A 61-year-old man with a medical history of coronary artery disease and symptomatic urolithiasis presented to the emergency department with new onset gross hematuria and 3 months of low back pain, urinary symptoms, and lower extremity edema. He described the back pain as throbbing and 8/10 in severity. The back pain was in the midline, lower thoracic area with radiation down both legs and to his left flank. The pain was worse when lying flat and improved when sitting in a chair. Acetaminophen, ibuprofen, transcutaneous electrical nerve stimulation, and chiropractic intervention did not provide relief. The pain would occasionally awaken him at night. He denied bowel or bladder incontinence or retention, saddle anesthesia, and leg weakness. Hematuria began the morning of presentation, and he had experienced 3 months of worsening urinary hesitancy, decreased stream, and urinary frequency. The lower extremity edema began in his left leg and was now bilateral. The edema had not improved with compression wraps, and weeping wounds had developed over his left shin.

Notably, he had 3 previous health care visits over the past 2.5 months for back pain, urinary symptoms, and lower extremity edema. During these visits, he was noted to have an enlarged left inguinal lymph node. A urinalysis and ultrasound of his left leg had been unremarkable, and a lumbar radiograph revealed degenerative changes in his spine. The patient’s medications included aspirin, acetaminophen, ibuprofen, atorvastatin, lisinopril, and metoprolol tartrate.

In the emergency department, vital signs were within normal limits. The patient was hunched over and unable to lie flat because of severe back pain. Physical examination revealed tenderness over his lower thoracic vertebrae. Examination of his lower extremities revealed asymmetry with the left leg exhibiting 4+ pitting edema and multiple erosions with surrounding erythema and the right leg exhibiting 2+ pitting edema without other abnormality. Left inguinal lymphadenopathy was also present. Scrotal swelling with normal sized testes and no palpable testicular masses were appreciated on genitourinary examination. Rectal examination revealed a hard, abnormal prostate with normal rectal tone. He had no neurological deficits.

Laboratory evaluation revealed the following results (reference ranges provided parenthetically): hemoglobin level, 12.9 g/dL (13.2 to 16.6 g/dL); leukocyte count, 7.0×10^9/L (3.4 to 9.6)×10^9/L; platelet count, 163×10^9/L (135 to 317)×10^9/L; creatinine level, 1.36 mg/dL (0.74 to 1.35 mg/dL); calcium level, 9.3 mg/dL (8.8 to 10.2 mg/dL); alkaline phosphatase level, 543 U/L (45 to 115 U/L); aspartate aminotransferase level, 20 U/L (8 to 48 U/L); alanine aminotransferase level, 19 U/L (7 to 55 U/L); erythrocyte sedimentation rate, 26 mm/h (0 to 22 mm/h). Urinalysis with microscopy revealed a protein level of 73 mg/dL (<26 mg/dL) and nondysmorphic red blood cell count of 51 to 100 per high-power field (<3 per high-power field). Urinalysis and urine Gram stain were otherwise unremarkable.

A chest radiograph revealed trace pleural effusion and multiple lytic lesions in the lower thoracic vertebral bodies. An ultrasound of the left lower extremity revealed bilateral lower extremity edema and left inguinal lymphadenopathy measuring up to 1.9 cm, but was negative for acute
deep venous thrombosis. Computed tomography of the abdomen and pelvis without intravenous contrast was notable for 3 and 5 mm obstructing stones in the distal right ureter near the ureterovesical junction with right hydronephrosis. In addition, destructive lytic lesions in the T10 and T11 vertebral bodies with pathologic fracture, innumerable osteoblastic lesions, and extensive retroperitoneal, pelvic, and left inguinal lymphadenopathy were noted.

1. Which one of the following is the most likely etiology of this patient’s presentation?
   a. Multiple myeloma
   b. Metastatic renal cell carcinoma
   c. Metastatic prostate cancer
   d. Metastatic urothelial carcinoma of the bladder
   e. Metastatic colon cancer

At the time of diagnosis, 58% of patients with multiple myeloma have bone pain, most commonly located in the back or chest, and approximately half of patients will have an elevated creatinine level. However, we would not expect to see considerable lymphadenopathy and lower extremity edema. In addition, osteoblastic lesions are rare compared with osteolytic lesions in multiple myeloma.

Metastatic renal cell carcinoma may present with back pain due to vertebral metastases. The lungs, bone, and liver are the organs most likely to harbor metastases, with about 30% to 40% of patients having skeletal metastases. Marked lower extremity edema can also occur with involvement of the inferior vena cava. In addition, hematuria can occur after the tumor invades the collecting system. Renal cell carcinoma, however, is not likely to form osteoblastic lesions. Also, a renal mass on computed tomography of the abdomen and pelvis with thickened irregular walls or septa would be expected.

Metastatic prostate cancer is the most likely cause of this patient’s presentation. Metastases from prostate cancer affect bone before other organs, with the most common sites of skeletal metastases being the pelvis and vertebrae. Lymphedema in the lower extremities can occur as a result of metastases to the pelvic lymph nodes and reduction in lymph flow at these sites. Although osteoblastic lesions are more common in prostate cancer, it has been increasingly reported that prostate cancer should also be in the differential diagnosis of osteolytic bone lesions.

Patients with urothelial carcinoma most commonly present with painless gross hematuria, but they may also present with skeletal metastases. Up to 47% of patients with metastatic urothelial cancer will have metastases to bone, and about 7% of these patients will have vertebral fractures leading to spinal cord compression. Although metastatic urothelial cancer shares many presenting symptoms with metastatic prostate cancer, it is considerably less common. Metastatic colon cancer may present with anemia and marked lymphadenopathy with resultant lymphedema, but metastases are most frequently located in the liver or lung.

A prostate-specific antigen (PSA) was ordered and found to be elevated to 184 ng/mL (%22C 4.5 ng/mL). Given the markedly elevated PSA level, prominent osteoblastic lesions in the axial skeleton, and inguinal lymphadenopathy, metastatic prostate cancer was considered to be the most likely diagnosis.

2. For this patient, which one of the following is the best way to diagnose prostate adenocarcinoma?
   a. No further testing given a marked elevation in PSA level
   b. Prostate biopsy
   c. Inguinal lymph node biopsy
   d. Retroperitoneal lymph node biopsy
   e. Vertebral osteoblastic lesion biopsy

An elevation in PSA level may be secondary to multiple etiologies, including benign prostatic hypertrophy, prostatitis, perineal trauma, and rarely salivary gland tumors. In this case, the considerable elevation in PSA level in the case of metastatic lesions provides a clinical diagnosis of prostate cancer. However, tissue diagnosis is still important to further understand prognostication, delineate histology, and guide therapy. Prostate biopsy is
often performed after an elevated PSA level is discovered, but in cases of diffuse metastatic disease, biopsy of other affected organs may be performed to prevent the morbidity associated with prostate biopsies. The benefit of prostate biopsy is the ability to obtain a Gleason score for prognostic purposes and to rule out small cell carcinoma of the prostate.

Marked inguinal lymphadenopathy was found in this patient. Fine needle aspiration of an inguinal lymph node reduces morbidity and can lead to a relatively quick tissue diagnosis of prostate adenocarcinoma. Biopsies of the retroperitoneal lymph nodes or vertebral osteoblastic lesions may lead to a correct pathological diagnosis but are less accessible and associated with increased morbidity. Bone biopsies particularly may be less sensitive.

Fine needle aspiration of an inguinal lymph node was completed, which revealed adenocarcinoma of prostatic origin. During his hospitalization, the patient continued to have significant lower back pain requiring hydromorphone patient-controlled analgesia. There was no sign of neurological impairment on physical examination, and magnetic resonance imaging of the spine was completed, which revealed no nerve or spinal cord compression. Computed tomography of the spine was also completed to further evaluate mechanical stability and the possibility of other vertebral metastases. It revealed fusion of the T10 and T11 vertebral bodies and a large lytic lesion involving T11 and T12 without evidence of vertebral instability.

3. At this point, which one of the following is the most appropriate next step to provide pain relief for this patient’s vertebral metastases?
   a. External beam radiation
   b. Inpatient surgery
   c. Zoledronic acid
   d. Denosumab
   e. Teriparatide

   Prostatic metastases in the vertebrae frequently result in considerable pain and occasionally spinal instability. External beam radiation therapy is the primary treatment used in patients with painful osteoblastic vertebral metastases. It provides some degree of pain relief in about 80% to 90% of patients and complete pain relief in 50% to 60% of patients. In some instances, spine surgery is needed before external beam radiation therapy. When patients present with lower extremity weakness, numbness, or bowel or bladder dysfunction, an emergent surgical evaluation should occur because of concern for spinal cord compression. Surgery may also be indicated in cases of spinal instability or impending pathological fractures. A Spinal Instability Neoplastic Score can be calculated to help determine the need for surgery. In this patient, spinal stability was intact.

   In general, osteoclast inhibition is integral in the management of solid tumor skeletal metastases. In metastatic prostate cancer that is castration resistant (progression of disease on androgen deprivation therapy [ADT]), osteoclast inhibition with zoledronic acid or denosumab is used to prevent skeletal-related events and decrease pain. However, there are little data supporting the use of these 2 medications in patients presenting with metastatic hormone-sensitive prostate cancer (prostate cancer that is metastatic at diagnosis or that continues to respond to ADT). One trial found no improvement in time to the first skeletal-related event or overall survival with zoledronic acid compared with placebo in patients who presented initially with metastatic prostate cancer. There are no data on the use of denosumab in metastatic hormone-sensitive prostate cancer. Teriparatide is contraindicated in patients with skeletal metastases and may increase the risk of further skeletal metastases.

   At follow-up 5 days after discharge, our patient’s pain regimen included frequent use of hydromorphone, naproxen, and acetaminophen. While using these pain medications, the patient had a baseline pain level of 5/10 with frequent escalation to 8/10. After 1 round of palliative external beam radiation therapy to T9 through T12, the patient’s pain dramatically improved to 2/10. He was
seen 3 days later by an oncologist to determine therapeutic options.

4. Which one of the following is the best treatment regimen given this patient’s diagnosis?
   a. Androgen deprivation therapy
   b. Docetaxel
   c. Androgen deprivation therapy + abiraterone
   d. Androgen deprivation therapy + docetaxel
   e. Androgen deprivation therapy + docetaxel + prostate radiation therapy

Androgen deprivation therapy is the cornerstone treatment of metastatic prostate cancer, but progression of disease while taking ADT is seen at a median interval of 1 year. In 2015, 2 studies—Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) and ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)—found that patients may benefit from additional treatment with either abiraterone + glucocorticoids or docetaxel, particularly those with high volume disease. The survival benefit of adding abiraterone + glucocorticoids with ADT was confirmed again in Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer (LATITUDE) published in 2017.

Docetaxel is a taxane chemotherapeutic agent used in the treatment of various solid tumors. It was first approved for metastatic breast cancer in the 1990s and since then has been used for various cancers including prostate cancer. However, docetaxel alone should not be the initial therapy for metastatic hormone-sensitive prostate cancer without combining a form of ADT.

The STAMPEDE, CHAARTED, and LATITUDE trials revealed that patients with metastatic hormone-sensitive prostate cancer had increased survival when ADT was combined with other agents. The decision to add additional therapies to ADT should be personalized. It may be reasonable for patients with decreased functional status, advanced age, significant comorbidities, or low volume disease to continue with ADT alone. Given our patient’s good functional status, younger age, and high volume disease, he would benefit from a treatment plan containing ADT and an additional agent.

When abiraterone is combined with ADT, it is always used in conjunction with glucocorticoids. Abiraterone blocks 17α-hydroxylase and causes mineralocorticoid precursors to accumulate upstream from this enzyme, resulting in hypokalemia and hypertension unless glucocorticoids are simultaneously administered.

A docetaxel-containing regimen, as compared with the abiraterone-containing regimen, would be more beneficial because abiraterone has been found to increase lower extremity edema, which was considerable in this patient. The addition of radiation therapy to docetaxel and ADT was also evaluated in the STAMPEDE trial, which reported no overall survival benefit.

Before his initial discharge, our patient began taking ADT. At his follow-up appointment with an oncologist, it was decided to pursue combination therapy with ADT and 6 cycles of docetaxel.

5. Given this patient’s diagnosis and his current therapy, which one of the following most accurately represents his expected length of survival?
   a. 3 months
   b. 12 months
   c. 15 months
   d. 34 months
   e. 51 months

Three-month predicted survival is an underestimate of this patient’s prognosis and instead reflects more similarly the median overall survival of metastatic pancreatic cancer. The overall survival of patients with metastatic hormone-resistant prostate cancer after failing subsequent docetaxel and who choose no further treatment have a prognosis of about 10 to 14 months. However, if these patients subsequently choose further treatment with abiraterone + glucocorticoids or
another chemotherapeutic agent such as cabazitaxel, prognosis is about 15 months. If our patient was to be treated with ADT alone, as was standard practice before 2015, 34 months would be the expected survival. However, he is being treated with combined ADT and docetaxel. Based on follow-up of patients with high volume disease in CHAARTED, his overall prognosis is about 51 months with combination therapy.1,1

Our patient had an infusion reaction after his first cycle of docetaxel. His course was further complicated by neutropenic fever and Escherichia coli bacteremia in the case of an obstructive kidney stone. Docetaxel is known to cause neutropenic fever in 8% to 12% of patients. Eventually, he was able to complete all 6 cycles of docetaxel. His final PSA level while being treated with long-term ADT was 1.4 ng/mL.

DISCUSSION
Prostate cancer is the most common solid organ cancer in men with a lifetime risk of 11%. Age, race, and family history are the predominant risk factors. The incidence in black men is 60% higher than that in white men. Those with a first-degree relative diagnosed are twice as likely to develop prostate cancer than the general population. Most commonly, prostate cancer in its early stages is asymptomatic. When symptoms are present, the most common include nonspecific urinary symptoms such as frequency, urgency, hematuria, or hematospermia.

In men presenting with new, progressing, and unremitting back pain in the case of other signs and symptoms such as inguinal lymphadenopathy, hematuria, and lower extremity swelling, metastatic cancer should be in the differential diagnosis. Because the benefit of prostate cancer screening is unclear despite prostate cancer being the second leading cause of cancer death in men, clinicians must have a high index of suspicion. Prostate cancer is most frequently diagnosed and treated while still localized, though the proportion of patients who present with metastatic disease may increase as guidelines for screening change.

Most men with metastatic prostate cancer have metastases to bone, particularly the vertebrae and pelvis, and regional lymph nodes. Once metastatic prostate cancer is suspected, biopsy of the prostate is helpful to determine a Gleason score, eligibility for clinical trials, and for prognostic purposes. Occasionally, biopsy is completed at other metastatic sites for diagnostic confirmation. Skeletal metastases frequently are a source of considerable pain and can lead to spinal cord compression. If spinal cord compression is noted, urgent surgical intervention is warranted. The primary treatment of vertebral metastases is external beam radiation. In regard to systemic therapy, the backbone has been ADT for several decades. In 2015, additional therapies for metastatic hormone-sensitive prostate cancer were noted to provide significant survival benefit, such as docetaxel or abiraterone with a glucocorticoid. These combination therapies have been found to improve overall survival by about 13 to 17 months.7-9,12

Potential Competing Interests: The authors report no competing interests.

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REFERENCES


**CORRECT ANSWERS**: 1. c. 2. c. 3. a. 4. d. 5. e