Lecture 9 in hematology by Dr.Alaa F. Alwan

Non-Hodgkin's lymphomas

Non-Hodgkin's lymphomas (NHLs) are malignant proliferations of the lymphoid tissues that can be distinguished from Hodgkin's lymphoma by a variety of clinical and histological features. NHLs are a disease of predominantly elderly persons, with a median age around 50–70 yr, often have an extranodal involvement. About 90% of the NHLs are derived from a malignant B-cell, the remaining cases from T-cells, natural killer (NK) cells, or undifferentiated cells.
NHLs are more frequent than Hodgkin's lymphoma and have an annual incidence of about 15–20 new cases per 100,000 people.

ETIOLOGY

The etiology of NHLs cannot be determined in most cases. viral or bacterial infections increases the likelihood of NHLs. HIV, Epstein-Barr virus (EBV) A human retrovirus (HTLV-1) that is associated with acute T-cell leukemias or lymphomas. Helicobacter pylori and mucosa-associated lymphoid tissue (MALT)-type gastric lymphomas Chronic infection with the hepatitis C virus has been associated with the development of NHL predominantly of the marginal zone type. Infections with Borrelia burgdorferi the etiological agent of Lyme disease, are associated with some forms of cutaneous lymphomas.

Cytogenetic and Molecular Markers in Non-Hodgkin's Lymphomas
Follicular lymphoma t(14;18)
Mantle cell lymphoma t(11;14)
B-cell chronic lymphocytic leukemia Trisomy 12
Burkitt's lymphoma t(8;14)(q24;q32), c-myc t(2;8)(p12;q24) t(8;22)(q24;q11)
Anaplastic large-cell lymphoma t(2;5) Alk

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

Patients with lymphoma present most frequently with lymph node swelling (lymphadenopathy) that may be either peripheral (e.g., axillary, cervical, inguinal) or involve central locations (e.g., mediastinal tumor, abdominal lymph nodes).
In most cases, the enlarged lymph nodes are painless, but also other lymphoma subtypes, may have an extranodal spread: the gastrointestinal tract or solid organs such as the liver; rarely, the CNS can be involved. In such cases, the clinical symptoms may be different. For example, the first symptoms of gastric lymphoma may be dyspepsia or discomfort in the upper abdomen. When the bone marrow is involved, the patient may present with anemia, leukopenia, or thrombocytopenia. Similarly to patients with Hodgkin's lymphoma, patients with NHL may also have systemic or B-symptoms (fever, night sweats, or weight loss).
The different categories of NHL can be divided into two major groups:
1. Low-grade (indolent) NHL: these lymphomas have an indolent course, do not always need treatment, but cannot be cured by most present approaches. Examples are the follicular lymphomas and CLL.
2. High-grade (aggressive) NHL: these lymphomas have an aggressive clinical course and, if untreated, are rapidly fatal. In a fraction of these NHL, cure is achieved with chemotherapy. Examples are Burkitt's lymphomas and diffuse large B-cell lymphomas (DLBCLs).

Diagnostic Strategies for the Non-Hodgkin's Lymphomas

1. History and clinical examination Ask for B symptoms and palpate all lymph nodes, liver, and spleen
2. Laboratory studies Obtain complete laboratory status, including blood counts, sedimentation rate, white cell differential, clotting tests, lactate dehydrogenase, B2-microglobulin, total protein, serum electrophoresis, quantitative immunoglobulins, immunoelectrophoresis if a monoclonal protein is suspected, creatinine, urea, uric acid, GOT, GPT, alkaline phosphatase; haptoglobin, Coombs' test; HIV serology
3. Chest radiograph (in two planes) CT scan of the thorax
4. CT scans of the abdomen Ultrasound of the abdomen and the neck FDG-PET scan
5. Lymph node biopsy should be excisional or incisional or tru-cut biopsy no role for fine needle biopsy just in selected cases
6. Bone marrow biopsy Bone marrow aspiration (with immunophenotyping to detect lymphoma infiltration) (if leukemic presentation, immunophenotyping can be done from blood)
7. ECG, Echo

DIFFUSE LARGE B-CELL LYMPHOMA

This is the most frequently occurring NHL. It includes lymphomas predominantly classified in the former Working Formulation as diffuse large-cell, diffuse mixed-cell, or immunoblastic, and lymphomas classified as diffuse centroblastic, diffuse centroblastic/centrocytic, and immunoblastic in the Kiel classification. Histopathologically, a diffuse proliferation of large, transformed lymphoid cells is found. The nuclei have a vesicular chromatin, prominent nucleoli, basophilic cytoplasm, and a moderate to high proliferation fraction.

Prognostic Factors in High-Grade NHL

Factors (each contributing one point) that enter into this International Index are age greater than 60 yr, reduced performance status, clinical stage III or IV, increased lactate dehydrogenase (LDH), and extranodal manifestation in two or more locations.

Treatment

The treatment of large-cell lymphomas depends on the stage of disease. Patients with disseminated disease (generally stages III and IV) are given six to eight cycles of R-CHOP (Rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin® [vincristine], and prednisone) or a comparable regimen..

FOLLICULAR LYMPHOMA

The combined group of follicular lymphomas or follicle center lymphomas makes up the second most frequent type of NHL (approx 20–30% of all cases of NHLs). In many countries, an increased incidence of follicular lymphomas has been observed. Pathologically, the follicular lymphomas have a characteristic picture that resembles normal germinal centers. Centrocytes are mixed with centroblasts and form a neoplastic germinal center. The growth pattern is usually follicular

At the molecular level, about 90% of patients with follicular lymphomas have the t(14;18) (q32;q21) translocation. Translocation t(14;18) leads to an overexpression of the bcl-2 protein. The immunophynotype of follicular lymphomas (as determined on tissue sections or in cell suspensions) is CD19+, CD20+, CD10+ in most cases, CD3-ve , and CD5-ve.

Clinical Symptoms

The clinical course of follicular lymphomas is indolent in most cases. The median age of patients with follicular lymphomas is around 50–60 yr. The disease most often begins with peripheral lymphadenopathy, and the mediastinum is rarely enlarged. Less than one-fifth of the patients have B-symptoms. The bone marrow is involved in about half of the patients, typically showing nodular infiltration. The clinical symptoms are often subtle and caused by the enlarged lymph nodes; para-aortic lymph nodes or an enlarged spleen may cause abdominal fullness or other local symptoms. An extranodal manifestation is observed in about 10% of the patients (gastrointestinal tract, rarely in the skin).

Treatment

1. OBSERVATION (WATCH-AND-WAIT STRATEGY)

indicated for asymptomatic patients with advanced disease (stage III–IV) who do not have B-symptoms or other complications caused by thelymphoma..

2. RADIOTHERAPY

indicated in stages I and II without bulk (usually as involved or extended-field radiation with 30–40 Gy).

3. SYSTEMIC CHEMOTHERAPY like R-CHOP

MANTLE CELL LYMPHOMA

The mantle cell lymphomas have a specific cytogenetic marker, the t(11;14) translocation,

Clinical Symptoms

The major symptom of mantle cell lymphomas is the enlargement of lymph nodes. About 80% of patients at diagnosis are already at an advanced stage (III or IV). About 30% of patients have B-symptoms. Almost two-thirds of the patients have an enlarged spleen. The bone marrow is involved in two thirds of the cases, and in some patients a leukemic dissemination can be found already at diagnosis.

Treatment

The optimal chemotherapy is R-CHOP achieved superior remission rates greater than 90%.