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Original Research Article

Varied Presentations of Classical Hodgkin's Lymphoma and Review of Literature – Case Series

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ABSTRACT

BACKGROUND

Most Hodgkin lymphoma (HL) patients present with disease in the nodal regions. Extranodal forms are rare. 40% of them present with B symptoms characterized by fever, night sweats and weight loss. This study was carried out to identify the characteristics of patients with primary HL.

METHODS

A retrospective analysis was done of 20 patients over a time period of 2 years (2017-2019).

RESULTS

Hodgkin's lymphoma is a common type of lymphoma affecting the young to middle aged adults, with mean age being 38-39 yrs. The most common subtype in our cohort was nodular sclerosis. The uncommon presenting complaints like low back ache (due bone involvement by Hodgkin's lymphoma) and pruritus were noted in our study group, apart from the common clinical presentation of B symptoms, and lymph node enlargement. The tumour microenvironment and wise use of immunos like characteristic dim pax 5, negative to very dim cd20 and cd30 Golgi and membrane expression will help in diagnosis of unsuspected and rare presentation of Hodgkin's lymphoma cases.

CONCLUSION

CHL (Classical Hodgkin Lymphoma) is a curable disease. However, there is still a lack of understanding of its pathogenesis, which may lead to less effective therapies for the smaller subset of patients who are destined to die of their disease. cHL is a tumour with only variable EBV association. We think it's appropriate to re-examine EBV's involvement in the pathophysiology of cHL in light of current advancements in immunotherapeutics and medicines that target EBV.

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KEYWORDS: Hodgkin's Lymphoma, EBV, B Symptoms, PD 1- PD-L1, Reed Sternberg Cell, Nodular Sclerosis, Mixed Cellularity, Pruritus in Hodgkin's Lymphoma, Bone Metastasis in Hodgkin's Lymphoma.

MeSH Terms

EBV, PD 1- PD-L1, Reed Sternberg Cell, Pruritus and Bone Metastasis in Hodgkin's Lymphoma.

INTRODUCTION

Hodgkin's lymphoma was first described by Thomas Hodgkin in 1832 and first proposed to be called Hodgkin's disease by Samuel Wilks. The most common way to describe it is as a type of malignant lymphoma that has Reed-Sternberg cells mixed in with reactive inflammatory cells of different types and fibrosis of varying degrees.[1] To attract reactive cells, the RS cells release TGF-Beta (Transforming Growth Factor-Beta) and IL-5.

These diagnostic RS (Reed-Sternberg) represent tumour cells that are large (20–60 μm in diameter) with a large rim of cytoplasm and mirror nuclei with acidophilic or amphophilic nucleoli, covering more than 50% of the nuclear area. Variant Hodgkin's cells (HCs) show similar cytological features to classical RS cells, each of which corresponds to a specific subtype of HL. Condensed cytoplasm and pyknotic, reddish nuclei with smudgy chromatin are features of mummified cells. Small nucleoli, a lot of pale cytoplasm, and multilobulated nuclei are characteristics of lacunar cells. During tissue fixation, the cytoplasm frequently retracts, leaving the nucleus in a lacune-like area. According to molecular research, RS cells, Hodgkin's cells, and cell variations are typically all members of the same clonal population that originates from peripheral B cells.[2]

NL-BCL is characterised by bigger cells with folded multilobulated nuclei (sometimes called "popcorn cells" or LP cells) instead of the typical RS cells. The nucleus of the LP cells has several tiny basophilic nucleoli. Immunoglobulin genes have been clonally rearranged in LP cells. They exhibit characteristics of B cell lymphomas and are positive for C020, CD45, EMA, CD79a, CD75, BCL6, BOB.1, OCT2, and J chain.

Clinically, HL is primarily a nodal disease that disseminates in a predictable manner to contiguous nodes.

It constitutes fewer than 1% of all yearly de novo neoplasms that arise globally.[3]

One of the malignancies that can be cured other than childhood leukaemias is Hodgkin's lymphoma, with a curable rate of approximately 90%. Relapse in cases is the most hindering factor in the success stories of Hodgkin's lymphoma. Recent advances in the treatment of all malignancies are directed based on good and bad prognostic factors.[4]

The current WHO classification divides Hodgkin lymphoma into:

I Nodular lymphocyte predominant B-cell lymphoma

II Classical Hodgkin lymphoma.

1. Nodular sclerosis.
2. Lymphocyte rich class Hodgkin's lymphoma.
3. Mixed cellularity Hodgkin's lymphoma.
4. Lymphocyte depletion Hodgkin's lymphoma.

Classic Hodgkin lymphoma CHL accounts for the majority of all HL cases.Hodgkin's lymphoma is generally commonly present as a nodal mass. Extranodal forms of HL are rare and accounts for only less than 1% of all HL cases, with the most common locations being the lung, digestive system, liver and bone. Bone involvement is seen only in 5% of all CHL cases.

The age range for which Hodgkin's lymphoma incidence peaks is 15–40 years, with a second peak for subtypes other than nodular sclerosis occurring in later life.

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Schwab et al.[5] published the first report on a novel monoclonal antibody known as Ki-1 in 1982. Its reactivity appeared to be limited to H&RS cells and a tiny fraction of normal lymphocytes that were located perifollicularly.

Subsequently, however, it was found that the ki1 antibody loses its sensitivity and specificity when expressed in nonlymphoid tumours as nasopharyngeal undifferentiated carcinoma, pancreatic carcinoma, embryonic carcinoma, and malignant melanoma, as well as ALCL (Anaplastic Large-Cell Lymphoma).[6] As a result, a panel of antibodies should always serve as the basis for the immunophenotypic diagnosis of HL. HRS cells lack a functioning BCR (B-Cell Receptor) and differ phenotypically from B cells; in approximately 25% of instances, this is due to mutations that impair the immunoglobulin genes' ability to code.[7]

RS cells usually lack CD45 and EMA expression. CD20 is usually weak to negative in classical RS cells. Additionally, cHL has varying BCL6 molecule expression. Furthermore, they typically test negative for BOB.1 and OCT2 and positive for PAX5/BSAP, IRF4, and both.[8] More than 98% of cHLs have CD30 molecule expression by H&RS cells, however the degree of immunostaining varies from case to case and even within a single example. Additionally, the CD30 molecule has been suggested as a potential target for certain antibodies. Antibodies against CD30 in Hodgkin lymphoma.[9]

The RS cell has no cytogenetic abnormalities and is aneuploid. Most isolated RS cells have been shown to have clonal Ig gene rearrangements. Apart from CD15 and CD30, PAX5-dim, CD25, HLA-DR, ICAM-1, Fascin, CD95 (apo-1/fas), TRAF1, CD40, and CD86 are also commonly positive in RS cells (1). Most H&RS cells are stained by antibodies against PCNA (Proliferating Cell Nuclear Antigen) and nuclear-associated antigens (Ki-67), indicating that a significant proportion of neoplastic cells enter the cell cycle.

Even then, RS cells are not the majority of tumour cells in the affected lymhnode. The majority of cells are composed of reactive inflammatory cells.[10] Leoncini and coworkers showed that RS cells have a defect in cytokinesis. The BCL2 and p53 gene products closely regulate the process of apoptosis, which occurs in a portion of cells that do not complete the cell cycle.[11] In EBV-positive HL, a B lymphocyte's latent infection by the virus represents an early transforming event.[12] The pathophysiology of certain subtypes, especially lymphocyte-depleted and mixed cellularity forms, is significantly influenced by EBV infection. EBV often behaves as a benign passenger and fits into the typical developmental paths of B cells. The virus may have a significant impact on B cell differentiation. The BCR generally provides survival signals. BCR-deficient B cells can survive when EBV substitutes the survival signals during the germinal centre reaction and skips the typical apoptotic route.[13]

Classical EBV-positive RS cells have been shown to contain EBV-induced compounds. These so-called molecules include two short RNAs, EBER 1 and 2, EBNA1, LMP1 (Latent Membrane Protein-1), and LMP2. Due to its vital role, EBNA1 is expressed in all EBV-associated tumours and EBV latency stages. In addition to anchoring the viral episome to mitotic chromosomes, the EBNA1 protein starts EBV episome replication prior to mitosis. This preserves EBV-encoded short RNA genes and aids in the spread of EBV DNA in dividing cells, both of which contribute to the oncogenicity of BL.[14]

Most often, patients have peripheral lymphadenopathy, which is limited to one or two lymph nodes. Most commonly affected are the cervical lymph nodes. B symptoms consisting of fevers greater than 101°F (38.3°C), drenching night sweats, and unexplained weight loss of more than 10% of body mass over 6 months are present in as many as 40% of patients. Their incidence varies in different subtypes of Hodgkin’s lymphoma and is more frequent with the nodular sclerosis subtype.

In this study, we will be dealing with the incidence of B symptoms and various other clinical parameters among various subtypes.

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MATERIALS AND METHODS

We reviewed 20 patients with cHL diagnosed at the Amala Institute of Medical Sciences in Thrissur from 2017–2019. Demographics, laboratory studies, and disease statuses were recorded. Data were collected from the institutional database and electronic medical records. Herein, we discuss 20 cases that presented in our hospital from 2017 to 2019.

RESULTS

Case No.	Age	Sex	Fever	Weight Loss	Night Sweats	LN Largest	Other Symptoms	Diagnosis
1	27	F	+	+	-	+ Left axillary swelling	Cough, Generalized itching	HL-NS
2	44	F	+	+	-	+ inguinal	Back ache	HL-Classical
3	43	M	-	-	-	+ Left axilla	-	HL
4	31	M	+	-	-	+Right cervical	-	HL-MC
5	75	F	-	+	-	+Right iliac fossa	-Abdominal pain, loss of appetite	HL-MC
6	34	F	+Evening rise in temp	-	-	+ Left? Cervical		HL -NS
Case Nos.	**Age**	**Sex**	**Fever**	**Weight Loss**	**Night Sweats**	**Largest LN**	**Other Symptoms**	**Diagnosis**
7	59	M	+	+	-	+ Left axillary LN	Generali zed itching	HL-Classical
8	51	M						HL-LR
9	48	M	-	-	-	+Left cervical	Cough, breathlessness	HL-MC
10	23	F						HL-NS
11	15	F						HL-NS
12	60	F						HL-LR
Case Nos.	**Age**	**Sex**	**Fever**	**Weight Loss**	**Night Sweats**	**Largest LN**	**Other Symptoms**	**Diagnosis**
13	22	F	-	-	-	+ Left cervical	Left ileum lytic lesion -	HL-NS
14	16	F	-	-	-	+B/l cervical LN	-	HL-NS
15	34	M						HL-Classical
16	18							HL-NS
17	17	F				+Left supraclavicular		HL-NS
18	40	M				+Left Supraclavicular		HL-NS
19	66	M						HL Classical
20	61	M				+Left inguinal		HL

Table 1

The main clinical characteristics of these patients at the time of diagnosis are shown in Table 1.

Histology types included nodular sclerosis (45%), mixed cellularity (15%), and lymphocyte-rich (10%). 25% were only diagnosed with Hodgkin's lymphoma. The mean age of

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HL manifestation was approximately 38 years. The average age of presentation in our cohort was 39 years. The median age for nodular sclerosis histology was 22 years in our study group.

The majority of the patients presented were females (11 out of 20) and of the age group 15–40 years old (11 out of 20).

The major pathologic types were NSCHL (Nodular Sclerosis Classical HL) and MCCHL (Mixed Cellularity Classical HL).

The presence of B-symptoms was more common in patients with mixed cellularity.

All the patients had nodal involvement, but one of them had a left ileum lytic lesion as the presenting complaint (case nos. 13). The majority (5/20, -25%) were with cervical LN enlargement. 5 out of 20 cases, or 25%, had symptoms other than B symptoms.

Pruritus was found in 2/20 cases (-10%). In the microscopy of lymphnodes, typical and mononuclear RS cells were seen in a background of lymphocytes, plasma cells, eosinophils, and histiocytes (tumour microenvironment.) IHC pattern in classical HL is cytoplasmic CD20 dim to negative, Fig. 2, Fig. 3, Pax 5 cytoplasmic dim positive, Fig. 4, Golgi, and nuclear positivity of CD 30 Fig. 5.

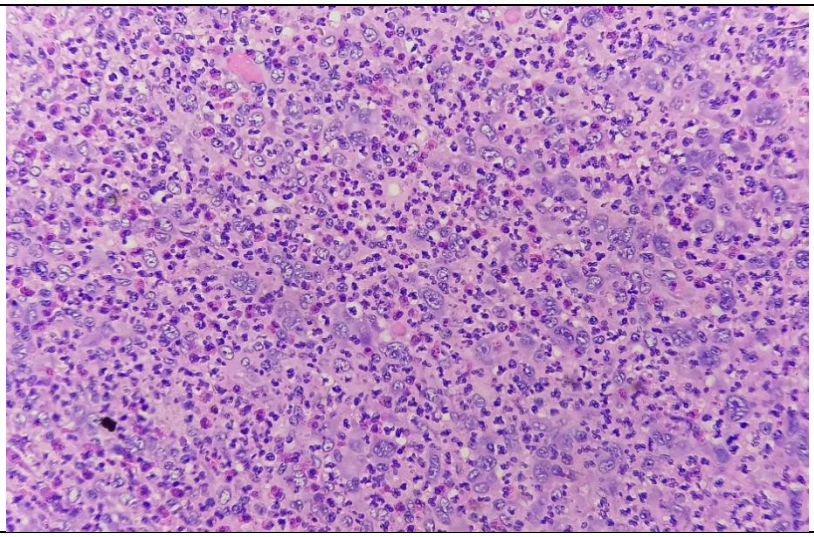

Figure 1: H/E 40x. Foot Note - Classical RS Cells and the Tumour Microenvironment

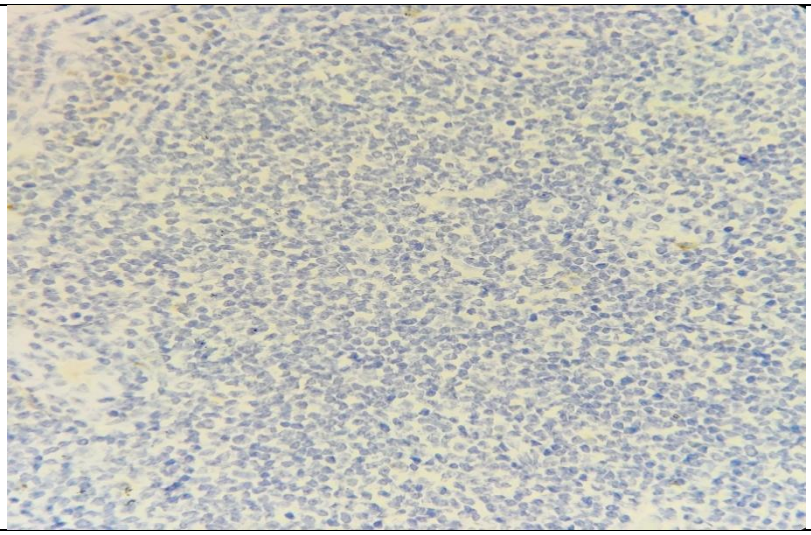

Figure 2: 40x , RS Cells with Cytoplasmic CD20 nagative

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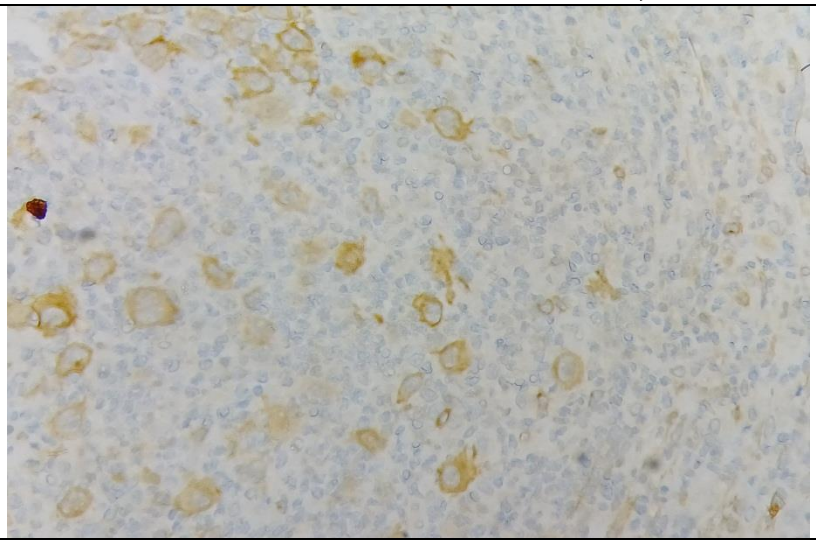

Figure 3: 40x Classical RS Cells Showing CD 20 dim

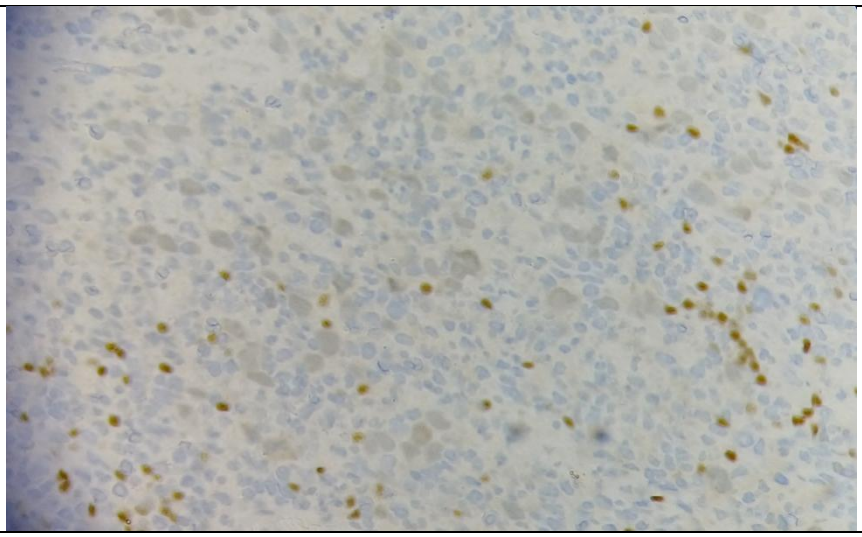

Figure 4: RS Cells Show Characteristic Cytoplasmic Dim Positive Pax 5

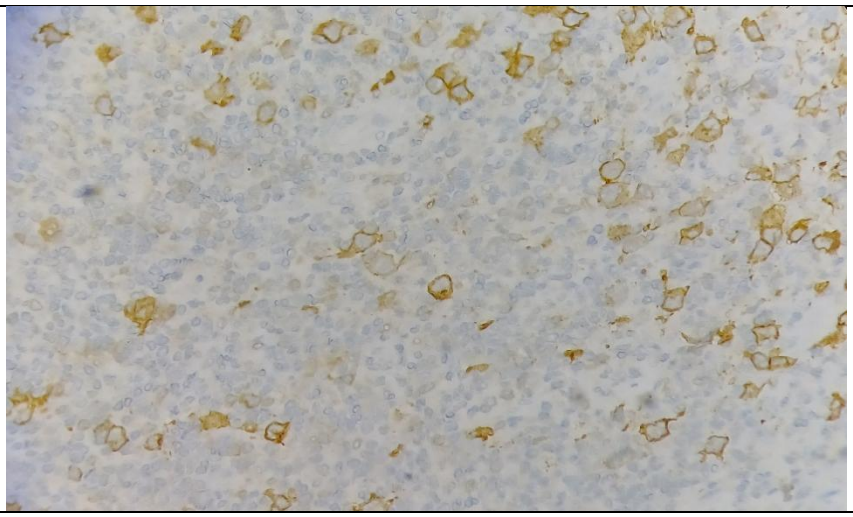

Figure 5: Golgi and Nuclear Positivity of CD 30 in RS Cells

X-rays, CT, and 18F-FDG PET-CT scans were used to assess the extent of the disease.

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DISCUSSION

Hodgkin's lymphoma is well known for its characteristic histology and the presence of B-symptoms in the majority of cases. Owing to its occurrence in young children and adults, there is intense research based on its microenvironment for its targeted treatment. Molecular pathogenesis has led to a better understanding of phenotype, histogenesis, and mechanisms of development. With recent research and development, a complete consensus on the B cell derivation of the tumour, Epstein-Barr virus infection, and defective cytokinesis is better understood.[11]

Hodgkin's lymphoma has a bimodal age group distribution, with the first peak between 15 and 40 years of age and the second peak after 60 years in our study group. Males and females were almost equally affected by the classical type.

Clinically, Hodgkin's lymphoma presents as a painless enlargement of peripheral lymph nodes. Cervical lymph nodes were more commonly involved in our group. The three commonest sites of disease presentation were mediastinal involvement or nodal enlargement in the neck. In decreasing order of frequency, additional locations include the splenic, axillary, abdominal, hilar, or inguino-femoral. Before a diagnosis is obtained, mediastinal masses can enlarge significantly. Bulky disease, which is indicated by a tumour mass's transverse diameter greater than 10 cm, has a worse prognosis for patients in its early stages.[15] The B symptoms, which are seen in approximately 40% of the cases are fever, night sweats and loss of weight. Pruritus is also frequently reported.

In addition to being resistant to topical and systemic medications, severe persistent pruritus without evident skin pathology on examination can be a precursor to clinically occult HL.[16]

Elevated Inflammatory markers, such as the ESR (Erythrocyte Sedimentation Rate) can serve as a useful lab marker of disease response. In patients with extensive disease, which portends a poorer prognosis, there is leukocytosis/neutrophilia and anemia. An excisional biopsy of the complete node that is affected is preferred for a definitive diagnosis.

In core biopsy specimens, HRS cells could be overlooked, and the architectural assessment might not be as good as it could be. However, in situations where the node is difficult to access, core biopsies will aid in the diagnosis; fine needle aspirates are not preferred because RS cells of HL are not detected by flow cytometry; and also, the architecture cannot be assessed.[15] The mixed cellularity subtype with abdominal involvement presented with B symptoms.

The nodular sclerosis subtype was the most common subtype of Hodgkin's lymphoma seen more commonly among young adolescents presenting with stage I or II disease and frequently involved the cervical lymphnodes in our study.

Abdominal involvement was more common in mixed cellularity and in lymphocyte depletion cases and least common in nodular sclerosis.

B symptoms were less frequent in nodular sclerosis and more common in mixed cellularity subtypes.

Lymphocyte depletion Hodgkin lymphoma usually shows up in older people as a feverish illness with low lymphocyte or pancytopenia levels, a swollen liver with abnormal liver function tests, and no lymph nodes in the periphery. However, it can also show up in the usual way that Hodgkin lymphoma does. No cases were diagnosed in our one-year study, which further suggests the rarity of the subtype.

Lymphocyte-rich HL also presents mostly with peripheral lymph node enlargement and presents with stage I or II disease. In our study group, only two cases were diagnosed to have lymphocyte-rich Hodgkin's lymphoma, and both patients showed a wide age range of distribution.

The majority of NLPHL patients exhibit peripheral lymph node enlargement and are asymptomatic. B-symptoms occur in less than 10% of cases. In the present study, no cases were

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diagnosed to be of the nlphl subtype (now renamed NLBCL nodular lymphocyte predominant B-cell lymphoma).

Hepatic involvement is almost always associated with retroperitoneal lymph node and splenic involvement and with B symptoms.

The enlarged lymph nodes show a soft, fleshy appearance on the cut section. In nodular sclerosis, enlarged lymph nodes show thickened capsules and fibrous bands dividing the lymph nodes into lobulations, which can be taken as a telltale sign for nodular sclerosis HL. None of the other types show prominent nodularity with dense fibrous bands. They consist of mature, non-neoplastic inflammatory cells surrounding mono- or multinuclear RS cells under a microscope. There may be a lot of diffuse or band-like collagen fibrosis.

The classic Reed-Sternberg cell is a large cell with abundant acidophilic or amphophilic cytoplasm. The nucleus is bilobed or polylobed and gives a binucleated or multinucleated appearance. The nucleus is vesicular, with coarse chromatin clumps and a thickened nuclear membrane. They have a clear halo surrounding their very sizable, highly acidophilic central nucleoli. In most typical cases, the two nuclear lobes are mirror images, resulting in an owl's eye appearance. Fig 2

The initial extranodal osseous presentation of CHL is extremely rare. In our study group, only one patient presented with an initial bone lytic lesion and, a few months later, cervical lymphnode enlargement.

Chemotherapy and radiation are the mainstays of cHL treatment. Before the advent of combination chemotherapy, HL had a 5-year survival rate of less than 10%.[17] Every stage of cancer survival has increased due to improvements in radiation and chemotherapy techniques, as well as advances in our understanding of the disease's biology.[18]

Initial staging is essential for detecting any extranodal involvement and thus will affect therapeutic decisions. Contiguous spread of disease (E stage) requires local radiation therapy with less extensive chemotherapy, whereas stage IV disease is treated with chemotherapy alone or is combined with radiation therapy. Immunotherapy has significantly improved the course of treatment for patients with cHL who were either resistive to treatment or experienced a rapid relapse following therapy (relapsed cHL).

The programmed death-1 (PD-1)-PD-1 ligand (PD-L1) signalling pathway is responsible for the functional impairment of T cells as a tumour's method of immune evasion. The PD-1 receptor on T cells is occupied by tumour cells that express the PD-1 ligand, which prevents T cell activation and proliferation. PD-L1 expression is high in HRS cells that are cancerous, while PD-1 expression is greatly increased in cHL T cells that are infiltrating tumours.[19]

EBV (Epstein-Barr Virus) infection also induces PD-L1 expression in cHL.[20] The main risk factors in the development of EBV positive cHL are:

1) A prior history of symptomatic IM (Infectious Mononucleosis).
2) Elevated antibody levels to viral capsid anigen and early lytic antigens.
3) Immune suppression.[21]

CHL is caused by three EBV-encoded proteins (LMP1, LMP2A, and EBNA) and viral microRNA (miRNA) that are found in HRS cells that have been infected with the virus. EBNA 1 as an episome promotes the growth and survival of HRS cells. LMP1 induces NF-κB, and JAK/STAT and other multiple cell signalling pathways will finally activate the HRS cells.[22] A BCR mimic called LMP2A permits B-cell growth even in the absence of regular BCR signalling.[23] Most people with cHL can be cured with combination treatments.

Immune checkpoint inhibitors that target the PD-1 pathway in this situation demonstrate impressive clinical results, even in patients who have received a lot of previous treatment. PD-1 antibody Nivolumab and Pembrolizumab, a PD-1 inhibitor, are the immunotherapy drugs currently being used.[24-26]

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Immune checkpoint inhibitors combined with EBV-specific treatments may increase these clinical results even more. Targeting EBV-associated cancers, such as cHL, therapeutically has become possible because of EBNA1 inhibitors.[27]

The extent of extranodal involvement is important and should be evaluated because it influences the prognosis. Primary extranodal HL patients have a favourable survival rate, according to one study conducted by Jing Ma et al.[28]

CONCLUSION

CHL is a curable disease. The classic Reed-Sternberg cell is a large cell with abundant acidophilic or amphophilic cytoplasm and very large, highly acidophilic central nucleoli surrounded by a clear halo. cHL is a tumour with variable EBV ssociations. EBV infection also induces PD-L1 expression. The development of cHL is connected to three EBV-encoded proteins (LMP1, LMP2A, and EBNA) and viral microRNA (miRNA) that are found in HRS cells that have been infected with the virus. Combination chemotherapy is able to cure most patients with CHL. Immune checkpoint inhibitors that target the PD-1 pathway in this situation demonstrate impressive clinical results, even in patients who have received a lot of previous treatment. PD-1 antibody Nivolumab and Pembrolizumab, a PD-1 inhibitor, are the immunotherapy drugs currently being used.

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