal integrity and bone strength[21]. Therefore, dysregulation of the OPG-RANK-RANKL system could lead to a wide spectrum of pathological conditions ranging from predominantly osteoblastic to osteolytic lesions[22] although other molecules including growth factors, endothelin-1, BMP-2 or BMP-6 are also involved in bone metastases.

The treatment modalities of advanced prostate cancers are focused on palliative care. Androgen receptor inhibitor (bicalutamide in this patient) or androgen deprivation therapy is a standard of care for this purpose[23]. Surgical castration or medical suppression of luteinizing hormone-releasing hormone (LHRH) production has been another treatment option. Leuprolide, a LHRH analogue was found to be equivalent to diethylstilbestrol in reducing testosterone with similar efficacy to surgical castration[24], though it has lower cardiovascular toxicity than diethylstilbestrol. Therefore, leuprolide is a preferred treatment of choice for androgen deprivation over diethylstilbestrol or surgical castration. Osteolytic nature of bone metastases in prostate cancer also endorses the use of bisphosphonate or denosumab, a monoclonal antibody against RANKL. Denosumab is known to increase bone-metastasis-free survival[9].

Conclusions

Although most of reported bone lesions of metastatic prostate cancer are osteoblastic, patients with prostatic cancer can present with a wide range of bone lesions ranging from osteoblastic to osteolytic pathologies. Therefore, physicians are to consider metastatic prostate cancer as a differential diagnosis for patients with osteolytic bone lesions.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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