Clinical Manifestations and Natural History of Hodgkin's Lymphoma

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Abstract: Hodgkin's lymphoma usually presents with typical lymphadenopathy that has been detected either incidentally by the patient or by imaging procedures performed for assessment of other conditions. Occasionally, it may be detected when investigation of nonspecific symptoms, such as fever, fatigue, or unexplained pain prompt assessment that, in turn reveals a mass lesion. The diagnosis must be confirmed with an appropriate biopsy. Nowadays, clinicians usually have little difficulty making the diagnosis of Hodgkin's lymphoma. Knowledge of the usual pattern of spread of this lymphoma, with its orderly progression through lymph node groups and its typical forms of extranodal involvement, facilitates timely diagnosis, staging, and treatment planning. Rare manifestations due to involvement of unusual sites or presentation with paraneoplastic organ dysfunction can prove challenging but a search for mass lesions and an appreciation of these uncommonly encountered findings as potential clues to the presence of Hodgkin's lymphoma usually prompts appropriate investigation and correct diagnosis. Finally, an understanding of the usual pattern and timing of relapse and knowledge of the typical types of late toxicity expected after successful eradication of the lymphoma allow the patient's physicians to detect recurrence in a timely fashion and to identify or prevent secondary complications enabling appropriate management plans to be developed.

Key Words: Hodgkin's lymphoma, lymphoma, lymphadenopathy, paraneoplastic syndrome, pattern of spread, late complication, late toxicity

(*Cancer J* 2009;15: 124–128)

Hodgkin's lymphoma was recognized as a unique illness almost 2 centuries ago. By the early 1900s, detailed descriptions of the typical microscopic appearance allowed confident separation of this type of lymphoma from other diseases causing similar symptoms and lymphadenopathy. Finally, and most importantly in terms of making clear the need for definite identification of the disease, curative treatments, initially with radiation therapy, and later multiagent chemotherapy, became available more than 50 years ago. Thus, Hodgkin's lymphoma has been sufficiently, dependably, and accurately diagnosed that its specific patterns of presentation and clinical behavior are well understood.

It is important to distinguish 2 major variants of Hodgkin's lymphoma, the classic variety including the nodular sclerosing, mixed cellularity, lymphocyte rich and lymphocyte depleted subtypes, and nodular lymphocyte predominant Hodgkin's lymphoma, a rare subtype seen in approximately 5% of cases.[1] Each of these 2 major variants, classic and nodular lymphocyte predominant, has a unique set of presenting symptoms and natural history. An understanding of the typical and unusual ways in which each of these 2 main variants of Hodgkin's lymphoma can present and how the disease spreads throughout the body is essential to their timely diagnosis and initiation of appropriate treatment. In addition, appreciation of the typical patterns of spread and relapse of this lymphoma equips the clinician with the knowledge needed to choose the best and most efficient diagnostic tests to stage the disease correctly and plan a course of treatment that best balances the need to cure this otherwise fatal illness with the need to minimize the impact of late, potentially serious toxicities.

Hodgkin's lymphoma typically, but not exclusively, presents in younger patients, usually between the ages of 20 and 60 years. Patients may feel well but note anatomic changes such as localized lymphadenopathy or they may become ill with constitutional symptoms, such as fever, night sweats, unexplained weight loss or fatigue or nonspecific organ-related symptoms, such as cough, pruritus, or localized bone pain or unexpected laboratory abnormalities, such as anemia, hypoalbuminemia, or an elevated erythrocyte sedimentation rate. Diagnosis may be straightforward, based on the results of a lymph node or bone marrow biopsy, or challenging because of the nonspecific nature of presenting symptoms or laboratory findings. Appreciation of the typical and unusual modes of presentation of the lymphoma is necessary for its timely recognition.

COMMON SYMPTOMS AND PRESENTING ABNORMALITIES OF CLASSICAL HODGKIN'S LYMPHOMA

Classical Hodgkin's lymphoma almost always causes mass lesions, most typically in centriaxial lymph nodes, but occasionally in other organs, such as the spleen, bone marrow, liver, bone, or lungs. However, because several of these sites are anatomically deep within the body, indirect evidence of the presence of the lymphoma, such as constitutional symptoms, local organ-specific abnormalities, such as cough or bone pain or incidentally discovered laboratory abnormalities, may precede detection of such mass lesions by physical examination or imaging. Thus, the most common manifestation of Hodgkin's lymphoma, especially in younger patients, is the development of persistent, painless, firm but not hard, supradiaphragmatic lymphadenopathy, usually but not exclusively in the neck or supraclavicular fossa or, less often, axilla (Table 1). However, similar lymphadenopathy may develop within the mediastinum where it does not come to attention until it causes a localizing symptom, such as cough, substernal chest pain, or anterior chest wall swelling. In older patients, retroperitoneal lymphadenopathy may present as an abdominal mass or abdominal or back pain.

Hodgkin's lymphoma typically spreads in a predictable fashion from one set of lymph nodes to adjacent groups, most often starting in supradiaphragmatic nodes (90%) and much less commonly in infradiaphragmatic nodes (10%). Two types of extranodal spread are recognized. Localized extension, presumably by direct invasion or through local lymphatic vessels, may involve any anatomic structure nearby involved lymph nodes, accounting for almost

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ISSN: 1528-9117/09/1502-0124

TABLE 1. Common and Uncommon Manifestations of Hodgkin's Lymphoma at the Time of Initial Diagnosis

Common	
Lymphadenopathy	
Supradiaphragmatic	90%
Infradiaphragmatic	10%
Extranodal disease	
No extranodal extension	75%
Localized, contiguous with involved lymph nodes	10%
Disseminated (liver, lung, bone, and bone marrow)	
Classical	15%
Nodular lymphocyte predominant	5%
B symptoms	35%
Uncommon	
Pruritus	<5%
Pain after alcohol ingestion	<2%
Rare	<1%
Autoimmune	
Hemolytic anemia	
Thrombocytopenia	
Paraneoplastic	
Neurologic	
Cerebellar degeneration	
Limbic encephalitis (Ophelia syndrome)	
Subacute myelopathy	
Subacute motor neuropathy	
Guillain-Barre syndrome	
Central pontine myelinolysis	
Diffuse cerebritis	
Renal	
Glomerulonephritis	
Minimal change	
Membranous	
Proliferative	
IgA associated	
Nephrotic syndrome	

all involvement of the thyroid, pleura, pericardium, perihilar lungs, subcutaneous tissue, skin, epidural tissue, and other similar sites. Such localized contiguous spread is common, especially when the original lymph node involvement is bulky and has a special designation in the staging system applied to Hodgkin's lymphoma.[2,3] For example, involvement localized to neck lymph nodes and the nearby thyroid is designated stage II E. Such localized spread of Hodgkin's lymphoma should be distinguished from more distant spread into extranodal organs, such as, the bone marrow or liver, because such localized extranodal extension does not necessarily imply widespread metastases and measures suitable for the treatment of localized disease, such as radiation, can be curative.

Spread of Hodgkin's lymphoma to distant extranodal organs is almost always preceded by splenic involvement, although the involvement of the spleen may be occult. Such distant extranodal Hodgkin's lymphoma occurs almost exclusively in 4 organs: liver, bone marrow, lung, or bone. Although rare cases of isolated involvement at other extranodal sites, such as skin, brain, gastrointestinal tract, or musculoskeletal tissue have been reported they are quite exceptional and constitute less than 1% of Hodgkin's lymphoma presentations.[1] Even in the presence of confirmed Hodgkin's lymphoma in lymph nodes involvement of such exceptional sites should be accepted as part of the presentation of the Hodgkin's lymphoma only if proven by an appropriate biopsy. Often such associated lesions prove to be due to another neoplasm or infectious disease, not the underlying Hodgkin's lymphoma.

As appropriate for the detection of any new mass lesion, either by physical examination or imaging tests performed to investigate a localizing symptom, such a finding should prompt an appropriate biopsy. It is quite important that such a biopsy consist of either an entire-involved lymph node or a generous excisional biopsy of a deeper mass lesion to provide the pathologist with sufficient material to search for the expected Reed-Sternberg cells and find the typical mixed inflammatory background changes.[4] A definitive diagnosis is a cornerstone of modern oncologic management and should not be compromised by an inadequately small or crushed biopsy.

Manifestations of Hodgkin's lymphoma other than a mass lesion can be divided into localized symptoms, nonspecific constitutional or organ-related symptoms, and laboratory abnormalities. Although not a common cause of such localized symptoms as cough, substernal chest pain, bone pain, or abdominal swelling, Hodgkin's lymphoma should remain on the list of possible explanations until a specific diagnosis is made. An appropriate combination of imaging tests and directed biopsies should provide the needed diagnostic answer. More challenging can be nonspecific constitutional symptoms, such as fever, night sweats, weight loss, or fatigue. Before the availability of modern imaging techniques, especially fine-detailed computerized tomographic scanning, Hodgkin's lymphoma was appropriately included in any list of differential diagnoses of such nonspecific abnormalities. However, currently such scans, occasionally complemented by functional imaging tests such as radionucleotide gallium scanning or positron emission tomography, almost always allow localization of a mass lesion appropriate for biopsy if Hodgkin's lymphoma is present. Similarly, such imaging techniques straightforwardly assist the assessment of organ-specific symptoms, such as localized pain or cough, quickly identifying appropriate next steps to confirm a diagnosis.

One organ-specific symptom, pruritus, continues to challenge physicians because of its nonspecific nature and the infrequency with which it is caused by Hodgkin's lymphoma. Clinicians, especially family practitioners, primary care internists, and dermatologists, need to remember Hodgkin's lymphoma as a possible cause of intractable itching. Finally, incidentally discovered anemia, thrombocytopenia, neutropenia, lymphopenia, hypoalbuminemia, or elevated erythrocyte sedimentation or similar findings encountered either incidentally or in the assessment of fatigue, unexplained weight loss, fever, night sweats, or other constitutional symptoms may suggest the presence of Hodgkin's lymphoma. Imaging tests followed by an appropriate biopsy or performance of a bone marrow biopsy should provide the additional information necessary to pin down a diagnosis of Hodgkin's lymphoma, if present.

UNCOMMON SYMPTOMS AND PRESENTING ABNORMALITIES OF CLASSICAL HODGKIN'S LYMPHOMA

Uncommonly, Hodgkin's lymphoma may cause a variety of potentially confusing symptoms or findings. Pain at a site of involved lymph nodes may occur immediately after alcohol ingestion. Although traditionally associated with Hodgkin's lymphoma, such alcohol-related pain is rare (<1%–2% of cases) and not specific, occasionally being caused by other neoplasms or inflammatory diseases such as systemic lupus erythematosis or rheumatoid arthritis.[5] Persistent alcohol-related pain should be investigated with imaging studies focused on the lymph node

areas near the pain. If due to Hodgkin's lymphoma, lymphadenopathy should be readily evident.

Although autoimmune hematologic conditions have been reported with Hodgkin's lymphoma in the past, such manifestations are now rare, perhaps in part because such past reports may have been based on mistaken diagnoses of what was actually a non-Hodgkin's lymphoma. Autoimmune hemolytic anemia and thrombocytopenia have been rarely reported with Hodgkin's lymphoma and should be appropriately investigated.[6,7] Most often such conditions are linked to other conditions besides Hodgkin's lymphoma or remain unexplained. Rarely, Hodgkin's lymphoma is found to be present and, if so, appropriate treatment should resolve the autoimmune phenomenon.

Paraneoplastic syndromes have infrequently been reported in association with Hodgkin's lymphoma. Several neurologic manifestations have been described including cerebellar degeneration, which usually presents as a gait abnormality but may involve dysarthria, nystagmus, diplopia, or dysphagia.[8,9] This syndrome seems to be caused by cross-reacting autoantibodies that irreversibly damage nerve fibers within the cerebellum.[10] Arrest of progression and occasional improvement with control of the underlying Hodgkin's lymphoma have been reported.[8] Other uncommon neurologic associations have rarely been reported in association with Hodgkin's lymphoma including limbic encephalitis (also referred to as the Ophelia syndrome),[11] subacute myelopathy,[12] subacute motor neuropathy,[13] Guillain-Barre syndrome,[14] central pontine myelinolysis,[15] and diffuse cerebritis.[16]

The kidneys, although virtually never invaded by metastatic spread of Hodgkin's lymphoma and only occasionally by direct extension, may display paraneoplastic involvement. Glomerulonephritides of various types have been described including minimal change, membranous, proliferative, or IgA-associated glomerulonephritis.[17–22] Clinically, patients may have all or some of the findings of nephrotic syndrome,[23–25] sometimes predating the lymphoma by months to years. The timing of these renal abnormalities is not tightly connected to the lymphoma. They may occur, before, coincident with, after successful treatment of, or at the same time as relapse of the lymphoma.[23–25] In addition, these glomerulonephritides may persist despite control of the lymphoma or regress independently.

Many additional syndromic abnormalities or organ dysfunctions have rarely been reported coincident with Hodgkin's lymphoma including hepatitis, cholangitis, vasculitis, conjunctivitis, uveitis, hypertension, hypercalcemia, hypoglycemia, the syndrome of inappropriate antidiuretic hormone secretion, coagulopathies, and hemophagocytosis.[26] These abnormalities have usually been associated with advanced, often recurrent or neglected, disease and none is diagnostic of Hodgkin's lymphoma. Thus, their presence is not likely to lead to the diagnosis of Hodgkin's lymphoma unless additional findings are present, such as a mass lesion in lymph nodes, spleen, liver, bone, or lungs or an abnormal infiltrate is found in the bone marrow.

Two situations in which Hodgkin's lymphoma is diagnosed deserve special comment because of their unusual modes of presentation. First, Hodgkin's lymphoma coincident with infection due to human immunodeficiency virus (HIV) much more frequently involves extranodal organs and causes coincident B symptoms (night sweats, fever, and weight loss) than ordinary Hodgkin's lymphoma.[27–33] In addition, the extranodal lymphoma may involve unusual organs, such as the central nervous system, musculoskeletal tissue, pleura, or abdominal viscera and may do so in the absence of splenic involvement, both characteristics infrequently encountered with Hodgkin's lymphoma in the absence of HIV infection.[27–30,34,35] This unusually aggressive pattern of metastatic involvement partially explains the poorer response to treatment seen in patients with Hodgkin's lymphoma and HIV infection.[27–30,34,35]

The other situation in which Hodgkin's lymphoma may present atypically is when it affects older patients above the age of 60 to 70 years, which occurs in about 5% of patients.[36–43] In such patients, presentations with systemic symptoms such as weight loss and fatigue are much more common as is subdiaphragmatic involvement. Also, in contrast to younger patients, in which approximately 75% of cases are of the nodular sclerosing subtype, at least 50% of older patients present with the mixed cellularity subtype.[37] This combination of findings associated with advanced age including subdiaphragmatic presentation, which less often presents with an obvious mass that might prompt medical assessment and is therefore harder to detect, prominent constitutional symptoms and mixed cellularity subtype may partially explain the poorer prognosis seen in elderly patients.[36–39]

CLINICAL MANIFESTATIONS OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN'S LYMPHOMA

Nodular lymphocyte predominant Hodgkin's lymphoma is seen in approximately 5% of cases of newly diagnosed disease. This variant typically occurs in younger patients with a 2:1 male predominance. More than 80% of cases present with limited stage disease, usually supradiaphragmatic stage I A or II A, or less commonly III A, with minimal bulk.[44–47] Apparent involvement of extranodal organs, bulky splenic or subdiaphragmatic disease, or constitutional symptoms should prompt additional biopsies, because such findings are unusual in nodular lymphocyte predominant Hodgkin's lymphoma and are often a sign of coincident non-Hodgkin's lymphoma, particularly diffuse large B-cell lymphoma or T-cell rich B-cell lymphoma.[48] Nodular lymphocyte predominant Hodgkin's lymphoma typically has very indolent behavior often persisting as palpable peripheral lymph nodes for months to years before a definite diagnosis is made. It may be preceded or followed by persistent lymphadenopathy due to progressive transformation of germinal centers, a non-neoplastic condition that may prove self-limiting or may be a prodrome to nodular lymphocyte predominant Hodgkin's lymphoma or other lymphocytic neoplasms.[49,50]

NATURAL HISTORY OF HODGKIN'S LYMPHOMA

Before discovery of reliably curative treatments, Hodgkin's lymphoma was a uniformly fatal illness with patients succumbing to a combination of progressive bulky lymphadenopathy that eventually compromised vital organ function and a wasting syndrome with steadily worsening constitutional symptoms, weight loss, cachexia, inanition, and death. Currently available chemotherapy and radiation treatments cure at least 80% of patients, usually with the first choice of regimen. Thus, fortunately, late manifestations of the disease have become uncommon. However, recurrence does affect a minority of patients. When Hodgkin's lymphoma relapses it typically recurs in sites of previous disease, if those sites were not treated with radiation, or novel sites if the original disease was irradiated. Even if novel sites are involved they are usually in lymph node regions nearby original sites of disease or in the usual extranodal sites, lung, liver, bone, or bone marrow. At recurrence, the histologic subtype most often matches the original diagnosis but a progression to greater numbers of Reed Sternberg cells and a tendency to develop the syncitial variant of nodular sclerosing disease may become evident. Eventually, despite application of the current best available treatments, involvement of vital organs, such as the lungs, liver, and bone marrow, often complicated by systemic infections, marked nutritional compromise and generalized weakness leads to the patient's demise. At autopsy extensive involvement of extranodal

TABLE 2. Potential Late Nonneoplastic Complications of Treatment of Hodgkin's Lymphoma With Appropriate Clinical Responses and Preventive Strategies

Risk/Problem	Incidence/Response
Dental caries	Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.
Hypothyroidism	After external beam irradiation that encompasses the thyroid with doses sufficient to cure Hodgkin's lymphoma at least 50% of patients eventually develop hypothyroidism. All patients whose TSH level becomes elevated should be treated with life-long thyroxine replacement in doses sufficient to suppress thyroid-stimulating hormone (TSH) levels to low normal. This is necessary to correct the hypothyroidism and to assure that the radiation damaged thyroid is not subjected to long-term stimulation by thyroid stimulating hormone, which may increase the risk of thyroid neoplasm.
Infertility	ABVD is not known to cause any permanent gonadal toxicity although oligospermia for 1 to 2 yr after treatment is common. Other regimens may cause gonadal damage, especially if alkylating agents or procarbazine was included. Direct or scatter radiation to gonadal tissue also may cause infertility, amenorrhea, or premature menopause but this seldom occurs with the current fields used for the treatment of Hodgkin's lymphoma. Thus, with the current chemotherapy regimens and radiation fields used, most patients will not develop these problems. In general, after treatment, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer. High-dose chemoradiotherapy and hematopoietic stem-cell transplantation almost always cause permanent infertility in both genders although some young women occasionally recover fertility.
Impaired immunity to infections	Hodgkin's lymphoma and its treatment can lead to life-long impairment of full immunity to infection. All patients should be given annual influenza immunization and pneumococcal immunization after treatment and again 5 yr later. Patients whose spleen has been irradiated or removed should also be immunized against meningococcal types A and C and *Hemophilus influenza* type B. As for all adults, diphtheria and tetanus immunizations should be kept up to date and appropriate immunizations given to prevent infections such as hepatitis A or B when traveling or if the patient's occupation or activities suggest heightened risk of exposure.

organs, including those seldom involved in the earlier stages of the disease, such as the central nervous system, can be documented.

For the clinician, the most important aspect of the later natural history of Hodgkin's lymphoma has to do with the anticipation of relapse, if it is going to occur. Fortunately, most recurrences become evident soon after the completion of primary treatment. Currently, at least half of all recurrences are noted within 1 to 2 years of primary treatment completion and 80% to 90% within 5 years. Patients who remain free of recurrence for more than 10 years rarely develop recurrence and after 15 years the risk of recurrence drops to match the risk of developing the lymphoma independently.[51] Thus, after the first decade of follow-up the most important aspect of continued management is anticipation of late complications of treatment, the majority of which is development of secondary neoplasms.[52–56] Irradiation is the treatment most likely to induce second cancers but chemotherapy, especially if it included alkylating agents such as mechlorethamine or cyclophosphamide, and even the underlying defects that led to the development of Hodgkin's lymphoma in the first place may also play a role. It is important to screen for cancers of the head and neck, thyroid, lung, breast, skin, uterine cervix, pleura (mesothelioma), and soft tissues (sarcoma) and to counsel against exposure to any additive factors such as use of tobacco products. Symptoms suggestive of such second cancers should be promptly evaluated.

Optimal follow-up management of a patient with cured Hodgkin's lymphoma also requires an understanding of other late toxicities besides second neoplasms.[57] Table 2 lists the major such late complications and appropriate steps to minimize their negative effects. In an era when most patients are cured correct management of the late infectious, endocrine, reproductive, dental, and other complications of the chemotherapy and radiation required to cure the original lymphoma is integral to ensuring each patient's long-term health.

CONCLUSIONS

Most cases of Hodgkin's lymphoma present with typical lymphadenopathy detected either incidentally by the patient or by imaging procedures performed for assessment of other conditions or as part of investigation of localized symptoms such as cough or pain. Occasionally, nonspecific constitutional symptoms such as fever or fatigue prompt assessment which, in turn, reveals a mass lesion. The diagnosis is confirmed with an appropriate biopsy. Nowadays, aided by remarkably detailed imaging procedures such as modern computerized tomographic scanning, the clinician usually has little difficulty identifying the site to be biopsied and, thus, the diagnosis of Hodgkin's lymphoma is readily established. Knowledge of the usual pattern of spread of this lymphoma, with its orderly progression through lymph node groups and typical forms of extranodal involvement, facilitates timely diagnosis and informs the choice of procedures necessary to complete staging and plan treatment. Rare manifestations with involvement of unusual sites or presentation with paraneoplastic organ dysfunction can challenge the evaluating physician but a search for mass lesions and an appreciation of these uncommonly encountered findings as potential clues to the presence of Hodgkin's lymphoma eventually prompts appropriate investigation and correct diagnosis of the underlying lymphoma. Finally, an understanding of the usual pattern and timing of relapse and knowledge of the typical types of late toxicity expected after successful eradication of the lymphoma allow the patient's physicians to detect recurrence or secondary complications and devise appropriate management plans.

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