Subject: e.g. HLS-Pathology

Topic: e.g. WBCs Neoplasms

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In the previous Lecture (lecture 7) we discussed Hodgkin Lymphoma and we talked about 2 types of Non-Hodgkin Lymphoma. Now, we will continue talking about the rest of NHL and other types as well. Now, let us start.

Burkitt Lymphoma

General info:

- **Extra nodular Lymphoma**
- **Origin**: **B-cells of germinal center**. So, they do express **CD20, CD10 & Bcl-6.**
- Has 3 types :
  1) Endemic in parts of Africa *100% of cases are associated with EBV*. This type involves the **Jaw**.
  2) Sporadic in the rest of the world (20% EBV +)
  3) Immunodeficiency (+ HIV) associated BL
- Both type (2) and (3) involve the **terminal ileum, retroperitoneum, ovary, CNS.**
- Sometimes it manifests as a leukemic disease (in the blood and BM)
- Aggressive, but responsive to chemotherapy.

Pathogenesis:

- **t(8;14) MYC→ IgH** => Overexpression of MYC transcription factor (which is a potent regulator of Warburg metabolism) .

Morphology:

- Intermediate size cells
- Round or oval nuclei [unlike DLBCL and FL] with Multiple small nucleoli
- ***Starry sky appearance***
- Monomorphic
- Presence of tangible body macrophages
- Lipid vacuoles can be found in the leukemic phase.

Extra-nodal marginal zone lymphoma

General info:

- Extra nodular lymphoma
- Origin: Marginal zone B cells
- Indolent (slow growing)

Pathogenesis

- Arises in the setting of **chronic inflammation** (H pylori gastritis, Hashimoto thyroiditis, and Sjogren's syndrome)
- Infiltrates the epithelium and causes its destruction

Mantle cell lymphoma

General info:

- Commonly arises in **lymph nodes** and affects them in addition to **Waldeyer ring** (oral and nasal cavity)
- **Origin**: naïve B-cells in mantle zone, Bcl6 and CD10 are **negative**
- Most commonly in older men
- Commonly involves BM, blood in 20%, sometimes in GIT [it appears as submucosal nodules → **lymphomatoid polyposis**]

Pathogenesis

- t(11;14) that fuses cyclin D1 gene to IgH => Overexpression of cyclinD1, promotes progression of cell cycle

Morphology

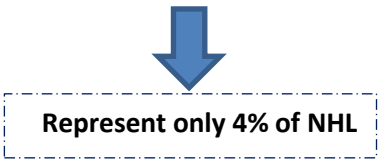
- looks like follicular lymphoma→ small centrocytes, BUT in diffuse pattern [no follicles]

Small Lymphocytic Lymphoma (SLL)

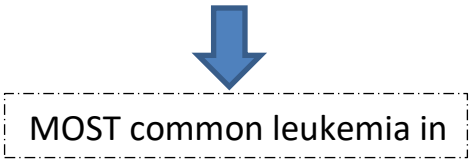
- Chronic lymphocytic leukemia (CLL): When it arises in and circulates the blood

General info:

- SLL arises in LNs and solid tissues



- CLL arises in BM and peripheral blood



- Affects elderly
- Low-grade B-cell neoplasm
- Lymphoma cells express CD20 [B-cell origin] AND Bcl2 and **CD5.**
- for confirmation of CLL, flow cytometry is used.

Pathogenesis

- Increased Bcl2 protein, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators that counteract Bcl2.
- B-cell receptor (BCR), is autonomously active => Bruton Tyrosine Kinase is activated => activate genes that promote cell survival

Morphology

- SLL: Most of neoplastic cells are **small** in **size, round**, dark chromatin, along with few large cells with central prominent nucleolus [**prolymphocyte**].
- CLL: Leukemic cells appear similar to lymphocytes, but they are high in number. Occasional prolymphocytes. **Smudge cells** which are Broken and dead lymphocytes.

Clinical Features

- Many patients are asymptomatic
- 50% have additional generalized lymphadenopathy & hepatosplenomegaly.
- **Thrombocytopenia**
- 50% have **hypogammaglobulinemia.**
- **Richter transformation:** in 10%, the disease becomes very accelerated with predominance of large cells
- Very poor prognosis, patients survive < 1 year.
- **Leukocytosis**
- Variable outcome (p53 mutation worsens the case)

Precursor B & T Cell neoplasms

General info:

- Precursor neoplastic cells: lymphoblasts, express CD34 and TDT.
- Lympho**blastic** lymphoma: when occurs in solid tissue (T type is more common than B)
- Acute Lympho**blastic** Leukemia(ALL): when circulates peripheral blood and involve bone marrow (B>T), it is aggressive & progresses rapidly.
- T-ALL presents in adolescents, arises in the thymus, is more common in boys.
- B-ALL tends to disseminate to solid organs (brain, testis, spleen)

Pathogenesis:

- Mutations in transcription factors for genes responsible for maturation of blasts
- Mutations in RAS signaling and tyrosine kinase proteins => cell survival
- In **T-LL**: 70% have mutations in **NOTCH1 gene**
- In **B-LL**, mutation is in **PAX5 gene**
- **T-ALL** shows mutation in **PTEN gene** (tumor suppressor) and **CDKN2A** (promotes cell cycle)
- Most childhood **B-ALL** have **hyperdiploidy** (>50 chromosomes) and t(12;21), involving **ETV6** and **RUNX1 genes**, creating new transcription factor.
- *Adult* **B-ALL** exhibits t(9;22) between **ABL** and **BCR genes**, similar to **chronic myeloid leukemia**, creating a new tyrosine kinase protein (**imatinib** inhibits this protein)

Morphology (ALL)

- Blasts are large, high N/C ration
- Chromatin is open (pale)
- Nucleolus sometimes present
- Cytoplasm is not granular

Clinical Features:

- Acute Aggressive
- Anemia, thrombocytopenia
- Good prognosis of B-ALL: hyperdiploidy, low WBC count, age between 2-10 years
- Poor prognosis of B-ALL: age < 2 years, age in adolescents or adults, WBC count >100k

Hairy Cell Leukemia

General info:

- **Uncommon** low-grade **B-cell** leukemia. It affects older patients, more common in men, smokers.
- Affects **BM** and **spleen** (Pancytopenia & Splenomegaly), LN involvement is very rare.
- Leukemic cells are biologically active; they inhibit hematopoiesis and cause BM fibrosis
- Characteristic: Leukemic cells are few in number, have prominent cytoplasmic projections [hair]
- Very sensitive to chemotherapy

Pathogenesis

- Mutation in **serine/threonine kinase BRAF gene** [found in solid tumors]

Plasma Cell Myeloma (Multiple Myeloma)

General info:

- Origin: plasma cells
- Commonly in elderly, more common in men, African origin
- Slowly growing, which is why they're NOT curable with conventional chemotherapy.
- **Lenalidomide**: which inhibits oncogenic proteins
- **Proteasome inhibitors**: which inhibit degradation of misfolded proteins → accumulation of these misfolded proteins → cause apoptosis in plasma cells.
- Malignant plasma cells secrete a large amount of monoclonal proteins (IgG mostly then IgA)
- Sometimes, they only secrete Lambda or kappa chains in large amounts which are detected in urine, these proteins are called **[Bence Jones proteins]**

Pathogenesis

- **t(11;14) cyclinD1** or **cyclinD3** fusing with IgH gene. MYC gene mutation occurs late in disease
- *BM macrophages and fibroblasts* supply these active cells with **IL-6** required for their survival
- They activate the expression of receptor activator of NF-kB ligand (**RANKL**) => osteoclasts are activated leading to more bone resorption. Other products inhibit osteoblast=> hypercalcemia=> pathologic fracture
- Malignant plasma cells Suppress normal B-cell function [**immune suppression**]
- Directly inhibits erythropoiesis (early onset **anemia**) → V.common
- **Renal failure**

Morphology:

- In Peripheral blood: characteristically RBCs show **rouleaux formation**
- In BM: more than 10% of BM cells are plasma cells (to make diagnosis)
- Abnormal figures with multi nuclei and cytoplasmic vacuoles containing Igs can also be observed.

Clinical Features:

- **Very high Erythrocyte sedimentation rate**
- **CRAB** (hyper**C**alcemia, **R**enal failure, **A**nemia, **B**one fracture)
- Some patients may suffer from **Amyloidosis**
- Advanced Disease: **Pancytopenia** [due to destruction of BM], **Plasma cell leukemia** & **Visceral damage**.

Peripheral T-Cell lymphoma

General info:

- Express T-cell markers: **CD2, CD3, CD5, CD7** and are **negative** for **TDT** [because they're mature]
- Aggressive, poor prognosis
- Simple diagnosis by exclusion of T-lymphoblastic or cutaneous lymphoma
- Neoplastic cells secrete inflammatory cytokines like normal cells, causing severe inflammation

Cutaneous Lymphoma

General info:

- Neoplastic **CD4+ T-cells**, that home to skin
- Patients present with a long history of **erythema**, which progresses to **plaque** then **tumor**
- Infiltrate epidermis and dermis, but most commonly it happens at the **junction** between them.
- With disease progression, lymphoma disseminates to **LNs** and **viscera.**
- **Sezary syndrome**: a variant of **Mycosis Fungoides**. From the beginning, patients present with widespread erythema and we see these cells in the skin, but they also have blood leukemia of neoplastic cells in which they're called [**Sezary cells**]

Morphology

- Neoplastic lymphocytes have irregular nuclear membrane [**cerebriform**]

Adult T cell Leukemia/Lymphoma

General info:

- Neoplastic CD4+ T-lymphocyte. Uniquely, these cells express **CD25 (IL-2 receptor**)
- Caused by a retrovirus; human T-cell leukemia virus1 (HTLV-1)
- Virus is similar to HIV: transmitted through body fluids (blood, breastfeeding, sexual intercourse)
- Poor prognosis

Pathogenesis

- **Tax protein**, which is essential for viral mRNA transcription, also causes proliferation of the cell through the following pathways: **PI3 kinase and cyclin D1, represses expression of CDK inhibitors, and activates NF-kB, all promote cell survival**.
- Tax also causes **genomic instability, inhibiting DNA-repair**

Clinical Features:

Patients present with *skin lesions, lymphadenopathy, lymphocytosis, hepatosplenomegaly, and hypercalcemia.*