



Confusing Presentations of Hodgkin Lymphoma

Matthew A. Lunning D.O* and Joel D. Armitage

Department of Hematology and Oncology, University of Nebraska Medical Center, USA

Abstract

The disease we today call Hodgkin lymphoma was named after Thomas Hodgkin, a physician at Guy's Hospital in London who in the 1830's did autopsies on 7 patients who died of an illness characterized by progressive lymphadenopathy. His description of these patients was presented at the Royal College of Physicians in 1832, and in 1856. Samuel Wilks referred to a group of similar patients as having "Hodgkin's disease." The discovery by Dorothy Reed and Sternberg at the turn of the 20th Century made it possible to recognize this specific type of lymphoma, known as Reed-Sternberg cells. The development of effective radiotherapy techniques and, more recently, effective combinations of chemotherapeutic agents have made Hodgkin lymphoma one of the most curable malignancies. Today more than 80% of all patients with Hodgkin lymphoma are cured and approximately 90% of those who present with early stage disease are cured. Given this excellent treatment outcome, it is important that patients be diagnosed in a timely manner so they can benefit from currently available treatments.

Hodgkin lymphoma usually presents with lymphadenopathy in the neck, mediastinum, or axilla and is relatively easily diagnosed upon excisional biopsy with modern techniques. However, this is an illness that can present with obscure symptoms that can lead to great delay in diagnosis. The unusual presentations of Hodgkin Lymphoma are not covered well in literature, particularly in literature that is oriented to primary care providers; it should be noted there has been literature oriented to oncologists discussing unusual presentations of Hodgkin Lymphoma. If primary care providers recognize these unusual presentations as possibly representing Hodgkin lymphoma, patients could be treated earlier, often with less extensive disease, and be spared prolonged and unpleasant periods of suffering from symptoms. This manuscript will present several illustrative cases of characteristic, but unusual, presentations of Hodgkin lymphoma.

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*Correspondence:

Matthew A. Lunning D.O, Department of Hematology and Oncology, University of Nebraska Medical Center, 601 S. Saddle Creek Rd, Omaha, NE 68198-6840, USA, Tel: 402-559-8500;

E-mail: mlunning@unmc.edu

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Case Presentation

Case 1 – pruritus

A 28-year-old woman had the onset of pruritus involving her feet. This gradually worsened and spread to the rest of her body. The itching was continuous, kept her from sleep, and she was excoriating her skin. Changing lotions, soap, and detergents did not help. Her primary care provider gave her antihistamines and topical creams without benefit. She then saw a dermatologist who tried a topical steroid – again without benefit. Six months after the onset, she saw an allergist who examined her, felt neck nodes and arranged for a chest x-ray which showed a bulky (>7 cm) mediastinal mass [1,2,3]. An excisional biopsy show nodular sclerosing, classical Hodgkin lymphoma.

Comments: Pruritus can have many causes including dry skin, psychiatric conditions, intolerance to chemicals in the environment, renal disease, liver disease, scabies, diabetes, thyroid disease, and specific hematologic disorders such as polycythemia vera, AIDS, and lymphomas. Some degree of pruritus is frequently seen in patients with Hodgkin lymphoma, and it has been described to occur in well over half of the patients with Hodgkin Lymphoma sometime in the course of their disease [4,5].

Pruritus as the beginning manifestation of Hodgkin lymphoma is unusual. Patients have often seen several physicians before someone feels a lymph node or orders a chest x-ray that shows a mediastinal mass. It appears to be more frequent in women than in men. Historically, pruritus was denoted as a systemic symptom of Hodgkin lymphoma with prognostic significance referred to as "B symptoms," but has been deleted leaving only fevers, drenching sweats, and unintentional weight loss as official B symptoms. The etiology of pruritus in patients with Hodgkin lymphoma is unknown.

Case 2 – Intermittent (pel-ebstein or ebstein-cardarelli) fevers

A 35-year-old man's wife complains to her husband that he has been warm while sleeping and his snoring has been worse over the last month regardless of repositioning. He blamed the new comforter on the bed and being overly tired from work. His wife checked his temperature at night which ranged from 101.5 °F to 102.5°F for several days. She prompted him to see her primary care provider, but he noted the fevers resolved after taking ibuprofen for arthralgias and no further work up was undertaken. However, a week later his fevers returned, this time with sweats that soaked the sheets. He was subsequently seen and on examination found to have fullness in the left supraclavicular region. A subsequent ultrasound demonstrated a 3 cm lymph node. An excisional biopsy demonstrated lymphocyte rich, classical Hodgkin lymphoma.

Comments: Fevers, drenching night sweats, and unintentional weight loss (>10% body weight in 6 months) are classically described as B symptoms. Any of the B symptoms will change the Ann Arbor staging criteria by adding an additional description: A (absent) or B (present) [5]. The findings of all 3 symptoms are uncommon. Fevers can be seen in Hodgkin lymphoma and may either be present and then subside without intervention (Ebstein-Pel Fevers) or be treated with Non-Steroidal Anti-Inflammatories (NSAIDs) for the fever or other complaints which may abrogate the fevers [6]. Often NSAIDs can be used to improve symptoms while the patient is undergoing diagnostic or staging evaluation. Nevertheless, fevers should resolve with appropriate Hodgkin directed treatment [7]. Any fever during treatment should be evaluated immediately given concern for neutropenic fever which can be life-threatening.

Case 3 – Erythema nodosum

A 19-year-old woman developed painful, red nodules on her shins. The diagnosis of erythema nodosum was made on clinical presentation and it was originally felt that this was related to her recently starting oral contraceptives. However, changing the contraceptive prescription and the use of NSAIDs did not resolve the issue. The patient then developed abdominal pain and hematemesis that resolved without further intervention. Four months after the initial symptoms, she became tired and developed a respiratory infection. She was treated with azithromycin but then developed axillary lymphadenopathy and worsening fatigue. A biopsy of a lymph node in the neck revealed nodular sclerosing, classical Hodgkin lymphoma.

Comments: Erythema nodosum presents with tender, reddish, raised nodules on the anterior lower legs. Erythema nodosum is associated with drugs, various infections, inflammatory diseases such as inflammatory bowel disease, and with lymphomas – particularly Hodgkin lymphoma [8,9]. The erythema nodosum may precede the diagnosis of Hodgkin lymphoma and precede relapse. Symptoms resolve with effective treatment of Hodgkin lymphoma.

Case 4 – Alcohol induced pain

A 23-year-old man developed progressive fatigue and transient abdominal discomfort. His discomfort slowly increased in intensity, but became dramatically more severe when he drank beer. When he stopped drinking beer for a week the pain did not completely resolve. Two months later, while shaving he felt a lump in his neck and saw his primary care provider who diagnosed infectious mononucleosis and GERD. He did not improve over the next two months and his

abdominal pain persisted despite the use of acid blocking agents. Two months later, he became jaundiced and was referred to a hepatologist who recognized the association of alcohol induced pain and Hodgkin lymphoma and arranged for a biopsy of the residual cervical lymph node which showed nodular sclerosing, classical Hodgkin lymphoma.

Comments: Alcohol induced pain is an unusual manifestation of Hodgkin lymphoma [10]. The pain typically begins shortly after ingestion and occurs in areas of nodal involvement. The pain is severe and patients have almost always stopped drinking alcohol by the time the diagnosis is made [11,12]. Occasionally, other symptoms may accompany the pain such as pruritus, flushing, nausea, vomiting, and dizziness. Alcohol induced pain can also occur rarely in other disorders such as tuberculosis. The mechanism of alcohol induced pain is unknown.

Other Unusual Presentations

These are not the only unusual presentations of Hodgkin lymphoma. Hodgkin lymphoma has been described with a variety of rare neurologic disorders such as sub-acute cerebellar degeneration, limbic encephalitis, sub-acute necrotic myelopathy, and sub-acute motor neuropathy [13]. These disorders can precede the diagnosis of Hodgkin lymphoma.

Hodgkin lymphoma can present with nephrotic syndrome [14]. A variety of hematological manifestations can precede the diagnosis of Hodgkin disease including autoimmune hemolytic anemia, immune thrombocytopenia, and immune neutropenia [15-17]. Hodgkin lymphoma can present with cholestatic jaundice – even with no involvement of the liver [18,19]. Other immune disorders such as polymyositis and scleroderma can precede the diagnosis of Hodgkin lymphoma [20].

Conclusion

Hodgkin lymphoma is a malignancy arising from a B lymphocyte that commonly affects individuals in their second or third decade of life. As described above Hodgkin lymphoma competes with conditions that are more common like work/school related fatigue, sport/exercise induced symptoms/injuries, and viral infections. Therefore, many individuals afflicted with Hodgkin lymphoma are often diagnosed after being treated for other conditions. It is an unrealistic expectation for primary care providers to add Hodgkin lymphoma to the differential for the majority of individuals; however appropriate questioning and acknowledgement of unique scenarios which may raise the pre-test probability of finding Hodgkin lymphoma is very important to avoid a delay in diagnosis and perhaps improve overall survival by avoiding stage migration.

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