A 73-year-old man presented to primary care for an annual examination. Four days prior, he noted right-sided sharp jaw pain such that he could not open his mouth nor chew solid food; it radiated from the right mandible to the ipsilateral temple. He also noted bilateral aching hip pain for several years that increased in severity in the prior 2 months. He reported an intentional weight loss of 9 kg over the past year, achieved through dietary modification. He denied fever, chills, and visual disturbance.

Acute onset of unilateral jaw pain that is worsened by chewing is a feature consistent with a temporomandibular disorder (TMD). TMD consists of musculoskeletal and neuromuscular conditions that affect the temporomandibular joints (TMJs), masticatory muscles, and associated tissues. Common symptoms of TMD include facial or ear pain, temporal headache, and TMJ dysfunction or discomfort. In addition to TMD, craniofacial pain has many possible etiologies such as dental pathology, neuralgias, sinus and otologic disorders, headache and migraine disorders, infections, rheumatologic conditions, and neoplasms.

Systemic etiologies for this patient’s symptoms are a consideration given his age and concomitant worsening of chronic hip pain. Rheumatologic conditions such as giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are more common in adults older than 50 years of age and cause headache, jaw claudication, and pelvic girdle pain. Rarely, hematologic malignancies (eg, lymphoma), solid tumor metastases (eg, breast cancer, melanoma), and primary tumors of the head and neck (eg, nasopharyngeal carcinoma) can involve the mandible, TMJ, or parotid gland and result in symptoms of TMD.

Medical history was notable for hypertension and type 2 diabetes mellitus complicated by peripheral neuropathy. He smoked one pack of cigarettes daily for 40 years but quit 15 years prior. He drank 4 ounces of vodka each night.

On examination, temperature was 36.5°C, heart rate 92 beats per minute, blood pressure 127/60 mmHg, respiratory rate 12 breaths per minute, oxygen saturation 98% on ambient air, and weight 118 kg. Extraocular movements were intact, pupils were equal and reactive to light and accommodation, and there were no visual field deficits. Nondilated funduscopic examination revealed normal blood vessels, optic disc, and optic cup-to-disc ratio. Dentine was good with pink gingiva. Bilateral temples were nontender. There was normal range of motion and strength in the shoulders, hips, and lower extremities with no tenderness over the trochanters. Patellar and ankle reflexes were present and symmetric bilaterally. He had no rashes or ecchymoses.

The appointment occurred during evening hours and the patient declined further evaluation until the following morning, at which time laboratory studies revealed normal serum levels of electrolytes, blood urea nitrogen, and creatinine. White blood cell (WBC) count was 6,800/mm³ with an immature granulocyte ratio of 1.8% (normal, 0.0-0.5%), hemoglobin 13.2 g/dL, and platelet count 163,000/mm³. ESR was 118 mm/hr (normal, 0-15 mm/hr) and CRP was 1.5 mg/dL (normal, 0-0.75 mg/dL). Radiographs of the hips and pelvis showed osteoarthritis of the bilateral hip joints and degenerative disc disease of the lower lumbar spine.

Granulocytosis may occur in response to infection, rheumatologic conditions, and hematologic malignancies such as chronic myelogenous leukemia. While infectious etiologies (eg, abscess, osteomyelitis) are the most common cause of an extremely elevated ESR level, this patient does not have other signs or symptoms of infection such as fever or leuko-
A 10-day course of prednisone 60 mg daily was prescribed for empiric treatment of GCA. The patient was discharged home with follow-up scheduled in rheumatology and primary care clinics. Pain in the jaw and temple resolved within several days.

Two weeks later, he presented to the rheumatology clinic. He noted 1 week of lower right back pain described as dull, aching, radiating to the lateral right hip, and occurring when transitioning from sitting to standing. He had no leg numbness, weakness, or change in bowel habits. Bladder habits were also unchanged, although he reported chronic urinary frequency and occasional incontinence. He reported further weight loss, this time an unintentional loss of 9 kg. He noted frequent sweating but no fever.

He reported a normal colonoscopy within the prior 5 years.

Because these records were not available for review, a fecal immunochemical test was obtained and negative for hemoglobin. He had previously declined prostate cancer screening.

The resolution of jaw and temple pain with prednisone supports the presumed diagnosis of GCA. Up to half of patients with GCA may also have PMR, which can cause aching and stiffness in the arms, hips, and lumbar region, and pain may be abrupt in onset. However, PMR-related pain would be expected to improve rather than develop or worsen in the setting of high-dose glucocorticoid use. Therefore, other causes of acute-onset back pain must be considered.

While localized musculoskeletal etiologies such as lumbar muscle strain, radiculopathy, and vertebral compression fracture are possible, co-occurrence of unintentional weight loss and diaphoresis with elevated inflammatory markers suggests a systemic etiology. A neoplastic process with bony metastasis is possible. The reportedly normal colonoscopy and the negative fecal immunochemical test make colorectal cancer less likely. Inflammatory conditions such as ankylosing spondylitis and rheumatoid arthritis are also possible. Ankylosing spondylitis usually presents at a much younger age, however, and axial skeletal involvement in rheumatoid arthritis often involves the cervical spine and is usually seen after longstanding disease. Additionally, the hallmark of inflammatory back pain is morning stiffness which the patient does not endorse. Nonetheless, additional laboratory testing should include antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP) antibody. Vertebral osteomyelitis remains on the differential diagnosis, and repeat WBC count and inflammatory markers should be assessed. Lumbosacral radiographs should be obtained to rule out fracture.

Physical examination in the rheumatology clinic revealed a temperature of 37.0°C, heart rate 100 beats per minute, blood pressure 146/72 mmHg, respiratory rate 12 breaths per minute, and oxygen saturation 98% on ambient air. Weight was 109 kg. He was pale and diaphoretic. There was diffuse tenderness to palpation of the right-sided lumbar paraspinal muscles. Straight leg raise was negative bilaterally. Patellar reflexes and gait were normal.

Blood chemistries, renal function, and aminotransferase levels were normal. WBC count was 7,100/mm³, hemoglobin 8.0 g/dL, mean corpuscular volume 88.9 fL, platelet count 128,000/mm³, ESR 66 mm/hr, CRP 0.57 mg/dL, alkaline phosphatase 438 IU/L (normal, 30-130 IU/L), and thyroid-stimulating hormone 0.925 mU/L (normal, 0.34-5.60 mU/L). Testing for antinuclear antibodies, rheumatoid factor, and anti-CCP antibody was unremarkable. Prostate-specific antigen (PSA) level was 2.2 ng/mL (normal, 0-4 ng/mL). Urinalysis was unremarkable. Antibodies to hepatitis C and Treponema pallidum were negative. Interferon gamma release assay was negative.

Findings of new onset anemia and thrombocytopenia, in combination with elevated ESR and alkaline phosphatase level, are concerning for disseminated intravascular coagulation (DIC).
and microangiopathic hemolytic anemia (MAHA), bone marrow infiltration of a metastatic neoplasm, or ineffective hematopoiesis caused by myelodysplastic syndromes or myelofibrosis.

Laboratory evaluation should include iron studies, lactate dehydrogenase (LDH), haptoglobin, fibrinogen, D-dimer, reticulocyte count, and peripheral blood smear to assess for hemolysis and erythrocyte morphology. Advanced imaging with lumbosacral magnetic resonance imaging (MRI) should be obtained to evaluate for focal etiologies of back pain such as disc herniation, abscess, marrow infiltration, and infarction.

Additional laboratory studies revealed a gamma-glutamyl transferase level of 49 IU/L (normal, 8-56 IU/L), LDH 288 IU/L (normal, 98-192 IU/L), haptoglobin 495 mg/dL (normal, 32-240 mg/dL), fibrinogen >700 mg/dL (normal, 225-550 mg/dL), D-dimer 693 ng/mL (normal, 200-250 ng/mL), serum iron 57 mcg/dL (normal, 33-150 mcg/dL), total iron binding capacity 286 mcg/dL (normal, 250-450 mcg/dL), ferritin 1,012 ng/mL (normal, 17.9-464 ng/mL), and reticulocyte count 2.9% (normal, 0.5-2.5%). Coagulation studies and serum protein electrophoresis were normal. Erythropoietin level was 109 mIU/mL (normal, 4.0-20.0 mIU/mL). Peripheral blood smear demonstrated moderate anemia with 8% nucleated erythrocytes per white blood cell (normal, 0%) and no circulating blasts.

MRI of the thoracolumbar spine and pelvis revealed diffusely abnormal bone marrow signal with multiple superimposed focal and poorly defined enhancing lesions along the lumbar spine marrow, sacrum, and bilateral iliac bones (Figure 1). Positron emission tomography/computed tomography (PET/CT) scan showed no scintigraphic evidence of metabolically active neoplastic, paraneoplastic, or inflammatory disorder.

The elevated haptoglobin, normal coagulation studies, and absence of fragmented erythrocytes on peripheral smear exclude an intravascular hemolytic process. The patient’s lower than expected reticulocyte count for the degree of anemia, elevated erythropoietin, and nucleated erythrocytes constitute a pattern that can be seen with bone marrow infiltration. There are no circulating blasts, making leukemia less likely. A solid organ tumor with bone metastases may cause enhancing lesions on MRI since this form of imaging is more sensitive than radiography for detecting skeletal malignancies. The negative PET/CT, however, does not reveal a primary tumor. Myelofibrosis is an infiltrative myeloproliferative disorder associated with nonspecific laboratory abnormalities, bone pain, weight loss, and night sweats that could cause diffuse MRI bone marrow signal alterations with normal PET/CT findings. However, myelofibrosis would not typically cause a significantly elevated ESR, and thus would be an unlikely cause for this patient’s presentation.

Given the constellation of symptoms, hematologic abnormalities, and bone marrow infiltration on imaging, hematology should be consulted to perform a bone marrow biopsy to assist with definitive diagnosis.

Bone marrow biopsy demonstrated metastatic adenocarcinoma consistent with prostatic origin (Figure 2). Bone scan demonstrated widespread osteoblastic metastases, which included the skull and temporal regions. These lesions were thought to be the cause of the patient’s original presenting symptom of jaw pain.

The patient was started on androgen deprivation therapy, initially with degarelix and subsequently leuprolide shots and abiraterone with prednisone. PSA was 0.08 ng/mL after 3
months of androgen deprivation therapy. His back and hip pain slowly improved.

DISCUSSION
Prostate cancer is the most common cancer in men with one out of every nine men diagnosed in his lifetime. While most men initially present with localized, curable disease, present with metastatic disease, an incidence that has been increasing since 2004. Despite available treatments, metastatic prostate cancer has a poor prognosis, with an average overall survival of approximately 5 years.

Prostate cancer can be challenging to diagnose. Men with prostate cancer are commonly asymptomatic. Rarely, patients may present with hematuria, bony pain caused by metastasis, or obstructive urinary symptoms like hesitancy or incomplete bladder emptying. Our patient presented with jaw pain, which was ultimately attributed to osteoblastic lesions of the skull. Additionally, his history of urinary frequency and incontinence may have been clues to his underlying diagnosis of prostate cancer.

Prostate cancer screening remains highly nuanced and relies on shared decision-making between patients and healthcare providers. Clinical practice guidelines for early detection of prostate cancer recommend individualized PSA-based serologic screening. Specifically, the United States Preventive Services Task Force recommends screening men aged 55 to 69 years who desire screening and understand the potential harms associated with a positive test result. These harms may include psychological distress and complications from prostate biopsy (eg, pain or infection) or prostate cancer treatment (eg, erectile, urinary, and/or bowel dysfunction). The decision to screen can be guided by individuals’ risk factors including African American race, family history, and older age.

While our patient elected not to undergo routine prostate cancer screening, a PSA level was obtained during his diagnostic evaluation and highlights the limitations of PSA-based screening. A PSA level ≤4.0 ng/mL has 21% sensitivity and 91% specificity for detecting prostate cancer. PSA levels above 4.0 ng/mL warrant repeat testing and, if persistently elevated, referral to urology for possible prostate biopsy. PSA levels often correlate with burden of disease, and patients with PSA levels >20 ng/mL are referred for CT imaging to evaluate for metastatic disease. PSA’s poor sensitivity was underscored in a study by Thompson et al who evaluated the incidence of prostate cancer in men participating in the Prostate Cancer Prevention Trial with PSA levels of <4 ng/mL. In this study, 15% of men diagnosed with prostate cancer never had a PSA level >4 ng/mL. While most of the cancers in this study were low grade and may have been clinically insignificant, 15% demonstrated histologic signs of at least intermediate-risk disease. Our patient’s PSA level of 2.2 ng/mL was below the threshold that triggers additional evaluation even though he had widely metastatic prostate cancer.

Our patient’s severe jaw and temple pain, weight loss, and progressive hip pain were concerning for GCA. This vasculitis of large- and medium-sized arteries predominantly affects older adults with greatest incidence among those 70 years of age and older. Symptoms occur because of cranial artery inflammation and may include headache, visual disturbance, erythema or tenderness of the temporal artery, and jaw claudication. Extracranial inflammation may affect the thoracic aorta and its branches and rarely the abdominal aorta and lower limb arteries. Pelvic girdle pain more typically results from associated PMR. Patients may also note systemic symptoms such as fever, weight loss, and fatigue.

Prompt diagnostic testing is important when considering GCA. Most patients with GCA have ESR levels greater than 40 mm/hr. ESR is a laboratory test that measures the vertical distance erythrocytes travel in a column of blood over 1 hour; in the setting of inflammation, cells form clumps and travel more quickly than individual cells, resulting in a higher value. While moderate elevations in ESR may occur without an identifiable cause, extreme ESR levels—those above 100 mm/hr, as observed in our patient—are highly suggestive of certain serious conditions, including infection, malignancy, and autoimmune disease such as GCA. Temporal artery biopsy is the gold standard test to diagnose GCA. However, because of noncontiguous inflammation of the temporal artery, biopsies may be falsely negative. Thus, sampling of the contralateral temporal artery may be warranted if suspicion remains high.

As was the case for our patient, PET/CT is not reliable for diagnosing prostate cancer. In contrast to other malignancies (eg, lymphoma, lung cancer), prostate cancer typically does not display increased glucose metabolism. Moreover, the close proximity of the bladder and prostate can interfere...
with imaging interpretation because the fluorodeoxyglucose (FDG) tracer is excreted in the urine.14 The reported sensitivity of PET/CT for the diagnosis of prostate cancer ranges from 17%-65%.15,16 In a small study of men with metastatic prostate cancer, only 18% of bony metastases were FDG avid, and there was no correlation between FDG avidity and PSA level.15 Notably, although PET/CT includes CT imaging, this CT is used to map anatomic landmarks and is not separately interpreted by the radiologist. Thus, even if evidence of prostate cancer was apparent on traditional CT, it may be overlooked on PET/CT.

Several important points regarding diagnostic testing are raised by this case. First, PSA-based screening for prostate cancer may be falsely negative, even in the setting of widely metastatic disease. Second, extreme ESR elevation is a marker for serious underlying disease and warrants a thorough diagnostic evaluation. Finally, PET/CT has limited diagnostic utility in evaluating metastatic prostate cancer because of the normal rates of glucose metabolism. Our patient initially presented with jaw pain, yet his progressive physical symptoms and laboratory abnormalities prompted an evaluation which ultimately revealed the jaw-dropping diagnosis of PSA-negative, metastatic prostate cancer.

**KEY TEACHING POINTS**

- ESR levels greater than 100 mm/hr are highly suggestive of certain serious conditions including infection, autoimmune disease, and malignancy.
- PSA-based screening for prostate cancer can result in false negative test results. In one study, 15% of men diagnosed with prostate cancer never had a PSA level greater than 4 ng/mL (ie, the level at which repeat laboratory testing and/or referral to urology for possible prostate biopsy is advisable).
- PET/CT has limited diagnostic utility in evaluating metastatic prostate cancer, because prostate cancer cells typically demonstrate normal glucose metabolism.

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**References**