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Precision Molecular Pathology of Hodgkin Lymphoma

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Precision Molecular Pathology of Hodgkin Lymphoma

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Preface

This new multiauthored text is designed to be the most up-to-date authoritative text on the molecular pathology and pathobiology of Hodgkin lymphoma currently available. Chapters have been written by an internationally recognized team of experts. While the emphasis is on molecular pathobiology, the text includes chapters covering all aspects of the disease. All chapters are generously referenced and, where appropriate, illustrated with tables, figures, and histopathologic images.

Chapter topics include clinical features (SM Ansell, Mayo Clinic, USA), histopathology (SD Hudnall, Yale University, USA), pathogenesis and molecular genetics of classical Hodgkin lymphoma (R Küppers, University of Duisburg-Essen, DE), targeting the microenvironment in Hodgkin lymphoma (L Visser, A Diepstra, A van den Berg, University Medical Center Groningen, NL, and C Steidl, BC Cancer Institute, CAN), the role of EBV in classical Hodgkin lymphoma (P Murray and M Ibrahim, University of Birmingham, UK), pathobiology of nodular lymphocyte predominant Hodgkin lymphoma (S Hartmann and M-L Hansmann, Goethe University, Frankfurt/Main, DE), composite lymphomas and the relationship of Hodgkin lymphoma to non-Hodgkin lymphomas (M Weniger and R Küppers, University of Duisburg-Essen, DE), epidemiology and genetic risk factors (W Cozen and T Mack, University of Southern California, USA), treatment and prognosis (F Montanari and CM Diefenbach, NYU Medical Center, USA), and development of targeted therapies (RW Chen, City of Hope, CA, USA).

We hope the text will prove to be of value to students, teachers, clinical practitioners, and research scientists interested in Hodgkin lymphoma.

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Contents

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Chapter 1
Clinical Features of Hodgkin Lymphoma

Stephen M. Ansell

Presenting Symptoms

The majority of Hodgkin lymphoma patients present with lymphadenopathy at the time of diagnosis (Ansell 2016). For many patients, the site of lymphadenopathy is supradiaphragmatic, and most commonly patients present with cervical, mediastinal, supraclavicular, and axillary lymph node involvement (Kaplan 1971; Kaplan et al. 1973). Less frequently, inguinal lymph nodes and intra-abdominal lymph nodes are the presenting sites of disease (Krikorian et al. 1986). Additional symptoms, which commonly occur at the time of diagnosis, may include fevers, night sweats, and weight loss (Ekstrand and Horning 2002). Many patients may present with a history of chronic pruritus. These symptoms are present in at least one-third of newly diagnosed patients. While mediastinal lymphadenopathy resulting in large mediastinal masses is often seen, this is rarely the only site of disease. More commonly, mediastinal masses occur in conjunction with cervical or supraclavicular lymph nodes. Infradiaphragmatic disease alone is uncommon, and this presentation constitutes only 3% of newly diagnosed patients (Krikorian et al. 1986; Leibenhaut et al. 1987).

Splenomegaly is present in approximately 10% of newly diagnosed patients. Initial studies suggested that clinical splenomegaly may be a nonspecific manifestation, as only half of the patients with splenomegaly were found to have confirmed involvement of the spleen by active Hodgkin lymphoma (Kaplan et al. 1973). These data, however, were generated in an era of staging laparotomies. More recent data has suggested that splenic involvement may be seen in the absence of splenomegaly in approximately 20–30% of patients when computerized tomography (CT) scans or positron emission tomography (PET) scans are used (Hancock et al. 1994).

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Extranodal disease can occur at any site. The most common extranodal presentations include lung, liver, bone, and bone marrow involvement. Extranodal involvement by Hodgkin lymphoma is a relatively uncommon phenomenon at diagnosis and is seen in approximately 5–10% of cases (Musshoff 1971; Rosenberg 1971). Other sites of involvement such as central nervous system involvement or testicular involvement are very rare. Primary extranodal Hodgkin lymphoma is extremely uncommon, the diagnosis of Hodgkin lymphoma should be questioned in these cases, and a pathology review should be requested.

Patterns of Disease Progression

Hodgkin lymphoma is somewhat unique among lymphomas in that the disease tends to spread in a contiguous fashion (Kaplan 1971; Mauch et al. 1993). Most commonly, the disease presents in the neck or chest and spreads to regional lymph nodes. Disease in the supraclavicular region can spread to sites in the upper abdomen in a contiguous fashion via the thoracic duct. Involvement of the hilar lymph nodes is extremely rare in the absence of mediastinal disease, and similarly, involvement of lung parenchyma is very rare if the mediastinal and hilar nodes are not involved (Diehl et al. 1991). Splenic involvement is a relatively common abdominal site of disease and most likely represents hematogenous spread. Liver involvement is very uncommon, particularly in the absence of splenic involvement (Fialk et al. 1979).

Clinical History

An accurate clinical evaluation is important in this disease. The presence of systemic symptoms is associated with a poor prognosis and may be a clue that more advanced disease than suspected is in fact present. The clinical evaluation may also direct the treating physician to include additional testing to exclude other comorbid diseases that may impact the patient's outcome. These include further evaluation for cardiovascular disease, exclusion of immune deficiencies such as those induced by HIV infection, and further evaluation of smoking and autoimmune diseases. Furthermore, a complete history of prior medical conditions is important. Previous medical conditions such as a history of breast cancer or severe asthma may influence decisions to incorporate treatments such as radiation therapy or the inclusion of bleomycin in the treatment regimen.

Constitutional symptoms have been shown to be of prognostic value. These include an unexplained fever of 101 °F, drenching night sweats, or weight loss ≥10% of the patient's weight. These symptoms have been included in the original Cotswolds staging system (see Table 1.1) and have been denoted as a "B" attached to the numeral to identify the presence of these systemic symptoms (Lister et al. 1989;

Table 1.1 Cotswold staging classification for Hodgkin lymphoma

Stage I	
Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)	
Stage II	
Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes are lateralized)	
Stage III	
Involvement of lymph node regions of structures on both sides of the diaphragm	
Stage IV	
Involvement of extranodal site(s) beyond the designated *E*	
A	No symptoms
B	Fever, drenching sweats, weight loss
X	Bulky disease, greater than one-third widening of the mediastinum, >10 cm maximum dimension of nodal mass
E	Involvement of a single extranodal site, contiguous or proximal to a known nodal site
CS	Clinical stage
PS	Pathologic stage

Lister and Crowther 1990). Other unique symptoms associated with Hodgkin lymphoma include pain or flushing at the sites of involved lymph nodes with the ingestion of alcohol. The mechanism for the phenomenon is unknown, and thus far no prognostic significance has been attached to these findings. Generalized pruritus is also commonly seen but is not felt to be a constitutional symptom. Pruritus may be present, however, in 10–15% of patients but does not have any known prognostic importance. Other symptoms that are commonly seen include fatigue and weakness, but these symptoms are frequently seen with other diseases and are therefore not incorporated into any staging evaluation.

Evaluation and Recommended Testing

The management of patients is largely dependent on the stage of the disease and the presence of unfavorable characteristics. A complete staging evaluation, as well as the inclusion of specific laboratory tests to allow for prognostication, is critically important. Aside from a comprehensive physical exam and clinical history, additional testing of importance includes a set of baseline imaging studies. Typically, these include PET with integrated CT scanning (PET-CT) as this has in large part supplanted the use of CT scan alone. Studies have suggested the use of PET-CT scan compared to CT alone changes the stage of disease in up to 20–40% of cases and changes the treatment in approximately 5–15% of patients (Jerusalem et al. 2001; Seam et al. 2007; Kostakoglu et al. 2004). If a CT-PET is unavailable, CT scans of at least the chest, abdomen, and pelvis should be used. In rare cases, additional or alternative imaging modalities can be used, and these could include

ultrasound or MRI scan. A bone marrow aspirate and biopsy have typically been used as a part of the staging evaluation in the past. These have been more relevant in patients with advanced-stage disease. Recent data has suggested that early-stage patients with normal blood counts have a very low likelihood of bone marrow involvement (Munker et al. 1995). With the routine use of PET-CT scans, a negative PET-CT with no bone or bone marrow positivity has been associated with a negative bone marrow test, and therefore, in patients with a negative PET scan, a bone marrow aspirate and biopsy could be omitted (Cheson et al. 2014).

Laboratory testing that needs to be included includes a complete blood count with differential count, an erythrocyte sedimentation rate, liver function testing, as well as measurement of the serum albumin. Additional testing for renal function and thyroid function should be considered. Thyroid function testing is needed to serve as a baseline value particularly if radiation to the neck is considered. Serology testing for human immunodeficiency virus (HIV) is appropriate in selected cases. A pregnancy test should always be performed in any female patient of childbearing potential. In view of the fact that many patients are young, fertility preservation should be considered, and the patient should be counseled regarding cryopreservation of sperm or ova. Additional assessments could include an assessment of the ejection fraction by echocardiogram or radio nucleotide study as most regimens incorporate anthracycline chemotherapy. A baseline pulmonary function test is commonly included if the chemotherapy will contain bleomycin. As newer agents such as brentuximab vedotin and others are incorporated into frontline therapy, an assessment of baseline neuropathy should also be undertaken.

Prognostic Factors

Clinical Factors. An accurate assessment of the stage of disease in Hodgkin lymphoma is vitally important to select appropriate treatment. The stage of this disease is a major prognostic factor for Hodgkin lymphoma, based on the fact that it determines the selection of treatment. The staging system for Hodgkin lymphoma is based on sites of lymphadenopathy with specific attention paid to whether the disease occurs on one or both sides of the diaphragm (see Table 1.1) (Lister et al. 1989). Further attention is paid to the number of involved sites and whether the sites of involvement are bulky in size. Additionally, the staging system takes into consideration contiguous extranodal spread or disseminated extranodal disease, and furthermore as mentioned above, it takes into consideration systemic symptoms (B symptoms) that may be present. Further prognostication with prognostic indices takes staging into account, and there are separate prognostic factors for limited-stage and advanced-stage disease.

In patients with limited early-stage Hodgkin lymphoma, clinical prognostic factors of importance are the presence of a large mediastinal mass, an elevated sedimentation rate, involvement of extranodal sites, involvement of multiple nodal sites, age greater than 50 years, and significant splenic enlargement (see Table 1.2). Both

Table 1.2 Unfavorable characteristics for limited-stage Hodgkin lymphoma

Risk factor	GHSG	EORTC
Age		≥50 years
ESR and B symptoms	>50 if A >30 if B	>50 if A >30 if B
Mediastinal mass	MMR > 0.33	MTR > 35
# of nodal sites	>2	>3
E lesions	Any	

GSHG German Hodgkin Study Group, *EORTC* European Organisation for the Research and Treatment of Cancer, *MMR* mediastinal mass ratio (maximal width of mass/maximal intrathoracic width), *MTR* mass to thoracic width at T5–T6 interspace on standing chest radiograph, *E lesions* involvement of a single extranodal site contiguous to a known nodal site

the European Organisation for the Research and Treatment of Cancer (EORTC) and the German Hodgkin Lymphoma Study Group (GHSG) have utilized these prognostic factors and have differentiated patients into favorable and unfavorable subsets with differing approaches to treatment based on these categories (Tubiana et al. 1989; Diehl et al. 2003).

In patients with advanced-stage Hodgkin lymphoma, the disease bulk and other typical prognostic variables have been less predictive of outcome. Therefore, the International Prognostic Factors Project on Advanced Hodgkin Disease developed a different prognostic scoring system (Hasenclever et al. 1998). In this study, seven variables were identified as prognostically relevant. These include age greater than 45 years, the presence of stage IV disease, male gender, white cell count greater than 15,000/μL, lymphocyte count less than 600 cells/μL, albumin less than 4 g/dL, and hemoglobin less than 10.5 g/dL. The outcome of patients with none of these negative prognostic factors is excellent with an 84% likelihood of being free from disease progression at 5 years. In contrast, patients with 5 or more of these poor prognostic factors have a 5-year freedom of progression of only 42%.

PET Scan. A more recent prognostic factor, which has proven to be as important as many of these clinical features, has been the response to treatment as defined by PET scan. An interim PET scan, typically done after two cycles of treatment, has been highly prognostic as far as overall outcome of patients is concerned (Hutchings et al. 2006; Gallamini et al. 2007). Similarly, a PET scan that is negative upon completion of treatment is also being shown to be associated with a favorable overall survival and progression-free survival (Jerusalem et al. 1999; Zinzani et al. 1999). A negative PET scan after two cycles of treatment predicts a favorable progression-free survival and overall survival and is in fact a better predictor of patient outcome than stage of disease, presence of extranodal disease, or other prognostic factors. The prognostic importance of PET scans has resulted in the utilization of PET scan as method to adapt initial treatment based on risk. Patients with positive PET scans after two cycles of treatment are typically receiving a de-escalation in treatment intensity or duration, compared to patients with a positive PET scan after two cycles of treatment who are receiving more intensive or prolonged treatment or the addition of other modalities of therapy.

Specific Presentations

Hodgkin Lymphoma in Pregnancy. Because Hodgkin lymphoma is often seen in women of childbearing potential, it is not surprising that Hodgkin lymphoma can occur in a woman who is pregnant. Studies have been done to access whether the pregnancy affects the course of Hodgkin lymphoma, and these studies have not suggested a different outcome for Hodgkin lymphoma in patients who are pregnant when compared to age-adjusted controls with Hodgkin lymphoma who are not pregnant (Barry et al. 1962). The management of pregnant Hodgkin lymphoma patients however does present some challenges. Staging of a pregnant patient must be modified to avoid risks to the fetus, and the treatment should also be tailored to optimize the care of the mother but avoid additional injury to the child (Doll et al. 1989). The workup is typically tailored to avoid exposure of the fetus to additional radiation. Ultrasound is often used to access abdominal disease, and imaging of the chest should be done with very careful screening of the fetus. The overall plan is to delay treatment until delivery, unless there is bulky disease that would require urgent treatment.

Hodgkin Lymphoma in Immunocompromised Patients. Although Hodgkin lymphoma is not an AIDS-defining illness, the incidence of Hodgkin lymphoma is significantly increased in patients with HIV infection (Shiels et al. 2009; Engels et al. 2006). In contrast to patients without any immunosuppression, Hodgkin lymphoma in patients who are HIV positive is more commonly mixed cellularity subtype and is often associated with advanced-stage and constitutional symptoms (Levine 1998). Bone marrow involvement can also be seen more commonly. HIV-positive patients may have an excellent outcome, but it is important to ensure that the HIV infection is adequately managed by optimizing treatment of the immune deficiency with highly active antiretroviral therapy (Xicoy et al. 2007; Hartmann et al. 2003). Staging and further management thereafter are typically the same as what is administered to patients who are HIV negative (Okosun et al. 2012).

Elderly Patients. Older patients with Hodgkin lymphoma are understudied, particularly because they are uncommonly included in clinical trials. Overall, the outcome of this population is inferior to younger patients primarily due to comorbid conditions that are more common in this population (Evens et al. 2013; Ballova et al. 2005; Boll et al. 2011). Advanced patient age often leads to modifications in dose intensity of treatment, and less therapy often results in poorer outcomes. To combat this, fit elderly patients should be managed in a similar fashion to younger patients. Those with comorbid disease should have their underlying diseases aggressively managed so that they can be treated with similar therapy as to what is administered to younger patients. Specific clinical trials are being developed for frail elderly patients that omit agents such as bleomycin and doxorubicin to avoid the potential heart and lung toxicity that may impact their outcome. This makes it particularly important to evaluate elderly patients for cardiac and pulmonary compromise prior to therapy. Patients with low ejection fractions may require treatments that contain less or no anthracyclines. Furthermore, in patients with compromised