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Pathology

Study of association of Epstein Barr virus, LMP in Hodgkin lymphoma in south India

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Original Research Article

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Abstract: Hodgkin lymphoma is a lymphoproliferative malignancy. Originally described by Thomas Hodgkin in 1982. It has great potential for adding years of productive life by giving curative therapy as Hodgkin lymphoma are often cured. Overall, cure can be achieved in approximately 80% of patients with Hodgkin lymphoma. Etiology of Hodgkin lymphoma is unknown. There is however considerable evidence suggesting Epstein Barr - to play a role in etiopathogenesis of Hodgkin lymphoma. EBV genomes have been identified in Reed-Sternberg cells of Hodgkin lymphoma**.** To study its association with Epstein - Barr virus.
Keywords: Hodgkin, lymphoma, CD15, CD30, Epstien Barr Virus and LMP.

INTRODUCTION

Hodgkin lymphoma is a lymphoproliferative malignancy. Originally described by Thomas Hodgkin in 1982 [1].

It has great potential for adding years of productive life by giving curative therapy as Hodgkin lymphoma are often cured. Overall, cure can be achieved in approximately 80% of patients with Hodgkin lymphoma [1].

Pathologically, HL is distinguished from other lymphomas by the presence of large binucleated or multinucleated cells (i.e., Reed-Sternberg cells) generally surrounded by a benign reactive host response consisting of lymphocytes, histiocytes, granulocytes, eosinophils, and plasma cells.

Reed-Sternberg cells are large cells with abundant cytoplasm and generally contain two or more nuclei and two or more inclusion like nucleoli. Variant forms of Reed-Sternberg cells exist, especially in the nodular sclerosis subtype of HL and the nodular form of lymphocyte- predominant Hodgkin lymphoma.

In addition to the use of standard hematopathologic criteria, immunostaining for CD15 (Leu -M1) and CD30 (Ki-1) may be helpful in confirming the diagnosis of HL. The neoplastic cells of Hodgkin lymphoma, both classic Reed-Sternberg cells and Reed-Sternberg variants, tend to stain positively with these antibodies [3].

As classified by the World Health Organization (WHO), Hodgkin disease (Hodgkin's lymphoma) exists in 5 types.

Four of these, nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte rich, are referred to as classic Hodgkin disease (Hodgkin's lymphoma).

The fifth type, nodular lymphocyte predominant Hodgkin disease (NLPHD), is a distinct entity with unique clinical features and a different treatment paradigm.

Etiology of Hodgkin lymphoma is unknown [2]. There is however considerable evidence suggesting Epstein Barr - to play a role in etiopathogenesis of Hodgkin lymphoma. EBV genomes have been identified in Reed-Sternberg cells of Hodgkin lymphoma [2].

Primary infection of Epstein-Barr virus (EBV), which is primarily transmitted by saliva, actively replicates in the epithelial cells of the oropharynx and can subsequently infect recirculating B lymphocytes which may lead to acute infectious mononucleosis (glandular fever).

Infection with Epstein-Barr virus is associated with lymphoproliferative disorders, especially in immunocompromised hosts, and is associated with various tumors, including Nasopharyngeal carcinoma and Burkitt lymphoma.

MATERIALS AND METHODS

We studied 50 cases of Hodgkin lymphoma, from MEHDI NAWAZ JUNG tertiary hospital, Osmania medical college over a span of 1 year, from May 2009 to May 2010, with clinical correlation. Lymph node biopsies received were collected in 10 % neutral buffered formalin along with detailed clinical history. The tissue was then examined for gross appearance and noted down. Representative tissue was sampled and submitted for processing. Hematoxylin and eosin staining was done on paraffin sections and studied microscopically.

Cases diagnosed as Hodgkin Lymphoma were subdivided according to WHO classification 2004 and subjected to immunohistochemistry using antibody CD30 and CD15 for confirmation.

50 cases of classic Hodgkin lymphoma, independent of age, sex or clinical details were subjected to immunohistochemistry using antibody LMP – 1 Latent membrane protein –1, to demonstrate Epstein Barr Virus. Were subjected to immunohistochemistry- Latent Membrane Protien-1, primary antibody to know the prevalence of EPSTEIN - BARR VIRUS in our population. Lymph node biopsies received were collected in 10 % neutral buffered formalin

RESULTS

Immunohistochemistry was done on 50 cases – to known the prevalence of Epstein Barr Virus
in Hodgkin lymphoma
LMP – positivity observed in 31 cases (31/50) – accounting for 62%
CD 30 – positivity observed in 45 cases (45/50) – accounting for 90%
CD 15 – positivity observed in 40 cases (40/50) – accounting for 80%
Out of 50 cases diagnosed in one year span were – subjected to immunohistochemistry with Latent

Membrane Protein -1,
Mixed cellularity (45 cases) – 27/45 positivity
Nodular sclerosis (5 cases) – 4/5 positivity

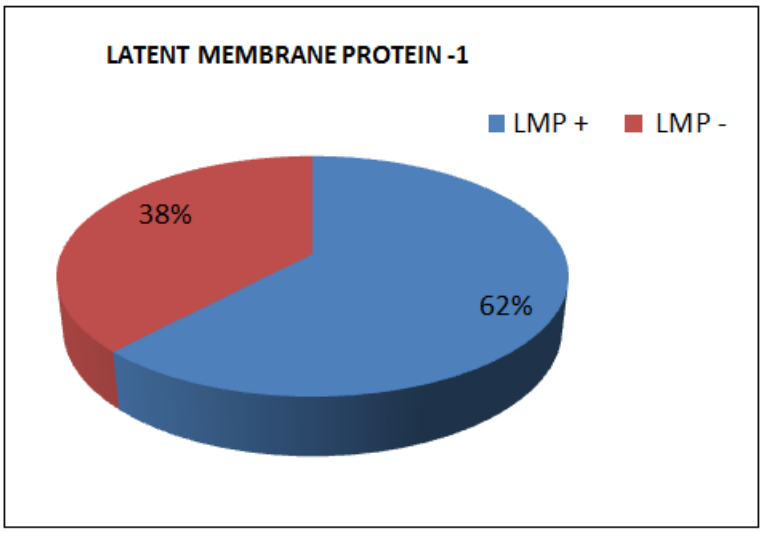

Fig-1: Latent Membrane Protien -1

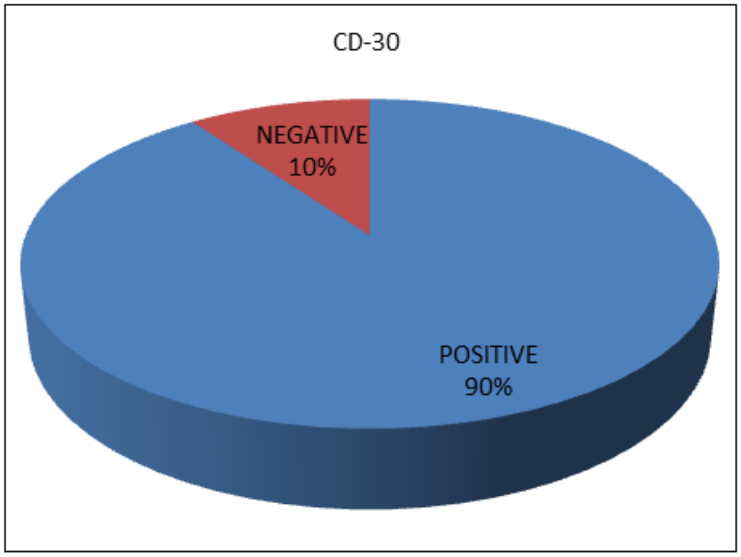

Fig-2: CD 30

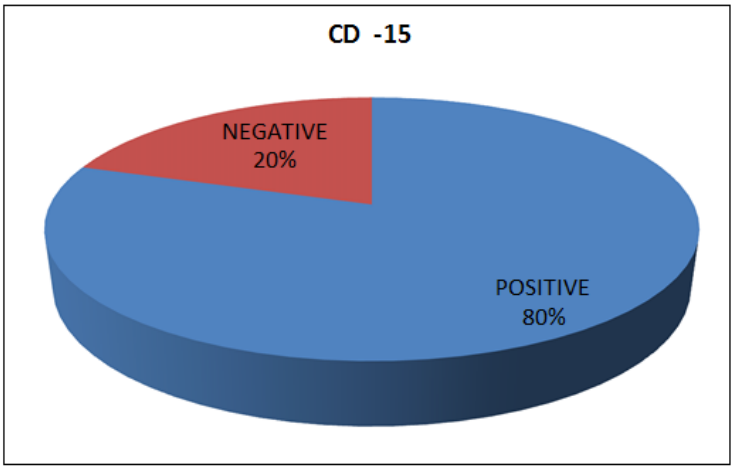

Fig-3: CD 15

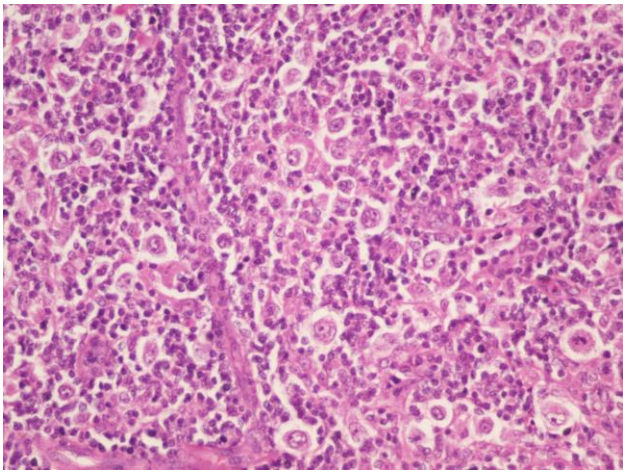

Fig-4: Hodgkin Lymphoma - Lymphocyte Rich.

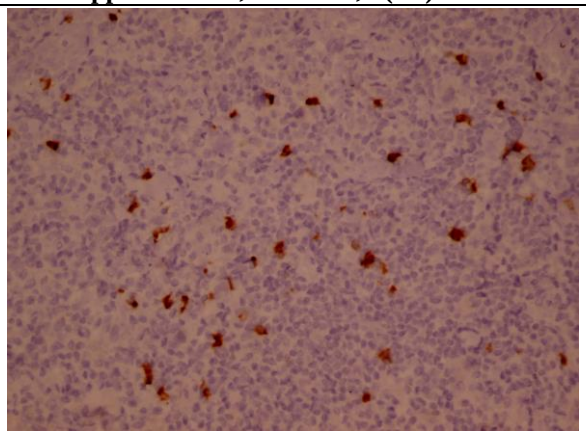

Fig-5: CD – 15 – Paranuclear (Golgi Area), Diffuse Cytoplasmic, and Corresponding To Membrane Immunostaining

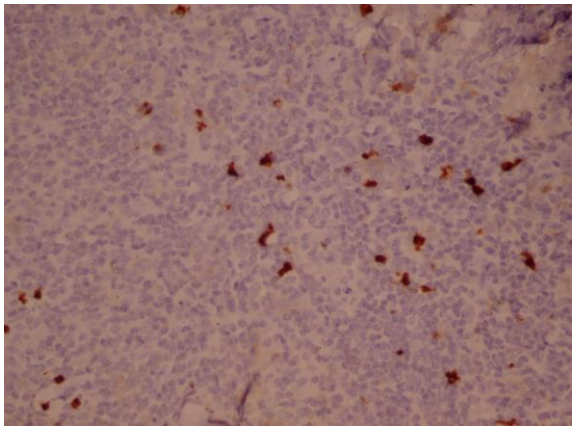

Fig-6: CD – 15 – Paranuclear (Golgi Area), Diffuse Cytoplasmic, And Corresponding To Membrane Immunostaining

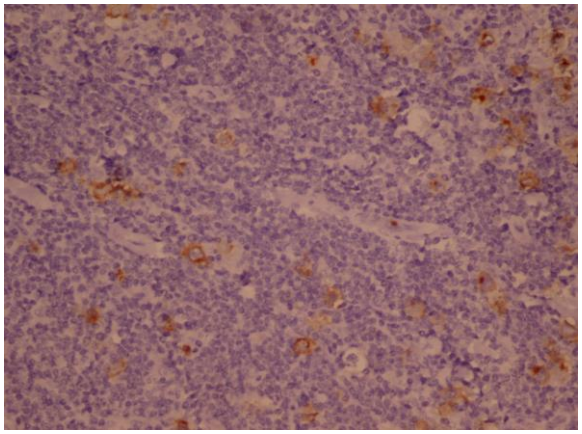

Fig-7: CD – 30 – Membrane and Golgi Type Immunostaining

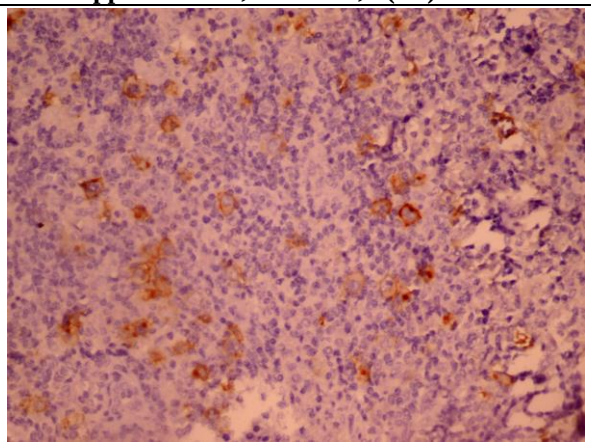

Fig-8: CD – 30 – Membrane and Golgi Type Immunostaining

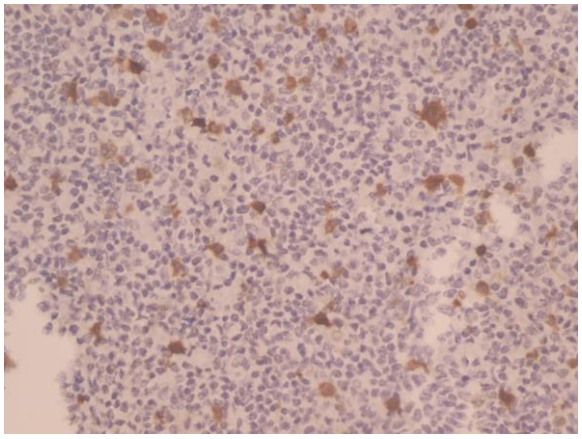

Fig-9: Latent Mambrane Protien-1 Cytoplasmic Positive in Rs Cells

Table-1: Tabulation of Fifty Cases Subjected To Immunohistochemistry with Results

Sl. No	Age	Sex	Histological type	CD30	CD15	LMP-1
1	45	M	Mixed	+	+	+
2	4	M	Mixed	+	-	+
3	25	M	Mixed	+	-	+
4	10	M	Mixed	+	+	+
5	32	M	Mixed	+	+	+
6	30	M	Mixed	+	+	-
7	32	F	Mixed	+	+	-
8	32	M	Mixed	+	+	-
9	8	M	Mixed	+	+	-
10	19	F	Mixed	+	+	+

Table-2: Tabulation of Fifty Cases Subjected To Immunohistochemistry with Results

Sl. No	Age	Sex	Histological type	CD30	CD15	LMP-1
11	27	M	Mixed	+	+	-
12	8	M	Mixed	+	+	-
13	33	M	Nodular sclerosis	+	+	+
14	10	M	Mixed	+	+	+
15	27	M	Mixed	+	+	-
16	36	M	Mixed	+	+	-
17	47	M	Mixed	+	+	-
18	13	M	Mixed	+	+	-
19	35	M	Nodular sclerosis	+	+	+
20	14	M	Nodular sclerosis	+	+	-

Table-3: Tabulation of Fifty Cases Subjected To Immunohistochemistry with Results

Sl. No	Age	Sex	Histological type	CD30	CD15	LMP-1
21	9	F	Mixed	+	-	+
22	25	M	Mixed	-	+	+
23	40	M	Nodular sclerosis	+	+	+
24	7	M	Mixed	+	+	+
25	19	M	Nodular sclerosis	+	-	+
26	14	F	Mixed	+	+	-
27	13	M	Mixed	+	+	+
28	38	M	Mixed	+	+	+
29	46	M	Mixed	+	+	+
30	18	M	Mixed	+	+	-

Table-4: Tabulation of Fifty Cases Subjected To Immunohistochemistry with Results

Sl. No	Age	Sex	Histological type	CD30	CD15	LMP-1
31	18	M	Mixed	+	-	+
32	25	M	Mixed	-	+	+
33	50	M	Mixed	-	+	+
34	44	M	Mixed	+	-	-
35	16	M	Mixed	+	-	+
36	23	F	Mixed	+	+	+
37	26	M	Mixed	+	+	+
38	19	M	Mixed	-	+	+
39	32	F	Mixed	-	+	-
40	40	M	Mixed	+	+	-

Table-5: Tabulation of Fifty Cases Subjected To Immunohistochemistry with Results

Sl. No	Age	Sex	Histological type	CD30	CD15	LMP-1
41	22	M	Mixed	+	+	+
42	32	F	Mixed	+	+	+
43	30	M	Mixed	+	+	-
44	17	F	Mixed	+	-	-
45	18	M	Mixed	+	+	+
46	22	M	Mixed	+	+	+
47	16	F	Mixed	+	-	-
48	14	M	Mixed	+	+	+
49	12	M	Mixed	+	+	+
50	36	M	Mixed	+	-	+

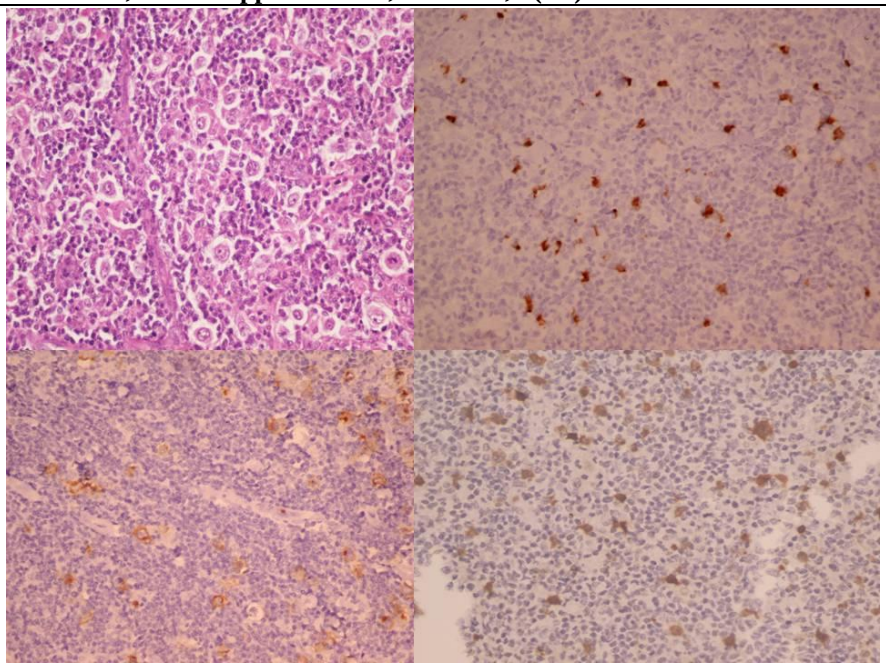

Fig-10(a): RS cells in Hodgkin Lymphoma ,H&E (40X),1(b) CD – 15 – Paranuclear (golgi area), diffuse cytoplasmic, and corresponding to membrane immunostaining,1(c) CD – 30 – Membrane and golgi area immunostaining,1(d) Cytoplasmic posivity for Latent Menbrane protein -1 in RS cells

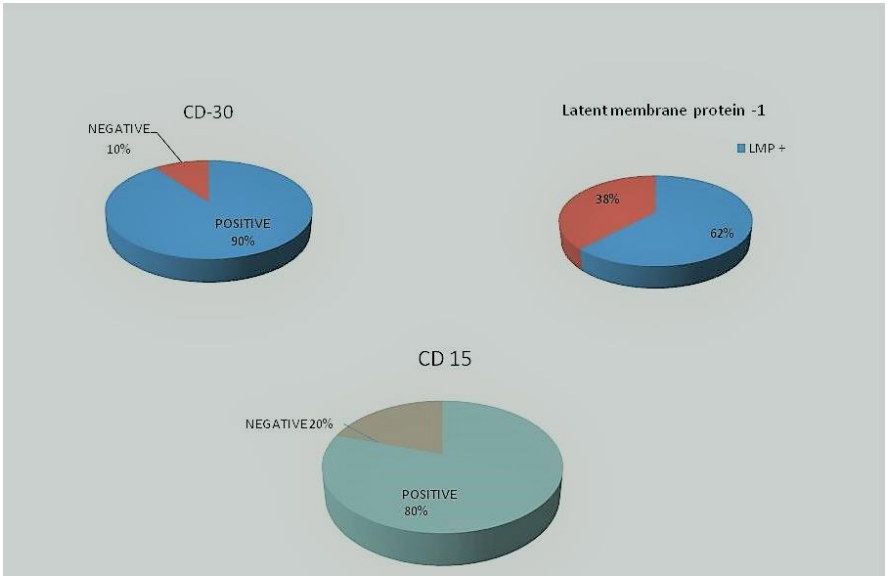

Fig-11(a): Pie Chart of CD30, 2 (b) Pie Chart Latent Membrane Protien1 – IHC,2(c) Pie Chart of CD15

DISCUSSION

EPSTEIN BARR VIRUs [9, 15]

Epstein-Barr virus (EBV), or human herpesvirus 4, is a gammaherpesvirus that infects more than 95% of the world's population. The most common manifestation of primary infection with this organism is acute infectious mononucleosis, a self-limited clinical syndrome that most frequently affects adolescents and young adults.

Classic symptoms include sore throat, fever, and lymphadenopathy. Infection with Epstein-Barr virus in younger children is usually asymptomatic or mild.

Epstein-Barr virus is also a human tumor virus, the first virus associated with human malignancy. Infection with Epstein-Barr virus is associated with lymphoproliferative disorders, especially in immunocompromised hosts, and is associated with various tumors, including Nasopharyngeal carcinoma and Burkitt lymphoma.

Primary infection of Epstein-Barr virus (EBV), which is primarily transmitted by saliva, actively replicates in the epithelial cells of the oropharynx and can subsequently infect recirculating B lymphocytes which may lead to acute infectious mononucleosis (glandular fever).

Infectious mononucleosis is a benign lymphoproliferative disease that is usually seen in children, although most cases of EBV infection occur in early childhood and have no symptoms. It is characterized by transient immunosuppression and an unusual expansion of atypical lymphocytes, the majority of which are not B cells but $CD8^+$ T cells.

Instead, in these cells EBV establishes a latent infection that persists for life during which only a few viral genes are expressed. Latent infection is a common feature to other herpesviruses [5, 6]. EBV has a narrow tissue tropism limited to B lymphocytes, T lymphocytes and epithelial cells of primate origin. By the age of twenty, greater that 90% of humans are seropositive, demonstrating previous exposure to EBV.

EBV is potentially oncogenic and has been linked to Burkitt's lymphoma, Nasopharyngeal carcinoma, B cell lymphoma, X-linked lymphoproliferative disorder [4, 8], and more recently to other neoplasia, including Hodgkin's disease, peripheral T cell tumours, and gastric cancer[7]. In normal individuals, latent EBV infection is controlled by humoral immunity, cytotoxic T cells, and the interferon (IFN) system [8].

EBV MORPHOLOGY

The EBV genome isolated from virus particles is a linear, double stranded DNA molecule of about 175 kilobase pairs (kbp). It is characterised by a number of different repetitions. The termini consist of tandem repeats of approximately 540 base pairs (bp). A variable number of large internal repeats of about 3.1 kbp joins a short and a long unique region. Several different other repeats are interspersed in the genome. Two clusters of small tandem repeats of 125 and 102 bp show partial homology and have the same orientation on the genome. Each cluster is flanked by a highly conserved region of about 1 kbp. These left and right duplicated regions, which are denoted DL and DR respectively, are located about 100 kbp apart from each other in the viral genome [4, 9].

The entire genome persists in the proliferating lymphocytes as linear-integrated and covalently closed circular episomal DNA [9, 12].

The EBV genome has been mapped using Bam HI restriction endonuclease to produce fragments which have subsequently been denoted with a letter to identify specific fragments [10].The term tegument, which is common to all herpesviruses, was introduced to describe the structures between the capsid and envelope. These structures have no distinctive features in thin sections, but they may appear to be fibrous on negative staining. The available evidence suggests that the amount of tegument is more likely to be determined by the virusthan by the host. The tegument is frequently distributed asymmetrically [11].

The most abundant EBV envelope proteins are pg350 and gp220, which are encoded by the same viral gene. Additional viral envelope proteins expressed at much lower levels include gp85, gp25, gp42/38, gp43, and gp78/55 [6].

LATENT INFECTION [8, 33]

Like other herpesviruses, Epstein-Barr virus persists in its hosts through its ability to establish a latent infection that periodically reactivates. EBV establishes latent infection as a self-replicating extrachromosomal nucleic acid (an episome). EBV has shown to have three transcriptionally distinct forms of latency. These are known as latency I, II, and III [13]. The first two different forms of latency to be identified were latency I and latency III, and were detected in phenotypically distinct human B cell lines. All of the latent proteins, comprising of six EBV-specified nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C, and leader protein, EBNA-LP) and three latent membrane proteins (LMPs 1, 2A and 2B), are expressed in latency III which was the first form of latency to be detected. The EBNAs are all polymorphic, that is, their structure differs from one strain to the next [4].

The latent membrane proteins (LMPs) are expressed in all forms of latency. Therefore it would be expected that these proteins would play a major role in the maintenance of transformed cells. The LMPs may play a role in viral target antigen (LYMDA) recognised by those immune T lymphocytes which specifically kill latently infected B lymphocytes [14]. A significant feature of LMP1 in EBV transformed lymphocytes is its association with the vimentin cytoskeletal network [15]. LMP1 has been shown to upregulate the expression of the cellular oncogene *bcl*-2 [16] .The interaction between EBV infection and expression of this cellular oncogene has important implications for virus persistence and for the pathogenesis of virus .associated malignant disease. LMP1 transforms immortalised rodent fibroblasts and induces vimentin, *bcl*-2, and many of the activation markers and adhesion molecules that EBV induces in BL cells or primary B lymphocytes [17], giving further evidence that LMP1 is critical in cellular transformation. LMP1 interacts with the novel human proteins, LMP1 associated protein 1 and EBV-induced gene 6, which are related to the murine tumour-necrosis factor receptor associated factors, TRAF1 and TRAF2 [18].

1.1.1.

1.1.2. EBER1 and EBER2 [5, 32]

The genome of EBV encodes two Epstein-Barr virus-associated small RNAs, EBER1 (166 bases) and EBER2 (172 bases), which are expressed in all forms of latency. Both RNAs are transcribed by RNA polymerase III and are synthesised in large quantities. The EBERs exist as ribonucleoprotein particles complexed with the cellular La antigen. Because of the relative abundance of EBER1 and EBER2 (approximately 10 [7] copies per cell) and because they

are two of a the few EBV latent gene products, it would be expected that one or both of the EBERs are important in B cell transformation and/or maintenance of the latent state [19]. The EBERs have been shown to be capable of substituting for the VAI RNA function in adenovirus infected cells. Adenovirus VAI RNA is essential for the efficient initiation of viral mRNAs in the late phase of infection [20]. Therefore it can be predicted that the EBERs play major a role in the efficient initiation of EBV viral mRNAs. There is still very little data on the functions of the EBERs presently available, although studies suggest that the EBERs may work at the level of replication, transcription, or RNA processing [19]. In developed countries positivity of LMP -1 is ranging from 25 – 35 % [21-24].

Studies showing high positive where from Brazil (2010) and Egypt (2000) with 52.2 % and 63 % respectively [25].

Studies from India show positivity ranging from 31 to 82 %. K.Radha *et al*., - 31% positivity Swapnil Karthik *et al*., -82% and Naresh *et al*., - 78% [26, 27, 28].

Studies conducted to know the treatment response and survival advantage – to a extent have proved Epstein barr virus as an etiological factor, and has an impact on treatment response but is dependent on age. Younger age group < 35 years [23, 29-31] having a longer time for relapse, overall survival and disease free survival, compared to patients > 35 years with EBV positivity who have shown poor response to treatment and shorter duration of failure free survival . Few studies don't show survival advantage, associated with Epstein Barr virus in Hodgkin lymphoma [22, 30, 24, 23, 2, 32, 33].

Percentage positivity for Latent Membrane Positivity -1 varies in different studies from different geographical area. Studies from developed countries have shown less percentage positivity, compared to developing countries. Studies from India have shown high positivity, implying a role in pathogenesis. Overall survival in younger patients with EBV positivity is better compare to EBV positive older patients.

CONCLUSION

With high positivity for EPSTEIN BARR VIRUS in patients of Hodgkin lymphoma from developing countries, we can attribute an etiological role to Epstein Barr Virus in the pathogenesis of Hodgkin lymphoma. Presence of Epstein Barr Virus in tumor cells of Hodgkin lymphoma is associated with better survival in young patients and poorer survival in older patients according to various studies .Variation in outcome by age and histology could indicate biologically distinct disease entities. Evidence that Epstein Barr virus is a meaningful prognostic marker may have therapeutic relevance. Impaired immune status may contribute to the development of Epstein Barr virus positive Hodgkin Lymphoma in older patients, and strategies aimed at boosting the immune response should be investigated in the treatment of these patients.

REFERENCES

1. Wintrobe MM. Wintrobe's clinical hematology. Lippincott Williams & Wilkins; 2009.
2. Rosai J, Ackerman S. Surgical pathology. Eigth edition, Mosby. 1996.
3. Stein H, Mason DY, Gerdes J. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue. Evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985;66:848–858.
4. Wang D, Liebowitz D, Kieff E. The truncated form of the Epstein-Barr virus latent-infection membrane protein expressed in virus replication does not transform rodent fibroblasts. Journal of virology. 1988 Jul 1;62(7):2337-46.
5. Cayrol C, Flemington EK. Identification of cellular target genes of the Epstein-Barr virus transactivator Zta: activation of transforming growth factor beta igh3 (TGF-beta igh3) and TGF-beta 1. Journal of virology. 1995 Jul 1;69(7):4206-12.
6. Cooper NR. Early events in human herpesvirus infection of cells. Cold spring harbor monograph series. 1994;28:365-88.
7. Yoshiyama H, Shimizu N, Takada K. Persistent Epstein-Barr virus infection in a human T-cell line: unique program of latent virus expression. The EMBO journal. 1995 Aug 1;14(15):3706.
8. Jabs WJ, Wagner HJ, Neustock P, Klüter H, Kirchner H. Immunologic properties of Epstein-Barr virus-seronegative adults. Journal of Infectious Diseases. 1996 May 1;173(5):1248-51.
9. Kieff E. Epstein-Barr virus and its replication. Virology. 1990:1889-920.
10. Sample J, Lancz G, Nonoyama M. Use of Cloned Epstein-Barr Virus DNA to Identify Genes that Determine the Fate of Viral Infection. InViral Messenger RNA 1985 (pp. 127-146). Springer, Boston, MA.
11. Tyler KL, Fields BN. Reoviridae: a brief introduction. Virology (2nd ed.), Raven Press, NY. 1990:1271-3.
12. Fennewald SU, van Santen VI, Kieff EL. Nucleotide sequence of an mRNA transcribed in latent growth-transforming virus infection indicates that it may encode a membrane protein. Journal of virology. 1984 Aug 1;51(2):411-9.
13. Rowe M, Lear AL, Croom-Carter D, Davies AH, Rickinson AB. Three pathways of Epstein-Barr virus gene activation from EBNA1-positive latency in B lymphocytes. Journal of virology. 1992 Jan 1;66(1):122-31.
14. Liebowitz DA, Wang DA, Kieff EL. Orientation and patching of the latent infection membrane

protein encoded by Epstein-Barr virus. Journal of Virology. 1986 Apr 1;58(1):233-7.
15. Wang D, Liebowitz D, Kieff E. The truncated form of the Epstein-Barr virus latent-infection membrane protein expressed in virus replication does not transform rodent fibroblasts. Journal of virology. 1988 Jul 1;62(7):2337-46.
16. Henderson S, Rowe M, Gregory C, Croom-Carter D, Wang F, Longnecker R, Kieff E, Rickinson A. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. Cell. 1991 Jun 28;65(7):1107-15.
17. Birkenbach M, Josefsen K, Yalamanchili R, Lenoir G, Kieff E. Epstein-Barr virus-induced genes: first lymphocyte-specific G protein-coupled peptide receptors. Journal of virology. 1993 Apr 1;67(4):2209-20.
18. Longnecker R, Miller CL. Regulation of Epstein—Barr virus latency by latent membrane protein 2. Trends in microbiology. 1996 Jan 1;4(1):39-42.
19. Glickman JN, Howe JG, steitz JA. Structural analyses of EBER1 and EBER2 ribonucleoprotein particles present in Epstein-Barrvirus-infected cells. J Virol. 1988 Mar;62(3):902-11.
20. Bhat RA, Thimmappaya BA. Construction and analysis of additional adenovirus substitution mutants confirm the complementation of VAI RNA function by two small RNAs encoded by Epstein-Barr virus. Journal of virology. 1985 Dec 1;56(3):750-6.
21. Murray PG, Billingham LJ, Hassan HT, Flavell JR, Nelson PN, Scott K, Reynolds G, Constandinou CM, Kerr DJ, Devey EC, Crocker J. Effect of Epstein-Barr virus infection on response to chemotherapy and survival in Hodgkin's disease. Blood. 1999 Jul 15;94(2):442-7.
22. Glavina-Durdov M, Jakic-Razumovic J, Capkun V, Murray P. Assessment of the prognostic impact of the Epstein–Barr virus-encoded latent membrane protein-1 expression in Hodgkin's disease. British journal of cancer. 2001 May;84(9):1227.
23. Krugmann J, Tzankov A, Gschwendtner A, Fischhofer M, Greil R, Fend F, Dirnhofer S. Longer failure-free survival interval of Epstein-Barr virus–associated classical Hodgkin's lymphoma: a single-institution study. Modern pathology. 2003 Jun 1;16(6):566-73.
24. Flavell KJ, Billingham LJ, Biddulph JP, Gray L, Flavell JR, Constandinou CM, Young LS, Murray PG. The effect of Epstein–Barr virus status on outcome in age-and sex-defined subgroups of patients with advanced Hodgkin's disease. Annals of Oncology. 2003 Feb 1;14(2):282-90.
25. Souza EM, Baiocchi OC, Zanichelli MA, Alves AC, Assis MG, Eiras DP, Dobo C, Oliveira JS. Impact of Epstein–Barr virus in the clinical evolution of patients with classical Hodgkin's lymphoma in Brazil. Hematological oncology. 2010 Sep 1;28(3):137-41.
26. Radha K, Shanthi P, Madhavan M, Senthamarai A. Study of association of Epstein Barr-virus with Hodgkin's disease. Indian journal of pathology & microbiology. 1997 Jul;40(3):351-4.
27. Karnik S, Srinivasan B, Nair S. Hodgkin's lymphoma: immunohistochemical features and its association with EBV LMP-1. Experience from a South Indian hospital. Pathology. 2003 Jan 1;35(3):207-11.
28. Naresh KN, Johnson J, Srinivas V, Soman CS, Saikia T, Advani SH. Epstein-Barr virus association in classical Hodgkin's disease provides survival advantage to patients and correlates with higher expression of proliferation markers in Reed-Sternberg cells. . Ann oncol 2000 Jan;11(1):91-6.
29. Flavell KJ, Billingham LJ, Biddulph JP, Gray L, Flavell JR, Constandinou CM. The effect of Epstein-Barr virus status on outcome in age- and sex-defined subgroups of patients with advanced Hodgkin's disease. Mod Pathol. 2003 Jun;16(6):566-73.
30. Clarke CA, Glaser SL, Dorfman RF, Mann R, DiGiuseppe JA, Prehn AW. Epstein-Barr virus and survival after Hodgkin disease in a population-based series of women. Cancer 2001 Apr: 15;91(8):1579-87.
31. Diepstra A, van Imhoff GW, Schaapveld M, Karim-Kos H, van den Berg A, Vellenga E. Latent Epstein-Barr virus infection of tumor cells in classical Hodgkin's lymphoma predicts adverse outcome in older adult patients. J. clinical oncology - 2009 Aug 10;27(23):3815-21
32. Jarrett RF, Stark GL, White J, Angus B, Alexander FE, Krajewski AS. Scotland and Newcastle Epidemiology of Hodgkin Disease Study Group. Impact of tumor Epstein-Barr virus status on presenting features and outcome in age-defined subgroups of patients with classic Hodgkin lymphoma: a population-based study. Blood. 2005 Oct 1;106(7):2444-51
33. Keresztes K, Miltenyi Z, Bessenyei B, Beck Z, Szollosi Z, Nemes Z, Olah E, Illes A. Association between the Epstein-Barr virus and Hodgkin's lymphoma in the North-Eastern part of Hungary: effects on therapy and survival. Acta haematologica. 2006;116(2):101-7.