

Review Article

Hodgkin's Lymphoma: A Comprehensive Review for Oral Health Care Practitioners

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ABSTRACT

The proliferative disorders of lymphoid cells may be reactive or neoplastic. Among the neoplastic lymphoid diseases, the distinction between leukemias and lymphomas is merely in the general tissue distribution of the disease with varying and mixed presentations at times. The broad group of lymphomas has been segregated into two types - Hodgkin's and Non Hodgkin lymphoma. This differentiation is of great importance as each type is clinically and histologically different and unique from each other. Further, they are treated differently and hence of utmost practical importance. This article gives an overview of the Hodgkin's lymphoma, discussing its classification, clinical and histological features and various treatment modalities.

Key words: lymphoma, Hodgkin, Reed Sternberg Cell, Pel-Ebstein, lymph node, Ann Arbor.

INTRODUCTION

Hodgkin's disease/lymphoma is a malignant lymphoproliferative disorder described by Thomas Hodgkin in 1832. It is potentially a curable malignant lymphoma with distinct clinical characteristics, histology, and biologic behavior. Hence, its proper diagnosis aids in better patient management and prognosis. [1,2] The exact nature of this disease is still poorly understood, which is evident by the usage of a noncommittal term for the diseases for decades, because of the fact that the neoplastic cells i.e. Reed Sternberg (RS) Cells constitute only 1-3% of all the cellular population on histopathology. [3,4] Yet it is necessary to identify a RS cell in establishing the diagnosis of Hodgkin's

lymphoma (HL). Research has proved that RS cell is B lymphocyte in origin. [1]

The exact etiology for HL is still unknown. Research has shown that Epstein Barr Virus (EBV) is one major causative agent as it was seen to be positive in 50% of cases, especially in Mixed Cellularity HL (MCHL) than Nodular Sclerosis HL (NSHL). [4] It is also noted that HIV associated HL cases are 100% EBV positive. Further, genetic predisposition in its pathogenesis has been put forth as 1% patients with HL have a positive family history. Also siblings of the patients are known to have 3-7 fold increased risk of getting HL and HLA-DP is also more commonly seen in HL patients. [4,5]

Various pathogenetic mechanisms have been postulated for HL. It is said that the expression of EBV nuclear antigen (EBVNA1), which is essential for the replication of the episomal EBV genome in proliferating cells and of latent membrane protein (LMP1 and LMP2a), are responsible for this infection. LMP1 mimics CD40 receptor which is a co-stimulatory molecule for B cells. [6] Deregulation of nuclear factor kappa light chain of activated B cell (NF-Kappa B) transcription factor is also noted in this infection. NF-Kappa B is a protein complex which controls DNA transcription, cytokine production and cell survival in leucocytes. 30% cases of HL have a gene mutation which is proved by constitutive activity of NF-KB in RS cells. [7] Mutations in genes coding for NF-KB inhibitors like IKB alpha, IKB eta and A20 [8-11] and mutation of TNFAIP3 gene (a tumor suppressor gene) which codes A20 (protein which inhibits NF-KB) have also been reported. [12,13] Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway play a major role in the regulation of immune response of leucocytes and also helps in DNA transcription. Genetic lesions altering these pathways are seen in few IM patients. [14,15] 30% nodular lymphocyte predominant HL (NLPHL) cases show translocation of BCL6 proto-oncogene. [16] A strong familial association has been put forth because of the mutations seen in NPAT gene. [17,18] Another finding is the expression of deregulated micro RNA (miR135a) for target gene JAK2. [19-21] Microenvironment surrounding the malignant cells of HL is also a critical determinant of its initiation and progression. RS cells and its variants interact with CD4 and CD8 T cells, B cells, plasma cells, macrophages, mast cells, dendritic cells, eosinophils, neutrophils and fibroblasts. These cells indeed attract them via the secretion of cytokines and chemokines. [22,23]

HL is a disease common in western world with 2.4 and 2.8 cases per 100,000 in UK and USA respectively. [24] Around

7500-8000 cases are reported in the US annually. [1,3] The greatest recorded incidence rates of HL are in whites in San Francisco and Connecticut and in Italy whereas, it is a rare entity in India, China and Japan. [24] It always begins in a lymph node or a lymph node group. The most common affected group of lymph nodes are cervical and supraclavicular nodes (70-75%) or axillary and mediastinal nodes (5-10%). Abdominal and inguinal lymph nodes are affected in less than 5% of cases. [3] It is more common in men than women except the nodular sclerosis type, which is more common in women. [1] There is bimodal pattern of age in the occurrence of HL with one peak at 15-35 year and other at >50 yrs. The average age for HL is 27 yrs. [1] In India, 21% of all Hodgkin's disease was seen in children at the Tata Memorial Hospital, Mumbai, India with a marked male: female ratio of 5.5:1. [25] In developing countries, the incidence of MCHL is higher among children while in developed countries, NSHL is more common in young adults. [25]

Clinically, it presents as a persistent enlarging, non-tender, discrete mass in lymph node region. In the early stages of HL, lymph nodes are movable whereas in the later stages, the lymph nodes are matted and fixed to the surrounding tissues. [1,4] If it is untreated, it involves spleen and other extralymphatic tissues like bone, liver and lung. Systemic signs for HL are weight loss, fever, night sweats and general pruritus. Fever in HL is cyclical and may increase and build to a peak over several days. This pattern of fever is known as Pel-Ebstein fever. However, this is not pathognomonic of HL. [1] Chest pain and cough or shortness of breath due to large mediastinal mass or lung involvement may be present. The HL with no systemic signs is Category A and with systemic signs is category B. It is important to categorize HL, since absence of symptoms in HL have better prognosis. [1,3] Alcohol ingestion will cause pain at sites of nodal disease and patients will pin point a location in < 10% of cases. [1,4]

HL is primarily a disease of lymph nodes and hence, seldom occurs as a disease primarily in oral cavity. Oral involvement is rare but may get affected secondarily. A case of HL in which mandible and overlying alveolar mucosa was affected has been reported. ^[4]

The diagnosis of HL is based on the identification of characteristic neoplastic cell (RS cell) against a proper cellular background. RS cell is indeed a lymphoid cell which is B cell in origin. ^[1,3] The unique nature of HL is the paucity this neoplastic cell that are found against an inflammatory background. The background is of considerable importance in basic diagnosis and has a pivotal role in proper classification within HL, as RS like cells may be seen in reactive lymphoid proliferations other than in HL. ^[1,2] There is effacement of normal nodal architecture by a diffuse, often mixed infiltrate of inflammatory cells that is interspersed with large, atypical neoplastic lymphoid cells. ^[4] The variable quantities of these cells in different types of HL correlate with the aggressiveness of the tumor. The background component is made up of lymphocytes which are usually small in size with round and regular nuclei. Majority of the lymphocytes are T cells. In addition to lymphocytes, epithelioid cells, eosinophils, neutrophils, plasma cells and fibroblasts are also seen. Acellular collagen and cellular non collagenous fibrous tissue may also be found. The cytokines produced by neoplastic cells, dictates the histopathologic picture. The reason for systemic symptoms like fever and night sweats is because of presence of inflammation and necrosis. ^[1]

In evaluating HL on morphologic grounds, 3 elements - Neoplastic RS cells (quantity & aberrant types), reactive inflammatory cells (quantity of lymphocytes) and the stromal components (quality of fibrosis) have to be considered. ^[1]

The classic RS cell is a giant cell having a size of 60-80 microns and named after its founders, Dorothy Reed and Carl

Sternberg. It has a bi or multilobed nucleus with large eosinophilic nucleolus surrounded by a clear zone and a prominent nuclear membrane. It has a mirror image appearance and resembles the eyes of owl (owl's eye nuclei). The cytoplasm is eosinophilic. (Fig. 1 & 2) The presence of this cell is essential for initial diagnosis of HL. RS cells are CD 15 and CD 30 positive. As a general rule, the number of RS cells is inversely proportional to the number of lymphocytes in a particular histologic subtype. RS cells are also seen in other lesions such as Infectious Mononucleosis, Burkitt's lymphoma, Chronic Lymphocytic Leukemia and Benign immunoblastic proliferation. ^[1,4] RS cells are formed as the EBV proteins induce aberrant expression of cyclin A which leads to the multinucleation of virally infected cells. Studies have revealed that cyclin A is expressed in cytoplasm and nuclei of RS cell and Hodgkin cell respectively. ^[26] In non-infected cases of EBV, RS cells are formed by endomitosis. ^[27]

The typical RS cells show variations and these are Hodgkin cell, lacunar cell, lymphocytic & histiocytic (L&H) cell. Hodgkin cell is a mononuclear cell resembling RS cell but has a large nucleolus. (Fig. 2) The lacunar cell has multilobed nucleus, abundant cytoplasm and nucleolus. The nucleolus is less conspicuous than those in RS cell. They appear to lie in spaces or lacunae due to the artifact during tissue processing and hence are called as lacunar cells. Their appearance can be variable depending on background. (Fig. 2) The lymphocytic & histiocytic cells (L&H cell) cell has a multilobed nucleus with convoluted nuclei having small peripherally placed nucleoli. There is no perinuclear halo. They are also called as popcorn cells because their nuclei have resemblance to the exploded kernel of popcorn. According to some authors, RS cell and Hodgkin cell are fully neoplastic while Lacunar and L&H cells represent transformed/aberrant cells which have the potential to transform into neoplastic cells. ^[1] (Fig. 2)

Hodgkin Lymphomas are classified as ^[1,3]

- Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)
- Classic Hodgkin's Lymphoma
 - ❑ Nodular Sclerosing Hodgkin's Lymphoma (NSHL)
 - ❑ Lymphocyte Rich Hodgkin's Lymphoma (LRHL)
 - ❑ Mixed Cellularity Hodgkin's Lymphoma (MCHL)
 - ❑ Lymphocyte Depleted Hodgkin's Lymphoma (LDHL)

Occasionally, examples of Hodgkin's lymphoma are encountered that do not fit the criteria of any of the known subtypes and these are designated as unclassifiable. ^[3] The subtypes of Hodgkin's Lymphoma are given in the order of their decreasing prognosis. ^[1]

Nodular Lymphocyte Predominant HL (NLPHL) makes up about 5% of all HLs. ^[1,4] It can occur at any age. There is no

bimodal age distribution. It is more frequent in adults and involves peripheral lymph nodes. ^[1] 80% of the cases are diagnosed in stage I or II and 90% of the patients alive are at 10 years. ^[3] Late relapse is common. 2-3% of this subtype develops into large B cell lymphoma. ^[1] Classic RS cell is very rare or absent. Instead, a variant of RS cell, L&H cells is seen within the background of predominantly lymphocytes. Typically, they are arranged in a nodular pattern, although there may be diffuse areas. Clusters of epithelioid cells may be seen sometimes. ^[1,28] Immunophenotyping separates NLPHL from all other forms of HL. L&H cells are positive for B cell antigens i.e. CD 45, CD19, CD 20, CD22, CD79A & EMA and negative for CD 15 & CD 30. They differ from B cells of Non Hodgkin's Lymphoma (NHL) as they are immunoglobulin negative. ^[1,4] (Fig. 3)

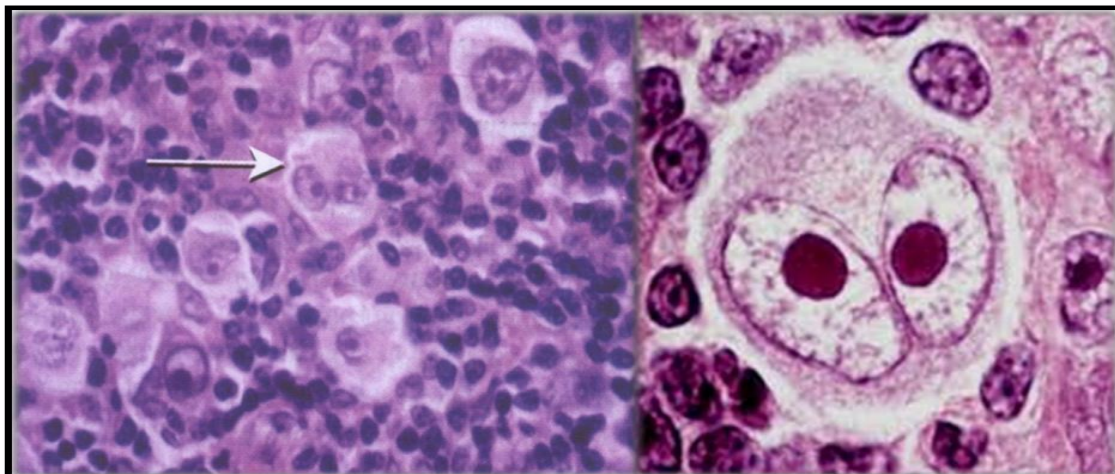


Figure 1: H & E section showing Reed Sternberg Cells (marked with arrow)

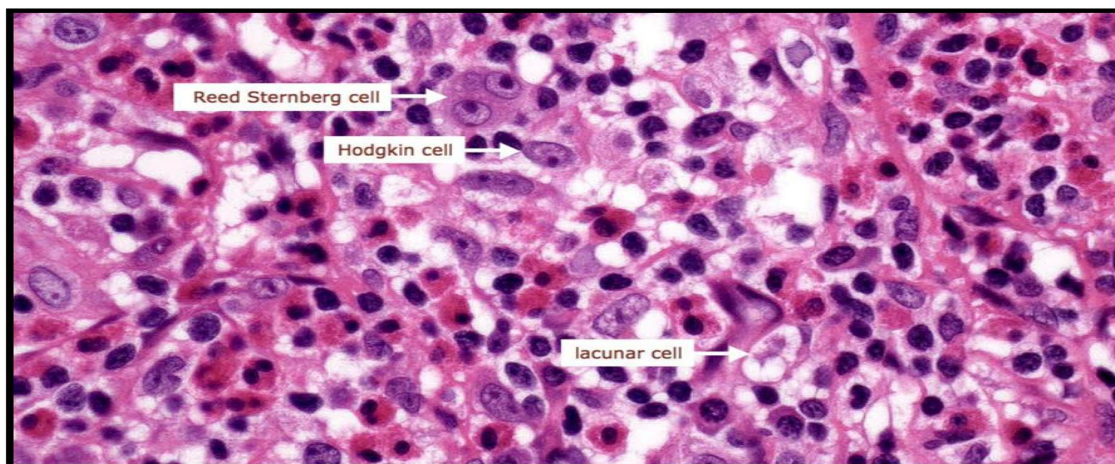


Figure 2: H & E section showing Reed Sternberg Cell, Hodgkin cell and Lacunar cell.

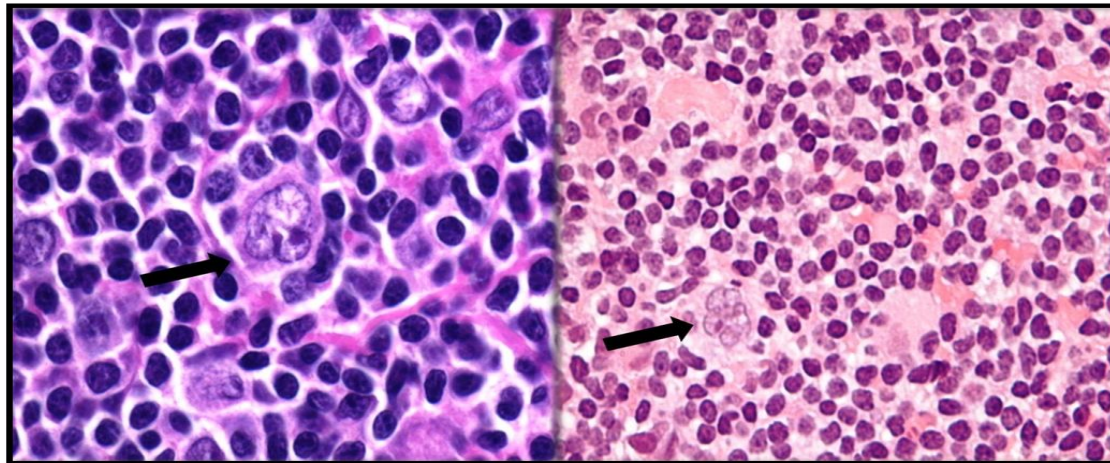


Figure 3: Microscopic picture of Nodular Lymphocyte Predominant HL showing popcorn cells (marked with arrow)

Classic Hodgkin's Lymphoma

Nodular Sclerosing HL is the most frequently occurring HL which constitutes 60-80% of all HLs. [4] Adolescents and young adults are most affected. Males and females are equally affected with slight female predilection. [1,28] It is often seen in mediastinum and other supradiaphragmatic sites. Patients with high socioeconomic background are most affected with survival rate of 80%. The distinguishing feature of this subtype is nodular pattern with bands of collagenous tissue that surround the nodules which are continuous with the thickened capsule of lymph node. They are often called C bands because of their shape. Their birefringence with polarized light is suggestive of collagenous nature. Characteristic cell is lacunar cell which are numerous in number. Classic RS cell is also seen but are uncommon. [4] (Fig. 4)

Lymphocyte Rich HL constitutes 5% of all HLs and presents at an early stage. [1,4] There is no fever or weight loss. Males are predominantly affected. Microscopically, it has a diffuse pattern. RS cells are infrequent. Lacunar cells may be seen. L&H cells are absent. Lymphocytes are numerous. Eosinophils and Plasma Cells will be more in this subtype than in NLPHL. [1,2,28] (Fig. 5)

Mixed Cellularity HL constitutes 15-30% of all HLs with adults being the most affected. It lacks usual bimodal age distribution. [1,3] Abdominal nodes and spleen are the most commonly affected

sites. Presentation is generally at late stage. Classic RS cells are readily seen and are the prominent cell type. Lacunar cells are occasionally seen. There is pleomorphic infiltrate of lymphocytes, epithelioid histiocytes, eosinophils, neutrophils and plasma cells. Fine interstitial fibrosis is also seen. [1,4,28] (Fig. 6)

Lymphocyte Depleted HL [1-4,28] Only 1% of all HLs are of this type. [1] Older Adults are affected majorly. It is more common in HIV positive patients. Patients from underdeveloped countries are commonly affected. Presentation is generally without peripheral lymphadenopathy but with abdominal lymph nodes, spleen, liver and bone marrow involvement. Generally, it is diagnosed at late stage. [1,2,28] Histopathologically, the infiltrate is diffuse with large number of RS cells which are often in bizarre sarcomatous forms. Lymphocytes and other inflammatory cells are sparse. The LDHL has two subtypes; reticular LDHL, also known as Hodgkin's Sarcoma when the tumor cells are arranged in sheet form and the diffuse LDHL. LDHL resembles anaplastic large cell lymphoma (ALCL) but the presence of t2:5translocation distinguishes the two as it frequently occurs in ALCL. [1] Diffuse fibrosis type shows diffuse and disorganized fine fibrosis with few classic RS cells and lymphocyte depleted background. Fibrosis here is non-birefringent and non collagenous in nature. Necrosis may be present. [1,4] (Fig. 7)

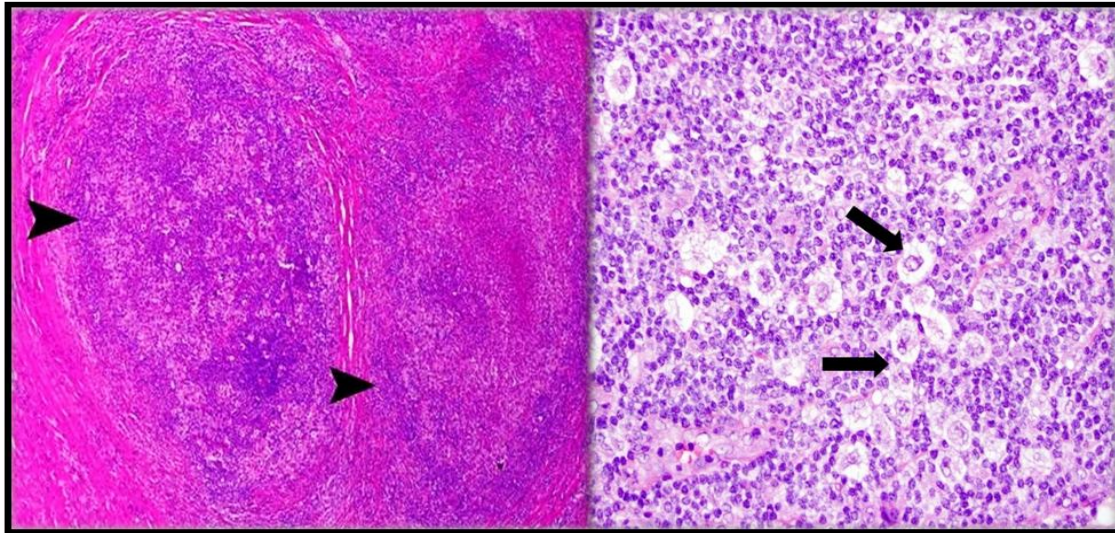


Figure 4: Microscopic picture of Nodular Sclerosing HL showing nodular pattern with bands of collagenous tissue that surround the nodules & characteristic lacunar cells (marked with arrows)

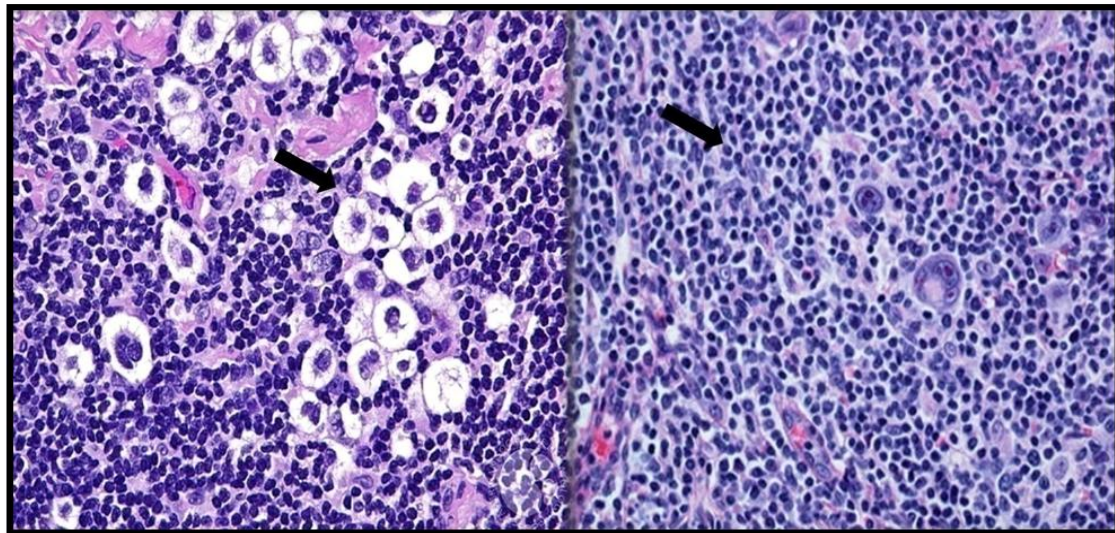


Figure 5: Microscopic picture of Lymphocyte Rich HL showing diffuse pattern with lacunar cells and numerous lymphocytes (marked with arrows)

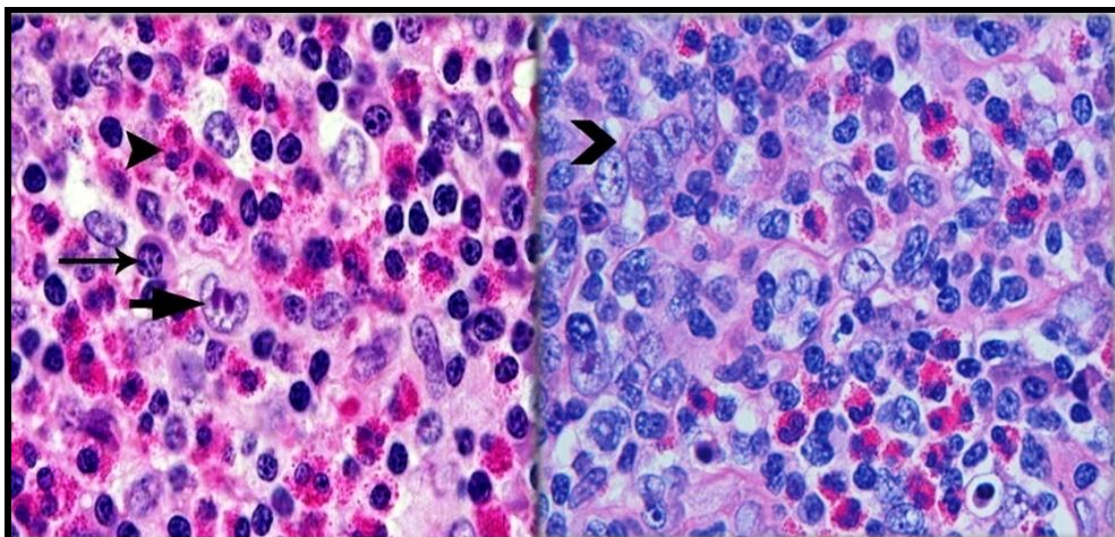


Figure 6: Microscopic picture of Mixed Cellularity HL showing Hodgkin cells in a background of lymphocytes, eosinophils, epitheloidhistiocytes, neutrophils & plasma cells (marked with arrows)

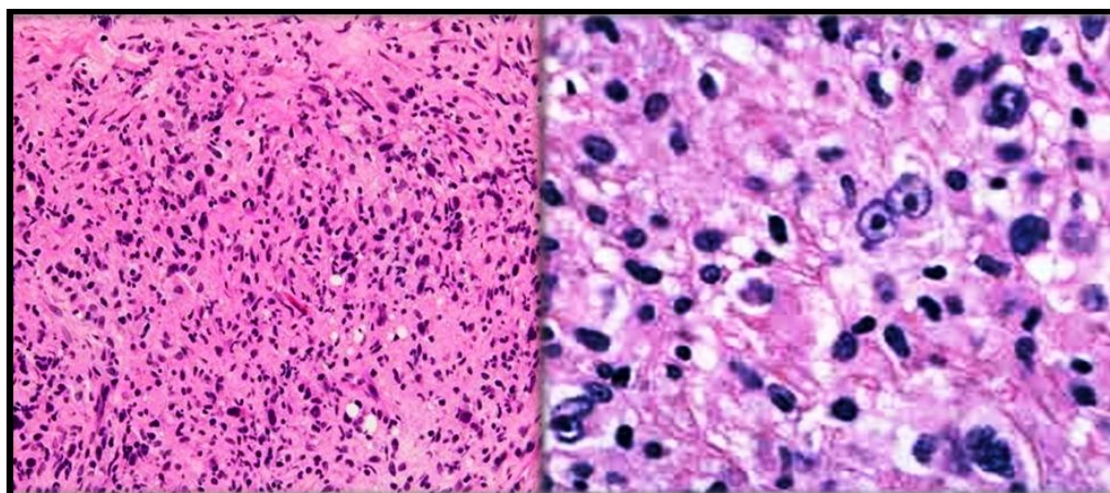


Figure 7: Microscopic picture of Lymphocyte Depleted HL showing diffuse infiltrate with large numbers of RS cells in bizarre sarcomatous forms

The histopathologic features are very important not only in categorizing the HL subtypes, but also aids in predicting the prognosis. Favourable prognosis for HL is seen with rare Classic RS cells, abundant lymphocytes and birefringent collagen. [1] Thus, the NLPHL has the best prognosis followed by NSHL, LRHL, MCHL and LDHL. [1,3,4]

In planning the treatment for HL, it is important to clinically stage the disease. This is done based on Ann-Arbor Clinical Staging System for Hodgkin's Lymphoma (HL). [1,3]

Stage	Definition
I	Involvement of a single lymph node region or of a single extranodal organ or site (I _E)
II	Involvement of two or more lymph node regions on the same side of diaphragm, or localized involvement of an extranodal site or organ (II _E) and one or more lymph node regions on the same side of diaphragm
III	Involvement of lymph node regions on both sides of diaphragm, which may also be accompanied by localized involvement of an extranodal organ or site (III _E), or spleen (III _S) or both (III _{SE})
IV	Diffuse or disseminated involvement of one or more distant extranodal organs with or without associated lymph node involvement

Treatment [1,3]

Radiotherapy is the mode of treatment for Stage I and II and combination of both radiotherapy and chemotherapy is the treatment modality used for Stage III and IV. Under chemotherapy, MOPP regime is followed which includes drugs Mechlorethamine, Oncovin, Procarbazine and Prednisone. This regime is given for a

time period of 6-12 months. Side effects of MOPP regime is hair loss, nausea, vomiting, peripheral neuropathies and leukemia inducement. Because of superior response and cure rates as well as lesser side effects of ABVD regime, it is used nowadays which includes Adriamycin, Bleomycin, Vinblastine and Dacarbazine. The complications which result because of treatment are mainly infections because of immunocompromised state of the patient. Patients undergoing treatment may present with herpes zoster, recurrent pneumococcal infections (if spleen involvement is there), dental abscess, pericoronitis, mucositis, hypersalivation and ulcerations.

CONCLUSION

Hodgkin's Lymphoma presents clinically with lymph node enlargements mainly the cervical and supraclavicular group and might be associated with general symptoms. Oral Health Care Practitioners (OHCPs) routinely come across lymph enlargements in their practice. Since the lymph node enlargements can be either due to reactive or neoplastic causes, it is important for OHCPs to be familiar with this disease so that early diagnosis may be possible. This will further help in early intervention and thus better prognosis of the patient. Not only is the OHCP called upon in its early diagnosis, but also plays an important role in management of associated

conditions due to treatment of HL.

REFERENCES

1. Marx RE and Stern D. Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment. 2nd Ed. Hong Kong: Quintessence; 2003. p. 829-844.
2. Kumar V, Abbas AK, Fausto N, Aster J. Robbins & Cotran Pathologic Basis of Disease. 8th Ed. Philadelphia: Elsevier Saunders; 2005. p. 668-710.
3. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 2nd Ed. New Delhi: Elsevier; 2005. p. 515-517.
4. Rajendran R and Sivapathasundharam B. Shafers's textbook of oral pathology. 7th Ed. New Delhi: Elsevier; 2012. p. 186-187.
5. Küppers R, Engert A and Hansmann ML. Hodgkin lymphoma The Journal of Clinical Investigation 2012; 122(10):3439-3447.
6. Kilger E, Kieser A, Baumann M, Hammerschmidt W. Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. EMBO J. 1998; 17(6):1700-1709.
7. Bargou RC et al. Constitutive nuclear factor-kappaB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. J Clin Invest 1997; 100(12):2961-2969.
8. Emmerich F et al. Overexpression of I kappa B alpha without inhibition of NF-kappaB activity and mutations in the I kappa B alpha gene in Reed-Sternberg cells. Blood 1999; 94(9):3129-3134.
9. Emmerich F et al. Inactivating I kappa B epsilon mutations in Hodgkin/Reed-Sternberg cells. J Pathol 2003; 201(3):413-420.
10. Jungnickel B, et al. Clonal deleterious mutations in the I kappa B alpha gene in the malignant cells in Hodgkin's disease. J Exp Med 2000; 191(2):395-401.
11. Lake A et al. Mutations of NFKBIA, encoding I kappa B alpha, are a recurrent finding in classical Hodgkin lymphoma but are not a unifying feature of non-EBV-associated cases. Int J Cancer 2009; 125(6):1334-1342.
12. Kato M et al. Frequent inactivation of A20 in B-cell lymphomas. Nature 2009; 459(7247):712-716.
13. Schmitz R et al. TNFAIP3 (A20) is a tumor suppressor gene in Hodgkin lymphoma and primary mediastinal B cell lymphoma. J Exp Med 2009; 206(5):981-989.
14. Joos S, et al. Genomic imbalances including amplification of the tyrosine kinase gene JAK2 in CD30+Hodgkin cells. Cancer Res 2000; 60(3):549-552.
15. Van Roosbroeck K et al. JAK2 rearrangements, including the novel SEC31A-JAK2 fusion, are recurrent in classical Hodgkin lymphoma. Blood 2011; 117(15):4056-4064.
16. Wlodarska I et al. Frequent occurrence of BCL6 rearrangements in nodular lymphocyte predominance Hodgkin lymphoma but not in classical Hodgkin lymphoma. Blood 2003; 101(2):706-710.
17. Saarinen S et al. Exome sequencing reveals germline NPAT mutation as a candidate risk factor for Hodgkin lymphoma. Blood 2011; 118(3):493-498.
18. Enciso-Mora V et al. A genome-wide association study of Hodgkin's lymphoma identifies new susceptibility loci at 2p16.1 (REL), 8q24.21 and 10p14 (GATA3). Nat Genet. 2010; 42(12):1126-1130.
19. Gibcus JH et al. Hodgkin lymphoma cell lines are characterized by a specific miRNA expression profile. Neoplasia 2009; 11(2):167-176.
20. Van Vlierberghe P et al. Comparison of miRNA profiles of microdissected Hodgkin/Reed-Sternberg cells and Hodgkin cell lines versus CD77+ B-cells reveals a distinct subset of differentially expressed miRNAs. Br J Haematol 2009; 147(5):686-690.
21. Gibcus JH et al. MiR-17/106b seed family regulates p21 in Hodgkin's lymphoma. J Pathol 2011; 225(4):609-617.
22. Kapp U et al. Hodgkin's lymphoma-derived tissue serially transplanted into severe combined immunodeficient mice. Blood 1993; 82(4):1247-1256.

23. Vockerodt M et al. Detection of clonal Hodgkin and Reed-Sternberg cells with identical somatically mutated and rearranged VH genes in different biopsies in relapsed Hodgkin's disease. *Blood* 1998; 92(8):2899-2907.
24. Mozaheb Z. Epidemiology of Hodgkin's lymphoma. *Health* 2013; 5(5A):17-22.
25. <http://www.medindia.net/patients/patientinfo/hodgkins-lymphomainscidence.htm>
26. Chang KC, Chang Y, Jones D, and Su IJ. Aberrant Expression of CyclinA Correlates with Morphogenesis of Reed-Sternberg Cells in Hodgkin Lymphoma. *Am J ClinPathol* 2009; 132:50-59.
27. Re D, Benenson E, Beyer M, Gresch O, Draube A, Diehl V and Wolf J. Cell Fusion Is Not Involved in the Generation of Giant Cells in the Hodgkin-Reed Sternberg Cell Line L1236. *American Journal of Hematology* 2001; 67:6-9.
28. Gobbi PG, Ferreri AJM, Ponzoni M, Levis A. Hodgkin lymphoma. *Critical Reviews in Oncology/Hematology* 2013; 85:216-237.

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