

# Hematopathology X

## Hodgkin Lymphoma and Immunoproliferative Disorders

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**UIC College of Medicine**

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### Important Concepts of Hodgkin Lymphoma

- 1) Clinical features of Hodgkin lymphoma.
- 2) Three main histologic subtypes of classical Hodgkin lymphoma and relative incidence of each.
- 3) Morphologic features of the Reed-Sternberg cell, L&H cell, and lacunar cell and prevalence of these cells in the various histologic subtypes.
- 4) Immunologic markers of the Reed-Sternberg cell and the L&H cell.
- 5) Nodular lymphocyte predominance, low grade B-cell lymphoma without Reed-Sternberg cells.

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### HODGKIN LYMPHOMA

In 1832 an English physician, Dr. Thomas Hodgkin, published a paper describing seven patients with enlargement of lymph nodes and spleen. Hodgkin lymphoma has subsequently become recognized as a distinct clinicopathologic entity. Gross tissues from the autopsies of Dr. Hodgkin's seven patients were preserved in a British medical museum. Microscopic examination of these tissues almost 100 years after the original report confirmed the presence of Hodgkin lymphoma in two of the seven with the remaining five representing cases of tuberculosis, syphilis, and non-Hodgkin lymphoma.

A useful way in which to describe the clinical features of Hodgkin lymphoma is to contrast it with non-Hodgkin lymphoma. Although Hodgkin lymphoma may occur at any age, it is primarily a disease of young adults with a peak incidence in the second, third, and fourth decades of life (ages 15-40). Non-Hodgkin lymphoma peaks in the fifth, sixth, and seventh decades (ages 40-65). Hodgkin lymphoma usually presents with localized lymph node involvement (stage I or II, see below) and spreads in a contiguous manner from one lymph node group to an adjacent lymph node group. It is most unusual for Hodgkin lymphoma to present with generalized lymphadenopathy whereas this is not uncommon for non-Hodgkin lymphoma particularly those of a low grade type. Hodgkin lymphoma virtually always presents within lymph nodes not as extranodal disease. The initially enlarged lymph nodes are usually in the cervical region. Waldeyer ring is seldom involved by Hodgkin lymphoma at diagnosis. Extranodal disease at presentation such as a mass in the gastrointestinal tract, cutaneous involvement, or central nervous system disease is more characteristic of non-Hodgkin lymphoma being seen in about 25% of patients at presentation. Having described a number of clinicopathologic differences between Hodgkin lymphoma and non-Hodgkin lymphoma, it must be stated that the two entities are coming closer together conceptually as will be highlighted below.

In 1966, Lukes and Butler proposed a new histopathologic classification of Hodgkin lymphoma which demonstrated a remarkable correlation with clinical stage and aggressiveness of disease. It is a testimony to Lukes and Butler that their classification, and the subsequent Rye modification, was rapidly accepted and has continued to be employed by both pathologists and clinicians throughout the world with only slight modification by the WHO in 1998.

WHO Classification of Hodgkin Lymphoma

Nodular lymphocyte predominant Hodgkin Lymphoma

Classical Hodgkin Lymphoma

Nodular Sclerosis

Mixed Cellularity

Lymphocyte Depletion

Lymphocyte Rich

The Reed-Sternberg cell, described at about the turn of the century by Sternberg (1898) and Reed



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In addition to the L&H cells demonstrating B-cell surface markers, a large proportion of the small lymphocytes can be identified as B lymphocytes which along with the nodular pattern suggests that this type of Hodgkin lymphoma is a variant of a follicular lymphoma of B-cell type. There is also clinical evidence that NLPHD behaves more like a low grade B-cell lymphoma as it has a tendency to recur after therapy although the survival is prolonged. Occasionally it will transform into a large B-cell non-Hodgkin lymphoma.

#### **Classical Hodgkin Lymphoma** **Nodular Sclerosis**

Nodular sclerosis is the most common type of Hodgkin lymphoma, comprising about 55% of cases. This form of Hodgkin lymphoma is more common in females and is unusual in patients over the age of 50 years. Nodular sclerosis tends to involve lower cervical, superclavicular and mediastinal lymph nodes; the majority of patients are stage II at presentation, often with a mediastinal mass, and have an excellent prognosis. The nodular sclerosis type exhibits birefringent collagen septa which typically arise from a thickened capsule and divide the lymphoid tissue into nodules containing lacunar variants of Reed-Sternberg cells. In formalin-fixed tissue, the lacunar variant of Reed-Sternberg cells is observed to have retracted cytoplasm around the nucleus causing the nucleus to appear to be situated in a clear space or lacuna. The nuclei vary from round to hyperlobated. Paradoxically, diagnostic Reed-Sternberg cells may be difficult to identify in nodular sclerosis, whereas lacunar cells are numerous. These cells are found in an inflammatory background comprised of lymphocytes, histiocytes, eosinophils, neutrophils, and plasma cells.

#### **Mixed Cellularity**

Mixed cellularity is slightly more common in males and is often associated with systemic symptoms. It occurs in all clinical stages. The mixed cellularity type is characterized by easily detectable Reed-Sternberg cells in presence of a wide variety of inflammatory cells including: mature lymphocytes, eosinophils, neutrophils, histiocytes, and plasma cells. The nodal architecture is often diffusely effaced in mixed cellularity Hodgkin lymphoma. This is the second most common subtype comprising 30% of cases.

#### **Lymphocyte Depletion**

Lymphocytic depletion is usually found in older symptomatic patients with stage III or IV disease at the time of diagnosis. This form of Hodgkin lymphoma is identified in less than 2% of cases. Historically, it has been the most aggressive with the shortest median survival, although some patients achieve prolonged remissions with newer modes of therapy. Lymphocytic depletion type is characterized by few lymphocytes and numerous diagnostic Reed-Sternberg cells. In recent years the entity of anaplastic large cell lymphoma, a non-Hodgkin lymphoma composed of numerous highly pleomorphic large lymphoid cells, has been described. The neoplastic cells are CD30 positive and further testing reveals the majority to be of a T-cell lineage. Awareness of this diagnosis has reduced the number of cases interpreted as lymphocyte depletion Hodgkin lymphoma to a very low level.

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#### Staging

The criteria for diagnosis of Hodgkin lymphoma in bone marrow are less stringent in patients with a previously established diagnosis of Hodgkin lymphoma. Multiple sections should be obtained to permit search for diagnostic Reed-Sternberg cells; if none is found, a mononuclear cell with a single large nucleolus is acceptable for an interpretation of involvement by Hodgkin lymphoma. These mononuclear cells should be found in a cellular environment appropriate for Hodgkin lymphoma. Fibrosis within the marrow is a common feature of Hodgkin lymphoma.

The stage of the disease bears some relation to histologic subtype of Hodgkin lymphoma and to the absence (A) or presence (B) of systemic symptoms. B symptoms are defined as: unexplained weight loss of greater than 10% of body weight in the six months prior to presentation, fever, and/or night sweats.

#### Clinical Stage and Systemic Symptoms vs Histopathologic Type

Histopathologic Type	Clinical Stage		Systemic Symptoms	
	I and II	III and IV	Absent (A)	Present (B)
Nodular lymphocyte predominant Hodgkin lymphoma	89%	11%	100%	0%
Nodular sclerosis	69%	31%	65%	35%
Mixed cellularity	57%	43%	54%	46%
Lymphocytic depletion	30%	70%	30%	70%

Staging is important for planning therapy particularly if one is considering radiation therapy for presumed localized disease. The absence of disease outside the radiation treatment field must be established. The stage of Hodgkin lymphoma does bear some relationship to prognosis with advanced stage obviously having a less favorable prognosis. Hodgkin lymphoma, particularly in advanced stage, may demonstrate peripheral blood lymphopenia and occasionally eosinophilia. Defects in cellular immunity are also common in advanced disease.

#### Relapse and Therapy

For those patients relapsing in untreated sites, the histologic appearance generally is similar to the original biopsy. In contrast, biopsies obtained from patients who relapse in treated sites demonstrate a more pleomorphic appearance and are more difficult to subclassify than the initial diagnostic biopsy. The pleomorphism is due predominantly to an increase in Reed-Sternberg cells.

Modern therapy for Hodgkin lymphoma involves multiagent chemotherapy and/or radiation

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therapy. The first effective chemotherapy regimen MOPP (nitrogen mustard, Oncovin [vincristine], prednisone, procarbazine) was pioneered in the 1960's. A second four drug combination ABVD (doxorubicin [Adriamycin], bleomycin, yinblastine; dacarbazine) introduced more recently has been shown to be quite effective. Megavoltage radiation therapy, primarily used for localized disease is effective by itself in cases with early stage Hodgkin lymphoma. The effectiveness of modern therapy has eliminated any prognostic differences between the histologic subtypes except for lymphocyte depletion type which is approaching the others in terms of median survival although it still does somewhat worse. Today overall there is a greater than 80% 5 year survival in Hodgkin lymphoma as a whole. Unfortunately, secondary malignant disease has been recognized in long term follow up of patients treated for Hodgkin lymphoma particularly those who have received combined modality therapy (radiation and chemotherapy). Acute myeloid leukemia is the most common therapy-related malignancy.

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##### Hodgkin Lymphoma

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Important Concepts of Immunoproliferative Disorders

- 1) Diagnostic features of myeloma.
- 2) Clinical features of Macroglobulinemia of Waldenstrom.

### IMMUNOPROLIFERATIVE DISORDERS

Multiple myeloma

Solitary plasmacytoma (Extramedullary plasmacytoma)

Macroglobulinemia of Waldenstrom

The immunoproliferative disorders are neoplasms of immunoglobulin-secreting cells which are plasma cells or plasmacytoid lymphocytes.

Multiple myeloma is a disseminated plasma cell malignancy with a peak incidence in the sixth and seventh decades (62 mean age at diagnosis). It is twice as frequent in blacks as whites.

Diagnostic features

10% or more plasma cells in the bone marrow often with abnormal forms

Monoclonal serum protein

Osteolytic bone lesions or diffuse osteoporosis

Bence Jones protein (75%)

Hypercalcemia

Depression of other Ig

The abnormal morphologic features of the neoplastic plasma cells of myeloma include; fine nuclear chromatin, a single central prominent nucleolus, and a centrally-placed nucleus surrounded by a regular rim of cytoplasm in contrast to the eccentric nucleus of a mature plasma cell. The monoclonal serum protein almost always quantifies at greater than 3.0 g/dl as opposed to the paraprotein of the benign monoclonal gammopathy which is typically less. The osteolytic lesions are characteristically located in areas of active red marrow including spine, ribs, skull, and pelvis. Hypercalcemia is a direct result of bone destruction.

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#### Immunologic subtypes of multiple myeloma

	<u>Incidence</u>	<u>Clinical Features</u>
IgG	55-60%	Highest levels of monoclonal Ig (usually 4-8 g/dl occasionally up to 15g/dl) and greatest depression of normal Ig; more frequent infection
IgA	20%	Hypercalcemia; hyperviscosity due to IgA polymer formation
IgD	1%	Younger patients; Bence-Jones proteinuria with associated renal failure; hypercalcemia
Light chain	20%	Osteolytic lesions; hypercalcemia, renal failure
Nonsecretory	<1%	Inability to secrete Ig

Occasionally a localized tumor of monoclonal plasma cells is found either in bone or in another site (extramedullary).

#### Features of solitary plasmacytoma of bone and extramedullary plasmacytoma

	<u>Solitary plasmacytoma of bone</u>	<u>Extramedullary plasmacytoma</u>
Mean age (M:F)	50 years (2.5:1)	61 years (3:1)
Location	Spine, pelvis, rib, and femur	Nasopharynx, upper respiratory tract
Ig	Monoclonal protein present in 40-50% at diagnosis	Monoclonal protein detected only rarely
Bone marrow	Uninvolved at diagnosis	Uninvolved at diagnosis
Treatment	Radiotherapy	Surgery, radiotherapy, Chemotherapy
Clinical course	Frequent progression to multiple myeloma although it may require years (progression in 58% by 10 years)	Occasional local recurrences (30%) and/or progression to multiple myeloma (20-30%)
Prognosis	68% 10 year survival (similar to myeloma when progression occurs)	50% 10 year survival

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Macroglobulinemia of Waldenstrom is an indolent disease closely akin to small lymphocytic lymphoma.

Clinical features

IgM monoclonal gammopathy  
(benign monoclonal gammopathies are  
seldom of the IgM class)

Lymphadenopathy, hepatosplenomegaly

Small lymphocytes, plasmacytoid lymphocytes, plasma cells

Hyperviscosity syndrome

Hemostatic abnormalities

Renal failure unusual

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Immunoproliferative Diseases

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