Burkitt Lymphoma Presenting as Thoracic Back Pain

David Heltzel, MD, LT, USN and Eric Brumwell, MD, LCDR, USN

This case illustrates the difficulty—and critical importance—of recognizing a malignant cause of back pain when benign etiologies are far more common.

Approximately 90% of adult Americans experience back pain at some point in their lives, and 50% of the country's working population experience back pain each year.[1,2] Moreover, acute back pain represents the fifth most common reason for all physician visits in the United States.[3] Less than 1% of the general population presenting for back pain, however, have cancer.[3,4]

As a result, primary care providers' suspicion for malignant etiologies in patients presenting with back pain is generally low. In the rare cases in which cancer is the culprit, though, the prospect of rapidly progressing, undiagnosed and untreated disease is sobering. Given the low prevalence on the one hand and the danger of unchecked progression on the other, the challenge to primary care providers is to develop a diagnostic approach that accurately identifies malignancies while using resources in an economically responsible fashion.

In this article, we present a case of progressive thoracic back pain that led ultimately to a diagnosis of Burkitt lymphoma. This type of lymphoma is quite rare, representing less than 1% of all adult cases of non-Hodgkin lymphoma—and even fewer cases of spinal metastases.[5] Nevertheless, the case illustrates how providers can pick up on certain clinical "red flags" to arrive at the diagnosis of cancer with a minimum of delay. Following the case presentation, we provide a brief review of Burkitt lymphoma and make recommendations on conducting a workup of back pain that is therapeutic, timely, and cost-effective.

Dr. Heltzel and **Dr. Brumwell** are both flight surgeons at Naval Health Clinic, Naval Air Station, Patuxent River, MD.

INITIAL EXAM

A 40-year-old man presented to our health clinic reporting four weeks of persistent and progressive thoracic back pain. He had initially attributed his pain to back strain after laying the foundation of an addition to his house, and over the four weeks prior to the current presentation, he had been evaluated by two providers in his primary care practice and an emergency department provider. These providers had diagnosed him with thoracic back strain and recommended progressive modalities of treatment, including naproxen, diazepam, tramadol, physical therapy, massage, and chiropractic care. After each of these modalities, the patient experienced moderate but short-lived improvement of his symptoms.

At the present evaluation, he reported having had no urinary incontinence, fever, chills, weight loss, focal weakness, or gait abnormalities. He described the pain as being located in the right, mid-thoracic region of his back and radiating anteriorly. The pain was worse when he was lying down and kept him from sleeping at night, but it was otherwise unrelated to position. It did not improve with sitting or standing, although he reported feeling slightly better when active. His pain was not associated with eating or urination. It had progressed in severity from mild to moderate to severe over the four-week period.

The patient's medical history was unremarkable except for a recent workup for abdominal pain one month prior to the start of his back pain. During this workup, a computed tomography (CT) scan revealed ileal and jejunal wall thickening, which raised suspicion for an intussusception or Crohn's disease. A colonoscopy was unrevealing. His ileocecal junction and ileal mucosa were normal, and his abdominal pain resolved after a brief hospital stay. There was no clinical evidence of a small bowel obstruction and no identifiable intra-abdominal pathology.

The patient reported no significant family history of cancer. Results of his physical examination were normal and revealed no significant focal tenderness or neurologic signs. A complete blood cell count revealed a mild normocytic and normochromic

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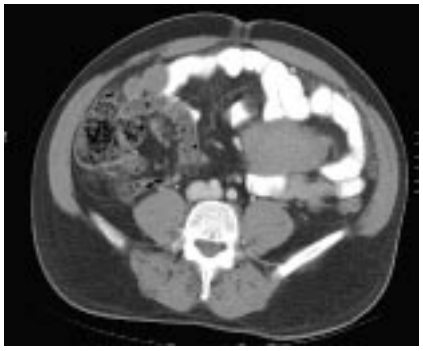

Figure 1. Computed tomography scan, showing a large, left mesenteric mass with jejunoileal involvement.

anemia. Results of blood chemistry studies, pancreatic enzyme studies, and urinalysis were all normal.

In order to evaluate the patient for possible urolithiasis or cholelithiasis, a CT scan was ordered. This scan revealed a left mesenteric mass with omental fat stranding. A follow-up CT scan of the patient's chest, abdomen, and pelvis with contrast was ordered for the next day. The next morning, he presented with lower extremity weakness, gait instability, and urinary retention. He appeared ill, but his neurologic examination was nonfocal and showed normal reflexes, normal rectal tone and sensation, normal lower extremity sensation, and a negative Babinski sign. His abnormal gait was attributed to generalized weakness. Results of testing for hip flexion and leg extension strength were 4/5 bilaterally, suggesting slight impairment.

At this point, it was determined that emergent magnetic resonance imaging (MRI) was not required, and the patient proceeded to undergo the scheduled follow-up CT scan. This scan confirmed a left mesenteric mass with jejunoileal involvement, omental caking, and a paraspinal soft tissue mass at the T6-T7 vertebral bodies (Figure 1).

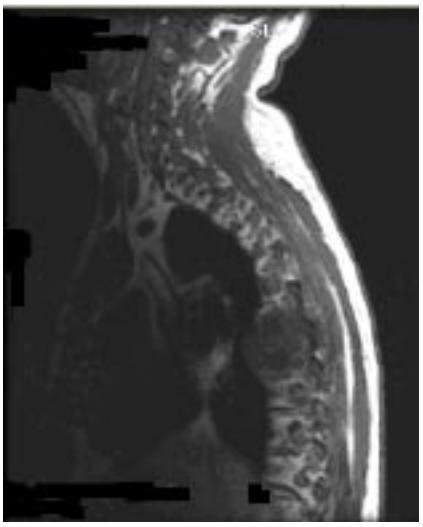

Figure 2. Magnetic resonance imaging scan, showing a paraspinal mass at the T4-T7 vertebral bodies.

Because his neurologic symptoms were progressing and 1 L of urine was drained on urethral catheterization, emergent MRI of his thoracic and lumbar spine was performed. This imaging confirmed a paraspinal mass at the T4-T7 vertebral bodies that extended through the T5-T6 and T7-T8 neural foramina (Figure 2). The mass was displacing his spinal cord anteriorly and to the left. The MRI also demonstrated multiple levels of vertebral body involvement and an extensive thoracic spinal cord syrinx.

TREATMENT COURSE

Intravenous dexamethasone therapy was initiated immediately, and the patient was transferred to neurosurgical care. The steroid treatment improved his neurologic symptoms significantly, and surgery was delayed to allow for aspiration of his paraspinal mass and a definitive diagnosis. Histologic and flow-cytometric analyses of the aspiration were consistent with Burkitt lymphoma (Figure 3). His serum lactate dehydrogenase (LDH) level was 729 U/L (normal range, 100 to 330 U/L).

At this point, the patient was transferred to the National Cancer Institute for treatment of a sporadic and rapidly progressive non-Hodgkin lymphoma. There, he was enrolled in a clinical trial investigating the high dose chemotherapy regimen of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R), without radiation or stem cell transplantation. Two months after the initiation of chemotherapy, the patient's disease was in complete remission.

ABOUT THE CONDITION

Burkitt lymphoma is classified in the highly aggressive subset of non-Hodgkin lymphomas and is found epidemiologically in three forms: endemic, immunodeficiency-related, and sporadic. Endemic Burkitt lymphoma was first described in African children in the mid 20th century by Dr. Denis Burkitt.[6] He noticed facial deformities and tumors of the mandibles in these children, with involvement of the intestines, kidneys, ovaries, and central nervous system (CNS). His analysis of the lymphoma led him to collaborate with a pathologist, Dr. Michael Anthony Epstein, who identified a virus in the lymphomas that is now known as the Epstein-Barr virus. This was the first time that a virus was implicated in the pathogenesis of a tumor.[7]

The same type of lymphoma was observed in homosexual men before HIV was fully characterized as a clinical entity. As more information on HIV and AIDS became available, Burkitt lymphoma was recognized as an AIDS defining illness. It often presented with CD4 counts greater than 200 and was the first clinical indication of HIV infection in many patients. In patients with Burkitt lymphoma

who are HIV positive, antiretroviral therapy combined with chemotherapy has resulted in better outcomes than chemotherapy alone, which suggests an indirect role for HIV in the pathogenesis of immunodeficiency-related Burkitt lymphoma.[8]

The patient described here had sporadic Burkitt lymphoma. This form represents almost 40% of all non-Hodgkin lymphomas in children but only 1% to 2% of all non-Hodgkin lymphomas in adults.[9] Only 10% to 20% of all cases have CNS involvement.[5] More typically, Burkitt lymphoma affects the intestines, specifically the ileocecal junction. Involvement of the kidneys, ovaries, and bone marrow also are common.

The pathogenesis of sporadic Burkitt lymphoma centers around the translocation of the c-Myc protooncogene, located on the long arm of chromosome 8 (8q24), to one of the immunoglobulin (Ig) heavy or kappa or lambda light chains.[10] The three classic translocations found in Burkitt lymphoma are t(8;14), t(2;8), and t(8;22) for heavy chain, kappa light chain, and lambda light chain involvement, respectively. The translocation results in tumor cells that constitutively express c-Myc, leading to almost 100% cell-cycle entry and cellular replication.[11] Other genetic abnormalities found in Burkitt lymphoma include p53 mutations and deletions in the long arm of chromosome 6.[12,13]

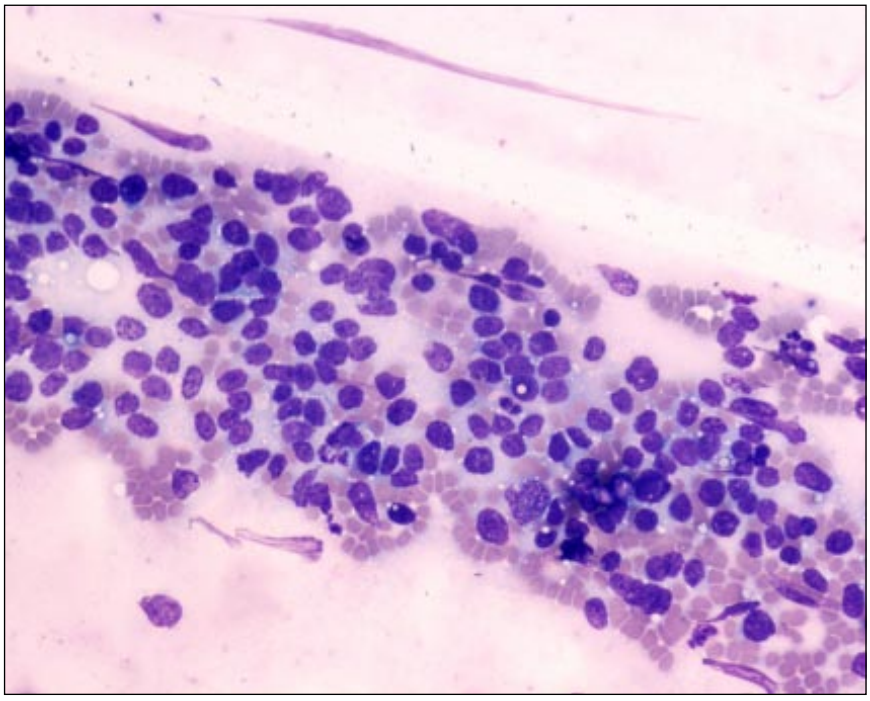

Figure 3. Histologic image of fine needle aspiration from the patient's paraspinal mass. There is a noticeable "starry sky" appearance from the tingible body macrophages.

A diagnostic challenge

The diagnosis of Burkitt lymphoma is often difficult to make in an adult because of significant overlap that exists between the diagnostic criteria for Burkitt lymphoma and diffuse large B-cell lymphomas (DLBCLs). To aid in this process, the World Health Organization (WHO) makes a distinction between classic and atypical Burkitt lymphoma.

Classic Burkitt lymphoma is characterized morphologically, by immunophenotype, and by cytogenetics. Morphologically, Burkitt lymphoma cells appear as medium-sized, uniform, round cells, each with a central nucleus, multiple nucleoli, moderate peripheral cytoplasm with multiple vacuoles, and many mitotic spindles. As seen in our patient's histologic studies, a "starry-sky" appearance is imparted by tingible body macrophages that have ingested apoptotic Burkitt cell debris. The immunophenotype of classic Burkitt lymphoma cells is similar to that of the germinal center B cells and is characterized by expression of monotypic surface IgM, CD 10, CD 19, CD 20, CD 79a, Bcl-6, and 100% Ki-67 (a protein expressed by proliferating cells)—but not CD5, TdT, or Bcl-2. Burkitt lymphoma cytogenetics can be recognized through fluorescent in-situ hybridization, which reveals the three classic chromosomal translocations.[7]

The diagnosis becomes challenging when tumor specimens resemble DLBCLs morphologically but have other features consistent with Burkitt lymphoma. Additionally, 5% to 10% of DLBCLs have c-Myc rearrangements. Because the vast majority of non-Hodgkin lymphomas in adults are not Burkitt lymphoma, a c-Myc rearrangement in itself is not specific or diagnostic for Burkitt lymphoma. A questionable case of Burkitt lymphoma is classified as atypical by the WHO when the histology is similar to DLBCL but the Ki-67 fraction is greater than 99%, representing a high rate of cell division, and when there is a c-Myc rearrangement with an Ig heavy or light chain.

The distinction between Burkitt lymphoma and DLBCL is very im-

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portant because the chemotherapy initiated for each condition is considerably different. Burkitt lymphoma is treated with high-intensity chemotherapy regimens, such as the French protocol of high dose cyclophosphamide, high dose methotrexate/leucovorin, cytarabine, vincristine, prednisone, and doxorubicin (LMB); the Magrath protocol of cyclophosphamide, vincristine, doxorubicin, and methotrexate cycles alternating with ifosfamide, mesna, etoposide, and cytarabine (CODOX-M/IVAC); or the MD Andersen protocol of fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone (hyper-CVAD) with rituximab. These high intensity regimens have significantly more success in adults compared with the standard regimen of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP), with two-year disease free survival rates of 60% to 80%. Treatment-related complications, however, are more likely with the high intensity regimens. These include myelosuppression, which may result in sepsis and death, and tumor-lysis syndrome. Patients with DLBCLs generally respond adequately to the less intense regimens (such as R-CHOP), which pose a lower risk of treatment-related death.[9,14,15]

The distinction between Burkitt lymphoma and DLBCLs is very important because the chemotherapy initiated for each condition is considerably different.

In an effort to improve diagnostic specificity and to avoid undertreatment or overtreatment through misclassification of Burkitt lymphoma, a number of researchers have developed molecular signatures of Burkitt lymphoma and DLBCLs.[16,17] Dave and colleagues used the technique of gene expression profiling to identify four groups of genes that are expressed differentially in Burkitt lymphoma and DLBCLs.[17] The results showed that c-Myc target genes were expressed in higher levels in Burkitt lymphoma, while major histocompatibility class 1 genes and nuclear factor-kappa B genes were expressed in higher levels in DLBCLs. Additionally, a subset of germinal center B-cell genes were expressed in higher levels in Burkitt lymphoma, while another subset of these genes were expressed in higher levels in DLBCLs.

The application of this genetic molecular signature to tumor biopsy specimens resulted in the accurate identification of Burkitt lymphoma and DLBCLs.[17] Nine lymphomas that were classified as DLBCLs by an expert panel of hematopathologists were reclassified as Burkitt lymphoma by this molecular signature. They had a poor response to standard chemotherapy regimens and a good response to the high intensity regimens.

The results of Dave and colleagues and others suggest that molecular diagnostic techniques can identify cases of Burkitt lymphoma that the standard diagnostic techniques cannot, possibly resulting in better outcomes through more accurate diagnosis and treatment. It is particularly encouraging that the signature developed by Dave and colleagues did not classify any of the DLBCLs with c-Myc translocations as a Burkitt lymphoma, a theoretical source of molecular overlap.

Determining prognosis

Long-term survival of patients with aggressive non-Hodgkin lymphomas, such as Burkitt lymphoma, can be extrapolated using one of two international prognostic indexes (an age-adjusted index for patients younger than 60 years and a general index for patients of all ages) that were published by the International Non-Hodgkin's Lymphoma Prognostic Factors Project in 1993.[18] Both of these indexes assign a risk value based on the patient's pretreatment performance status, LDH value, and Ann Arbor stage.

Performance status is measured according the Eastern Cooperative Oncology Group scale, in which a score of 0 indicates the patient has no symptoms, 1 indicates the patient has symptoms but is still ambulatory, and 2 to 4 indicates the patient has symptoms and is bedridden (to varying degrees). According to the prognostic indexes, risk factors are defined as a performance status score of 2 to 4, an Ann Arbor stage of III or IV, and a serum LDH level greater than the upper limit of normal (approximately 330 U/L).[18] The number of risk factors is then totaled and a patient is assigned a category of low risk (no risk factors), low-intermediate (one risk factor), high-intermediate (two risk factors), and high (three risk factors). Under the age-adjusted index, the five-year survival rates for these risk categories are 83%, 69%, 46%, and 32%, respectively.

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Using this model, our patient had two risk factors: elevated LDH and Ann Arbor stage III. (Since the patient had symptoms but was still ambulatory, his performance status was 1.) Therefore, he would be categorized as high-intermediate risk, making his chances of five-year survival approximately 46%.

Many other prognostic factors specific to Burkitt lymphoma have been proposed based on data from more recent clinical trials. These include age greater than 33, advanced disease stage (Ann Arbor stage III or IV), poor performance status (being bedridden or unable to complete activities of daily living), CNS or bone marrow involvement, anemia, the presence of circulating blasts, and an elevated LDH level. The one uniformly poor prognostic factor is the failure to achieve complete remission.[5,19] Prognostic factors for this type of lymphoma continue to evolve with improving molecular and biologic diagnostic techniques and therapeutics.

An efficient approach to identifying malignant back pain

Among patients with known cancer who present with acute back pain, 98% have underlying metastases to the spine.[4] Overall, Posner found that up to one third of patients with cancer develop metastases of the spine, frequently in the thoracic region.[20] While acute back pain due to an underlying malignancy is most commonly associated with metastases of prostate, breast, lung, and thyroid cancers,[20,21] the rare case of Burkitt lymphoma we describe here also presented with this symptom. Because of the serious nature of this potential diagnosis, it is wise to perform some type of cancer screening on all patients who present with back pain.

Primary care providers can enhance their ability to identify the small percentage of patients who present with acute back pain related to underlying malignancies through the use of thorough medical histories and physical examinations.[22] One way to maximize the cost- and time-efficiency of these evaluations is to look out for certain red flags in the history and physical examination that are particularly suggestive of underlying cancer or other serious, systemic disease (Table).

Table. Red flags in the evaluation of back pain

- Age greater than 50 years
- Personal history of cancer
- Constitutional symptoms, such as fever, chills, night sweats, and weight loss
- Symptoms that last longer than one month or are progressive and show no improvement with conservative therapy
- Bowel, bladder, or sexual dysfunction
- Claudication and neurologic symptoms, such as numbness; weakness; or pain that radiates to extremities, genitals, or the perianal region
- Pain that is unremitting or incompletely relieved by lying down, worse when the patient is at rest, or reported to wake the patient from a sound sleep
- Intravenous drug use
- Recent infection
- Immunosuppression from HIV, transplant, or chronic corticosteroid use
- Major trauma, or minor trauma in adults of advanced age (older than 65 years)
- Physical examination findings suggestive of cauda equina syndrome, such as loss of rectal tone, saddle anesthesia, and lower extremity weakness with either flaccidity and hyporeflexia or spasticity and hyperreflexia

In addition to these red flags, primary care providers can refer to clinical practice guidelines, such as those developed by Jarvik and Deyo.[23] Based upon their extensive review of the available medical literature, these authors recommended that, at the time of a patient's presentation, primary care providers try to distinguish between three general categories of back pain: that which represents serious systemic disease such as malignancy or infection, that which is associated with significant neurologic deficits, and that which is musculoskeletal or idiopathic in origin. Their recommendations for the initial diagnostic approach to back pain are similar to guidelines put forth by the U.S. Agency for Health Care Policy and Research.[24]

Consistent with Jarvik and Deyo's recommendations, if the history and physical examination raise no red flags for systemic disease in an adult under the age of 50, no further laboratory studies or imaging are necessary. For this group, the back pain will resolve in 90% of patients by four weeks and 95% by six weeks with conservative treatment. Plain x-ray films in this period do not result in better outcomes and rarely reveal significant abnormalities—instead, they often lead to misleading findings. In this population, a specific diagnosis often is not made, but common etiologies include spinal stenosis, herniated disk, lumbar strain, or facet joint and disk degeneration.[25]

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If the patient is older than 50 years, or suspicion for a systemic cause of pain is raised by the history and physical examination, plain x-ray films and a basic laboratory examination are indicated. A prostate examination, prostate-specific antigen testing, or a breast examination may be included when appropriate. If results of the evaluation are normal, the patient may be treated conservatively for four to six weeks with confidence that an underlying malignancy is not present. If the evaluation reveals abnormal findings, advanced imaging with CT or MRI is indicated. MRI is more sensitive and specific for detecting malignancy or infection, while CT is comparable to MRI for detecting spinal stenosis, facet joint arthrosis, or a herniated disk.[23,26]

Most patients with significant neurologic symptoms or examination findings consistent with sciatica can be treated conservatively for four to six weeks. In rare cases, however, a patient will present with radicular findings and bowel or bladder incontinence or retention, loss of rectal tone, and bilateral lower extremity weakness, indicating cauda equina syndrome. These patients must be referred immediately for imaging and neurosurgical care. The cause of cauda equina syndrome often is a centrally herniated disk compressing and trapping the nerve roots. Patients with sciatica, radicular pain, or symptoms consistent with spinal stenosis who do not respond to four to six weeks of conservative therapy should receive advanced imaging, usually an MRI. This is because these patients often benefit from invasive procedures, such as steroid injections at the facet joints, laminectomy, or diskectomy.[27]

Referred visceral pain also can present as isolated back pain. The primary care provider must identify these cases by history and physical examination findings that cannot be explained by spinal disease. Examples include pyelonephritis, perinephric abscess, abdominal aortic aneurysm, cholecystitis, and pancreatitis. Additionally, endometriosis and chronic pelvic inflammatory disease are possible etiologies in women. The workup for these conditions is substantially different and is beyond the scope of this article.

The case presented here highlights the importance of adequate follow-up to document resolution of the reported back pain. Significant red flag symptoms did not develop in this patient until four weeks into his care, at which point his inability to sleep and the progressive nature of the pain led to advanced imaging.

One possible clue to the severe nature of his back pain that is not a typical red flag was the history of a recent hospital admission for abdominal pain with a CT scan that revealed small bowel wall thickening. The differential diagnosis for these findings includes an intussusception, which can result from a mass such as a mesenteric lymphoma. In retrospect, it is possible that his abdominal pain was caused by an intussusception, which subsequently resolved spontaneously, resulting in both the cessation of his abdominal pain and the lack of obstructive symptoms. Had the pain progressed and obstructive symptoms developed, further evaluation likely would have uncovered the lymphoma at an earlier date, possibly preventing some neurologic disability. Since the abdominal pain had resolved, the colonoscopy was negative, the blood count and differential were normal, and he had no new or persistent abdominal symptoms at the time of presentation for back pain, however, this possibility was not readily apparent.

SUMMING UP

In the evaluation and treatment of back pain, the primary care provider must first rule out severe systemic disease, such as an underlying malignancy. Certain reported symptoms and physical findings can be assigned relevance as red flag items. The physician then can decide to implement conservative treatment for four weeks or proceed with a further workup.

The severe nature of this patient's condition was discovered in an appropriate amount of time, but his case illustrates how quickly an essentially benign presentation can turn critical. We advise screening for malignancy, paraspinal sepsis, or acute spinal compromise with an appropriate history and examination prior to proceeding with routine care of back pain. ●

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