A STUDY ON LYMPHOMA

Dissertation

Submitted in partial fulfillment of the regulations of

M.S. DEGREE EXAMINATION

BRANCH I GENERAL SURGERY

Department of General Surgery

GOVT. STANLEY MEDICAL COLLEGE AND HOSPITAL

CHENNAI - 600001

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2014

CERTIFICATE

This is to certify that this dissertation titled **A STUDY ON LYMPHOMA** is the bonafide work done by **Dr.VENGATESAN.S** Post Graduate student (2011 – 2014) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfillment of the regulations of The Tamil Nadu Dr. M.G.R Medical University, Chennai for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

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I, **Dr.VENGATESAN.S** solemnly declare that this dissertation titled **A STUDY ON LYMPHOMA** is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief.

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Place: Chennai.

Date: **Dr.VENGATESAN .S**

ACKNOWLEDGEMENT

I am grateful to **Prof. S. Geethalakshmi,** Dean, Govt. Stanley Medical College for permitting me to conduct the study and use the resources of the College.

My sincere thanks to **Prof. K. Kamaraj,** Professor and HOD, Department of General Surgery, for his valuable guidance throughout the study.

I am highly indebted to my guide **Prof. J.VIJAYAN** Professor of Surgery for his constant help, inspiration and valuable advice in preparing this dissertation.

I express my deepest sense of thankfulness to my Assistant Professors **Dr.THIRUMURUGANAND, Dr.CHANDRASEKAR** for their valuable inputs and constant encouragement without which this dissertation could not have been completed.

I am extremely thankful to my patients who consented and participated to make this study possible.

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INTRODUCTION

Lymphoma , involves cancers of the lymphatic system..The two main types of lymphoma are hodgkins lymphomas also known as hodgkins disease, and the non hodgkins lymphoma.

In hodgkins lymphoma` ,cells of the lymphatic system multiplying fastly. The cells of HL grow with out any order or without any control. HL can occur almost anywhere in the lymphatic system.HL may occur in lymphnodal site. They may also affect the other parts of the lymphatic system[bone marrow, spleen]

HL spread from one group of LN to next group of LN.

Non hodgkins lymphoma, accounts,comprises 3 percent of all malignancies.In NHL cells of lymphatic system become abnormal.They undergo division and multiplying without any control .they do not die normally .

They spreads to other group of lymph nodes and lymphoid organs in a non contigious manner.

The objective of this study is to evaluate clinical presentation ,organs involved , incidence among different age groups and incidence of different subtypes of lymphomas

AIM:

To evaluate

- the spectrum of clinical presentations in lymphoma patients
- organs involved and
- incidence among specific age groups
- the incidence/distribution of different subtypes of lymphomas

MATERIALS AND METHODS:

PLACE OF STUDY:

Department of General Surgery,

Govt. Stanley Medical College and Hospital.

DURATION:

MAY 2011 TO DEC 2013

STUDY DESIGN:

Prospective and retrospective

SAMPLE SIZE: 51

METHODOLOGY

Clinical data, imaging studies and biopsy material of the all the available patients diagnosed as having lymphomas in the institution .

REVIEW OF LITTERATURE

LYMPHOMAS

EPIDEMOLOGY

Nonhodgkins kymphomas and hodgkins lymphoma are the most common haematological malignancies in the world.they account for 4 to 55 of new cancer cases . fifth leading cause of cancer deaths and second leading cause of cancer mortality.united states ,Europe and Australia are associated with high incidence rates . asia is generally associated with low incidence rates.

A dramatic increase in the incidence of non hodgkins lymphoma has been reported in the last five decades.although there is increase in the incidence of most histologies ,largest increase is seen in aggressive lymphomas . This increase is due to occurrence of primary cns lymphomas in patients with AIDS. Increased incidence is also seen in non-aids patients also. Difference in histological sub types has also been attributed geographically. For example, endemic burkitt lymphomas are common in children of equatorial Africa.gastric lymphomas in Italy .nasal t cell lymphomas in china.small intestinal lymphomas in middle east. Adult t cell lymphomas in southern japan and carribean.Reports

follicular lymphomas are lower in asia and Asian immigrants to the united states.Inspite of this the reason for increase in incidence of Nhl lymphomas remain unexplained.

NON HODGLINS LYMPHOMAS

ETOLOGY

The cause is mostly unknown. Although several genetic disease, environtmental agents and infectious agents have been implicated .familial occurrence of lymphomas has also been described. Increased risk is seen in siblings and relatives of lymphomas and other haematological malignancies.

Several inherited immunodeficiency states are associated with risk of developing lymphomas .Some of this include

- severe combined immunodeficiency disease
- hypogammaglobulinemia,
- common variable immunodeficiency,
- wiskott Aldrich syndrome, and
- ataxia telengectasia.

Development of lymphomas in these are associated with Epstein barr virus.

Acquired conditions such as Aids and post organ transplant conditions are also associated with development of lymphomas .A variety of auto immune conditions like rheumatoid arthritis ,sjogrens syndrome

and psoriasis are also associated with lymphomas .In sjogrens most of this lymphomas are marginal lymphomas . They occur in salivary glands and other extra nodal sites such as the stomach and lung. Celiac sprue is associated with poor prognosis lymphomas classified as enteropahty type intestinal T cell lymphomas

INFECTIOUS AGENTS

Ebv Dna both type A and type B are associated with 95% of endemic burkitt lymphomas . Less commonly they are associated with sporadic type.the actual mechanism of development is unknown .it appears that early Ebv infection and environemental factors increase the number of infected precursors and the risk of genetic errors.

Ebv is also linked to

- post transplant lymphoproliferative disorders ,
- some Aids associated lymphomas and
- some lymphomas associated with immunodeficiency disease.

Ebv is associated with almost all cases of Aids associated primary cns lymphomas .Normal immune responses by T cell supress Ebv infected cells .In patients with depressed T cell function ,clones of ebv transformed cells can proliferate. This can lead to the development of

lymphomas.The pattern Ebv associated proteins in patients with Aids associated lymphomas differ from that in other lymphomas.c-myc activation in the absence of ebv infection can also occur in aids associated lymphomas. The Ebv latent membrane protein 1 is a viral analog of the tumor necrosis factor receptor. In ebv positive aids associated lymphomas LMP 1 binds to members of the TNF receptor. It then activates Nfkb transcription factor leading to cellular proliferation.

The human T cell lymphotropic virus type 1 was the first human retro virus associated with development of malignancy. It is a type c rna virus responsible for the development of ALT in addition to myelopathy and other disorders.it is primarily transmitted mainly by breast feeding ,sexual contact and blood transfusion.the latent period takes several decades for the development of lymphomas.Htlv associated ALT is most prevalent in southern japan,south America ,Africa and the carribean.The Htlv 1 genome has a regulatory tax gene which is a potent transcriptional activator. It is responsible for the transforming feature of the virus. The binding domains of the virus glycoproteins inhibit glucose transport by interacting with Glut1 . This contributes to the virus associated disorders.

A third virus associated is HHv8.It was discovered from Kaposi sarcoma lesions in aids patients. It is called kaposi’s sarcoma associated

herpes virus.It is also associated with multicenteric castleman's disease. In an analysis of 193 patients with lymphomas the virus was found in only 8 patients. All of these are primary effusion lymphomas.HHV 8 associated lymphomas lack c-myc expression and has different phenotype and expression. The actual mechanism of stimulation is unknown . It has been proposed that this virus is necessary for Ebv induced transformation.

Hepatitis c is also linked to lymphomas . Hcv infection is strongly associated with essential mixed cryoglobulinemia,which is associated low grade lymphomas.several analyses show higher incidence of Hcv infection in patients with B-cell NHL.The association appears strongest for patients with monocytoid lymphomas and lymphoplasmacytoid lymphomas .Neoplastic transformation is related to chronic antigenic stimulation of Bcells by HCV.

Simian virus 40 , a potential contaminant of salk polio vaccine may also be linked to the developement of NHL.

Several bacterial infection is also related to development of lymphomas .Helicobacter pylori is linked to the development os gastric mucosa associated lymphoid tissue(MALT) lymphomas. The development of gastric lymphomas includes several steps , colonisation

of gastric mucosa ,chronic antigenic stimulation leading to gastritis and subsequent development of malignant B cell clones.

Campylobacter jejuni is associated with small intestinal mmunoproliferative disease some cases of ocular adnexal lymphomas is associated with chlamydia psittacci infection.

ENVIRONEMENTAL AND OCCUPATIONAL EXPOSURES

There is increased risk of NHL in several occupation in farmers forestry and agricultural workers.Exposure to herbicides especially phenoxy herbicides like 2,4,-dichlorophenoxyacetic acid.NHL has been associated with organic solvents and high levels of nitrates in drinking water.

DIET AND OTHER EXPOSURES

Studies suggest that the risk of lNHL is increased in association with higher intake of meat and dietary fat. Recreational drug use has been associated with increased NHL risk and tobacco use has also been associated with increased risk . Risk of NHL in association with ionising radiation is minimal.solar ultra violet exposure has also been associated with NHL in some studies .

ANATOMY AND MORPHOLOGY OF NORMAL LYMPHOID TISSUES

Lymphoid tissues can be divided in to two major categories 1.central or primary lymphoid tissues,in which lymphoid precursor cells mature .

2.periphery or secondary lymphoid tissue ,in which antigen specific reactions occur

PRIMARY (CENTRAL) LYMPHOID TISSUES

BONE MARROW (bursa equivalent)

These are the antibody producing cells found in the bone marrow . they are equivalent to the bursa of fabricus found in the avian species.

THYMUS

Thymus is the site at which immature T-cell precursors which migrate from the bone marrow matures in to naïve T cells capable of responding to antigen. The thymus is divided in to cortex and medulla each which is characterised by special function.

SECONDARY (PERIPHERAL)LYMPHOID TISSUES

The lymph nodes are placed throughout the body to process the antigen present in the lymphdrained from tissues and lymphatics drained through lymphatics.lymph nodes have a capsule ,a cortex ,a medulla and sinuses(subcapsular ,cortical and medullary). The sinuses contain the macrophages which take up the antigens and process them in to peptides . these peptides are then presented to the lymphocytes in the major histocompatibility antigens.the cortex contains B cell follicles and paracortical T-0cell zones and the medulla contains medullary cords and sinuses.the paracortex contains endothelial venules through which T and B cells and the antigen presenting cells which present antigen to the T cells.the follicles also contain follicular dendritic cells that bind antigen – antibody complexes and help in regulating the differentiation of B cells in response tio antigens.

SPLEEN

The spleen has two major areas

1. Red pulp, which functions as a filter for particulate antigens and for the formed elements

2. White pulp, which is identical to the lymphoid tissue of the lymph node .

Follicle and germional centres are found in the malphigian corpuscles,

T cells and dendritic cells in the peri arteriolar lymphoid sheath . plasma cells are concentrated in the red pulp.

MUCOSA ASSOCIATED LYMPHOID

These are the specialised lymphoid tissue found in association with the epithelium in nasopharynx ,oropharynx as the waldeyers ring ,adenoids and tonsils . in the gastrointestinal tract as peyer patches in the distal ileum ,colon and the rectum. In the lung as bronchus associated lymphoid tissue . they have prominent B cell follicles and also discrete T cell zones .they function in response to intraluminal antigens . it can also be acquired in sites such as stomach ,thyroid in response to chronic infection or inflammation.

B AND T CELL DIFFERNTIATION

It includes 2 phases antigen dependent and antigen independent.

Antigen independent differentiation in primary lymphoid organs without exposure to antigens. The early stages of lymphocytes are called stem cells and lymphoblasts where as the later stages are differentiated cells. On exposure to antigens the naïve lymphocyte undergoes blast transformation and proliferates to hive rise to a progeny against the inciting antigen.the early stages are composed of proliferating cells and later stages are composed of differentiated cells.the neoplasms composed of proliferating cells are aggressive and neoplasms composed of differentiated cells tend to be indolent. Proliferatin g cell neoplasm such as luekemia/lymphomas are more common in children and those composed of mature cells such as lymphoplasmocytic lymphomas are common in adults .

ANTIGEN –DEPENDENT B-CELL DIFFERENTIATION

IMMUNOBLASTIC OR PLASMA CELL REACTION

When interacting with antigen the naive B cell transforms into a proliferating cell, which transforms into an antibody-secreting plasma cell. In T-cell independent reactions, and in the early primary immune

response, naive B cells transform into IgM positive blast cells in the T-cell zones, proliferate, and differentiate into IgM-secreting plasma cells, producing the IgM antibody in response to the antigen. Surface IgD is lost during blast transformation, and antigens associated with activation are up-regulated. With maturation to plasma cells, most surface antigens are lost and secretory cytoplasmic IgM are concentrated . The immunoblastic reaction occurs in the lymph node paracortex, and IgM-producing plasma cells accumulate in the medullary cords. Lymphoplasmacytic lymphoma, associated with Waldenstroms macroglobulinemia, may correspond to the IgM-producing plasma cell. However, they express low levels of variable region gene mutation and may thus derive from memory B cells.

IMMUNOPHENOTYPING

Antigens Useful in the Classification of Lymphoid Neoplasms			
CD	***Expression on Normal Cells***	***Useful Diagnostic Applications in These Neoplasms***	
1a	Cortical thymocytes (strong), Langerhans cells	Precursor T-lymphoblastic lymphoma/leukemia, Langerhans cell neoplasms	
2	T cells, NK cells	T- and NK-cell neoplasms	
3	T cells (surface and cytoplasmic), NK cells (cytoplasmic epsilon chain only)	T- and NK-cell neoplasms	
4	T subset (MHC class II restricted), monocytes	Some T-cell neoplasms	
5	T cells, naive B cells	T-cell neoplasms, CLL/SLL, mantle cell lymphoma	
7	T cells, NK cells	T- and NK-cell neoplasms	
8	T subset (MHC class I restricted), NK subset,	Some T- and NK-cell neoplasms	

	splenic sinus lining cells		
10	Precursor B cells, germinal center B cells, granulocytes, fibroblasts, kidney epithelium	Precursor B or T lymphoblastic lymphoma/leukemia, Burkitt lymphoma, follicular lymphoma, diffuse large B-cell lymphoma	
11c	T-cell and B-cell subsets, NK cells, dendritic cells	Hairy cell leukemia, CLL/SLL, splenic marginal zone lymphoma	
15	Granulocytes, monocytes	Reed-Sternberg cells of classic HL	
16	NK cells, granulocytes, macrophages	NK cell neoplasms, some T-cell neoplasms	
19	B cells in all stages of maturation	B-cell neoplasms	
20	Mature B cells (not plasma cells), T-cell subset	Mature B-cell neoplasms, some classic HL	
21	Mature B-cell subset, FDCs	Mature B-cell neoplasms, groups of background FDCs in some lymphomas, FDC neoplasms	

22	Nearly all stages of B cells (cytoplasm), B-cell subset (surface)	B-cell neoplasms, especially hairy cell leukemia	
23	IgE Fc receptor: activated B cells, monocytes, FDC	CLL/SLL, other B-cell lymphomas, groups of background FDCs in some lymphomas	
25	IL-2 receptor: activated T cells, activated B cells, activated monocytes	Hairy cell leukemia, adult T-cell leukemia/lymphoma, other T-cell neoplasms	
30	Activated T, B, and NK cells, monocytes	Reed-Sternberg cells in classic HL, ALCL, primary cutaneous CD30+ LPD	
35	Follicular dendritic cells, myeloid cells, B cells, T cells, monocytes, erythroid cells, glomerular podocytes	Follicular dendritic cell sarcoma	
38	Activated T and B cells, NK cells	Plasma cell neoplasms, B- and T-cell lymphoma	
43	T cells, B subset, NK cells, monocytes, plasma cells, and myeloid cells	T-cell neoplasms, some B-cell neoplasms, myeloid neoplasms	
45	Leukocyte common antigen, all leukocytes except plasma	Lymphoid and myeloid neoplasms	

	cells		
45RA	B cells, naive T cells, NK cells	B-cell neoplasms, T-cell neoplasms	
45RO	T cells (most), granulocytes, monocytes	T-cell neoplasms	
56	Neural cell adhesion molecule: NK cells, activated T cells	NK-cell neoplasms, T-cell neoplasms, plasma cell neoplasms	
57	T-cell and NK cell subset, neural tissue	NK-like T-cell neoplasms, T-cell neoplasms, NK-cell neoplasms	
68	Monocytes, macrophages, activated T cells	Myeloid and histiocytic neoplasms	
79a	B cells, including precursor B and plasma cells	B-cell neoplasms, rare T-lymphoblastic neoplasms, rare classic HL	
95	Fas (apoptosis receptor): activated T cells, B cells	Some B- and T-cell neoplasms, HL	
99	Cortical thymocytes	Precursor B- and T-cell neoplasms, Ewing's sarcoma	
103	Mucosal intraepithelial lymphocytes	Hairy cell leukemia; enteropathy-type T-cell lymphoma	

138	Syndecan-1 (stromal binding): plasma cells	Plasma cell neoplasms, plasmablastic lymphomas	

Recognising these antigens have become vital to diagnosis and residual disease monitoring in lymphoid neoplasms.

PRINCIPLES OF MANAGEMENT OF NONHODGKINS LYMPHOMAS

The phases of patient management include

1. obtaining an adequate biopsy for an accurate diagnosis,
2. a careful history and physical examination,
3. appropriate laboratory studies, imaging studies, and
4. possibly further biopsies to determine an accurate stage and to plan therapy.

Finally, taking into account factors related to the patient, type of lymphoma, and stage and pace of disease.

HISTORY AND PHYSICAL EXAMINATION

It determine the extent of the disease and a key factor in the therapeutic decision. The duration of symptoms and the pace of progression of the illness should be documented. waxing and waning lymphadenopathy could possibly be related to the lymphoma. Especially in follicular lymphomas, spontaneous regressions are not infrequent. The presence of specific symptoms known to have an adverse prognosis in some lymphomas. These include fevers, night sweats, and unexplained weight loss. Symptoms , such as pain in the chest, abdomen, or bones, might indicate specific sites of involvement. For example, symptoms like seizures,focal nuerological deficit is seen in CNS lymphoma .

concurrent illness such as diabetes or congestive heart failure might modify therapeutic decisions. Obviously, examination of all lymph node and search for hepatomegaly or splenomegaly are important. m Sites such as pharynx, lung,bones , abdomen and testis should also be examined.

LABAROTARY EVALUATION

Laboratory studies should include

- complete blood count
- renal and hepatic function studies,
- serum glucose, calcium, albumin,
- Serum lactate dehydrogenase (LDH), Ig and microglobulin level.

Serum protein electrophoresis is frequently appropriate.

The purpose of these studies is

- determining the prognosis
- identifying abnormalities in other organ systems (e.g., renal or hepatic dysfunction).

Almost all patients should have a bone marrow aspirate and biopsy performed. The chance of finding bone marrow involvement varies considerably among different subtypes of lymphoma. It is present in approximately 70% of patients with SLL, lymphoplasmacytoid lymphoma, and mantle cell lymphoma. Patients with follicular lymphoma have bone marrow involvement approximately 50% of the time. Bone involvement is seen in approximately 15% of patients with DLBCL.

In certain situations, cytologic evaluation of the cerebrospinal fluid is indicated. Patients with paranasal sinus, testicular involvement, epidural lymphoma, should have a diagnostic lumbar puncture. lumbar puncture is also recommended for highly aggressive histologies and in immunocompromised patients.

IMAGING STUDIES

CHEST RADIOGRAPHY AND COMPUTED TOMOGRAPHY

Chest radiography and computed tomography (CT) scans of the chest, abdomen, and pelvis should be performed . Identification of hilar or mediastinal adenopathy, parenchymal lesions, or pleural effusions is important a. CT scanning can identify nodal and extranodal sites of involvement. Thus help in monitoring the response to therapy. Involvement of intra-abdominal organs, such as kidney, ovary, spleen, can be identified on CT scans.

MAGNETIC RESONANCE IMAGING

MRI is particularly useful in identifying bone and CNS involvement. MRI can suggest leptomeningeal involvement when gadolinium has been used. MRI can also identify bone marrow involvement.But it is not acceptable as a substitute for bone marrow biopsy.

NUCLEAR MEDICINE STUDIES: POSITRON EMISSION TOMOGRAPHY IMAGING

Nuclear scintigraphy may improve staging, through the detection of occult abdominal or splenic disease. nuclear scintigraphy may detect a residual mass after therapy as either fibrosis or residual active lesion. gallium-67, binds to transferrin receptors in the tumor,is used as nuclear tracer. Bone scans can be useful for looking vertebral involvement and spinal cord compression.

Positron emission tomography (PET) is a functional imaging technique. It uses a glucose analog (2-fluoro-2-deoxy-D-glucose [FDG]) radiolabeled with the positron emitter fluorine-18. It evaluate the glycolytic activity, which is increased in malignancies, including lymphoma. PET provides several advantages compared with other nuclear imaging techniques. The short half-life of FDG allows patient convenience and improved imaging characteristics. With modern PET machines, a resolution of approximately 5 mm can be achieved.The majority of studies evaluating FDG-PET in NHL includes patients diffuse large cell NHL. Limited data are available on the role of PET in other histologies.

Persistently positive PET scans during and after chemotherapy indicates subsequent relapse of aggressive lymphoma. Therefore, persistently positive PET scans at the end of therapy, warrant close follow-up or additional diagnostic procedures .

PET is most useful in assessing response to therapy of curable lymphomas, specifically DLBCL and Hodgkin's lymphoma.

PET after completion of therapy should be performed

- at least at 3 weeks, and preferably at 6 to 8 weeks, after chemotherapy or chemoimmunotherapy,
- 8 to 12 weeks after radiation or chemoradiotherapy.

STAGING AND PROGNOSTIC SYSTEMS

The goal of initial evaluation of a patient with lymphoma is to provide information that allows

- intelligent planning of therapy,
- imparting the prognosis to the patient, and
- making possible comparisons between patients in clinical trials.

The studies to accomplish these goals can be aimed at

- identifying sites of involvement,

- characteristics of the patient (i.e., age, performance status, and so forth), or
- characteristic of the lymphoma (serum LDH, serum microglobulin) that predict treatment outcome.

Ann Arbor Staging System

Stage	***Description***[a]
I	Involvement of a single lymph node region or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Bone marrow and liver involvement are always stage IV

The Ann Arbor Staging System was developed for patients with Hodgkin's lymphoma. This system has a significant effect on prognosis and is important in treatment planning.’’

HODGKINS LYMPHOMAS

ETIOLOGY AND EPIDEMIOLOGY

There are approximately 7,500 new cases of Hodgkin lymphoma diagnosed each year in the United States. Slightly more men than women develop this malignancy (1.4:1). In economically developed countries, there is an age-related bimodal incidence for Hodgkin lymphoma. The first peak occurs in the third decade of life with a much smaller peak occurring after the age of 50. The incidence of Hodgkin lymphoma by age also differs by histologic subtype.

A number of studies have suggested that there appears to be a genetic predisposition for Hodgkin lymphoma. There is an increased incidence in Jews and also among first-degree relatives. Siblings appear to have a increased risk of developing the disease. There is an increased risk among parent-child pairs but not among spouses. Also, Hodgkin lymphoma has been linked to certain HLA antigens’’.

There is less support for most other potential causes of Hodgkin lymphoma. Hodgkin lymphoma is rarely seen as a second malignancy. It does not appear to be increased in patients with illness or treatment-related chronic immunosuppression. In AIDS patient with hodgkins there is lack of evidenceto correlate with immunosuppresion. It seems that under antiretroviral therapy the incidence of Hodgkin lymphoma seems to increase with CD4 cells. There is increasing evidence to suggest a viral etiology for Hodgkin lymphoma. There is association between Hodgkin lymphoma and c decrease exposure to infectious agents at an early age has led investigators to propose that the epidemiologic features of Hodgkin lymphoma appear to mimic those of a viral illness that has an age-related host response to infection.

BIOLOGY LINEAGE AND CELL OF ORIGIN

SPECIFIC MORPHOLOGIC FEATURES OF HODGKIN LYMPHOMA

Lymph nodes affected in Hodgkin lymphoma contain a mixture of lymphocytes, , plasma cells, fibroblasts, and other cells. The malignant mononuclear cells in hodgkin’s are called hodgkin’s cells. Their multinucleate counterparts are called Reed-stenberg cells. Except in lymphocyte-depleted these cells represent only 0.1% to 1% of the entire

cell population .In nodular and lymphocyte-predominant type the lymphocytic and histiocytic (L&H) cells represent only a small minority of the total cell population. This scarcity of the tumor cells makes it difficult to understand their nature.

HRS cells express

- B-cell specific surface antigens (CD19, CD20), in lymphomcyte-predominant type
- the activation marker CD30, and in the CD15, in classic hodgkins lymphomas. most cases lack B-cell or T-cell-lineage antigens in classic hodgkins lymphomas.

CELL LINES AND ANIMAL MODELS

outgrowth of a cell line is extremely rare in Hodgkin lymphoma. The first two permanent cell lines are designated as L428 and L540 . These cell lines grew out from a pleural effusion and bone marrow. So far, only 15 cell lines have been established that may be regarded as Hodgkin lymphoma-derived. Analysis of immunophenotype, karyotype, or TCR gene rearrangements of these cell lines revealed heterogeneous results. Recently, a novel Epstein-Barr virus (EBV)-negative cell line (L1236) was established . Using single-cell polymerase chain reaction

(PCR) it could be shown that the genomic sequences were identical to those detected in L1236 cells.[25] Thus, the derivation from the primary HRS cells could definitely be proved on the molecular level in this cell line.

HL-derived cell lines were successfully used for

- discovery of HRS cell-associated antigens, which include CD30 (Ki-1), CD70, and Ki-27
- for cloning the CD30 gene[28] and for studying the CD30 signal transduction pathway.

They also enabled the in vitro testing of new immunotherapeutic modalities such as

- Ricin A-linked anti-CD30 immunotoxins,
- anti-CD16/CD30 bispecific antibodies and
- CD30- anti-idiotype vaccine.

The Results of Single-Cell Analysis shows HRS Cells Are Clonal B Cells

Derivation of HRS Cells from Preapoptotic Germinal Center B Cells

The site of contact between a specific antigen (Ag) and a B lymphocyte is the germinal center (GC) of a lymph node.[44] This contact

results in somatic mutations accumulating in the Ig genes. This leads to the expression of antibodies with higher affinity for the respective Ag due to amino acid exchanges. However, somatic mutations often result in a lower affinity of the antibody or even in generation of a stop codon. B cells which lose their ability to express surface Ig or express sIg with low affinity undergo apoptosis . It is mediated through activation of the CD95/Fas cell surface receptor. B cells that accumulate favorable mutations clonally expand and c improve the affinity of their sIg for antigen. After leaving the GC, selected B cells differentiate into B memory cells or plasma cells. The clonal L&H cells revealed ongoing mutations, indicating they are are GC-derived B cells .Their whose survival depends on antigen binding and selection. L&H cells are thus similar to follicular lymphoma (FL) cells.

HRS cells of classic Hodgkin lymphoma differ from FL as well as from LPHL . They accumulate crippling somatic mutations that prevent expression of sIg.[25] These crippling mutations do not necessarily have to be located within the coding region of Ig genes. In addition to crippling mutations,HRS cells lack B-cell specific transcription factors. Thus they fail H to express Ig. Several groups have found no Ig gene expression in

HRS cells. These features suggest that HRS cells can grow independently from antigen selection and even antibody expression.

The mechanisms that prevent negative selection in the GC are therefore important in understanding the transformation process. Inherited Fas gene mutations in the autoimmune lymphoproliferative syndrome increase risk for the development of HL. Interestingly, c-FLIP protein has recently been shown to be strongly expressed by HRS . c-FLIP may interrupt transmission of the Fas death signal, thereby preventing negative selection.

GENETIC ALTERATIONS IN HODGKIN LYMPHOMA

CHROMOSOMAL INSTABILITY

In karyotype analyses , the percentage of abnormal karyotypes varied considerably, between 22% and 83%. Although a specific chromosomal marker of Hodgkin lymphoma has not yet been defined. In a study from untreated patients in about half of the cases numerical and/or structural aberrations were found.[64] Among the abberations, aneuploidy (100%) with hyperdiploidy (70%) is the most frequent. Trisomies of chromosomes 1, 2, 5, 12, and 21 are often present. Chromosomal translocations or deletions were found in two thirds of cases.Numerical

chromosomal aberrations in cHL were either clonal[66] or differed from metaphase to metaphase. several studies were able to show that specific gains (and less prominently losses) of chromosomal regions are a typical feature of cHL.Among the regions affected were loci containing the JAK2 and the REL genes. Both genes are involved in important stimulatory signaling pathways.A region that was recurrently affected in more than cHL cases was identified on chromosome 6q25. This region suspected to harbour a tumor suppressor gene for a long period of time. The causes underlying the genetic instability in cHL remain, however, elusive.

MOLECULAR GENETIC ANALYSES

In several studies, the t(14;18) translocation was found in 0% to 39% of Hodgkin lymphoma cases. The retinoblastoma tumor suppressor gene, is also not mutatedin most of the Hodgkin lymphoma cases.[7]Mutations in the p53 tumor suppressor are also not a typical feature of HRS cells as. Additionally, mutations in the BCL10 gene could not be detected in cHL. Importantly, the functionality of the most important mismatch repair system was recently demonstrated in HRS cells.[78]

CONSTITUTIVELY ACTIVE SIGNALING PATHWAYS IN CLASSIC HODGKIN LYMPHOMA

NFKB

The transcription factor NFkB was shown to be constitutively active in cultured as well as in primary HRS cells.[80,81] Moreover, NFkB activity lead to down-regulation of a highly antiapoptotic and proproliferative gene expression program.[5] Thus, NFkB seems to be a central modulator of survival and proliferation in cHL. NFkB may thereby directly lead to disruption of the principal apoptosis pathway that is needed for negative selection in the GC. This allowing the preapoptotic HRS cell precursor to survive. Several mechanisms were identified that cause constitutive activation of NFkB. Examples are

- Constitutively active CD30- or CD40-signaling,
- autonomous RANK signaling, and EBV-encoded LMP1 or LMP2a expression.

They lead to nuclear translocation of NFkB and to induction of transcription of its target genes. NFkB is retained in the cytoplasm by its inhibitors. Activation of distinct signaling pathways leads to activation of Ik-kinases, subsequent phosphorylation which in turn releases NFkB .

This NFKB translocates to the nucleus and induces the transcription of its target genes.

In the mutated cases, cytoplasmic retention of NFkB is abolished. This facilitating its constitutive transcriptional activity. These findings suggest that these mutations may be important transforming events in cHL . Thus constitutively active NFkB is a central mediator of survival and proliferation of HRS cells of cHL.. Multiple mechanisms were identified that may contribute to its constitutive activation.

STATS AND AP-1

The signal transducer and activator of transcription (STAT) family includes several members. Among them, STAT3, STAT6, and STAT5a were found to be constitutively active in HRS cells of cHL. STAT3 activity was found to be disrupted from its physiological regulatory circuits. It did not depend on interleukin (IL)-6 receptor signaling and the subsequent activation of Janus kinases (Jaks). Importantly, the Jak2 genomic locus was shown to be recurrently amplified in cHL. STAT6 was, however, dependent on IL-13 signaling. As IL-13 and its adequate receptor are expressed by HRS cells, this may account for the observed STAT6 activation. AP-1 was recently identified as an additional constitutively active transcription factor in cHL.

EPSTEIN-BARR VIRUS INFECTION IN HODGKIN LYMPHOMA

ASSOCIATION OF HODGKIN LYMPHOMA AND EPSTEIN-BARR VIRUS INFECTION

Individuals with a history of infectious mononucleosis have a two- to threefold increased risk of developing Hodgkin lymphoma.[61] Elevated IgG and IgA titers against the viral capsid antigen in predisease sera were also shown . Weiss et al were the first to detect EBV DNA in total lymph nodes affected by Hodgkin lymphoma u. EBER1- and 2-RNAs are small EBV-encoded, nonpolyadenylated transcripts of high abundance . In several developing countries more than 90% of case carry the virus in their tumor cells.HRS cells show a specific expression of LMPs (latent membrane protein) 1 and 2a and EBNA (Epstein-Barr nuclear antigen) 1. This pattern is identical to that found in nasopharyngeal carcinoma endemic .It differs from that of other EBV-associated neoplasias like endemic Burkitt's lymphoma. Except EBNA1, all latent viral proteins represent targets for cytotoxic T lymphocytes. Thus, EBV-infected lymphoma cells in immunocompromised hosts may express the complete set of latent viral genes. In immunocompetent hosts they down-regulate these proteins to escape the host's immune response.

The functional relevance of expression of LMPs in HRS cells is undoubted. LMP1 has transforming potential for epithelial cells. In lymphocytes, apoptosis can be prevented by LMP1 via up-regulation of the bcl-2 gene. In addition, LMP1 up-regulat numerous cellular genes, like CD23, CD30, CD39 and ICAM-1, LFA-3. Thus, it may render a cell indirectly more susceptible for a T-cell response.[38] Knecht et al. described some mutations in the carboxyterminal part of the LMP1 gene . Both LMP1 and LMP2a, can activate NFkB, a transcription factors that is constitutively active in cHL. LMP1 mimick a constitutively active CD40 receptor and LMP2a,, shuts down B-cell receptor expression. Thus, EBV may hide the infected B cell from immune recognition. EBV is present in the HRS cells of only about 50% of the cHL cases in the Western world. Integration of fragments of the EBV genome into the nuclei of HRS cells might prevent its detection..

IMMUNOLOGY OF HODGKIN LYMPHOMA

CELLULAR IMMUNE DEFICIENCIES

Hodgkin lymphoma is characterized by the predominance of a reactive infiltrate. The infiltrate consists of T cells, B cells, neutrophils, and eosinophils surrounding few malignant HRS cells. This morphology suggests a major role of the interplay between the tumor and the host

immune system. Although HRS cells express several molecules necessary for efficient antigen presentation immune response is not mounted. The T cells, lack CD26 and CD25, the IL-2 receptor. This may be due to the concerted interplay of various chemokines and cytokines secreted by HRS cells. The predominant secretion of Th2-favoring cytokines and chemokines may inhibit an effective cytotoxic Th1 response. Moreover, secretion of IL-10 and TGF by the HRS cells and inability of T cells to secrete IL-2 suppresses immune reaction. Thus HRS cells escape the host immune system by modulating the immune response. Immune response is directed towards an impaired Th2 response.

PATHOLOGY

DEFINITION OF HODGKIN LYMPHOMA

The clinical features and responses to treatment of Hodgkin lymphoma differ from those of NHLs. In nodular lymphocyte predominance Hodgkin lymphoma (NLPHL), the RS cell variants express B-cell-associated antigens. while those of nodular sclerosis (NS) and mixed cellularity (MC) Hodgkin lymphoma lack these antigens. NLHPL differ in immunophenotype, and have a more indolent clinical course. This suggests that NLPHL was a low-grade B-cell lymphoma.

CYTOKINES AND CHEMOKINES EXPRESSED IN HODGKIN-REED-STERNBERG (HRS) CELLS AND THE SURROUNDING T CELLS

Cytokine/Chemokine	*Expression in HRS Cell Lines*	*Expression in HRS Cells (%)*
IL-4	2/8	2
IL-13	4/5	93
IL-5	2/6	95
IL-6	5/7	75
IL-9	0/1	58
IL-10	2/7	32
IL-12	ND	85
IL-2	0/7	22
IFN	2/3	47
TARC	4/4	88
MDC	ND	87
Eotaxin	1/5	63
IP-10	ND	100
Mig	ND	100

MIP	ND	100
IL-8	ND	61
TNF	7/7	69
LT	5/6	77
CD40L	0/4	100
CD30L	0/3	100
RANKL	2/2	100
IL-1	3/6	58
TGF alpha	1/1	61
IL-3	0/6	25
IL-7	ND	77
GM-CSF	2/6	0

IL, interleukin; ND, no data; IFN, interferon; TARC, thymus and activation-regulated chemokine; MDC, macrophage-derived chemokine; IP, interferon-inducible protein; Mig, monokine induced by interferon; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor; LT, lymphotoxin; RANKL, receptor activator of nuclear factor kB ligand;

TGF, transforming growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Current classifications of Hodgkin lymphoma include:

- classic Hodgkin lymphoma (nodular sclerosis Hodgkin lymphoma [NSHL],
- mixed cellularity Hodgkin lymphoma [MCHL],
- lymphocyte-rich [LRCHL] and lymphocyte depletion [LDCHL]) and NLPHL.

The Hodgkin lymphomas are defined as lymphomas containing one of the characteristic types of Reed-Sternberg (RS) cells. The RS cells are seen in a background of nonneoplastic cells

CLASSIFICATIONS OF HODGKIN LYMPHOMA (HL)

Jackson and Parker[a]	*Lukes and Butler*[b]	*Rye Classification*[d]	*REAL Classification*[d]	*WHO Classification*[e]
Paragranuloma	Lymphocytic and/or histiocytic, nodular Lymphocytic and/or histiocytic, diffuse	Lymphocyte predominant	Nodular lymphocyte predominant Classic HL Lymphocyte-rich classic HL[f]	Lymphocyte predominant, nodular Classic HL Lymphocyte-rich classic H
Granuloma	Nodular sclerosis Mixed cellularity[g]	Nodular sclerosis Mixed cellularity[g]	Nodular sclerosis Mixed cellularity	Nodular sclerosis Mixed cellularity
Sarcoma	Diffuse fibrosis Reticular	Lymphocytic depleted	Lymphocyte depleted	Lymphocyte depleted Unclassifiable classic HL

NODULAR LYMPHOCYTE PREDOMINANCE HODGKINS LYMPHOMA

MORPHOLOGIC FEATURES

NLPHL is defined as having at least a partially nodular growth pattern. diffuse areas are present in a minority of the cases . The RS cell

variants differ from mononuclear and classic RS cells. They have vesicular, polylobated nuclei and distinctperipheral,nucleoli without perinucleolar halos; These have been called L&H cells (lymphocytic and/or histiocytic of Lukes and Butler) or popcorn• cells. They are called so because of resemblance of their nuclei to an exploded kernel of corn.[110] In fact, they resemble exploded centroblasts. A better name for these cells is LP cells for lymphocyte-predominant type. Although LP cells may be very numerous, usually no classic, diagnostic RS cells are found. In occasional cases, however, the neoplastic cells may resemble classic or lacunar types. In such cases, immunophenotyping may be essential in establishing the diagnosis and excluding lymphocyte-rich cHL. The background is predominantly lymphocytes. clusters of epithelioid histiocytes may be numerous. plasma cells, eosinophils, and neutrophils are rarely seen . Occasionally, sclerosis may cause some cases to resemble NSHL’’.

MORPHOLOGIC AND IMMUNOPHENOTYPIC FEATURES OF NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NLPHL) AND CLASSIC HODGKIN LYMPHOMA (HL)

	Classic HL	***NLPHL***
Pattern	Diffuse, interfollicular, nodular	Nodular, at least in part
Tumor cells	Diagnostic RS cells; mononuclear or lacunar cells	L&H or popcorn cells
Background	Lymphocytes, histiocytes, eosinophils, plasma cells	Lymphocytes, histiocytes
Fibrosis	Common	Rare
CD15	+	+
CD30	+	+
CD20	±	+
CD45	-	+
EMA	-	+

EMA	-	+
EBV (in RS cells)	+ (approximately 50%)	-
Background lymphocytes	T cells > B cells	B cells > T cells
CD57+ T cells	-	+
Ig genes (single-cell PCR)	Rearranged, clonal, mutated, crippled•	Rearranged, clonal, mutated, ongoing

Progressive Transformation of Germinal Centers

A distinctive type of follicular lymphoid hyperplasia is seen in NHPHL. It is known as progressive transformation of germinal centers .PTGCs are enlarged follicles that contain numerous small B cells of mantle zone type. These follicles may closely resemble the nodules of NLPHL. This phenomenon has given rise to speculation that NLPHL may arise from PTGCs. PTGCs are usually seen as single or only a few enlarged follicles in a setting of nonspecific reactive follicular lymphoid hyperplasia.

NODULAR LYMPHOCYTE PREDOMINANCE HODGKIN LYMPHOMA AND LARGE B-CELL LYMPHOMA

Patients with NLPHL have a slightly higher risk of development of NHL than patients with other types of HL. The DLBCL may consist of typical L&H cells, but usually resembles other DLBCLs.[1] In some cases, a clonal relationship between the LP and the DBCL has been shown by molecular genetic analysis. The prognosis of these patients appears to be similar to that for usual DLBCL.

Immunophenotype

Atypical cells in NLPHL are

- CD45+
- express B-cell associated antigens (CD19, 20, 22, 79a, PAX5, the transcription factors Oct2 and BOB.1,
- and the GC-associated protein Bcl6)[50] and EMA
- but lack CD15 and CD30.

Immunoglobulin J-chain and in some cases, light chain mRNA can be detected,.[1] Recently, IgD expression has been reported occurring predominantly young males. LP cells also express CD40 and CD86, which are involved in B-cell interaction with T cells.

The nodules of NLPHL are actually altered follicles or GCs.The T cells in reactive or transformed follicles, are scattered singly and often concentrated in the light zone. The T cells in NLPHL form small aggregates, often giving the follicle a broken up, moth-eaten, or irregular contour.They typically surround the neoplastic B cells, forming rings or rosettes. A prominent concentric meshwork of CD21+ FDC is present within the nodules. CLINICAL FEATURES

NLPHL accounts for 4% to 5% of the cases of Hodgkin lymphoma in most series. The median age is in the mid-30s, but cases may be seen both in children and the elderly. The male-to-female ratio is 3:1 or greater. NLPHL usually involves peripheral lymph nodes, with sparing of the mediastinum. About 80% of the patients in most series are stage I or II at the time of the diagnosis. but rare patients may present with stage III or IV disease, with a concomitantly worse prognosis. More than 90% of the patients have a complete response to therapy, and 90% are alive at 10 years. The cause of death is often NHL, other cancers, or complications of treatment, rather than Hodgkin lymphoma.

CLASSIC HODGKIN LYMPHOMA

cHL is defined by the presence of classic, diagnostic RS cells. The RS cells are in a background of either nodular sclerosis, mixed cellularity, or lymphocyte depletion. They have the immunophenotype of cHL (CD15+ CD30+). cHL includes nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted types.

NODULAR SCLEROSIS HODGKIN LYMPHOMA

Morphologic Features

NSHL by definition has at least a partially nodular pattern. The characteristic cell is the lacunar type RS cell.It has multilobated nuclei, small nucleoli, and abundant, pale cytoplasm. The cytpoplasm retracts in formalin-fixed sections, producing an empty space, or lacune. Diagnostic RS cells may be rare. The background usually contains lymphocytes, histiocytes, plasma cells, eosinophils, and occasionally neutrophils.

Grading of Nodular Sclerosis Hodgkin Lymphoma

The British National Lymphoma Investigation (BNLI) developed a system for grading NSHL (grade 1 and grade 2). It is based on the number and atypia of the RS cells in the nodules.[139] About 75% to 85% of the cases in most series are grade 1 and 15% to 25% are grade 2. Grade 2

(NS2) tumors were associated with a worse prognosis than grade 1 (NS1) tumors. NS2 tumors having an increased rate of relapse, shorter survival and worse response to initial therapy . The impact of NS2 on survival is most evident in patients who relapse. Those with NS2 have significantly shorter survival postrelapse than those with NS1. Taken together, these results suggest that more aggressive therapy benefits grade 2 patients. They also suggest the possibility that patients with NS1 could be treated less aggressively and still do as well.

Differential Diagnosis of Hodgkin Lymphoma (HL)

Diagnosis	***Morphology (Large Cells)***	***Immunophenotype (Large Cells)***	***T-Cell Rings***	***Genetics (Southern Blot)***
NLPHL	Popcorn cells	CD20+, EMA+, CD15-, CD30-	+	Ig polyclonal
Classic HL, lymphocyte-rich	Classic RS cells	CD20-, EMA-, CD15+, CD30+	+	Ig polyclonal
PTGC	Centroblasts	CD20+, EMA-, CD15-, CD30-	-	Ig polyclonal
Follicular	Centroblasts	CD20+, EMA- (Ig	-	Ig

lymphoma		monoclonal)		monoclonal
T-cell, histiocyte-rich large B-cell lymphoma	Centroblasts, immunoblasts, popcorn cells	CD20+, EMA+, CD15-, CD30- (Ig monoclonal Â±)	-	Ig monoclonal
Anaplastic large-cell lymphoma (T cell)	Horseshoe-shaped nuclei, paranuclear hof	CD20-, EMAÂ±, CD15-, CD30+,T-AgÂ±	-	TCR monoclonal
Large B-cell lymphoma, anaplastic subtype	Bizarre, large cells, RS-like cells	CD20+, EMAÂ±, CD15-, CD30+	-	Ig monoclonal

More recently, the GHSG has reported that increased tissue eosinophilia is an adverse prognostic factor in advanced-stage NSHL,.

Clinical Features

NSHL is the most common subtype of Hodgkin lymphoma in developed countries. It is most common in adolescents and young adults,

but can occur at any age; affected females equal or exceed males. The mediastinum and other supradiaphragmatic sites are commonly involved.''

MIXED CELLULARITY HODGKIN LYMPHOMA

MORPHOLOGIC FEATURES

In MCHL, the infiltrate is usually diffuse or at most vaguely nodular, without band-forming sclerosis, . RS cells are of the classic, diagnostic type, and are usually easily identified. Many mononuclear variants are usually also present. rarely lacunar cells may be seen.

Diagnostic RS cells are large cells with

- bilobed, double, or multiple nuclei,
- a large, eosinophilic, inclusionlike nucleolus .

The infiltrate typically contains lymphocytes, epithelioid histiocytes, eosinophils, and plasma cells.[110]

MCHL comprises 15% to 30% of Hodgkin lymphoma cases in most series. It may be seen at any age, and lacks the early adult peak of NSHL. Involvement of the mediastinum is less common than in

NSHL.abdominal lymph node and splenic involvement are more common.

LYMPHOCYTE DEPLETED HODGKIN LYMPHOMA

MORPHOLOGIC FEATURES

Lymphocyte-depleted Hodgkin lymphoma (LDHL) produces a diffuse and often hypocellular infiltrate. There is presence of diffuse fibrosis and necrosis. There are large numbers of RS cells, and bizarre sarcomatous• variants. There is a paucity of other inflammatory cells. Confluent sheets of RS cells and variants may occur and rarely predominate. They are called reticular• variant or Hodgkin sarcoma. Clinical Features

LDHL is the least common variant of Hodgkin lymphoma, comprising less than 1% of the cases in recent reports. It is most common in older people, in (HIV+) individuals,[98] and in nonindustrialized countries. LDHL frequently presents with abdominal lymphadenopathy, spleen, liver, and bone marrow involvement. It presents without peripheral lymphadenopathy.[145] The stage is usually advanced at diagnosis; however, response to treatment is reported not to differ from other subtypes .

IMMUNOPHENOTYPE OF CLASSIC HODGKIN LYMPHOMA

The tumor cells are CD 15+, CD30+, CD45-. The frequency with which CD15 and CD30 is detected varies. 83% of cases positive for CD15, 96% positive for CD30, and 5% for CD20. Expression of CD20 occurs in a variable number of cases, usually weakly and not in all of the cells.[147] Nonetheless, expression of CD20 does not exclude a diagnosis of Hodgkin lymphoma if the morphologic features are typical. Other B-cell antigens such as CD79a and OCT2 and BOB.1 are typically absent.

The diagnosis of Hodgkin lymphoma is still made on routine sections, and immunophenotyping studies are an adjunct to the diagnosis. In a morphologically typical case, immunophenotyping studies are not absolutely needed.. Failure to detect CD15 or expression of a B-cell associated antigen does not preclude a diagnosis of Hodgkin lymphoma. Absence of both CD15 and CD30 and expression of CD20 should prompt re-examination of the slides.In these situation consideration of either NLPHL or LRCHL is considered. Expression of T-cell antigens is di unusual, and should prompt both re-review of the slides and molecular genetic analysis .

In EBV+ cases, the tumor cells express EBV latent membrane protein (LMP) but not EBNA2.

LYMPHOCYTE-RICH CLASSIC HODGKIN LYMPHOMA

MORPHOLOGIC FEATURES

It has RS cells of classic type, have a background infiltrate that consists predominantly of lymphocytes.They contain rare or no eosinophils. Some cases have a nodular pattern, mimicking NLPHL. This has been termed follicular Hodgkin lymphoma, or nodular lymphocyte-rich classic Hodgkin lymphoma.

426 cases initially diagnosed as LPHL, were reviewed and by the European Task Force on Lymphoma (ETFL) . It revealed that only 51% were confirmed as NLPHL, while 27% were LRCHL with a nodular pattern.

Thus, cases of LRCHL may very closely resemble NLPHL, and require immunophenotyping for differential diagnosis.

IMMUNOPHENOTYPE

The cells express CD15 and CD30 similarly to other types of cHL.CD20 is coexpressed in 3% to 5% of cases.[151] In nodular areas, the background lymphocytes are predominantly B cells, similar to LPHL. Staining for FDC often reveals a small, dense aggregate of FDC with more loosely spaced FDC processes. The RS cells are found within the

mantle area or at the junction of the mantle and interfollicular regions. CD57+ T cells may also be present and may rim the RS cells. Thus, it is really the immunophenotype of the RS cells that distinguishes this from NLPHL.

Clinical Features

The clinical features at presentation of LRCHL seem to be intermediate between those of LPHL and cHL. similar to NLPHL, patients had early stage disease and lacked bulky disease or symptoms. They lacked mediastinal disease and had a predominance of males. They had an older median age than either NLPHL or NSHL.. However, cases of NLPHL had an increased frequency of multiple relapses and better survival after relapse.

ASSOCIATION OF CLASSIC HODGKIN

LYMPHOMA WITH OTHER LYMPHOMAS

Classic HL may be associated with other lymphomas, most often of B-cell type. They either before, simultaneously with, or after Hodgkin lymphoma. Patients treated for Hodgkin lymphoma are at risk for development of high-grade B-cell lymphomas. They presumed to arise in a setting of immune suppression secondary to therapy for Hodgkin

lymphoma.The estimated risk ranges from 1% to 5%. Numerous cases of cHL associated with follicular lymphoma or DLBCL have been reported. The Hodgkin lymphoma may precede, follow, or occur simultaneously with the NHL.'

Rare cases of B-cell chronic lymphocytic leukemia may contain classical RS cells. patients with typical chronic lymphocytic leukemia may go on to develop Hodgkin lymphoma. The condition is called Hodgkin lymphoma variant of Richter's syndrome. These cases may be clonally related or unrelated to the chronic lymphocytic leukemia.Finally, cases of mycosis fungoides or lymphomatoid papulosis may be associated with Hodgkin lymphoma .

THE GREY ZONE BETWEEN CLASSIC HODGKIN LYMPHOMA AND LARGE B-CELL LYMPHOMA

There are lymphomas that seem to have features of both cHL and DLBCL. This phenomenon is most common in the mediastinum, and the term mediastinal grey-zone lymphoma is used. Recent gene expression profiling suggest that mediastinal large B-cell lymphoma may be more closely related to. Thus, this phenomenon may reflect true biological overlap between these two diesases.

DIAGNOSIS AND STAGING

NATURAL HISTORY AND PATTERNS OF SPREAD

Hodgkin lymphoma spread by contiguity from one lymph node chain to adjacent chains. The development of new radiographic studies and staging laparotomy improved understanding of the presentation and evolution of Hodgkin lymphoma. Hodgkin lymphoma begins in a single group of lymph nodes and then spreads to contiguous lymph nodes. Eventually the malignant cells may become more aggressive, invade blood vessels, and spread aggresively. This is more likely to occur in patients with stage III than with stage I-II Hodgkin lymphoma.

Evidence for contiguous spread was most convincing for patients with NS or MC histology. The mediastinum, left side of the neck, and right side of the neck were involved in more than 60% of patients . There was a negative association between the right and left neck if the mediastinum was not involved. This suggests that spread from one neck to the other occurred through the mediastinal nodes. It appears that when the spleen is involved there is a high risk of extranodal involvement. This suggests that spread from diaphragm to the spleen, is perhaps through the vascular system. splenic involvement may herald spread to extranodal sites through a similar process.’’

Clinical Presentation

In general, Hodgkin lymphoma patient present with peripheral lymphadenopathy. The nodes usually are not tender, and changes in the overlying skin are unusual. Otherwise, tenderness and skin changes are thought to reflect rapid growth with stretching of nodal capsules. In most cases, the nodes are discrete and freely movable. Occult presentation with central (chest and abdomen) lymphadenopathy, visceral involvement, or with systemic symptoms of the disease is more uncommon. The most characteristic clinical presentation of Hodgkin lymphoma is enlarged superficial lymph nodes in young adults. The most frequent locations being cervical/supraclavicular (60% to 80%), high in the neck, or axillary. Less often it is found in the inguinal-femoral region.

A mediastinal involvement is discovered often by routine staging chest radiography. Even fairly large masses may occur without producing local symptoms. Otherwise, symptoms of retrosternal chest pain, cough, or shortness of breath may be present

Involvement of the liver in a newly diagnosed patient is uncommon. IT occurs almost always with concomitant splenic involvement. Hodgkin lymphoma limited to the spleen is rare. Patients may present with abdominal swelling secondary to hepato- or

splenomegaly or, with ascites. Infradiaphragmal lymphadenopathy may give cause discomfort and pain in the retroperitoneum, the paravertebral, or loin regions. Symptoms are particularly in the supine position by nodular compression of nerves or nerve roots. Advanced intra-abdominal disease may cause obstruction of the ureters or compression of the renal vein, and/or ascites.

Bone marrow infiltration is usually focal.In most cases is associated with extensive disease including systemic symptoms.

Laboratory findings like

- leukopenia, anemia, thrombocytopenia,
- an elevated alkaline phosphatase level

may give indications of bone marrow infiltration.

Involvement of the central nervous system is rare, although invasion of the epidural space can occur. This by nodular extension from para-aortic region through the intervertebral foramina. Several paraneoplastic neurologic syndromes have been reported, but all are very rare’’.

Complaints from extranodal manifestations of disease may occur, such as

- cough from pulmonary infiltration,

- jaundice from hepatic involvement, or
- abdominal pain from disease adjacent to the bowel.

Gastrointestinal involvement is extremely rare and occur as infiltration from mesenteric lymph nodes.

A significant proportion presents systemic symptoms prior to enlarged lymph nodes. Typical symptoms are fever, drenching night sweats, and weight loss. They are called B-symptoms, relating to the Ann Arbor classification. fever occurs intermittently and recurs at variable intervals for several days or weeks. Fever and drenching night sweats are found in 25% of all patients at first time of presentation. It increases to 50% in patients with more advanced disease. Other nonspecific symptoms are pruritus, fatigue, and pain shortly after drinking alcohol. This pain is usually transient at the site of nodal involvement and may be severe. Pruritus, may be an important systemic symptom of disease. It often occurs months or even a year before the first diagnosis of Hodgkin lymphoma.[1] The underlying pathophysiologic mechanisms leading to pruritus may be due to an autoimmune reaction. The reaction activates a number of cytokines by tumor lysis.

TREATMENT METHODS

CHEMOTHERAPY

A number of different drugs including chlorambucil, cyclophosphamide, procarbazine, vinblastine, and vincristine were developed and showed efficacy in Hodgkin lymphoma.

Combined Modality

It has the advantage of interaction and summing of effects when they are combined. The purpose of adding a second modality is to overcome resistance to the first.

HIGH-DOSE CHEMOTHERAPY PLUS STEM CELL SUPPORT

High-dose chemotherapy (HDCT) has been used extensively in patients with relapsed and refractory Hodgkin lymphoma.

CONDITIONING REGIMENS

The most commonly used are 1.CVB (cyclophosphamide, carmustine [BCNU] and etoposide) or

- BEAM (carmustine [BCNU], etoposide, cytarabine and melphalan) given in different dose schedules.

RESULTS AND OBSERVATION

TABLE .1 SEX INCIDENCE

SEX	NO OF PATIENTS	PERCENTAGE
MALE	34	66.6%
FEMALE	17	33.3%

In my study out of 51 patients 34 were male and 17 were female the ratio of male to female is 2:1.sex incidence is almost similar to the western studies.

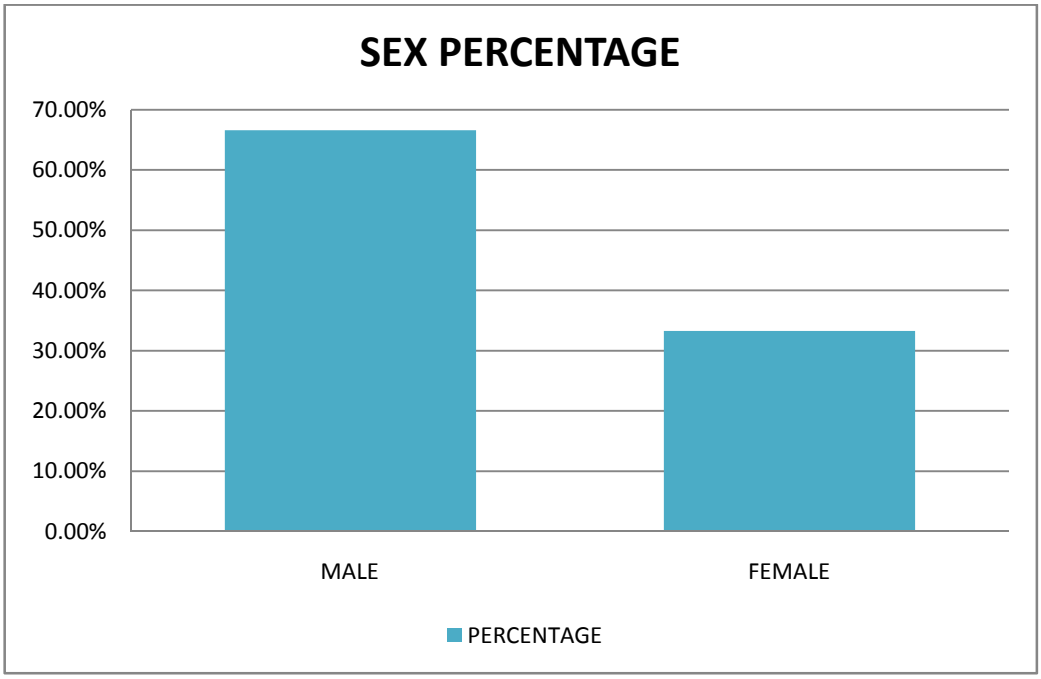
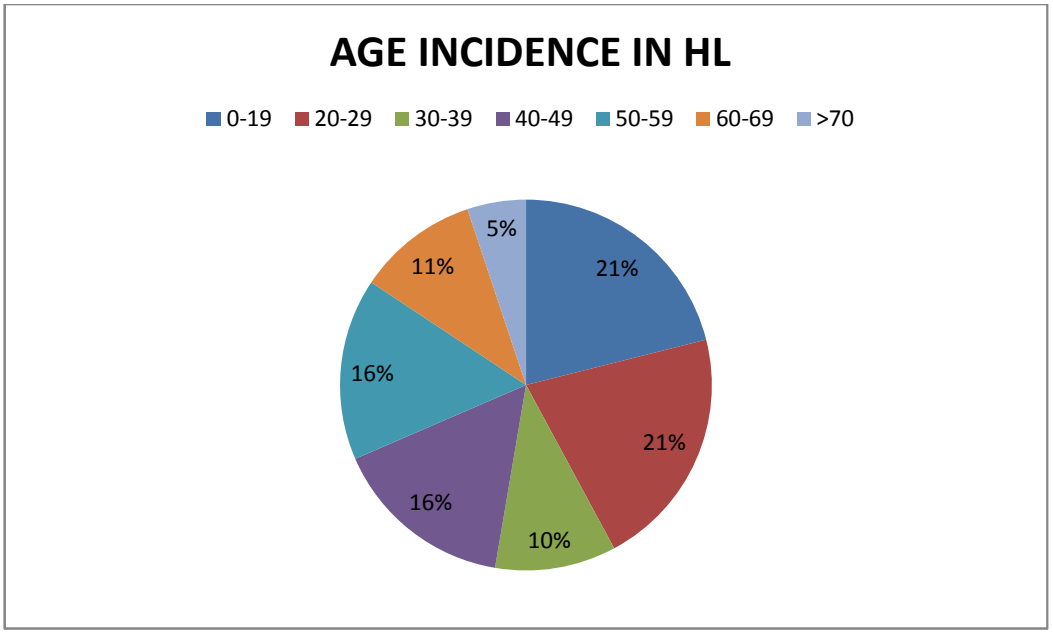


TABLE .2 AGE INCIDENCE IN HL

AGE in years	NO OF PATIENTS	PERCENTAGE% IN HODKINS
<19	4	21%
20-29	4	21%
30-39	2	10.5%
40-49	3	15.8%
50-59	3	15.8%
60-69	2	10.5%
>70	1	5.1%

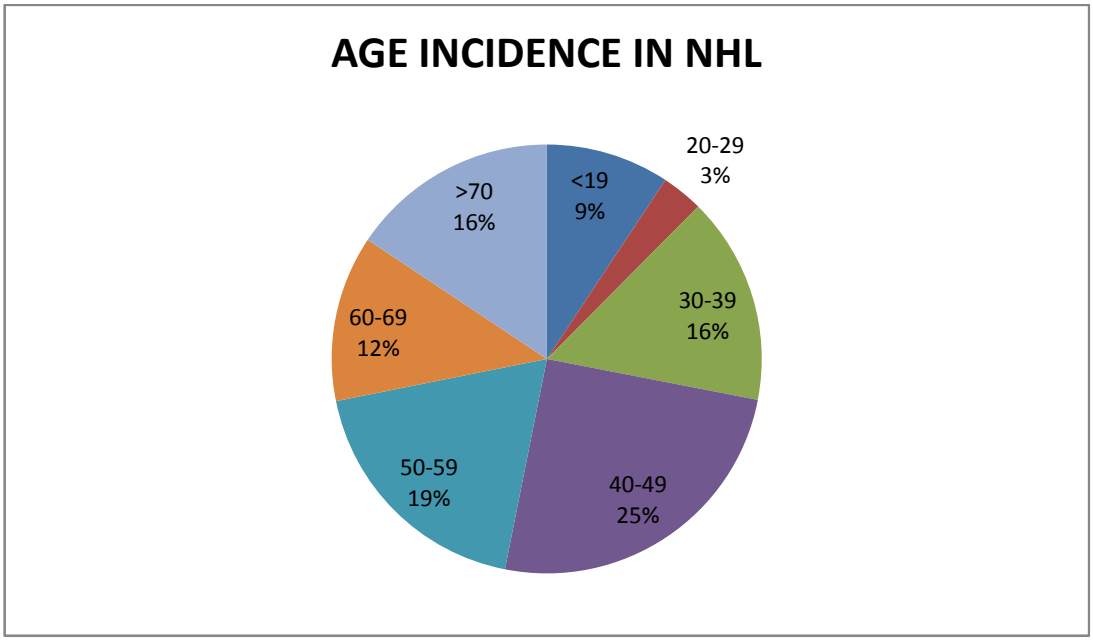
In this study I have found that the most commonly involved people in Hodkins belong to the age group of between 20-29(21%) and <19(21%) YEARS



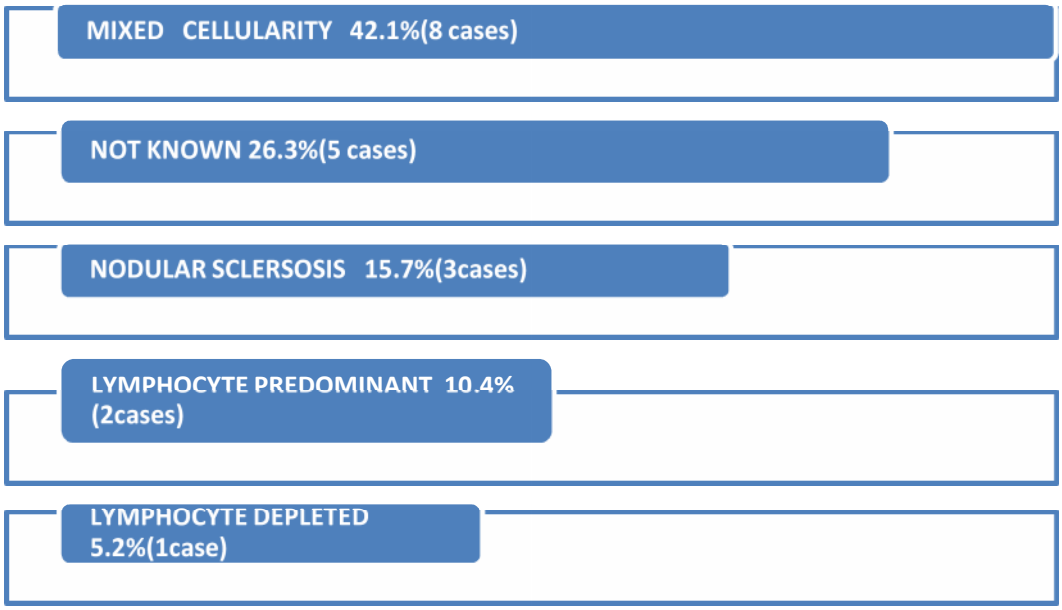
AGE INCIDENCE IN NHL

AGE	NO OF PATIENTS	%OF PATIENTS IN NHL
<19	3	9.3%
20-29	1	3.1%
30-39	5	15.6%
40-49	8	25%
50-59	6	18.7%
60-69	4	12.5%
>70	5	15.6%

In this study I have found that the most commonly involved people in NHL belong to the age group of between 40-49(25%) YEARS.

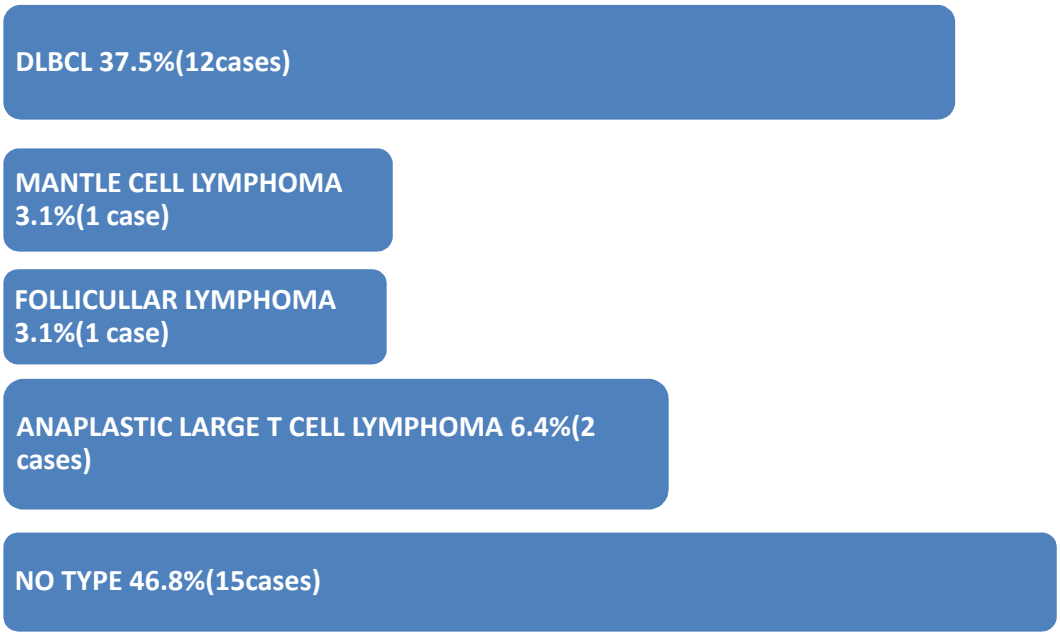


SUB TYPE DISTRIBUTION IN HL



Among 19 cases most common type of HL is mixed cellularity-8 cases(42.1%) ,nodular sclerosis found in 3 cases(15.7%) ,lymphocyte predominant found in 2 cases(10.4%),lymphocyte depleted in 1case(5.2%) and type not specified in 5 cases(26.3%)..

SUB TYPES IN NHL

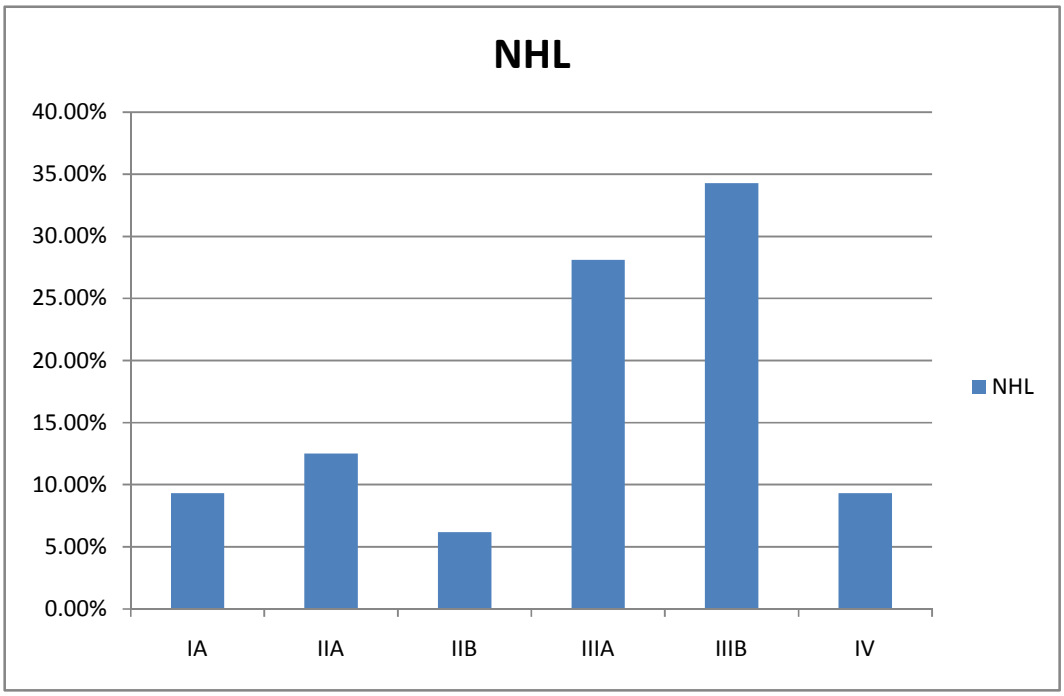


Among 32 cases the most common subtype of NHL is found to be Diffuse large B-cell lymphoma-12 cases (37.5%) ,Anaplastic large T cell lymphoma - 2 cases(6.4%), mantle cell lymphoma -1 case (3.1%), Follicullar lymphoma-1 case(3.1%) and Type not specified in 15 cases(46.8%).

STAGE DISTRIBUTION IN NHL

STAGE	NO OF PATIENTS	% OF PATIENTS
IA	3	9.3%
IIA	4	12.5%
IIB	2	6.2%
IIIA	9	28.1%
IIIB	11	34.3%
IV	3	9.3%

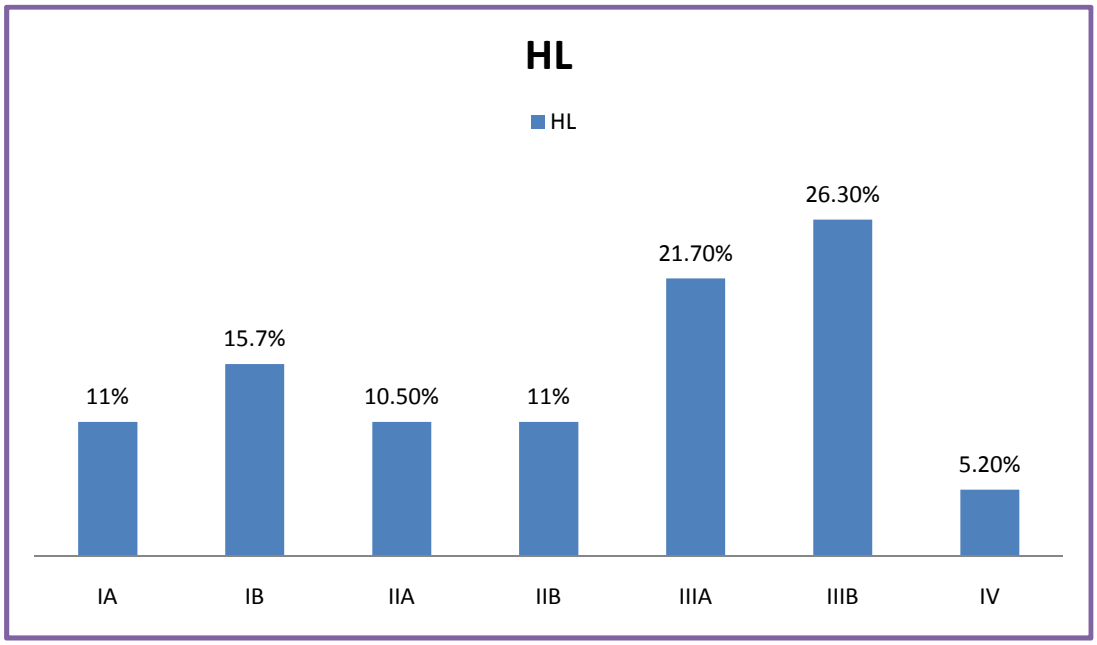
STAGE DISTRIBUTION



Maximum number of cases were also found to be in Stage IIIB-11cases(34.3%),followed by stage IIIA-9 cases(28.1%),stage IIA-4 cases(12.5%),stage IA & IV -3cases (9.3%) and stage IIB-2 cases(6.2%).

STAGE DISTRIBUTION IN HL

STAGE	NO OF PATIENTS	% 0F PATIENTS
IA	2	10.5%
IB	3	15%
IIA	2	10.5%
IIB	2	10.5%
IIIA	4	21.7%
IIIB	5	26.3%
IV	1	5.2%



Maximum number of cases were found to be in Stage IIIB -5 cases (26.3%),followed by stage IIIA-4 cases (21.7%),Stage IB-3cases(15.7%),Stage IA,IIA,IIB were 2 cases(10.5%) and Stage IV-1 case(5.2%).

VARIOUS PRESENTATIONS

SYMPTOMS	**NO OF PATIENTS**	**% OF PATIENTS**
LYMPHADENOPATHY	39	76.4%
FEVER	15	29.4%
ABDOMINAL PAIN	10	19.6%
ABDOMINAL MASS	3	5.8%
JAUNDICE	1	1.9%
LOSS OF WEIGHT & APPETITE	7	13%
DYSPHAGIA	1	1.9%
BACK PAIN	1	1.9%

Lymphadenopathy[76.4%] is the most common presentation followed by fever[29.4%]

ORGANS INVOLVED:

IN NHL:

Git involvement found in 5 patients

Spleenomegaly found in 3 patients

Hepatomegaly found in 2 patients

Lung infiltration seen in 1 patient

IN HL:

Spleenomegaly found in 3 patients

Hepatomegaly found in 1 patient.

DISCUSSION:

In this study group which comprised of 51 patients taken from surgery department shows 66.6%{n=34} were male and the rest 33.37%{n=17}were female.

Among this group, age group between 15-30yrsand 40-60yrs are the more common age groups in HL .

In NHLthe age group most commonly involved is 5^{th} decade

The HPE study of the HL patients among 19 showed that 8 cases were reported as mixed cellularity , 3cases as nodular sclerosis ,2 cases were lymphocyte predominant type ,1 case as lymphocyte depletion type and subtypes of 5 cases not done.

Among 32 cases of NHL ,HPE report of 12 cases were found to be DLBCL ,1case as mantle cell lymphoma ,1 case as follicular lymphoma and 2cases as anaplastic large T cell lymphoma ,and subtype of 15 cases could not be made out

In this study group of 51 patients most patients presented as stage lllB disease

In both HL and NHL lymphadenopathy{76.4%} is the commonest clinical presentation,followed by fever

The most common site of lymphadenopathy is cervical region followed by axilla

In 5 patients of this study group GIT involvement seen ,4 of them with the involvement of stomach seen and 1 case involving the small intestine and mesentry

CONCLUSION

Total number of patients included in our study is 51.male patients are dominating in numbers

Male, female ratio is 2:1

In HL,high incidence is found in 2^{nd} and 3^{rd} decades followed by 5^{th} and 6^{th} decades.

In NHL,High incidence is found in 5^{th} decade followed by 6^{th} decade.

In HL,mixed cellularity is common than other types

Lymphocytic depletion type is least common

In NHL,diffuse large B cell lymphoma is common than other types

In both HL and NHL stage lllB is the frequent stage of presentation

Lymphadenopathy is the commonest clinical presentation

The most common site of Lymph node involvement is cervical region followed by axillary

GIT is the most frequently involved extranodal site

Stomach is most frequently involved in GIT,followed by small intestine

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PROFORMA

SL. NO:

- **NAME :**
- **AGE /SEX:**
- **IP NO:**
- **ADDRESS WITH CONTACT NUMBER:**

- **DATE OF ADMISSION:**

- **DATE OF DISCHARGE:**

HISTORY OF PRESENTING ILLNESS:

H/o fever

H//o RTI/UTI

H/o pallor/jaundice

H/O rashes /itching

H/O bleeding tendencies

H/O abdomen pain- onset

duration

progression

radiation

aggravating/relieving factors

H/o vomiting/ loose stools

H/o hametemesis/melenna

H/o abdominal distention / constipation

H/o edema

H/o disturbances in bladder habits/urine output

H/o convulsions/neurological deficit

H/o unexplained loss of weight /loss of appetite

PAST HISTORY:

H/O Diabetes mellitus/hypertension/asthma/TB/epilepsy/cardiac illness /immunocompromised states

H/o similar episodes in the past, if any:

H/o similar illness in the past

H/o major illness/ hospital admissions, if any

PERSONAL HISTORY:

Whether a smoker or an alcohol consumer

FAMILY HISTORY:

TREATMENT HISTORY:

CLINICAL EXAMINATION:

General examination:

Systemic examination:

CVS

RS

CNS

Per abdomen

Local examination of swelling if any

Per rectal examination and Proctoscopy

Clinical diagnosis:

INVESTIGATIONS:

Complete blood count

Peripheral smear

Random blood sugar

Renal function test: Blood urea, serum creatinine

Liver function test

Chest X ray, ECG

FNAC and biopsies

USG abdomen and pelvis

CT abdomen and pelvis,chest,

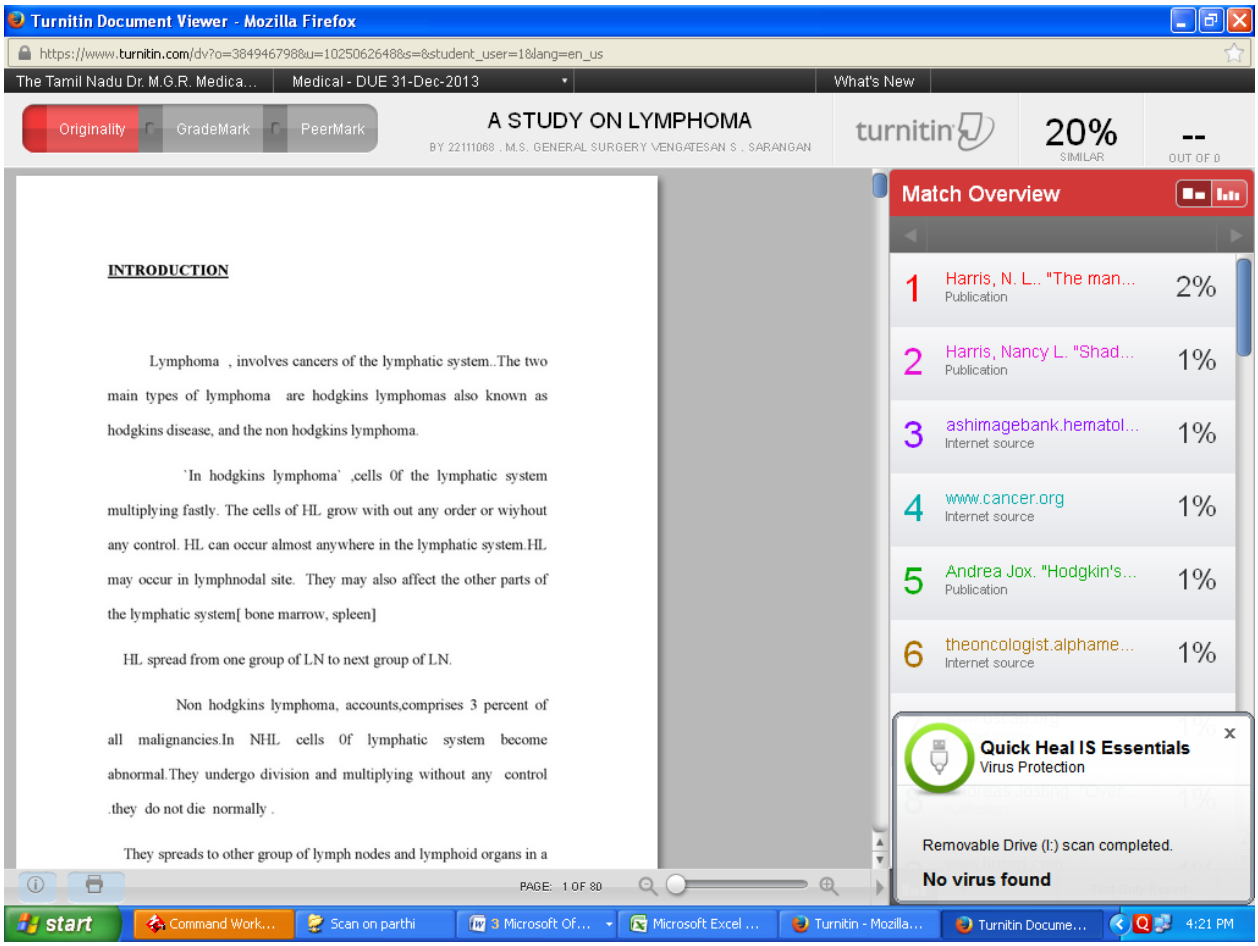
MRI and skeletal survey

Upper and lower gastrointestinal endoscopy

FINAL DIAGNOSIS:

NAME	AGE	SEX	IPNO	COMPLAINTS	HISTOPATOLOG	CT	USG	OGD	COLONOSCOPY	SYSTEM
kalaiarasi	15	f	373/13	cervical lymphadenopathy	NHL-DLBCL	normal	normal			nodal
prabakara	16	m	19866	cervical adenopathy	HL-HISTIOCYTIC	normal	normal			nodal
abdulla	17	m	724/13	neck swelling/	HL-MC	normal	normal			nodal
sathish	17	m	17537	abdominal pain/loss of wei	NHL-ND	diffuse somach wall thickening				GIT
mukesh	17	m	337/11	abd pain/loss of appetite	NHL-DLBCL	mesentric lymphadopathy				GIT
keerthana	17	f	456/11	cervical adenitisfever/chills	HL-LPD	normal	normal			nodal
karthik	20	m	831/11	abdominal pain/loss of wei	NHL-ND	preaortic ln	normal			nodal
aswath	21	m	471/11	genaralised lymphadenopa	HL-MC	para aoric ln				nodal
prasanna	24	m	54632	cervical adenitis/fever	HL -NS	mediastinal LN	normal	candidal oesophagitis		nodal
velmuruga	25	m	417/12	cervical lymphadenopathy	HL-NS	mediastinal LN	normal			nodal
samuvel	28	m	25732	cervical adenitis/headache	HL-LD	normal	normal			nodal
anandhan	32	m	383/12	cervical/axillary	NHL-TCELL	normal	normal			nodal
chandram	35	f	713/13	dysphgia	NHL-LC	diffuse stomach wall thickening/lung infirates		ulcero proliferative growth LC		GIT
baby	36	m	18283	hypogastric mass/loss weig	NHL -LC	lesoin in mesentry of small bowe	mesentric mass			GIT
esther	38	f	453/	cervical/axillary lymphader	HL-LP	mild spleenomegaly				nodal
senthil	39	m	718/13	cervical lymphadenopathy	NHL-TCELL	hepatomegaly,spleenomegaly		monilial esophagitis		nodal
thangama	40	m	783/13	epigastric mass/vomiting/a	NHL-DLBCL	multiple enlarged ln para aortic		extrinsic compresion at antrum		GIT
rajendran	41	m	129/13	abd pain/fever	NHL-ND	circumferential stomach wall thi	stomach wal	ulceroproliferative growth		GIT
balaganes	45	m	187/13	inguinal/cervical LN/fever	HL-NS	mild spleenomegaly	normal			nodal
meheraj b	45	f	573/11	abd pain/fever/cervical ln	NHL-DLBCL	multiple peripancreatic LN				GIT
manickam	45	m	236/12	generalised adenopathy/fe	NHL-ND	normal	normal			nodal
indra	47	f	17738	cervical ln	HL-ND	normal				nodal
ragavan	47	m		neck swelling	NHL-DLBCL	normal	normal			nodal
vengatesa	48	m	19940	cervical/axillry adenitis/hea	HL-MC	normal				nodal
fushia	48	f	20063	generalised adenopathy	HL-MC	mediastinal LN	para aortic LN			nodal
rajathi	49	f	59158	inguinal/cervical lymphade	NHL-LC	para aortic LN	para aortic LN			nodal
venugopa	50	m	225/13	cervical,axillry LN/fever	NHL-ND	hepatospleeno megaly	hepatospleeno megaly			nodal
babu	50	m	57733	inguinal/cervical lymphade	NHL-LC	spleenomegaly	spleenomegaly			nodal
arjunan	50	m	779/11	genaralised lymphadenopa	NHL-ND	normal	normal			nodal
rajendran	52	m	920/11	genaralised lymphadenopa	NHL-ND	normal	normal			nodal
murali	52	m	802/11	abd pain/axillry ln/fever	NHL-DLBCL	biliary obstruction/hepatospleenomegaly				GIT
ameerjoh	55	f	45757	cervical/axillary adenitis	HL-MC					nodal
mohan	57	m	10498	rt axillary swelling/loss of v	HL-LP	mediasinal pre aorticnodes				nodal
ruthrappa	60	m	530/11	abd pain/wt loss/cervical ln	HL- MC	gastro hepatic ln	normal			GIT
rajammal	60	f	22980	gasric growh/cervical ln	NHL-ND	wall thickening of stomach		growth body of stomach		GIT
shanthi	60	f	455/11	abd pain/vomitingaxillry ln	NHL-DLBCL	si growh				GIT

subbaiah	62	m	843/11	cervical/axillry lymphaden	NHL-ND	normal	normal			nodal
kannagi	62	f	49922	abd distension/back pain/g	HL-NS	para vertebral soft tissue lesion/	multiple paraaortic ln			vertebral
eswaraih	66	m	536/11	dysphagia/ioss of appeiite/	NHL-ND	mediastinal node				GIT
jayalakshr	70	f	344/11	abd pain/loss of appetite/c	NHL_BCL	normal		growth body of stomach		GIT
umavathy	70	f	28705	cervical/axillary adenitis	NHL-DLBCL	normal				nodal
natarajan	72	m	715/13	cervical /inguinal LN	HL- MC					nodal
riyas	72	m	25939	cervical adenitis/fever	MANTLE CELL LY	normal				nodal
navamani	74	f	243/12	cervical adenitis/abd pain/	NHL-FOLLICULAI	multiple retro peritoneal ln		mild esophageal compression		nodal
kannan	75	m	592/11	generalised lymphadenopa	NHL -ND	multiplepara aortic nodes				nodal
vasanthar	33	m	342/13	Cervical/axillary lymphade	HL-NS					nodal
srinivasn	39	m	607/12	abdominal pain	NHL-ND	multiple para aortic lymph nodes				GIT
thennaras	43	m	987/11	cervical lymphadenopathy	NHL-ND	spleenomegaly				nodal
EZHILARA	51	f	522/12	generalised lymphadenopa	HL- MC	mediastinal ln	normal			nodal
kovalan	54	m	135/13	generalised lymphadenopa	NHL-ND	normal	normal			nodal
asaithamb	63	m	621/11	cervical lymphadenopathy,	HL- MC	normal	normal			nodal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INTRODUCTION
Lymphoma , involves cancers of the lymphatic system..The two main types of lymphoma are hodgkins lymphomas also known as hodgkins disease, and the non hodgkins lymphoma.
`In hodgkins lymphoma` ,cells 0f the lymphatic system multiplying fastly. The cells of HL grow with out any order or wiyhout any control. HL can occur almost anywhere in the lymphatic system.HL may occur in lymphnodal site. They may also affect the other parts of the lymphatic system[bone marrow, spleen]
HL spread from one group of LN to next group of LN.
Non hodgkins lymphoma, accounts,comprises 3 percent of all malignancies.In NHL cells 0f lymphatic system become abnormal.They undergo division and multiplying without any control .they do not die normally .
They spreads to other group of lymph nodes and lymphoid organs in a
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