

HEMATOLOGIC NEOPLASIA LECTURE IV HODGKIN'S DISEASE

- I. DEFINITION: Hodgkin's disease is a malignancy of the para-axial or mediastinal LN. It rarely arises below the diaphragm, in peripheral LN or extranodal tissues. Spread from LN to LN by contiguity is characteristic. Monoclonal Reed-Sternberg (RS) cells are a defining feature, but usually represent a minor component of the tumor mass. The RS cells are surrounded by polyclonal lymphocytes and plasma cells, histiocytes (= tissue macrophages) and reactive inflammatory cells.
- II. HISTORY: An English physician, Thomas Hodgkin wrote of this entity in 1832. Dorothy Reed an American pathologist described the characteristic RS cells ca. 1900.
- III. REED-STERNBERG CELLS: The origin of these binucleate or multinucleate cells is not fully understood. Despite considerable heterogeneity in morphology and expression of leukocyte markers, recent microdissection and molecular genetic studies indicate that they are monoclonal and predominantly of B cell origin. Many express the granulocyte marker CD15 or CD 30 which is a marker of activated B and T cells. Multiple cytokines secreted from the RS cells may recruit a variety of inflammatory cells (see NEJM 337:495, 1997).
- IV. EPIDEMIOLOGY
- A. Incidence: estimated 40-60 cases / 1,000,000/ yr
In USA = 35 to 50% of all malignant lymphomas
 - B. Bimodal age of onset:
 - 1. uncommon at < 15 y/o, 85% M,
 - 2. first peak at 25-29 y/o, 45% M
 - 3. second peak at 65-74 y/o, 65% M
 - C. Risk factors
 - 1. upper socioeconomic status, small sibships
 - 2. sibling, monozygotic twin
 - 3. HIV infection
- V. ETIOLOGY & PATHOGENESIS:
- A viral agent has been suspected due to case "clusters" and frequent history of prior infectious mononucleosis. In > 50%, EBV sequences are detected in RS cells by PCR. This itself is consistent with a B cell origin for most RS cells. The membrane-associated LMP1 antigen of EBV protects cells from apoptosis. Expression of macrophage, granulocyte, or T cell antigens also occurs in some classical RS cells and suggests RS cell derivation from an abnormal common stem cell prior to B cell maturation.
- VI. **STAGING IS ESSENTIAL FOR PROGNOSIS AND TREATMENT**
- A. Based upon extent of anatomic spread
 - 1. Physical exam
 - 2. BM biopsies (bilateral iliac crests)
 - 3. Radiography / CT scans: chest and skeleton, ± lymphangiogram
 - 4. Liver function tests, biopsy
 - 5. Splenectomy: thorough gross and microscopic examination
 - B. Based upon symptoms: A = asymptomatic,
B = fever, night sweats, pruritus, excess weight loss

VII. HISTOPATHOLOGY:

A. Topography: **typically arises in a single group of para-axial or mediastinal LN, spreads regionally.**

B. Gross appearance: can resemble TB granulomas when growing the in the spleen, liver or BM (good case example in NEJM 336: 1235, 1997)

VIII. SUBTYPES: Determined by ratio of lymphocytes to RS cells, other cell types, and evidence of fibrosis. Note some differences in presentation, histopathology and prognosis.

A. Nodular sclerosis

1. Incidence: pattern found in 40% of adolescents/young adults F > M
2. Typical presentation: lower cervical or supraclavicular & mediastinal LN (stage I or II)
3. Histopathology: LN partitioned by broad collagenous bands. RS cells are multilobate and relatively prominent. Due to fixation artefact, they appear to reside in lacunae and the jargon is *lacunar cells*. These may have a granulocytic marker CD-15. IL-5 production by the RS cell is a factor in the attraction of eosinophils. Eosinophil production of TGF-beta leads to LN fibrosis with focal necrosis.
4. Prognosis: a generally excellent response to chemotherapy.

B. Lymphocyte & histiocyte (L&H) predominance

1. Incidence: pattern found in 5-15% of cases
2. Typical presentation: stage I or II
3. Histopathology LN are replaced by small lymphocytes with admixed histiocytes. Interspersed Reed-Sternberg cells (<1% of all cells) are relatively small and can be difficult to identify (see Robbins Fig. 15-24, 15-27). PCR analyses of microdissected L&H cells indicates a germinal center B cell origin.
4. Prognosis: this is the most indolent subtype of Hodgkin's disease, excellent prognosis
transformation of to a diffuse large cell lymphoma of B cell type can occur.

C. Mixed cellularity

1. Incidence. 30% of cases
2. Typical presentation: stage II or III
3. Histopathology: ca. 1-2% classical Reed-Sternberg cells within a sea of lymphocytes, eosinophils, histiocytes and plasma cells. Occasional foci of necrosis or fibrosis
4. Prognosis: A relatively indolent subtype with a favorable prognosis in early stage

D. Lymphocyte depletion

1. Incidence. 15% of cases, most common in elderly
2. Typical presentation:
stage III or IV
3. Histopathology: can be numerous Reed-Sternberg cells with increasing atypia and sparse lymphocytes or inflammatory cells. More diffuse fibrosis than other types
4. Prognosis: least favorable of all subtypes
NB: progression of the histologic subtypes correlates with the advancement of stage

PLASMA CELL NEOPLASMS and RELATED DISORDERS

I. DEFINITION: abnormal clonal expansions of B-cells which secrete whole Ig molecules or molecular fragments (fragments. can be H or L chains). Major clinicopathologic entities are defined by predominant tissue locations, laboratory data, and pathophysiologic complications of the abnormal Ig production.

II. PLASMA CELLS AND NEOPLASTIC TRANSFORMATION:

A. The normal precursors of BM plasma cells: slowly proliferating plasmablasts in LN germinal centers are stimulated by antigen and T helper cell cytokines, then migrate to the BM. Somatic mutation switches Ig class production from IgM to IgG or IgA. While in the BM, mature plasma cells no longer divide. They produce most of the serum IgG and IgA. IL-6 helps to maintain their viability.

B. Monoclonal expansion and neoplastic transformation:

Monoclonal gammopathies can begin in young adult life (see MGUS below). When a plasma cell clone constitutes just 3-5% of the total lymphocyte population it may be detected by Southern blot due to an identical rearrangement of the VDJ genes for assembly of H chains. PCR for the rearranged DNA sequences increases the sensitivity of clonal detection.

Malignancies typically arise after age 50. The age-dependent increase suggests a role of persistent immunologic stimulation. A controversial hypothesis holds that virus infection of dendritic stromal cells can cause production of an IL-6-like protein which sustains plasma cell precursors. Paradoxically, neoplastic plasma cells may lack the CD19 marker for mature B cells. and may express markers for pre-B cells or the myeloid lineage. This suggests an origin from abnormal stem cells. IL-6 is essential for survival and growth of the neoplastic cells.

III. DYSPROTEINEMIA:

A. Laboratory methods for detection of abnormal Ig:

1. Immuno-electrophoresis and immunofixation: Applied to samples of blood or urine, gellectrophoresis separates Ig proteins by net charge (see Robbins Fig. 15-19).

Monospecific antibodies discriminate IgA, IgG, IgM, , or .

2. RBC rouleau: formation observed on blood smears due to RBC coating by excess Ig

B. Serum M-protein (= paraprotein): Monoclonal expansions of plasma cells secrete Ig of a single H-chain class (isotype), single L-chain subtype (L-chain restriction), and "one-of-a-kind" idiotype (immunogenic variable regions). Serum electrophoresis shows a "monoclonal spike" =M-protein in the region of -globulin electrophoretic migration.

C. Free L-chain: **Neoplastic cells secrete unattached L-chains**

The low MW allows them to percolate through the glomerular filter and appear in urine where they were initially discovered over 100 years ago by Bence-Jones (he detected a unique biophysical property of precipitation at 56 °C and resolubilization by boiling).

Modern detection is by electrophoresis with a concentrated urine sample. Routine urine dipsticks are insensitive. Blood levels increase as associated renal disease advances.

D. Immune (AL) Amyloid: Excess L-chains are processed by macrophages and are deposited around capillaries and small veins as abnormal microfibrils. The microfibrils consist of betapleated protein sheets. In tissue sections they exhibit a red-green birefringence after staining with cotton dyes (e.g., congo red) and polarization analysis.

E. Cryoglobulins: These are circulating paraproteins which reversibly precipitate at low body temperatures. Most are IgM or IgG. Blanching, pain and cyanosis occur in the fingers or toes

during exposure to cold (Raynaud's phenomenon). Tissue deposition of cryoglobulins around nerve fibers can cause polyneuropathy and patients may lose mobility.

F. Truncated H-chains: Abnormally secreted fragments of H chains detected by serum electrophoresis. Rare glomerular accumulation = heavy chain deposition disease.

IV. MAJOR CLINICAL CATEGORIES

A. Monoclonal Gammopathy of Unknown Significance (MGUS):

1. Incidence / Age of onset: 0.5-1% of adults between 30 - 65 y/o, ~3% of adults at > 70 y/o
2. Clinical presentation: chance laboratory detection or evidence of a polyneuropathy
3. Laboratory Diagnosis:
 - a. presence of an M-protein: > 90% IgG isotype
 - b. normal serum albumin and γ -globulin levels
 - c. < 10% plasma cells in BM and few atypical forms
no anemia, no B-J protein, no bone or tissue lesions
4. Course/Prognosis: patients may develop multiple myeloma after a latent period up to 30 yr.

B. Multiple Myeloma = Plasma Cell Myeloma

1. Incidence: 3-4 / 100,000/yr (incidence comparable to CLL), 1% of all cancer deaths typically 50-60 y/o African-Americans are more susceptible than other groups in USA
2. Clinical presentation: signs/symptoms of anemia, bleeding, bone pain or Fx, infections
3. Histopathology / Laboratory Diagnosis:
 - a. BM: multifocal osteolytic lesions (punched-out)
BM replacement by > 25% plasma cells (> 10% atypical plasma cells)
 - b. PB: severe replacement anemia
plasma cell leukemia (>2,000 plasmablasts/mm³) is rare
 - c. Immunodiagnosis
 - i. serum M-protein in > 85%, typically IgG or IgA
 - ii. normal serum Ig is depressed
 - iii. urine Bence-Jones protein occurs in up to 70%
 - iv. cells may express CD38 or a myelomonocytic antigen CD33
 - d. Hypercalcemia and hypercalcuria
4. Nasty complications:
 - a. bone destruction and life threatening hypercalcemia (50%)
osteoclasts activated by IL-6, IL-1 other cytokines
 - b. pathologic fractures: vertebral collapse w/ spinal cord compression and paralysis
 - c. nephrotoxicity (60-80% of cases) = myeloma nephrosis
severe renal insufficiency and azotemia
 - i. L chain glomerular deposition & ii. tubular protein casts (L chain)
 - ii. AL amyloid fiber deposition (10-35% of cases)
begins in the glomeruli and around other small blood vessels.
 - iii. tubular uric acid precipitates, metastatic calcification
 - d. recurrent bacterial/ fungal infections due to depression of Ig
5. Pathogenesis: IL-6 may play a role. ? genetic predisposition
Mixed myeloid markers suggest probable cell origin from a multipotent stem cell
6. Course & Prognosis: patients may suffer terrible bone pain,
~ 50% survival at 3 years

C. IgM Monoclonal gammopathy = Waldenstrom's macroglobulinemia

1. Incidence up to 10% of all plasma cell neoplasms, patient typically > 60 y/o
2. Clinical presentation: diffuse lymphadenopathy, hepatosplenomegaly
3. Histopathology / Lab Diagnosis:
 - a. BM: diffuse infiltration of lympho/plasmacytic cells
no evidence of punched-out bone lesions on X-ray

b. LN: lympho/plasmacytic infiltrates morphologically similar to SLL cells characterized by rearrangement of the μ -H chain
the absence of isotype switching suggests origin in the LN rather than BM

c. Serum / urine: M-protein = IgM = "macroglobulin"
Bence-Jones protein in 20-30% of cases

4. Complications:

a. cryoglobulinemia with Raynaud's phenomenon, peripheral neuropathy

b hyperviscosity syndrome:

i. distended retinal venules visual disturbances,

ii. bleeding diathesis, purpura

5. Course & prognosis: with repeated plasmapheresis a patient can survive several years

VI. SIGNIFICANCE OF SPLENOMEGALY

A. Normal white pulp - functions as a giant lymphoid organ, and mononuclear phagocytes are active in removal of circulating microorganisms as well as senescent RBCs. While pulp enlarges during virus (e.g. infectious mononucleosis) or bacterial infections, systemic auto-immune diseases (e.g. Felty's syndrome in RA).

REM: Loss of the spleen due to trauma or by autosplenectomy (multiple infarcts) in sickle cell disease can predispose to bacterial infection, especially *streptococcus pneumoniae*.

B. In leukemia / lymphoma

1. The spleen and liver often are involved in lymphocytic malignancies of all types

2. This is very important in staging, but not especially helpful in differential diagnosis.

3. massive splenomegaly can occur in CML.

other causes of massively splenomegaly are malaria, Kala-Azar (leishmaniasis), and Gaucher's disease (lipid storage in sinusoidal lining cells).

**HISTIOCYTOSIS X (a true histiocytic neoplasm)
= LANGERHANS CELL HISTIOCYTOSIS**

I. DEFINITION: Proliferative disorders of Langerhans histiocytes . Normal Langerhans histiocytes are specialized for antigen-presentation = dendritic cells. They form part of the cutaneous mononuclear-phagocyte system.

II. CLINICAL PRESENTATION relatively rare diseases

A. Letterer-Siwe syndrome = *acute disseminated form* (infants)

Extensive skin eruption is accompanied by systemic infiltration of liver, spleen, LN, BM. May respond to chemotherapy or resolve spontaneously

B. Hand-Schuller-Christian syndrome = *multifocal* (children)

Milder than acute disseminated form, but often involves posterior pituitary stalk

Disease triad: osteolytic lesions of calvarium. diabetes insipidus, exophthalmos

C. Eosinophilic granuloma = *unifocal* (young adults)

Indolent disease of skeletal system. Bone lesions respond to curettage or radiotherapy

D. Pulmonary disease - rare in adults

III. HISTOPATHOLOGY

A. Mixed tissue infiltrate: variable mixture of bland mononuclear cells, foamy histiocytes and eosinophils

B. Electron microscopy: **tubular Birbeck granules show a characteristic periodicity**
Robbins Fig. 15-37

C. Immunodiagnosis: cells express CD1a marker of dendritic cells

