76-Year-Old Man With Back Pain and Progressive Leg Weakness

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A 76-year-old man, who was healthy until 1 month before hospital admission, tripped and injured his right hip and lower back while descending stairs. The patient experienced localized pain in the right lumbar region, superior to the iliac crest, which resolved initially with anti-inflammatory agents. He was fully ambulatory preceding and just after this event. The patient’s discomfort worsened during the next few days. Progressive lower extremity weakness ensued, impairing mobilization. The patient initially required use of a cane and then a walker. One week before admission, his pain radiated to his left knee, and he was unable to ambulate, even with the walker. The patient’s discomfort was rated at 6 on a 10-point scale of severity; his pain was sharp, exacerbated by movement, and relieved mildly by immobilization, although still noticeably present at rest. The patient denied numbness, tingling, treatment with saddle block anesthesia, and urinary or bowel dysfunction. He had no fevers, chills, myalgias, or appetite changes but noted a 4.5-kg weight loss during the preceding 2 months. A review of systems was notable for recent constipation while taking opioid analgesics but was otherwise unremarkable.

The patient’s history was remarkable for hyperlipidemia, bilateral knee arthroplasties, asthma, gastroesophageal reflux, hypertension, and benign prostatic hypertrophy. He underwent parathyroidectomy for a parathyroid adenoma 12 years previously. Medications on admission included diltiazem, atorvastatin, omeprazole, aspirin, and a multivitamin. The patient did not smoke, and alcohol intake was minimal. His family history was notable for a son with testicular cancer.

On examination, the patient’s temperature was 37.1°C, blood pressure was 140/90 mm Hg, heart rate was 72 beats/min, and respiratory rate was 12/min. Notable findings included tenderness overlying the lumbar spine and paraspinal muscles, with symmetrical weakness in the lower extremities and no paresthesia or extensor plantar responses. His pain radiated down both legs to each knee and was exacerbated by slight leg movement. Rectal examination revealed normal anal tone and sensation. Reflexes were bilaterally symmetrical.

1. Based on the patient’s medical history and physical examination on admission, which one of the following is the most likely cause of his back pain?
   a. Mechanical low back pain
   b. Neoplasm
   c. Spinal stenosis
   d. Osteoporotic compression fracture
   e. Psychiatric disease

Although mechanical back pain is a common presenting symptom that may lead to radicular pain, it rarely causes constant pain or progressive motor abnormalities. It is not associated with constitutional symptoms, making this choice unlikely. Neoplasm is the most likely choice in this patient because he presented with constitutional symptoms, continuous pain, and progressive motor symptoms. Buttock discomfort is seen usually in spinal stenosis and was characteristically absent in our patient; also, the patient’s discomfort was present continuously and not relieved on sitting or lying down, which is normally seen in this disorder. Radicular pain is exceedingly uncommon in osteoporotic compression fractures but is possible. However, patients with osteoporotic fractures do not lose weight and are asymptomatic except for focal pain that increases with movement. Moreover, our patient had no traditional risk factors for osteoporosis other than recent immobility, making this choice less likely. The patient had no psychiatric history and had objective features on physical examination, making a diagnosis of psychiatric-induced low back pain highly unlikely.

Initial laboratory data revealed normocytic normochromic anemia with a hemoglobin of 12.8 g/dL, platelets of 339 × 10^9/L, white blood cells of 9.1 × 10^9/L, bicarbonate of 31 mEq/L, chloride of 97 mEq/L, serum urea nitrogen of 35 mg/dL, creatinine of 2.1 mg/dL, calcium of 12.9 mg/dL, phosphorus of 4.6 mg/dL, and albumin of 2.8 g/dL. The white blood cell differential was normal with no evidence of blasts. Plain radiographs showed mild degenerative changes in the lower thoracic spine and a compression fracture in the L1 vertebral body with an approximate 30% to 40% loss of height. There was also compression of the right side of the body of L4 and left side of the body of L3.
Moreover, sclerotic changes were seen in the innominate bones bilaterally.

2. After evaluation of initial laboratory data, which one of the following is the most likely diagnosis?
   a. Lymphoma
   b. Mechanical low back pain
   c. Multiple myeloma
   d. Monoclonal gammopathy of undetermined significance
   e. Surrupitious use of vitamin D

Cortical bone involvement and hypercalcemia are not common presentations for lymphomas. Mechanical low back pain characteristically does not cause metabolic abnormalities and definitely would not result in compression fractures. Multiple myeloma is the most likely diagnosis based on our patient’s anemia, mild renal insufficiency, hypercalcemia, and x-ray findings. Monoclonal gammopathy of undetermined significance is not a reasonable diagnosis because characteristic hypercalcemia, renal failure, and bone lesions are absent. Excessive vitamin D use would cause hypercalcemia and hyperphosphatemia but would not account for renal insufficiency or the radiographic lesions.

Our initial clinical impression at this time was that the patient had multiple myeloma. The degree of hypercalcemia was concerning at the time of admission.

3. Which one of the following is the best initial treatment of this patient’s hypercalcemia at this stage?
   a. Intravenous fluids only
   b. Intravenous fluids and calcitonin only
   c. Intravenous fluids and furosemide
   d. Intravenous fluids, pamidronate, and calcitonin
   e. Hemodialysis

Patients with hypercalcemia are often intravascularly depleted, which can compromise renal function and impair calcium clearance. Intravenous fluid would restore hydration and promote calciuresis; however, normal calcium levels are rarely achieved in severe hypercalcemia with fluid alone. Calcitonin administered intranasally or subcutaneously, although expensive, is effective in early management, but its effects are fast-acting and short-lived; thus, this choice combined with fluids is inappropriate for achieving sustained normocalcemia. Furosemide with intravenous fluids can promote calcium excretion but cannot maintain it. Pamidronate is an effective bisphosphonate that, when given intravenously, can inhibit bone resorption by inhibiting osteoclast formation. Its onset of action is delayed, occurring within 24 to 48 hours of initiation. Coadministration of calcitonin and pamidronate with aggressive hydration is the best treatment option because it allows both short-term and long-term maintenance of normocalcemia. Although hemodialysis with use of a calcium-free dialysate may be effective, its indications are reserved for patients with severe renal or cardiac failure whose fluid balance is tenuous.

Normal saline at a rate of 250 mL/h was administered with careful monitoring of urine output and physical examination. Subcutaneous calcitonin, intravenous pamidronate, and oxycodone for pain control were given initially. The patient developed substantial lower extremity edema and some bibasilar crackles, prompting use of intravenous furosemide. Thyrotropin and prostate-specific antigen levels were within normal limits. The patient’s serum calcium level normalized on day 5.

4. Which one of the following imaging techniques is best for investigating our patient’s back pain, weight loss, lower extremity weakness, and possible malignant disease?
   a. Magnetic resonance imaging (MRI)
   b. Radionuclide bone scanning
   c. Positron emission tomography (PET)
   d. Computed tomography (CT)
   e. Myelography

Although back pain is a common complaint, emergent MRI is warranted for patients presenting with neurologic signs, recent spinal procedures, constitutional symptoms, bowel or bladder symptoms, or a history of cancer to rule out spinal cord compression or cauda equina syndrome. Radionuclide bone scanning depends predominantly on osteoblastic activity. The sensitivity of this technique is 40% to 60% for evaluation of osteclast-predominant bone activity in myeloma; hence, it may miss lesions that cause spinal cord compression and poorly visualizes thecal sac compression. PET is being used increasingly to manage malignant disease, but data regarding its use in spinal cord compression are inconclusive. Although PET is useful in fluorodeoxyglucose F 18–avid tumors, uptake may be detected in benign changes, causing difficulties in precise anatomical localization. Furthermore, PET may not be available on an emergent basis and therefore cannot be recommended at this time. Computed tomography is useful to better characterize and describe lesions seen on alternative forms of imaging but not to localize lesions in broad anatomical areas. Furthermore, CT poorly characterizes the epidural space, making a determination of whether there is compression more difficult. Myelography is certainly an alternative to MRI and is used commonly in patients with contraindications to MRI; however, it is an invasive procedure and is unlikely to be available on an emergent basis.

In our patient, MRI of the entire spine revealed numerous foci with increased signal enhancements of cortical bone at multiple levels in the cervical, thoracic, and lumbar
regions, with no evidence of spinal cord compression. He continued to receive intravenous hydration and responded to analgesia. Further laboratory work-up revealed the following (reference ranges shown parenthetically): a small abnormality in the gamma fraction, with a monoclonal IgG κ protein on immunofixation on both serum and urine electrophoresis; β₂-microglobulin level, substantially elevated at 4.30 μg/mL; parathyroid hormone level, suppressed at less than 0.4 pmol/L (1.1-5.8 pmol/L), as was parathormone–related peptide level at 0.5 pmol/L (<2.0 pmol/L); 25-hydroxyvitamin D level, elevated at 52 ng/mL (8-38 ng/mL); lactate dehydrogenase (LDH) level, substantially elevated at 611 U/L (122-222 U/L), as was alkaline phosphatase level at 191 U/L. Our working diagnosis was multiple myeloma, prompting a bone marrow biopsy as the next indicated test. It showed profoundly decreased hematopoietic elements, normocytic normochromic anemia, and a large B-cell lymphoma with extensive necrosis. A single viable focus was markedly hypercellular and reacted to CD20 monoclonal staining pattern for κ immunoglobulin light chains. All other markers, including CD3, CD30, CD34, CD138, keratin, and myeloperoxidase, were negative, supporting a diagnosis of malignant lymphoma. A core biopsy of a lytic lesion performed immediately before the marrow studies corroborated this diagnosis. Staging CT revealed no masses or lymphadenopathy. The hematology service evaluated the patient and suggested initiation of R-CHOP chemotherapy (rituximab-cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone) for his stage IV disease.

5. Which one of the following is least likely to be useful in this patient’s treatment before initiation of chemotherapy?
   a. Echocardiography
   b. Aggressive hydration and allopurinol administration
   c. Cerebrospinal fluid examination
   d. Liver function tests
   e. Pulmonary function tests

In patients who receive doxorubicin as part of their chemotherapeutic regimen, obtaining a baseline echocardiogram is warranted because cardiomyopathy may ensue in as little as 1 week, but more commonly within 1 year. Aggressive hydration and allopurinol are needed to prevent tumor lysis syndrome characterized by hyperkalemia, hyperuricemia, and hypocalcemia, which can be seen with large tumor burdens. Cerebrospinal fluid examination for cytology is important to exclude central nervous system (CNS) lymphoma involvement because the leptomeninges often are involved. Liver function tests are necessary for adjusting chemotherapy dosing because the liver metabolizes most agents. Pulmonary function tests are useful for baseline studies in patients receiving chemotherapeutic agents, such as bleomycin, which can predispose patients to fibrosing alveolitis or other restrictive lung diseases; however, these tests are not necessary.

The patient was transferred subsequently to the hematology service, where R-CHOP chemotherapy was initiated. The hypercalcemia and renal insufficiency resolved, and the patient was discharged. He has received 7 courses of chemotherapy with moderate improvement in his mobility and neurologic function.

DISCUSSION

Diffuse large B-cell lymphomas are the most common type of non-Hodgkin lymphomas, accounting for 40% of all lymphoma diagnoses yearly, with an increasing incidence among developed nations and with rates in African Americans and Asian Americans lower than those in white persons. Risk factors include family history; older age; exposure to infectious pathogens such as hepatitis C virus, human immunodeficiency virus, and Helicobacter pylori and to toxins such as hair dye; and occupational exposure to substances such as benzene, vinyl chloride, and pesticides. There is a slight preponderance in males.

Diffuse large B-cell lymphomas can develop de novo or may result from a prior indolent lymphoma that is diagnosed at the time of transformation into a large B-cell lymphoma. Morphologic variants include centroblastic, immunoblastic, anaplastic, plasmablastic, multilobulated, and histiocyte-rich B-cell lymphomas. Subtypes include primary mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, and pyothorax-associated pleural lymphoma.

In general, patients may present with either nodal or extranodal disease, usually in the sixth or seventh decade of life. Extranodal presentation occurs in approximately 40% of patients and may be seen in the gastrointestinal tract, skin, bone, sanctuary sites such as the CNS and testes, and other organs. Bone marrow and vessel involvement is exceedingly rare. These patients typically have disseminated disease. Large, rapidly enlarging masses usually but not exclusively cause local symptoms. Patients with disseminated malignancy and an elevated LDH level are at increased risk of CNS invasion, warranting cerebrospinal fluid examination and/or MRI for cytologic analysis and meningeval enhancement, respectively. The B symptoms include temperature higher than 38 C, night sweats, and unexplained weight loss of more than 10% within 6 months; they can be seen in up to half of patients. Interestingly, patients with multiple myeloma often may have similar presentations—weakness, fatigue, and bone pain.
Treatment is determined on the basis of disease extent and severity. Alkylating regimens such as CHOP are mainstay. Newer evidence suggests that the addition of CD20 monoclonal antibody antagonists such as rituximab will increase response rates and 2-year survival rates, with odds ratios of 76% vs 60% and 70% vs 57%, respectively, in R-CHOP vs CHOP treatment arms. This cell surface marker is expressed on most lymphomatous cells but not stem cells, with its expression varying minimally at differing stages of the cell cycle. Although there is evidence that radiotherapy is helpful in confined stage I or II disease, randomized controlled trials are lacking that suggest any benefit of radiation therapy for disseminated disease.

Prognostic indices, such as the International Prognostic Index, have been developed to allow patient and outcome stratification at time of diagnosis. It is composed of 5 clinical factors: age older than 60 years, elevated LDH level, performance status of 2 or more (indicating increased symptoms from the lymphoma), stage III or IV disease, and more than 1 extranodal site. Some authors have described the addition of β2-microglobulin as a predictor for R-CHOP treatment failure. Patients are categorized into low, intermediate-low, intermediate-high, and high risk, depending on their scores. Our patient’s 3 risk factors placed him into an intermediate-high risk range with a 5-year survival of 43%. Randomized studies are under way to determine whether use of stem cell transplantation as consolidation or up-front therapy improves clinical outcome in this intermediate-high–risk group of patients.

Approximately 10% of patients with a malignancy develop hypercalcemia. Patients with myeloma usually have evidence of bone involvement, and up to one third of these patients may have evidence of hypercalcemia. These features are rarer in other hematologic malignancies, other than human T-lymphotrophic virus-1-related lymphoma. Lymphomas involving bone tend to occur in only 5% to 15% of all cases and are usually due to large B-cell, diffuse, or mixed lymphomas. Our patient had an unusual complication with a presenting feature that included bone lesions and hypercalcemia. Incidence of hypercalcemia in lymphoma has been examined in few series and is seen in 2% to 10% of all cases. Canellos has the most comprehensive series, in which 108 patients with non-Hodgkin lymphoma were examined, 3 of whom had notable hypercalcemia at presentation. Median survival of patients with hypercalcemia was 10 months in a series by Majumdar, although none of these patients had bone lesions or renal failure at the time of diagnosis, and none experienced complete remission after conventional therapy. Lymphomas affecting bone often have a better prognosis, with 5-year survival rates ranging from 40% to 70%. Treatment of such lesions often involves treating the underlying malignancy with systemic chemotherapy, followed by local radiotherapy in selected patients, which often improves overall prognosis. Our patient had no localized tumor site; therefore, radiation therapy was not administered.

In summary, there are numerous causes of hypercalcemia, and the general internist must be aware of its broad differential diagnosis. Our patient presented in a manner that prompted us to suspect a plasma cell disorder causing destructive bone lesions, hypercalcemia, and renal insufficiency. Non-Hodgkin lymphoma can mimic the clinical presentation of multiple myeloma. Likely mechanisms of hypercalcemia in our patient included lymphoma-induced 1α-hydroxylase activity and direct tumor invasion of bone. Our patient’s clinical course further exemplifies the aggressive nature of multiple myeloma and the possible difficulties in diagnosing it.

REFERENCES

Correct answers: 1. b, 2. c, 3. d, 4. a, 5. e