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Brief Overview of Myeloid and Lymphoid Neoplasia: A Review Article

Huzaifa Saleem[1*]

[1]Nowshera Medical College, Khyber Pakhtunkhwa, Pakistan

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Abstract

Bone marrow neoplasia is a wide and diverse topic. Especially lymphoid and myeloid neoplasia, there is potential for confusion between them and their subtypes. This article aims to provides educational clarity and differentiation between lymphoid and myeloid neoplasia along with some of their subtypes. I searched databases like PubMed and Web of sciences along with the help of a reference book, Robins Basic pathology to achieve this goal. Articles were selected using a convenience sampling method without strict inclusion or exclusion criteria.

Keywords Myeloid neoplasia, Lymphoid neoplasia, Myeloproliferative syndrome

1. Introduction

Neoplastic proliferation of Haemopoietic stem cells that diffusely spread in the bone marrow and to other parts of the body through blood is called leukemia (1,2). Leukemia can be myeloid or lymphoid.

Neoplastic proliferation of Lymphocyte precursor cells that remains as a well-defined mass in the lymph nodes or wherever it may spread, is called lymphoma (1). It should be noted that granulocytic sarcoma also mimics lymphoma but is of myeloid lineages, seen in AML.

Lymphoid neoplasia Involves lymphoid lineage of Hematopoietic stem cells, therefore will affect B and T cells primarily. It includes:

- Hodgkin
- Non-Hodgkin lymphoma
- Acute lymphoblastic leukemia
- Chronic Lymphocytic leukemia.

Non-Hodgkin lymphomas includes B and T cell lymphomas. While Hodgkin lymphoma is purely a B cell lymphoma. Examples of NHL are:

- T cell lymphoma associated with HTLV1
- B cell lymphoma includes Follicular, Burkit, Mantel zone, Marginal zone, Diffuse large B cell Lymphomas (3)

Myeloid neoplasia Involves Myeloid lineage of Hematopoietic stem cells, therefore will affect Granulocytes primarily. It includes:

- Acute Myeloid leukemia
- Myeloproliferative syndromes like Chronic Myeloid leukemia, Primary myelofibrosis and Polycythemia vera.

Before proceeding further it is important to understand the types of genetic mutations that predisposes to blood neoplasms. Cancer transformations can be due to:

- Point mutations as in TP53 and RB tumorsupressor genes
- Translocations where two genes on different chromosomes fuse together. This will lead overexpression on one genes as in case of BCR-ABL translocation.

2. Myeloid Neoplasia

1. Acute Myeloid Leukemia

According to WHO classification it can due to:

- genotoxic chemotherapy
- progression from Myelodysplastic syndrome
- Mutations
- other causes

Corresponding author at: Huzaifa Saleem
Email address: gtx650tigddr5@gmail.com

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CLL can also progress to AML. Down syndrome is also associated with AML (13). A subtype of AML, Acute promyelocytic leukemia is due to 15:17t (RARA: PMLt) leading to inability of myeloblast cells to further differentiate. As a result, there is myeloblastosis and overcrowding of bone marrow causing anemia and thrombocytopenia (14). These myeloblast cells (in APL) contain Auer rods. Mutation in Isocitrate dehydrogenase is also associated with AML. This results in production of an oncometabolite that interferes in the differentiation of Myeloblast cells. On immunohistochemistry CD117 and 34 are positive (5). Flow cytometry can be used to check for 15:17t and PCR to quantify the gene confirming APL. Bone marrow biopsy will show more than 20% myeloblast cells. Gingival hyperplasia and leukemia cutis is present in AML (5, 15). Disseminated Intravascular Coagulation is also common due to production pf Tissue factor 3 and Tissue Plasminogen Activator by the tumor (16). This leads to consumptive loss of clotting factors. D-dimer and Partial Thromboplastin Time is positive (17). In AML there is no hepatosplenomegaly. Susceptibility to infection is high. Acute kidney injury secondary to tumor lysis syndrome can occur. All Trans Retinoic Acid (ATRA) is given as treatment in APL (18).

2. Chronic Myeloid Leukemia

95% of the 9:22t's are associated with CML (19). This leads to overexpression of ABL tyrosine kinase responsible cell growth. There are three phases of CML. In the Chronic phase, myeloblast cells have more propensity to differentiate into granulocyte so there is granulocytosis (Neutrocyte, Basophils and Eosinophils increase). This is associated with normal red blood cells and thrombocytosis. Usually, this phase is asymptomatic. In a leukemoid reaction there is increase in leukocyte alkaline phosphate, which helps to differentiate it from CML (in which there is 9:22t). Bone marrow biopsy will show less than 10% myeloblast cells. In accelerated phase, myeloblast cells have relatively low propensity for differentiation as a result on bone marrow biopsy there are 10-19% myeloblast cells, along with anemia and thrombocytopenia. Blast phase is an exacerbated phase of accelerated phase with more 20% myeloblast on bone marrow biopsy (5). On immunohistochemistry CD10 is

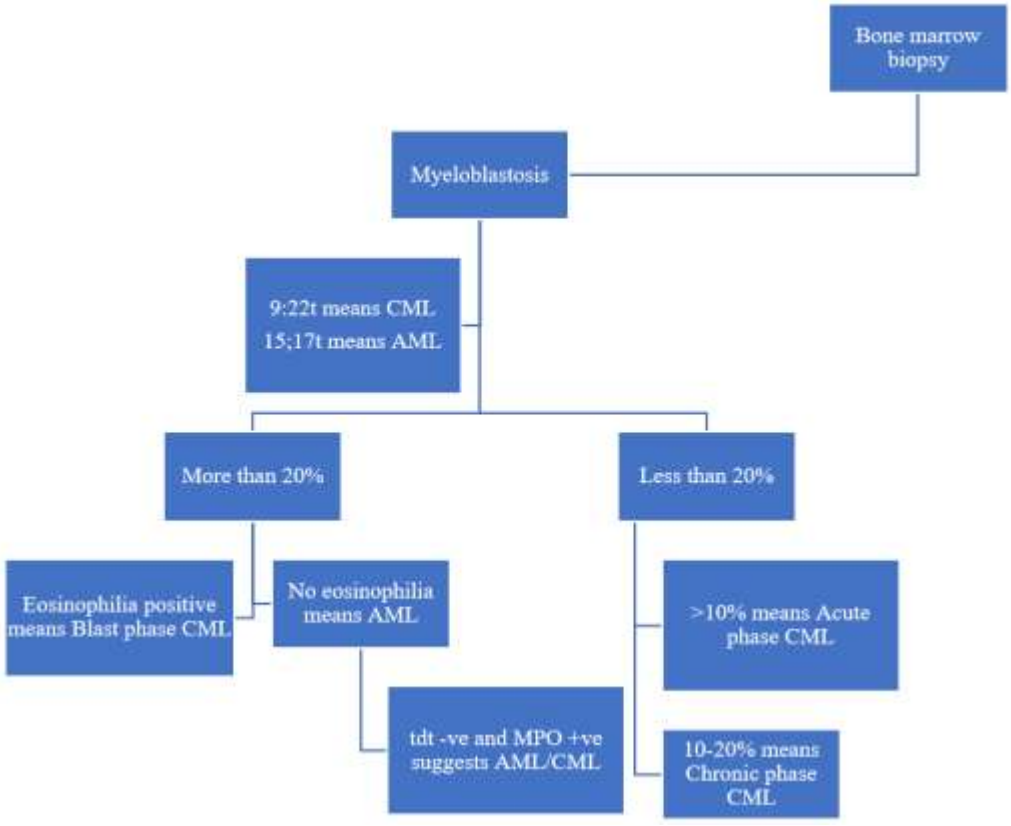

Figure 1: Diagnostic criteria for AML/CML

positive (20). Splenomegaly is present along with extramedullary hematopoiesis (21). Disorders with 9:22 translocations are treated with BCR-ABL Tyrosine kinase inhibitors, Now there are 1rst(Imatinib), 2nd (Dasatinib) and 3rd (Ponatinib) generations of TKIs. Newer generations of TKIs are better in terms of achieving Major, deep molecular responses and preventing Progression of the disease (Acute/Blast phase transformation in case of CML) but they have increased risk ratio for adverse effect (22,23). Newer generations of TKIs also increase liver enzymatic levels specifically Alanine and Aspartate transaminase (24).

3. Lymphoid Neoplasia

1. Acute Lymphoblastic Leukemia

Genetic defects in Lymphoid precursor cells prevent them from differentiating beyond lymphoblast stage, as a result there is excess production of lymphoblasts. This can involve both B and T lymphoblast cells as a result increased susceptibility to opportunistic infections like pneumonia and UTI etc. is present. T-ALL is due to mutation in PTEN and CDKN2A, the former inhibits Warburg metabolism and the later is composed of p14 that augments p53 tumor suppressor gene and p16 that is a cyclin dependent kinase inhibitor. P53 stops cellular proliferation in response to DNA damage and CDK inhibitor prevent progression of cell cycle from G1 to S and G2 to M phase. B-ALL has two subtypes. Adult (Leukemia) and Children (lymphoma) B-ALL. Adult B-ALL are less common and contain 12:21t (ETV6:RUNX1) while Children B-ALL are due to 9:22t (B-ALL in 20% of the cases, in 90% of the cases they cause CML) (4). 9:22t overexpresses a BCR-ABL Tyrosine kinase (Hence, treated with tyrosine kinase inhibitor) (5). Bone marrow hypercellularity due to lymphoblastosis causes anemia and thrombocytopenia (6). In severe cases Bone pain is present. If ALL spread by blood, hepatosplenomegaly is common due to lymphoblastic infiltration, causing nausea and vomiting. Meningococcemia may occur (more common in ALL than CML). T lymphoblastic infiltration of thymus causes thymic hyperplasia, compressing in trachea, esophagus and superior vena cava. Testicular enlargement is also common in ALL. Lymphadenopathy is also present. Is associated with down syndrome (7). 6th Cranial nerve palsy is present, manifesting itself as inability to abduct the eye. Mediastinal masses are present in T-ALL. Complications include tumor lysis syndrome (6).

If anemia and thrombocytopenia is present along with peripheral lymphoblastosis and Bone marrow biopsy show more than 20% lymphoblast then check for translocation in Flow cytometry. If 9:22t is present then use PCR to quantify BCR-ABL gene to confirm the disease, although the Prescence of 12:21 translocation also confirms it. On immunohistochemistry tdt is positive but MPO is negative. CD2-8 may be present in T-AL and CD10,19,20 in B-ALL (8).

2. Chronic Lymphocytic Leukemia

CLL only affects B cells. In CLL there is more differentiation than ALL, as one would find even mature lymphocytes (B and T cells) in peripheral smear. Although these cells are not as functional as in a normal, healthy individual. Hypogammaglobinemia is common as there is reduced antibody production leading to increased susceptibility to opportunistic infections like pneumonia, UTI etc. There is anemia and thrombocytopenia due to bone marrow crowding. Peripheral lymphocytosis is present (more than 5000 cells per mm3). On bone marrow biopsy small mature lymphocyte are found. Genetic defect involves BCL2 rearrangement leading to BCL2 overexpression (5). It is in individuals older than 70 years of age (9). Hepatosplenomegaly is present along with lymphadenopathy (5). On peripheral smear B cells tend to rupture giving rise to smudge cells. If CLL infiltrates lymph nodes and forms small tumors there it is called small cell lymphoma but if they enlarge, they can undergo ritchers transformation leading to Diffuse Large B cell lymphoma (10). On immunohistochemistry CD5 is present (11). Small lymphoblastic cells are present in bone marrow biopsy. Evans syndrome comprises of CLL, Autoimmune hemolytic anemia and thrombocytopenia which is of great diagnostic significance in case of CLL (12).

4. Hodgkin Lymphoma

Characterized by the presence of a large centroblast cell with multi-lobed nucleus. Involves the lymph nodes. In the germinal center centroblast cells with bad somatic hypermutation undergo apoptosis but in HL they don't (25) This can be due to upregulation of NFKB associated with HIV or EBV. These centroblast cells are called

Reed-Stenberg cells. There are 2 types of Hodgkin Lymphoma.

- Classical
- non-classical

Non-classical include Lymphocyte predominant HL, while classical HL has 4 subtypes:

- Nodular sclerosis
- mixed cellularity
- lymphocyte rich
- lymphocyte depleted

Classical Hodgkin Lymphoma are more common, especially nodular sclerosis. In classical Hodgkin Lymphoma RS cells are present but in Non-classical Hodgkin Lymphoma popcorn cells are present (26). Hodgkin Lymphoma upregulates PD1 so to prevent T cells from performing its action (that's why anti PD1 antibody is given). B symptoms (sweets, fever etc.) are present in stage 3 and 4 (5). Tomur cells secretes cytokines that act on hypothalamus to produce B symptoms. HL secretes cytokines that alter the function of hypothalamus causing B symptoms. In the skin basal cells secretes histamine leading to itching of the skin (Pruritis) and Lymphadenopathy is non-tender and rubbery except in alcoholics (27). Acute kidney injury secondary to tumor lysis syndrome is common along with hypercalcemia. Subtypes of HL incudes those without B symptoms (type A), with B symptoms (type B) and those with tumor >10cm (type X). In stage 1 only 1 lymph node is involved on one side of the diaphragm. In stage 2 more are involved. In stage 3 More lymph nodes but on both sides of the diaphragm. In stage 4 Both sides of the diaphragm and extra nodal involvement is present (although less common than non-Hodgkin lymphoma). Mainly mediastinal lymph nodes are affected (28).

5. Non-Hodgkin Lymphomas

Non-Hodgkin lymphomas includes B and T cell lymphomas. T cell lymphoma is associated with HTLV1 and B cell lymphoma includes:

- Follicular
- Burkit
- Mantel zone
- Marginal zone
- Diffuse large B cell Lymphomas (3).

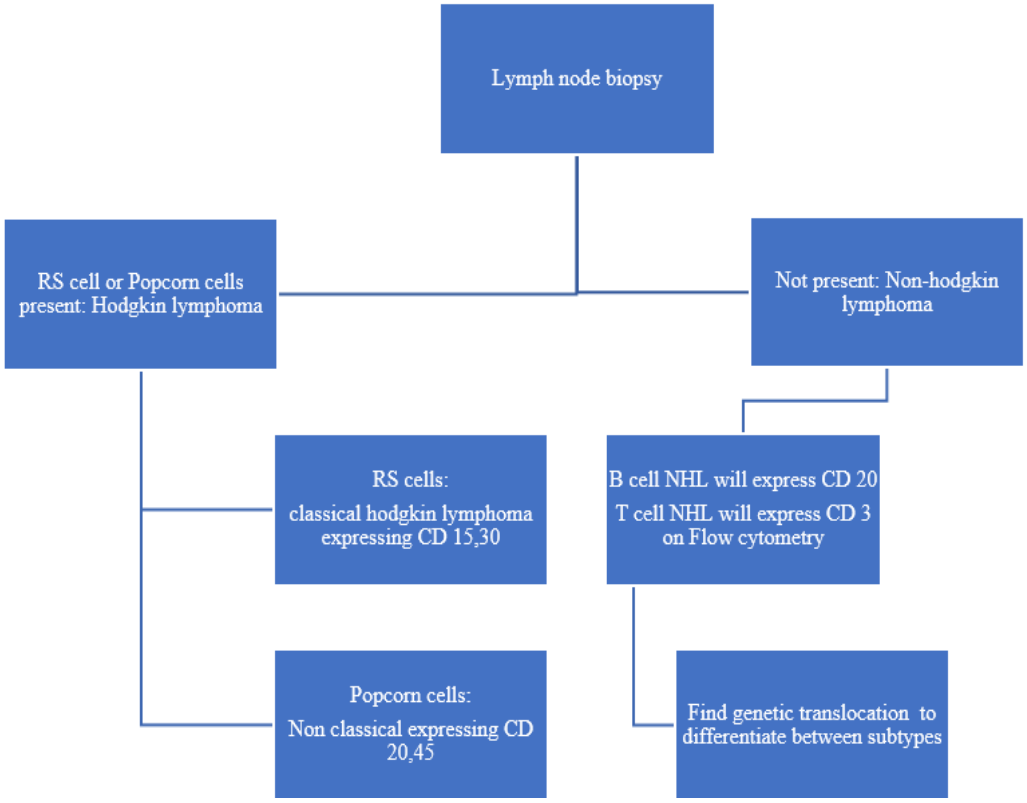

Figure 2: Diagnostic criteria Lymphomas

Hodgkin lymphoma accounts for 10% while non-Hodgkin lymphoma makes up 90% of all lymphoma (27).

Genetics:

T cell lymphoma is due to Human T cell leukemia virus type 1. Follicular lymphoma is due to 14:18t resulting in BCL2 overexpression. This is due to fusion of BCl2 and igH locus. Mantel zone lymphoma is due to 11:14t resulting in fast transition from G1 to S phase. This is due to fusion of Cyclin D1 gene and IgH locus resulting in overexpression of cyclin D1. Marginal zone lymphoma is due to chronic inflammation. Diffuse large B cell lymphoma is due to BCL6 overexpression ($1/3^{rd}$ of the cases), 14:18t (30%) and myc gene (rest of the cases). Burkit lymphoma is due to 8:14t resulting in overexpression of c-myc gene. This is due to fusion of c-myc gene and IgH locus (5).

Features:

Follicular and marginal zone lymphoma are due to decrease apoptosis of lymphocyte cells in the mantel zone and germinal center respectively. Marginal zone lymphoma associated with centrocyte cells surviving in the mantel zone of a lymph node. Follicular lymphoma is associated with centrocyte surviving in the germinal zone. Mantel zone, Burkit and Diffuse large B cell lymphomas are due to over proliferation of lymphocyte cells. In Mantel zone lymphoma naïve lymphocyte cells pre-exposure to any antigen (while residing in the mantel zone of a lymph node) undergo transformation, While in Diffuse large B cell and Burkit lymphoma centrocytes post-exposure to antigens (in the germinal center) undergo transformation (28).

- Follicular lymphoma is associated with centroblastosis and centrocytosis along with hepatosplenomegaly (more common than other NHL) (29).
- Mantel zone lymphoma is associated with lymphomatoid polyps in the GIT (5).
- Marginal zone lymphoma is associated with H. Pylori (Gastritis), Sjogren syndrome, gastric malt disease and Hashishmoto thyroiditis. Lymphoepithelial lesions are also present (30)
- Burkit lymphoma is associated with starry sky pattern of macrophages in the lymph node. EBV-associated (African subtype) causes large jaw masses, the sporadic type causes small bowel obstruction (31).
- Diffuse large B cell lymphoma is associated with Human Herpes Virus 8 (Kaposi sarcoma associated herpes virus), EBV and Mediastinal large B cell lymphoma (5).
- HTLV1 associated T cell lymphoma is associated with plaques of the skin (mucosis fungiodes). If infiltration of blood occurs Sezary (T) cells are seen in blood, further leading to Sezary syndrome (red rashes/erythroderma) (32).
- Hypercalcemia secondary to secretion of vitamin D by tumor and Acute Kidney Injury secondary to tumor lysis syndrome can occur (33,34)
- Stages is the same as Hodgkin Lymphoma.

Table 1: Differences between Hodgkin and Non-Hodgkin Lymphoma

Hodgkin lymphoma	**Non-Hodgkin lymphoma**
involves B cell	Involves B and T cells
RS cells or popcorn cells are present in the affected lymph node	Not present
Spreads to regional lymph node by contiguity.	Spread to lymph nodes in a haphazard manner
Commonly affects mediastinal lymph node	Less commonly affects mediastinal lymph node
Extra nodal involvements are uncommon	Extra nodal involvements are common
Eosinophilia is more common	Eosinophilia is less common

Conflict of interest The author declares no conflict of interest.

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