Orthopaedic Case of the Month: A 62-year-old Woman With Neck Pain and Neurologic Findings

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History and Physical Examination

A 62-year-old woman presented with 3 months of intractable neck pain with recent onset of upper extremity weakness and paresthesias. She reported no fever, weight loss, fatigue, or generalized malaise. She had subtle complaints of hand dexterity loss but said she had no problems with balance, and no bladder or bowel complaints. Analgesics and antispasmodic medications did not relieve her pain. Her medical history was significant for hypertension, hyperlipidemia, diabetes mellitus Type II, multiple sclerosis, depression, anxiety, obesity, and hypothyroidism. There was no history of antecedent trauma, previous rheumatologic phenomena, recurrent infections, or bleeding dyscrasia. There was no family history of cancer or congenital skeletal abnormalities. Review of systems was otherwise negative.

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On physical examination, the patient was afebrile with normal vital signs. She was oriented to person, time, and environment. The head was normocephalic and sclerae were anicteric. ROM of the neck was normal, and she had no pain with movement of her neck. She had no palpable lymphadenopathy. There was no tenderness to palpation of the posterior shoulder musculature. Cranial nerves II through XII were grossly intact; signs of hypocalcemia including Chvostek's sign and Trousseau's signs were not elicited. Abdominal examination was benign without hepatomegaly or splenomegaly. Neurologically, the patient had some mild weakness with wrist extension and finger extension on the left (C 4/5) but an otherwise normal examination with intact sensation and motor function in her lower extremities. Reflexes were brisk and symmetric. Hoffmann's sign was positive but symmetric suggesting an upper motor neuron lesion, but there was no elicitable clonus. Babinski response was plantar indicating a normal neurologic response in the lower extremities.

Laboratory examination showed a white blood cell count of 7.8, hematocrit of 37.3, mean corpuscular volume (MCV) of 84, with a normal differential (54% segmented neutrophils, 9% band neutrophils, 33% lymphocytes), normal chemistries including a serum calcium of 8.9 mg/dL, and an erythrocyte sedimentation rate of 100 mm/hour.

We obtained CT scans of the cervical spine (Fig. 1), head, and chest, abdomen, and pelvis, MR images of the spine (Fig. 2), and a whole-body bone scan.

Imaging Interpretation

The CT scan of the cervical spine showed a prevertebral lesion extending from C7 to T2 and a permeative pattern of bone destruction within the C7 vertebra (Fig. 1). MRI of

Fig. 1 An axial CT scan at the C7 level shows an inhomogeneous appearance of the vertebral body and lytic bone resorption (arrow).

the cervical, thoracic, and lumbar spine revealed diffuse marrow replacement and extension of a soft tissue mass into the prevertebral and epidural spaces from the C7 to T1 vertebrae (Fig. 2). The spinal cord signal was slightly increased on T2-weighted (Fig. 2A–B) and short-tau inversion recovery (STIR) sequences from C7 to T1 (Fig. 2C). Her head CT was negative for intracranial disorders and there were no signs of metastatic disease with whole-body imaging (bone scan, total spine MRI, and CT of the chest, abdomen, and pelvis). The bone scan showed no abnormal uptake in the cervical and thoracic spine.

Based on the history, physical findings, laboratory tests, and imaging studies, what is the differential diagnosis at this point?

Differential Diagnosis

Osteomyelitis
 Metastatic bone disease
 Myeloma
 Lymphoma
 Primary bone tumor (osteoblastoma, Ewing's sarcoma, osteosarcoma)
 Tuberculosis
 Hematologic-based malignancy with local epidural extension

A CT-guided biopsy was performed for histologic and microbiologic analyses, including hematoxylin and eosin

staining, immunostaining, flow cytometry, and cytogenetics (Fig. 3).

Based on the history, physical findings, laboratory tests, imaging studies, and histologic picture, what is the diagnosis and how should this lesion be treated?

Histology Interpretation

Cultures were negative for infection. Histopathologic analysis showed diffuse infiltrative atypical large lymphoid cells with prominent central nucleoli (Fig. 3A–B). Immunohistochemistry and flow cytometry were positive for CD20 (expressed by cells in the pro-B cell phase) and weakly positive for CD56 and BCL6. Ki67 (a protein measure of the degree of cellular proliferation) showed a 68% to 70% proliferation index. The histologic analysis was positive for terminal deoxynucleotidyl transferase (TDT) stain, which differentiates between acute lymphoblastic leukemia (positive) and acute myelogenous leukemia (negative).

Diagnosis

Acute lymphoblastic leukemia (ALL)

Discussion and Treatment

Our adult patient had a painful, aggressive-appearing bone lesion with epidural extension as the presenting complaint of ALL. To our knowledge, this is the first case of ALL initially presenting in an adult as either axial skeletal pain or myelopathy. This unusual presentation is attributable to the relatively low incidence of ALL in adults and the infrequency of ALL with axial skeletal or central nervous system (CNS) involvement. CNS involvement in this case is a result of bone involvement and epidural extension, not a primary intrathecal, intradural, or parenchymal insult.

Metastatic bone disease and infection as an etiology of our patient's presenting symptoms were higher on our differential diagnosis based on imaging alone and frequency of these diseases. CT and MRI findings showed a multilevel prevertebral involvement with marrow replacement and extension into the soft tissue that can be consistent with infection such as osteomyelitis or tuberculosis. The multilevel marrow changes raise suspicion that this may be a result of systemic disease. The combination of the bone scan, complete spinal MRI, and CT of the head, chest, abdomen, and pelvis decreased the likelihood of cervical metastasis from another primary solid tumor on the differential diagnosis. The absence of leukocytosis along with a negative microbiologic culture including

Fig. 2A–C (A) An axial T2-weighted image shows marrow replacement at the C7 level with an epidural mass extending from C7. The arrow on the left shows the bony lesion, while the arrow on the right shows the extension of the mass into the epidural space. (B) The sagittal T2-weighted image shows marrow replacement in multiple cervical levels (arrows), and (C) a sagittal STIR image shows cord compression at the T2 level with an increased cord signal (resultant edema) from C7 to T2. The arrow shows the affected levels with resultant edema.

acid-fast bacillus decreased the likelihood of infection in this patient. With the histologic analysis not showing glandular epithelial cells and cultures all being negative, both of these potential diagnostic categories were excluded. A comprehensive evaluation of the specimen with hematoxylin and eosin staining showing greater than 80% lymphoblasts, immunostains, flow cytometry, and cytogenetics establishing a B-cell lineage of rapid proliferation, and positive TDT stain confirmed the diagnosis to be ALL. Other primary bone tumors would reveal different histologic appearances, osteoid and irregularly shaped woven bone for example in osteoblastoma.

We reviewed the English literature describing pediatric and adult patients with ALL and “spinal cord compression” and “myelopathy” using a MEDLINE® database search between 1985 and 2012. The literature showed that a history of autoimmune disease increases the risk of cancer, not specifically hematologic-originating malignancies [16]. This is not a causal relationship as treatments for lupus and rheumatoid arthritis also are implicated.

B cell lymphoblastic neoplasms are classified as either acute lymphoblastic lymphomas or ALLs, depending on their presentation. If there is a mass lesion and less than 25% blasts in the bone marrow, then the disease is called acute lymphoblastic lymphoma. If there are greater than 25% blasts, regardless of the presence or absence of a mass lesion, then it is considered ALL. These entities represent the same disease with a different presentation, and both are treated with similar combination chemotherapeutic regimens [1]. Our patient had approximately 80% blasts on bone marrow biopsy from the iliac crest (Fig. 3A–B).

The diagnosis is made by bone marrow biopsy or biopsy of a mass lesion, which also allows for microbiology evaluation to rule out infection. Lymphoblasts have distinctive morphologic features on microscopy, but flow cytometry is essential for making the definitive diagnosis and classifying the disease. CBC laboratory values can vary, but approximately 50% of patients have normal or depressed white blood cell counts in peripheral blood evaluation on presentation [11].

Fig. 3A–C Histopathologic analysis showed the hypercellular marrow (**A**) with greater than 80% of cells represented by lymphoblasts (Stain, hematoxylin and eosin; original magnification, 600 $\times$), and (**B**) with lymphoblastic proliferation (Stain, hematoxylin and eosin; original magnification, 1000 $\times$). Atypical large lymphoid cells are

evident with prominent nucleoli. (**C**) An immunopathology slide shows a positive terminal deoxynucleotidyl transferase (TDT) stain. The TDT stain differentiates between ALL (positive) and acute myelogenous leukemia (negative) (Original magnification, 400 $\times$).

Expression of various B cell markers differentiates subforms of leukemia; T cell markers are negative in B cell disease. Many chromosomal translocations have been identified in adults with B cell disease, the most common of which is t(9;22)(a34;q11). This is commonly known as the Philadelphia translocation and is most commonly associated with chronic myelogenous leukemia. In adults with ALL, the Philadelphia chromosome occurs in 25% to 30% of patients and confers a poor prognosis when present [1]. Similarly, the presence of CNS involvement at the time of diagnosis has been found to be a statistically significant risk factor for mortality. In a cohort of 1500 adult patients with ALL, 5-year survival rates for patients with CNS involvement (approximately 5% of total patients) were 29% versus 38% for those without [10]. Cytogenetics performed in our patient were negative for Philadelphia chromosome or other rearrangements including myeloid and lymphoid or mixed lineage leukemia (MLL) gene.

ALL is the most common form of childhood leukemia, representing up to 80% of all childhood leukemias [3]. Less commonly, ALL can arise in adults, where it represents only approximately 2% of lymphoid neoplasms diagnosed yearly in the United States [4]. The demography of ALL is bimodal, with the majority of cases occurring in children aged 4 to 5 years (four to five per 100,000) and a second, smaller peak in the sixth decade (two per 100,000) [9, 13].

ALL initially presents with an acute and unexplained fever in approximately 50% to 60% of pediatric patients with the disease [13]. Other common presentations include symptoms involving the appendicular skeleton, including unexplained extremity pain, arthralgias, new-onset limping, or refusal to walk. This presentation of ALL occurs in approximately 1/2 of pediatric patients and generally is attributable to leukemic infiltration of appendicular bone, periosteum, marrow spaces, and/or joints [13, 15]. Compressive CNS symptoms or axial skeleton involvement at the time of ALL diagnosis is uncommon in children and

adults, with a reported prevalence of 3% to 7% [2, 9]. In the past, CNS involvement with ALL has been a telltale sign of disease recurrence, with up to 75% of recurrent cases presenting with new-onset compressive CNS symptoms. These numbers have significantly declined in recent years owing to the addition of CNS-prophylactic chemotherapies [9]. The number of adults with ALL CNS disease today is believed to be approximately 5% to 10% [2].

Epidural spinal cord compression is a potential presentation of virtually any metastatic disease; infections, trauma, and degenerative disc disease, of course, can cause this symptom, as well. Estimates suggest that about 5% of the approximately 500,000 patients who die from cancer annually in the United States have epidural spinal cord compression [1]. Skeletal malignancies associated with epidural spinal cord compression include breast, prostate, lung, renal cell, lymphoma, and myeloma. Together, these represent approximately 90% of spinal tumors [14]. Epidural spinal cord compression secondary to leukemias of any kind are thought to occur in less than 1% of patients with epidural spinal cord compression secondary to tumors [2].

Axial skeletal pain is a common first presentation for metastatic disease, with radicular or myelopathic complaints being somewhat less common. This presentation may be underappreciated, however (ie, people do not usually think of a tumor in a patient with radiculopathy or myelopathy). Some alarming studies have found that epidural spinal cord compression may be the presenting symptom in up to 30% of newly diagnosed lung cancers [14]. Lymphoma and myeloma also have a disproportionate likelihood of first presenting with spine-related symptoms. Leukemias, conversely, rarely present with spine-related symptoms. Despite the frequency by which breast and prostate cancers metastasize to the spine, rarely do they present with epidural spinal cord compression [14].

To our knowledge, only 10 patients who presented with symptomatic spinal cord compression from mass effects of ALL have been reported [7, 8]. These cases all involved children between 3 and 15 years of age. These patients initially were treated with high-dose dexamethasone and chemotherapeutic regimens with rapid resolution of symptoms. There were no significant risk factors or demographic commonalities reported. As far as we are aware, this is the first adult patient to initially present with epidural spinal cord compression secondary to an epidural ALL lesion. In the handful of patients described with ALL and symptomatic epidural leukemic masses, the most commonly involved levels involved the thoracic spine (73% of patients) [12]. Thirty-four percent of such patients had involvements of the lumbar spine, 23% of the sacral spine, and 5% of the cervical spine [6].

Surgical intervention in a patient with widespread hematologic disease and symptomatic spinal cord compression is

often controversial. In a review of 10 pediatric patients with ALL and epidural involvement, only three patients (aged 4–14 years) underwent decompressive laminectomy [8]. Two of three of these patients had lesions in the lower thoracic spine and one in the lower cervical spine. Two of these three patients died in less than a year from diagnosis; outcome for the third patient was not reported. The standard treatment for ALL is chemotherapy with or without radiation as most patients respond to these therapeutic modalities. Surgical decompression is reserved for patients who have progressive neurologic symptoms refractory to nonoperative therapy. Our patient did not undergo surgical decompression but instead responded well to radiation and chemotherapy with rapid resolution of neurologic symptoms. She remains disease free at 2-year followup. While the overall prognosis for ALL in adult patients is poor for longevity, adequate symptomatic management often can alleviate neurologic symptoms and confer an improvement in quality of life.

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