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stimulating factor, granulocyte-macrophage colony-stimulating factor) increase neutrophil counts, and erythropoietin increases RBC production in 20 to 25% of cases, but survival advantage has not been shown. Response of MDS to AML chemotherapy is similar to that of AML, after age and karyotype are considered.

139 / LYMPHOMAS

A heterogeneous group of neoplasms arising in the reticuloendothelial and lymphatic systems.

The major types are Hodgkin's disease and non-Hodgkin's lymphoma. An uncommon type is mycosis fungoides.

HODGKIN'S DISEASE

Localized or disseminated malignant proliferation of tumor cells arising from the lymphoreticular system, primarily involving lymph node tissue and the bone marrow.

Incidence and Etiology

In the USA, 6000 to 7000 new cases are diagnosed annually. The male:female ratio is 1.4:1. Hodgkin's disease is rare before age 10 and has a bimodal age distribution that peaks at ages 15 to 34 and after age 60. However, the second peak may be an artifact of inaccurate pathologic diagnosis, because most cases diagnosed after age 60 are intermediate-grade non-Hodgkin's lymphomas (NHL—see below). Epidemiologic studies find no evidence of horizontal spread. The cause is unknown, but patients with Hodgkin's disease appear to have a genetic susceptibility (as demonstrated in twin studies) and environmental associations (eg, occupation, such as woodworkers; Epstein-Barr virus infection; HIV infection).

Pathology

Diagnosis depends on identification of Reed-Sternberg cells (large binucleated cells) in lymph nodes or other sites. The background cellular infiltrate is heterogeneous and consists of histiocytes, lymphocytes, monocytes, plasma cells, and eosinophils. Hodgkin's disease has four histopathologic subtypes (see TABLE 139–1).

Reed-Sternberg cells are usually $CD15^+$ and $CD30^+$ on immunophenotyping. Lymphocyte-predominant Hodgkin's disease may be confused with T-cell–rich B-cell NHL; nodular sclerosis, mixed cellularity, and lymphocyte-depleted Hodgkin's disease may be confused with Ki-1 anaplastic large cell NHL.

TABLE 139–1. HISTOPATHOLOGIC SUBTYPES OF HODGKIN'S DISEASE

Type	Appearance	Incidence	Progression
Lymphocyte-predominant	Few Reed-Sternberg cells and many lymphocytes	3%	Relatively slow or indolent
Nodular sclerosis	Dense fibrous tissue* surrounds nodules of Hodgkin's tissue	67%	Intermediate or moderately progressive; relatively slow or indolent (occasionally)
Mixed cellularity	A moderate number of Reed-Sternberg cells with a mixed background infiltrate	25%	Intermediate or moderately progressive; aggressive
Lymphocyte-depleted	Numerous Reed-Sternberg cells and extensive fibrosis	5%	Aggressive

*Shows characteristic birefringence with polarized light.

Symptoms and Signs

Symptoms and signs primarily relate to the site, amount, and extent of nodal mass involvement. Most patients present with cervical and mediastinal adenopathy and without systemic complaints. Other manifestations develop as the disease spreads through the reticuloendothelial system, generally among contiguous sites. The rate of progression varies according to histopathologic subtype (see TABLE 139–1). Intense pruritus may occur early; fever, night sweats, and weight loss are frequent when internal nodes (bulky mediastinal or retroperitoneal), viscera (liver), or bone marrow is involved. Pel-Ebstein fever (a few days of high fever regularly alternating with a few days to several weeks of normal or subnormal temperature) occasionally occurs. Although the mechanism is unclear, immediate pain may occur in diseased areas after drinking alcoholic beverages, providing an early clue to diagnosis.

Bone involvement is often asymptomatic but may produce pain with vertebral osteoblastic lesions ("ivory" vertebrae) and, rarely, osteolytic lesions and compression fracture. Pancytopenia is occasionally caused by bone marrow invasion, usually by the lymphocyte-depleted type. Epidural invasion that compresses the spinal cord may result in paraplegia. Horner's syndrome and laryngeal paralysis may result when enlarged lymph nodes compress the cervical sympathetic and recurrent laryngeal nerves, respectively. Neuralgic pain follows nerve root compression. Intracranial, gastric, and cutaneous lesions occur rarely and, if present, suggest HIV-associated Hodgkin's disease.

Intrahepatic or extrahepatic bile duct obstruction by tumor masses produces jaundice. Leg edema may follow lymphatic obstruction in the pelvis or groin. Tracheobronchial compression can cause severe dyspnea and wheezing. Infiltration of lung parenchyma may simulate lobar consolidation or bronchopneumonia and may result in cavitation or lung abscess.

Most patients have a slowly progressive defect in delayed or cell-mediated immunity (T-cell function) that contributes in advanced disease to common bacterial and unusual fungal, viral, and protozoal infections (see in Ch. 151). Humoral immunity (antibody production) or B-cell function also is depressed in advanced disease. Cachexia is common, and patients frequently die of sepsis.

Laboratory Findings

Slight-to-moderate polymorphonuclear leukocytosis may be present. Lymphocytopenia may occur early and become pronounced with advanced disease. Eosinophilia is present in about 20% of patients, and thrombocytosis may be observed. Anemia, often microcytic, usually develops with advanced disease. In advanced anemia, defective iron reutilization is characterized by low serum iron, low iron-binding capacity, and increased bone marrow iron. Hypersplenism may appear, but mainly in patients with marked splenomegaly. Elevated serum alkaline phosphatase levels usually indicate bone marrow or liver involvement or both. Increases in leukocyte alkaline phosphatase, serum haptoglobin, ESR, serum copper, and other acute-phase reactants usually reflect active disease.

Diagnosis

The symptom complex of lymph node enlargement (especially cervical) and mediastinal adenopathy, with or without fever, night sweats, and weight loss, suggests lymphoma; however, Hodgkin's disease can be definitively diagnosed by lymph node biopsy that reveals Reed-Sternberg cells in a characteristic histologic setting. Hodgkin's disease is very rare in the absence of lymphadenopathy. Biopsy specimens then can be obtained from bone marrow, liver, or other parenchymal tissue. Monoclonal antibodies to certain antigens on Reed-Sternberg cells (eg, Leu-M1 [CD15] and CD30 [Ber-H2]) are important in cases that can be confused with NHL.

Hodgkin's disease may be difficult to differentiate from lymphadenopathy caused by infectious mononucleosis, toxoplasmosis, cytomegalovirus, NHL, or leukemia. The clinical picture can also be simulated by lung carcinoma, sarcoidosis, TB, and various diseases in which splenomegaly is the predominant feature (see Ch. 141).

Staging

Radiotherapy, chemotherapy, or a combination of both is potentially curative, but the extent or stage of disease must first be delineated. The Ann Arbor staging system is commonly used (see TABLE 139–2). The Cots-

wold modification of the Ann Arbor stage uses *X* to designate a bulky disease site (> 1/3 of the chest diameter or > 10 cm in diameter).

Noninvasive procedures for staging include CT of the thorax, abdomen, and pelvis and gallium scanning. Bone scanning and MRI are usually not required. Bipedal lymphangiography may be indicated in patients with normal abdominal and pelvic CT scans. Clinical studies attempting to detect disease below the diaphragm may be falsely positive or negative in 25 to 33% of patients. Laparotomy (including splenectomy), biopsy of mesenteric and retroperitoneal lymph nodes (especially those enlarged on CT or lymphangiography), and core biopsy of the bone marrow and liver should be considered when therapeutic decisions will be significantly affected. However, staging laparotomy indications have been narrowed significantly in recent years. Only patients whose clinical stage is IIA or less and in whom mantle radiation is planned may be considered. If the patient is to receive chemotherapy, staging laparotomy is not needed.

TABLE 139–2. ANN ARBOR STAGING OF HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA

Stage*	Criteria
I	In one lymph node only
II	In two or more lymph nodes on the same side of the diaphragm
III	In the lymph nodes, spleen, or both and on both sides of the diaphragm
1	Above the renal vessels (eg, spleen; splenic, hilar, celiac, and portal nodes)
2	In the lower abdomen (periaortic, pelvic, or inguinal nodes)
IV	Extranodal involvement (eg, bone marrow, lung, liver)

*Subclassification E indicates extranodal involvement adjacent to an involved lymph node (eg, disease of mediastinal nodes and hilar adenopathy with adjacent lung infiltration is classified as stage IIE). Stages can be further classified by A to indicate the absence or B to indicate the presence of constitutional symptoms (weight loss, fever, or night sweats). B symptoms generally occur with stages III and IV (20 to 30% of patients).

Treatment

Chemotherapy or radiotherapy regimens cure most patients. Nodal disease can be eradicated in > 95% of cases with 4 to 4.5 wk of 4000 to 4400 cGy within the treated field. In addition, irradiation of adjacent regions (extended field) to 3600 cGy is standard because the disease spreads by lymphatic contiguity. Patients with subclassification E may also respond to radiotherapy, although combined chemotherapy and radiotherapy is often recommended. Treatment is based mainly on pathologically staged patients, although selected patients may be considered for primary radiotherapy without pathologic staging.

Stage I and IIA disease can be treated with radiotherapy alone to an extended field that includes all lymph node–bearing areas above the diaphragm and, in most cases, the periaortic lymph nodes to the aortic bifurcation and spleen or splenic pedicle. Such treatment cures about 80% of patients. Cure refers to being disease-free at 5 years post-therapy, after which relapse is very rare. In patients with bulky mediastinal disease, radiotherapy alone has a high relapse rate; chemotherapy followed by radiotherapy results in a prolonged relapse-free survival in about 75% of patients. For selected patients with stage IA disease and nodular sclerosis or lymphocyte-predominant histology, mantle field radiotherapy alone may suffice.

For **stage IIIA1 disease,** total nodal irradiation (mantle and inverted Y) results in an overall survival of 85 to 90%, with disease-free survival of 65 to 75% at 5 years. In selected cases (eg, minimal splenic disease only), lesser radiotherapy (omission of the pelvic field) has been equally effective. However, for the majority of patients presenting with clinical stages IIB and IIIA1, chemotherapy and radiotherapy are indicated. For **stage IIIA2 disease,** combination chemotherapy is generally used with or without radiotherapy of bulky nodal sites. Cure rates of 75 to 80% have been achieved.

Because radiotherapy alone does not cure **stage IIIB disease,** combination chemotherapy alone or in conjunction with radiotherapy is required. Survival ranges from 70 to 80%.

For **stage IVA and B disease,** combination chemotherapy, particularly MOPP (mechlorethamine, vincristine, procarbazine, prednisone) or ABVD (doxorubicin,

bleomycin, vinblastine, dacarbazine), has produced a complete remission in 70 to 80% of patients, with > 50% remaining disease-free at 10 to 15 yr. ABVD has become the standard regimen for most cases based on the results of recent randomized studies. Alternating MOPP and ABVD or hybrid combinations have not proven superior to ABVD in prospective studies. Other effective drugs include nitrosoureas, ifosfamide, cisplatin or carboplatin, and etoposide. Patients who fail to achieve complete remission or who relapse within 6 to 12 mo have a poor prognosis. Autologous transplantation using bone marrow or peripheral cell products has been carried out in selected patients; conventional salvage regimens are generally not curative. Autologous transplantation can cure up to 50% of patients who are physiologically eligible for intensification therapy and responsive to salvage induction chemotherapy. Allogeneic transplantation has not been shown to be superior and is not recommended. Autologous transplantation is also being studied in selected high-risk patients at initial diagnosis.

NON-HODGKIN'S LYMPHOMAS

Malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver, and GI tract.

Pathologic classification of non-Hodgkin's lymphomas (NHLs) continues to evolve, reflecting new insights into the cells of origin and the biologic bases of these heterogeneous diseases. The course of NHL varies from indolent and initially well tolerated to rapidly fatal. A leukemia-like picture may develop in up to 50% of children and about 20% of adults with some types of NHL.

Incidence and Etiology

NHL occurs more often than Hodgkin's disease. In the USA, about 50,000 new cases are diagnosed annually in all age groups, the incidence increasing with age. Its cause is unknown, although, as with the leukemias, substantial experimental evidence suggests a viral cause for some lymphomas. For example, the retrovirus human T-cell leukemia-lymphoma virus (HTLV-I) has been isolated and appears to be endemic in southern Japan, the Caribbean, South America, and the southeastern USA. The acute illness of adult T-cell leukemia-lymphoma is characterized by a fulminating clinical course with skin infiltrates, lymphadenopathy, hepatosplenomegaly, and leukemia. The leukemic cells are malignant T cells, many with convoluted nuclei. Hypercalcemia often develops, related to humoral factors rather than to direct bone invasion.

The incidence of NHL, particularly immunoblastic and small noncleaved (Burkitt's lymphoma) cell types, is increased in HIV patients. Primary CNS involvement and disseminated disease have been reported. In about 30% of cases, the lymphomas are preceded by generalized lymphadenopathy, suggesting that polyclonal stimulation of B cells precedes lymphomagenesis. C-*myc* gene rearrangements are characteristic of some AIDS-associated lymphomas. Response to chemotherapy is possible, but toxicity is common and opportunistic infections continue to occur, resulting in short survival.

Pathology

The **Working Formulation** classifies NHL into prognostic categories having therapeutic implications as follows (NOTE: The prognostic designations are based on survival data of patients treated before 1980 and may not accurately reflect outcomes in patients undergoing modern therapy, as discussed under Treatment, below):

- **Low-grade lymphomas** (38%): diffuse, small lymphocytic; follicular, small cleaved cell; follicular mixed, small and large cell.
- **Intermediate-grade lymphomas** (40%): follicular large cell; diffuse, small cleaved cell; diffuse mixed, small and large cell; diffuse large cell.
- **High-grade lymphomas** (20%): Immunoblastic lymphoma; lymphoblastic lymphoma; small noncleaved cell lymphoma (Burkitt's and non-Burkitt's type).
- **Miscellaneous lymphomas** (2%): composite lymphomas, mycosis fungoides, true histiocytic, other, and unclassifiable types.

A new pathologic classification, the REAL (Revised European-American Lymphoma) Classification, has recently been introduced and is gradually being adopted. This classification is valuable for identifying entities

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