INTRODUCTION

Hodgkin’s lymphoma is a malignant tumor characterized by pleomorphic lymphocytic and histiocytic infiltrate with multinucleated Reed-Sternberg cells (RSCs). Hodgkin’s lymphoma (HL) was first described in an 1832 report by Thomas Hodgkin after studying seven patients with painless lymph node enlargement. Hodgkin’s lymphoma is a heterogeneous syndrome rather than a single disease.

RISK FACTORS FOR HODGKIN’S LYMPHOMA

Genetic predisposition
The relative risk for the development of HL increases approximately 100-fold in monozygous twins and 7-fold in siblings of patients less than 45 years of age. Human leukocyte antigen (HLA) associations have been described in familial HL including HLA A1, B5, B18, DPB1, DRB1, DQA1, and DQB1.

Epstein-Barr virus and classical Hodgkin’s lymphoma
A total of 20-100% of HL appears to be associated with Epstein-Barr virus (EBV) infection, the association varying with age (more frequent in children and older adults), gender (more frequent in males), geography (higher in Asia than in the US), and histology.

Sjogren syndrome and Hodgkin’s lymphoma
Sjogren syndrome (SS) is commonly associated with non-HLs but rarely with HLs.

SS is an autoimmune disease characterized by a lymphocytic infiltration of salivary and lacrimal glands leading to a progressive destruction of these glands and by production of autoantibodies. This disorder is either isolated (primary SS) or associated with other systemic diseases (secondary SS). SS is characterized histologically by mononuclear cellular infiltration of the salivary and lacrimal glands and serologically by the presence of many tissue component antibodies. The most serious complication of SS is the appearance of parotid gland lymphomas. The warning signs are the presence of persistent parotid gland swelling, regional or generalized lymphadenopathies, hepatosplenomegaly,
lung infiltrates, vasculitis, and hypergammaglobulinemia, particularly when accompanied by pancytopenia, an increased erythrocyte sedimentation rate, or the presence of monoclonal immunoglobulins. The correlation between SS and the development of malignant lymphoma may be due to a chronic state of immunological hyperactivity and B-cell hyperstimulation, both in cases of HLs and in non-HLs.\(^1\)

**HIV infection and Hodgkin’s lymphoma**

HIV-infected individuals (especially those with AIDS) have up to 10-fold increase in incidence of HL. In HIV-HL, there is intratumoral loss of CD4 + T cells and a decrease in intratumoral-activated cytotoxic T lymphocytes leading to a striking inversion in the CD4/CD8 ratio HL.\(^3\) The majority of HIV-HL cases are of the mixed cellularity HL subtype, whereas nodular sclerosis HL is most common for HIV-negative patients.\(^4\)

**Aspirin intake**

Low-dose aspirin use is inversely associated with HL risk but only among never/rare users of nonaspirin nonsteroidal anti-inflammatory drugs. This is due to the polymorphic variation in genes involved in nuclear factor-κB (NFκB) activation/inhibition, other inflammatory pathways, and aspirin metabolism.\(^4\)

**CLINICAL PRESENTATION**

Patients with HL may present with the night sweats (during the previous month), unexplained weight loss (more than 10% of body weight), painless, rubbery and swollen lymph nodes when examined. The nodes of the neck and shoulders (cervical and supraclavicular) are most frequently involved (80-90% of the time, on average), splenomegaly, hepatomegaly, pain following alcohol consumption (involved nodes are painful after alcohol consumption), back pain, red-cultured patches on the skin, easy bleeding, and petechiae due to low platelet count.\(^6\)

Systemic symptoms include low-grade fever, night sweats, itchy skin (pruritis) due to increased levels of eosinophils in the bloodstream; or fatigue (lassitude). Systemic symptoms such as fever, night sweats, and weight loss are known as B symptoms. A pattern of relapsing fever known as the Pel-Ebstein fever, or ‘P-E fever’ related to cytokine release is distinctive of HLs.\(^7\)

**REED-STERNBERG CELLS AND VARIANTS**

Hodgkin’s lymphoma is characterized by the presence of RSCs and variants in the characteristic mixed inflammatory background. Classical (diagnostic) RSC are an important component in identifying primary Hodgkin’s lymphoma.\(^8\)

The cells are large (15-45 μm in diameter) and have either multiple nuclei or a single nucleus with multiple nuclear lobes, each with a large eosinophilic inclusion like nucleolus about the size of small lymphocyte (5-7 μm in diameter) and have eosinophilic cytoplasm. The classic binucleate RSC was described by Carl Sternberg in 1898 and Dorothy Reed in 1902. The binucleation is an artifact seen as a result of deep indentation and folds in the nuclear membrane.\(^2\)

**VARIANTS OF REED-STERNBERG CELLS**

A. Mononuclear RSC: These cells have a single large nucleus and a prominent eosinophilic nucleolus [Figure 1].\(^9\)

B. Lacunar RSC: They are large, with a single hyperlobated nucleus, multiple, small nucleoli, and eosinophilic cytoplasm which is retracted around the nucleus, creating an empty space (“lacunae”) [Figure 2]. These retraction artifacts are caused by formalin fixatives. In other fixatives, lacunar cells have an abundant pale cytoplasm and prominent cytoplasmic membrane.

C. Pleomorphic RSC: They have multiple irregular nuclei.

D. “Popcorn” RSC: (Lympho-histiocytic variant) are small cells, with a very lobulated nucleus resembling popcorn kernels with a small inconspicuous small nucleoli [Figure 3].

E. Mummy” RSC: They have a compact nucleus, no nucleolus, and basophilic cytoplasm.

**CLASSIFICATION OF HODGKIN’S LYMPHOMA**

The Rye classification of Hodgkin’s lymphoma was developed at the International Symposium in Rye, NY in 1965. It divides Hodgkin’s lymphoma into four subtypes [Table 1]. The divisions lack objective, clear cut cytologic and histologic guidelines.\(^10\)

A further refinement in this classification was made in the 1980s, when immunohistochemistry was used to demonstrate that the RSCs typically displayed a characteristic immunophenotype. The RSCs and variants

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**Table 1: Rye classification of Hodgkin’s lymphoma**

<table>
<thead>
<tr>
<th>Rye classification</th>
<th>Histological features</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Lymphocyte predominant</td>
<td>Lymphocytes and RSCs</td>
<td>Best</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>Nodules of lymphoreticular cells and lacunar RSCs</td>
<td>Good</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>Mixture of lymphocytes, eosinophils, plasma cells, and RSCs</td>
<td>Fair</td>
</tr>
<tr>
<td>Lymphocyte depleted</td>
<td>Lymphocytes and RSCs</td>
<td>Poor</td>
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RSCs: Reed-Sternberg cells
could usually be shown to express both CD30 and CD15 but usually lacked markers associated with non-HLs, such as leukocyte common antigen (LCA; CD45/CD45RB), B-cell antigens (e.g., CD20), and T-cell antigens (e.g., CD3).

Later, the Revised European-American Lymphoma (REAL) classification of Lymphoid Neoplasms developed by the International Lymphoma Study Group adopted a new approach to lymphoma classification. In this approach, all available information—morphology, immunophenotype, genetic features, and clinical features were used to define a disease entity. This combined morphologic and immunophenotypic diagnosis of HL was reflected in the 1994 REAL classification.[11]

REAL classification included following subtypes:
- Lymphocyte predominance
- Mixed cellularity
- Lymphocyte depletion
- Nodular sclerosis, and
- Lymphocyte-rich classic (provisional entity).

Since 1995, members of the European and American Hematopathology Societies have been collaborating on new WHO classification of hematologic malignancies. It used an updated version of the REAL classification for lymphomas and expanded the principles of the REAL. The 1994 REAL classification of Lymphoid Neoplasms and the 2008 WHO classification of Hematopoietic and Lymphoid Tumors both add only the entity of lymphocyte-rich classic (LRC) HL (designated a “provisional entity” in the REAL) to the four Rye categories of lymphocytic predominant (LP), mixed cellularity (MC), lymphocyte depleted (LD), and Nodular sclerosis (NS) HL. LRC HL was added to emphasize that a predominance of background small lymphocytes is one of the least important features in the diagnosis of LP HL.[12,13]

Several changes were proposed for WHO version, these included some changes in the nomenclature, splitting some categories that were believed to be heterogeneous and adopting some ‘provisional’ entities as ‘real’. Thus, it is the WHO classification that is used worldwide.[14]

WHO Classification
1. Classical HL[9]
   - Nodular sclerosis HL (Grades 1 and 2)
   - Mixed cellularity HL
   - Lymphocyte-rich HL
   - Lymphocyte depletion HL
2. Nodular lymphocyte predominance HL

CLASSICAL HODGKIN’S LYMPHOMA

Nodular sclerosis Hodgkin’s lymphoma
Young adults are more often affected than the elderly. It differs from all other forms of classical HL as being more common in females than males, and less frequently associated with EBV. Clinically, mediastinal involvement is more common in nodular sclerosis Hodgkin’s Lymphoma than in other types of HLs.[21]

Nodular sclerosis Hodgkin’s Lymphoma is characterized by the presence of lacunar cells and birefringent fibrous bands [Figure 4]. These collagen bands subdivide the lymphoid tissue into cellular nodules. The birefringent character of the connective tissue readily permits its identification as collagen.
VARIANTS OF NODULAR SCLEROSIS

A. Cellular variant: This variant is predominantly cellular and the formation of collagen bands and isolation of cellular nodules may be limited to a small portion of the specimen. The distinctive feature of the cellular proliferation in nodular sclerosis is the unusually large variant of the RSCell (lacunar). The cellular proliferation accompanying the unusual RSC, both within the nodules and in the nonnodular tissue may be predominantly lymphocytic or of mixed composition with numerous eosinophils or mature granulocytes or both.[15,16]

B. Syncytial variant: This variant is characterized by numerous RSC and variants. These cells may form sheets and/or cohesive clusters often surrounding necrotic foci.[17]

C. Fibroblastic variant: This variant contains areas with numerous fibroblasts which may not be associated with deposition of thick collagen. The proliferation of fibroblasts may obscure the RSC variants and immunohistochemical studies may be necessary for their identification.[18]

D. Obliterative total sclerosis variant: This variant consists of nodules that have been obliterated by fibrous tissue and sclerosis. The nodules consist predominantly of fibrous tissue (nonbirefringent) and also contain few lymphocytes or RSC variants. The initial phase in this process is the appearance of numerous mature granulocytes associated with the loss of lymphocytes. Next, numerous small vessels extend from the periphery of the nodule from the circumscribing collagen bands, followed by the formation of cellular connective tissue and finally collagen.[9,19]

MIXED CELLularity HODGKIN’S LYMPHOMA

This histologic type is of heterogeneous composition and occupies a somewhat intermediate position between the predominantly lymphocytic proliferation at one extreme, and lymphocytic depletion with diffuse fibrosis and reticular types at the other. It is composed of mature neutrophils, eosinophils, plasma cells, histiocytes, and lymphocytes in varying proportions, usually with a slight to moderate degree of disorderly fibrosis, but without collagen formation. RSC and mononuclear variants are often numerous and prominent. Focal necrosis may be present but is usually not marked [Figure 5]. This form is more common in males and strongly associated with EBV, as RSC contain EBV genomes in at least 70% of cases. This is more commonly associated with older age.[9]

LYMPHOCYTE RICH HODGKIN’S LYMPHOMA

This is an uncommon form of classical HL in which reactive lymphocytes make up vast majority of the cellular infiltrate. In most cases, lymph nodes are diffusely effaced, but vague nodularity due to presence of residual B-cell follicles can sometimes be seen. This form is associated with EBV in about 40% of cases. It is more common in males and is more often seen in older adults.[20]
LYMPHOCYTE DEPLETION HODGKIN’S LYMPHOMA

This form consists of numerous variants of RSC against a sparse background population of small reactive lymphocytes [Figure 6].

Two subcategories have been recognized by Lukes and Butler: [9]
A. The diffuse fibrosis variant characterized by reticulin fibrosis that envelops individual cells, relatively low cellularity and few diagnostic RSC.
B. The reticular variant characterized by numerous diagnostic RSC and variants with few background reactive cells. This form accounts for about less than 5% of cases and is seen in older patients, HIV positive patients and is often EBV associated.

NODULAR LYMPHOCYTE PREDOMINANCE HODGKIN’S LYMPHOMA

This is an uncommon variant accounting for approximately 5% of all cases. It is characterized by nodal effacement by a nodular infiltrate of small lymphocyte admixed with variable number of benign histiocytes. Typical RSC are difficult to find but their variants popcorn cell are seen. Other cells such eosinophils, neutrophils, and plasma cells are scanty or absent and there is little evidence of necrosis or fibrosis [Figure 7]. It involves peripheral lymph nodes and is the only HL subtype to involve mesenteric lymph nodes; the mediastinum is nearly always spared. Other common sites of involvement are periparotid and inguinal lymph nodes. It is also seen in children, much more commonly in males.[2]

DIAGNOSIS OF HODGKIN’S LYMPHOMA

Proper interpretation of cytologic features, together with use of immunocytochemical parameters, can be used for HL diagnosis [Table 2, Figure 8]. The RSC are essential for diagnosis of HL, their identification alone is not enough for the subtyping of HL. The reactive background is an essential component. It may consist of small T and B lymphocytes, histiocytes, epithelioid histiocytes, neutrophils, eosinophils, plasma cells, and fibroblasts in varying proportions depending on the specific histologic subtype of HL.[19,21]

PATHOGENESIS OF HODGKIN’S LYMPHOMA

A. There are two possible pathways for malignant transformation [Table 3],[2,22] The Epstein-Barr nuclear antigen 3C disables retinoblastoma protein that

Table 2: Immunophenotyping in Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Markers</th>
<th>CHL (RSCs in all subtypes)</th>
<th>NLPHL (L and H cells)</th>
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<tbody>
<tr>
<td>CD 30</td>
<td>Positive</td>
<td>Usually negative</td>
</tr>
<tr>
<td>CD 15</td>
<td>Usually positive</td>
<td>Usually negative</td>
</tr>
<tr>
<td>CD 20</td>
<td>Occasionally positive (40%)</td>
<td>Usually positive</td>
</tr>
<tr>
<td>CD 45</td>
<td>Usually negative</td>
<td>Usually positive</td>
</tr>
<tr>
<td>EMA</td>
<td>Usually negative</td>
<td>Usually positive</td>
</tr>
<tr>
<td>EBV genome markers (LMP-I, EBER-I)</td>
<td>Frequently positive</td>
<td>Infrequently positive</td>
</tr>
</tbody>
</table>


Figure 7: Nodular lymphocyte predominant Hodgkin’s lymphoma with L and H details highlighted in the insert

Figure 8: Photomicrograph exhibiting strong cytoplasmic reactivity for CD30 by Hodgkin and Reed-Sternberg cell
provides a plausible connection between the virus and the endless and purposeless proliferation of infected cells.

B. The second pathway involves MP-1, which upregulates nuclear factor-κB (NF-κB), a transcription factor for lymphocyte activation which may play a role in allowing the survival of B cells in HL by rescuing them from apoptosis within the germinal center and further mutations in some B-cells lead to the formation of RSC.

RSC continues to proliferate as they also acquire the capacity to escape apoptosis, survive, and continue proliferating. Apoptosis appears to be inhibited by several means in RSC:

1. Constitutive activation of the transcription factor NF-κB either autonomously, by rosetting T-cells, by EBV or by inactivation of its inhibitors such as IκB.

2. Inactivation of the CD95 death receptor pathway.

3. Inhibition of executors of apoptosis by expressing X-linked inhibitor of apoptosis.

The characteristic accumulation of reactive cells occurs in response to cytokines secreted by the RSC, such as interleukin (IL)-5, IL-6, IL-13, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor. Once attracted by cytokines, the reactive infiltrate in turn supports the growth and survival of tumor cells. IL-5 leads to attraction and activation of eosinophils that express ligands for CD-30 receptor that produce signals for the activation of NF-κB which is essential for RSC survival. IL-13 leads to autocrine stimulation of RSC.

**STAGING**

The most common staging system for lymphoma is the Ann Arbor staging system which was developed in 1971 for HL. This system for lymphoma focuses on the number of tumor sites (nodal and extranodal), location, and the presence or absence of systemic symptoms noted with each stage designation [Table 4].

Designations applicable to any disease stage:

A: No symptoms

B: Fever (temperature, >38°C), drenching night sweats, unexplained loss of >10% of body weight within the preceding 6 months

X: Bulky disease (a widening of the mediastinum by more than one-third of the presence of a nodal mass with a maximal dimension greater than 10 cm)

E: Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

CS: Clinical stage

PS: Pathologic stage (as determined by laparotomy).

**TREATMENT OF HODGKIN’S Lymphoma**

With appropriate treatment, about 90% of patients with Hodgkin’s Lymphoma are curable. Radiation therapy is potentially curative for Stage IA, IIA, and some III A cases. In Stage IA and IIA disease, mantle field radiation is used that includes all the suboccipital, cervical, supravacular, mediastinal, and hilar nodes and usually is extended to the celiac axis and splenic hilum. The radiation dose is 40-45 Gray (Gy) to the involved areas and 30-35 Gy to surrounding areas. Stage IIB disease is treated with more extensive radiation, such as extended field irradiation or total nodal irradiation (TNI). Patients with IIIA disease limited to spleen or paraaortic nodes may also be treated with TNI. Combination systemic chemotherapy is the treatment of choice for Stage IIIB, IVA, and IVB Hodgkin’s Lymphoma. This treatment is also indicated for some patients with Stage IIB and IIA disease.  

**Combination chemotherapy**

i. ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine)

ii. MOPP (mechlorethamine, vincristine procarbazine, and prednisone)

iii. BEACOPP (bleomycin, etoposide, doxorubicin, dacarbazine, cyclophosphamide, vincristine, procarbazine, and prednisone)
cyclophosphamide, vincristine, procarbazine, and prednisone) iv. CEC (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin) v. Stanford V regimen: External beam radiotherapy (XRT) is administered to bulky sites 2-4 weeks following the end of chemotherapy.

(vinblastine, doxorubicin, vincristine, bleomycin, mechloretamine, etoposide, and prednisone)

Therapy of relapsed or refractory Hodgkin’s lymphoma

I. Salvage therapy: For primary refractory or relapsed disease

- ICE (ifosfamide, carboplatin, etoposide)
- DHAP (cisplatin, cytarabine, prednisone)
- GDP (gemcitabine, daunemethasone, cisplatin)
- GVD (gemcitabine, vinorelbine, doxil)
- IEV (ifosfamide, etoposide, vinorelbine)
- MINE (mitoguazone, ifosfamide, vinorelbine, etoposide), and
- IV (ifosfamide, vinorelbine).

II. High-dose chemotherapy with autologous stem cell transplantation can also be used. [29]

ACKNOWLEDGMENTS

Drs. Robin Sabharwal, Shaminda Sengupta, Bhudev Sharma, Shivangi Gupta contributed equally toward conception, design, and definition of intellectual content. Drs. Robin Sabharwal and Shaminda Sengupta did literature search. All the four authors coordinated in the preparation, editing, and in reviewing the manuscript, and are also equal guarantors.

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