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Infectious Aetiology of Cancer: Developing World Perspective

Shahid Pervez
Professor, Section of Histopathology,
Department of Pathology & Microbiology,
Aga Khan University Hospital Karachi,
Pakistan

1. Introduction

Infection attributable cancers contribute over 1/4th of all cancers in the developing countries (26.3%) compared to the developed countries (7.7%), (Parkin, 2006). Overwhelming majority are related to viral infections. In contrast to other carcinogens where it is usually a *'hit and run'* kind of situation, with infectious agents particularly viruses one may precisely demonstrate and prove its presence and integration within host neoplastic cells. Oncogenic DNA viral genome incorporates itself directly into host cells DNA while oncogenic RNA viral genome is transcribed into host cell DNA by reverse transcriptase. Neoplastic transformation usually follows. Oncogenic mechanisms include acting as promoter, transforming protooncogenes into oncogenes. Credit goes to Dr Peyton Rous, a noble laureate pathologist who demonstrated that it was possible to transmit tumours from one animal to other like transmission of an infection.

Human tumours with proven or proposed viral aetiology include 'Human papillomavirus (HPV)', Epstein-Barr Virus (EBV), Hepatitis B and C viruses, RNA retroviruses like 'Human T-lymphotropic virus (HTLV1)', 'Human Herpes Virus-8 (HHV-8). Bacteria with proven carcinogenic potential include 'Helicobacter pylori'. Among fungi aflatoxins produced by 'Aspergillus flavus' are potent carcinogens. Among parasites 'Schistosoma' and 'Clonorchis sinensis' are implicated in the causation of cancer.

2. Human papillomavirus (HPV)

HPV is a small epitheliotropic, non enveloped DNA virus belonging to papovaviridae family. Its genome comprises 7000-8000 base pairs of double-stranded closed-circular DNA. At least 70 genetically distinct types of HPV have been identified in humans. According to their oncogenic potential HPV is classified in a high oncogenic risk group (i.e., HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 65, 66) and low oncogenic risk group (i.e., HPV6, 11, 42, 43, 44). High risk HPV association with cervical and anogenital cancers is established beyond doubt. HPV16 and 18 are declared as human carcinogens by 'international Agency for Research on Cancer (IARC)'. HPV association with other cancers in particular with *'oral cancer'* is also being investigated with evidence of significant association.

2.1 HPV & cervical carcinoma

Cervical carcinoma is one of the most common malignancies in women worldwide. However with effective preventive measures like *'cervical screening'* programs in developed countries more and more cases are picked at an early stage where complete cure is possible. A significant recent breakthrough has come in the form of *'HPV vaccine'* against high risk HPV16 & 18. This is gaining momentum in developed countries with high risk and burden of disease. It is administered at age 11-13, three shots are given intramuscularly. In contrast in the developing countries data is patchy or non-existent. In most countries no cervical screening programs are in place. In developing muslim countries situation is even worse. For instance in Pakistan, a populous muslim country of about 170 million inhabitants there is no cervical screening program and the only source of cervical smears are the sporadic smears obtained at the time of consultation in obstetrics & gynecology clinics. The problem is further compounded by the social taboos on matters of sexual practices and sexually transmitted infections (STI). These socio-cultural prohibitions create a substantial barrier to such investigations.

Recently a study was carried out with the help of IARC in women of Karachi, Pakistan (largest port city of Pakistan with an estimated population of 15 million from diverse ethnic backgrounds), (Raza et al, 2010). A sum of 899 married women aged 15-59 years living in a densely populated suburb of Karachi consented to participate. HPV prevalence was found to be 2.8%. Cervical abnormalities were diagnosed in 2.4% of whom 27.3% were HPV positive. HPV16 was detected as the most common type among women with both normal (0.5%) and abnormal (9.1%) cytology. This study also included 91 invasive cervical carcinomas (ICC) from two major university hospitals of Karachi, Pakistan. HPV16 was also the predominant HPV type (75.8%) in ICC followed by HPV18 (6.6%). This study led to the suggestion of very low burden of HPV infection in general female population, considerably lower than neighboring India (17%, Franceschi et al, 2005), China (15-18%, Dai et al, 2006, Wu et al, 2007) and Nepal (9%, Sherpa et al, 2010).

In another study from Karachi, Pakistan (Khan et al, 2007) women visiting two major tertiary care hospitals in Karachi, diagnosed with ICC, sixty (60) paraffin-embedded biopsies were analysed for HPV subtypes by PCR. Out of the 60 samples only one was negative for HPV, the rest were positive excluding two samples where subtype could not be determined. Fifty six (56) were HPV16 positive and only one was HPV18 positive.

2.1.1 Conclusion

- In most developing countries particularly developing muslim countries data regarding sexually transmitted infections (STI) is either non-existent or sparse.
- A comprehensive well planned study utilizing samples from asymptomatic married women of Karachi, Pakistan revealed very low incidence of HPV (2.8%).
- Samples from both asymptomatic women as well as from invasive cervical cancer (ICC) showed overwhelming predominance of HPV16.
- Results from Karachi, Pakistan underscore the importance of cervical screening programs & HPV vaccination in resource constrained economies.

3. HPV and oral cancer

Oral cancer (OC) / Oral squamous cell carcinoma (OSCC) excluding salivary gland cancers ranks 6th overall in the world in both sexes with much higher incidence in the developing

countries. In Karachi it ranked 2nd with an identical risk in both genders (Bhurgri et al, 2003). However if combined with pharynx and larynx cancers which have the same histologic type (squamous cell carcinoma) & risk factors it ranks number 1. Major risk factors in the developed world include *'smoking'* and *'alcohol;* however in the developing world though smoking is a common major risk factor, role of alcohol drinking is possibly a minor risk factor particularly in developing muslim countries. In subcontinent (Pakistan, India & Bangladesh) alternate chewing habits like betel quid and areca nut are major risk factors. Areca nut is now declared by WHO as a bonafide carcinogen. People using paan (betel leaf) are about 8- 9 times more likely to develop oral cancers as compared to non-users (Merchant et al, 2000). Smokeless tobacco, including '*gudka*' and '*niswar*' is an extremely addictive substance with a high rate of use in younger age groups, as well is contributing toward endemic rise of oral cancers in Pakistan (Ali et al, 2009 & Nair et al, 2004). (Figure 1) This habit commonly leads to a pre-malignant condition '*Submucosal fibrosis*' which commonly transforms into OSCC. Poor oral hygiene is another contributory factor in this population.

A significant proportion of OSCC patients however deny exposure to conventional and well known risk factors. This has led to search of other risk factors and associations including microbes (Scully et al, 1985). The striking commonality between oral cavity and cervical cavity paved the way to look for epitheliotropic viruses like HPV. Although these two areas are anatomically different, the squamous epithelium found in both areas has several similarities. For instance the squamous epithelium of ecto-cervix and oral cavity including pharynx and larynx are composed of squamous epithelium with a thin layer of keratin or no keratin. In both areas the epithelium is subject to microtrauma of various types as well as to bacteria and varying chemical irritants. Most common malignancy at both anatomic sites is also SCC with varied differentiation. (Figure 2) These factors may directly expose to HPV infections of cells resulting in malignant transformation. Furthermore the HPV subtypes isolated from lesions of squamous epithelium of cervix are similar to the type found in both normal epithelium and various lesions of the oral cavity, pharynx and larynx. These include HPV subtypes16, 18, 31 & 33.

The reported prevalence of HPV in OSCC varies widely in various studies depending on the population and ethnicity studied and/or sensitivity of the methods used and viral DNA sequence targeted. HPV in particular HPV-16, like in cervix is implicated in the aetiology of OSCC (Gillison, 2004; Miller & Johnstone, 2001) About 40 – 60% of patients with tumours of oropharynx are reported to be positive for HPV infection (Gillison, 2004; Kreimer et al, 2005). HPV-positive tumours are distinct from HPV-negative tumours in their biological characteristics and clinical behaviour. Data from retrospective analyses as well as a prospective clinical trial demonstrated that HPV-positive oropharyngeal tumours are more sensitive to chemotherapy and radiation treatment and have a markedly improved prognosis and favourable clinical outcome compared with HPV-negative tumours (Fakhry et al, 2008; Settle et al, 2009)

Recently, another significant observation has emerged in terms of HPV status of oropharyngeal tumours and racial disparities. Black Americans are known to have a higher incidence of and mortality from head and neck squamous cell carcinoma (HNSCC) than the whites and present with more advanced disease at a younger age (Goodwin et al, 2008; Morse & Kerr 2006; Ryerson et al, 2008; Shiboski et al, 2007). The greatest survival difference between blacks and whites was detected specifically in oropharyngeal cancers, but there was no racial difference between the overall survival rates of patients with non-oropharyngeal tumours (Settle et al, 2009). Most importantly, the recently published

prospective analysis demonstrated that a marked difference exists between black and white Americans in terms of HPV infection. HPV positivity was about 9-fold higher in white (34%) than in black (4%) patients, directly correlating HPV infection with significant survival disparities between the two populations (Settle et al, 2009). Clearly, the HPV status of patients with OSCC would be an important determinant for prognosis and treatment options in the future.

Recently, in a retrospective study of 140 patients with primary OSCC and a long-term follow up, Ali et al reported from Karachi, Pakistan, 68% of cases to be positive for HPV (Ali et al, 2008). Approximately 90% of these cases were infected with HPV16, (Figure 3 & 4) the predominant subtype in the US population as well. HPV infection was detected entirely in tumours of the cheek and tongue in the oral cavity; this was consistent with the occurrence frequency in the Karachi population for oral cancers which is as follows: 55.9% for cheek, 28.4% for tongue, 6.8% for palate, 4.4% for gum, 3.1% for lip and 1.4% for floor of the mouth (Bhurgri et al, 2003). Furthermore, though HPV positive patients had comparatively prolonged overall survival when compared with HPV negative patients but the difference was not statistically significant (P=0.97) (Figure 5). Betel quid chewers were comparatively more prone to HPV positivity (OR=2.34; 95 CI= 1.1-4.31). These findings are in contrast with the results from US studies where the ratio of oropharyngeal tumours with respect to other sites was 2:1 and the HPV-positive tumours were consistently associated with a better clinical outcome in terms of both overall and disease-free survival (Fakhry et al, 2008; Settle et al, 2009). The reason(s) for these different findings are not clear.

3.1 Oncogenic HPV pathways

The chief oncoproteins of HPV16 are encoded by the genes E6 and E7. The E6 protein targets the tumour suppressor gene p53 for degradation. In fact, degradation of p53 in HPV positive cells is fully dependent on the presence of E6 (Ali et al, 2010, Figure 6). The E7 oncoprotein is involved in suppression of retinoblastoma protein (pRb) function. Reduced pRb expression is common in HPV-positive tonsillar cancer.

3.2 Mode of transmission

Two questions immediately come to mind, first how HPV gets there and second why patients with HPV association will have better survival. In response to question 1, haematogenous spread from genital tract is proposed besides atypical sexual habits. In response to question 2 one possible explanation is that HPV infection may lead to genome instability, paradoxically making tumour cells more susceptible to radiotherapy.

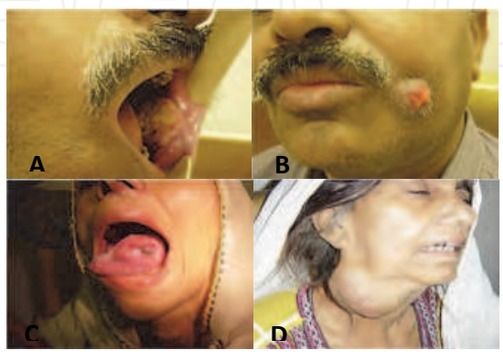

Fig. 1. Clinical presentations of patients with oral squamous cell carcinoma (OSCC) in Pakistani patients (Photographs were taken with patient's consent).

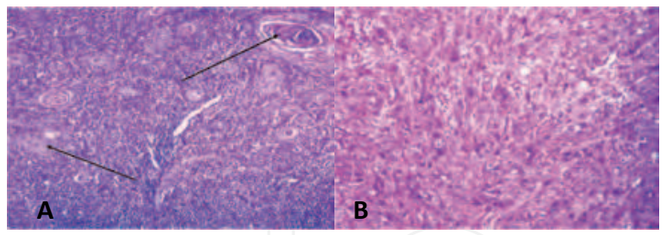

Fig. 2. Photomicrograph of H & E stained (A) well differentiated oral squamous cell carcinoma showing diffuse sheets of squamous cell with prominent keratinization and keratin pearl formations ↖ ↗, Magnification X 10. (B) poorly differentiated oral Squamous cell carcinoma, Magnification X 20.

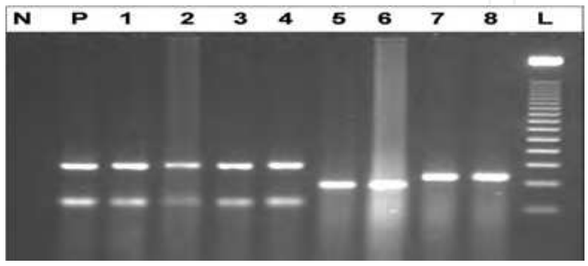

Fig. 3. PCR amplification of HPV general, HPV type 16 and HPV type 18 in OSCC samples. The products were electophoresed on 2% agarose gel and stained with ethidium bromide. Lane N: negative control, lane P: positive control, lanes 1-4 HPV (general primer) positive tumour samples, lanes 5-6 HPV 16 positive tumour samples, lanes 7-8 HPV 18 positive tumour samples, Lane L: molecular size marker (50-bp ladder marker).

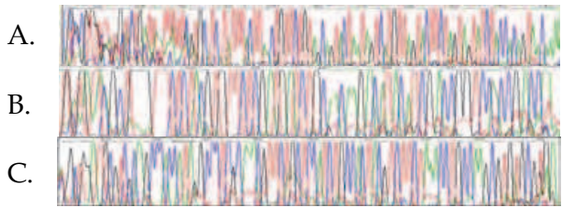

Fig. 4. Result of sequence analysis of PCR products, (A), Gene Sequencing HPV General. (B), Gene Sequencing HPV Type 16. (C), Gene Sequencing HPV Type 18.

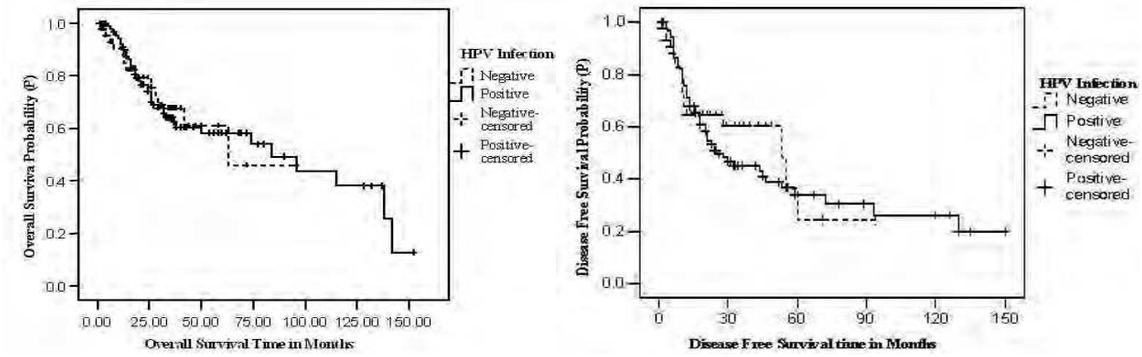

Fig. 5. Kaplan-Meier curves of overall survival (OS) of (A) human papillomavirus (HPV) positive patients as compared with HPV-negative patients. (B) Disease Free Survival of human papillomavirus (HPV) positive patients as compared with HPV-negative patients.

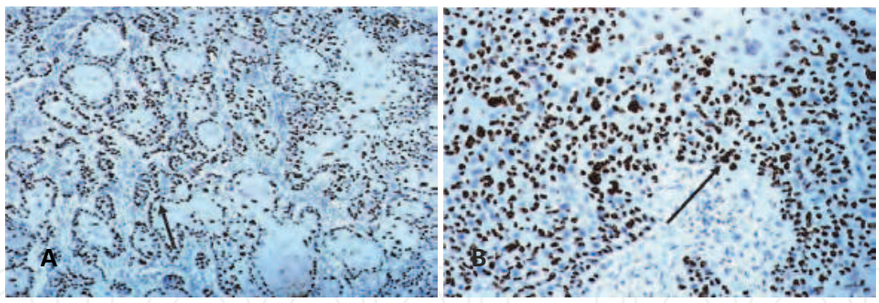

Fig. 6. Photomicrograph of a well-differentiated OSCC demonstrating diffuse strong nuclear TP53 staining. The arrows indicate positive dark brown intranuclear staining (magnification x 10 (A) & 20 (B)).

3.3 Conclusions

- Incidence of Oral Cancer in subcontinent (Pakistan, India & Bangladesh) is one of the highest in the world.
- Alternate chewing habits alongwith cigarette smoking are major risk factors in this part of the world.
- High risk HPV association was seen in 68% of the cases of OC in a high risk population of Karachi (Pakistan) with 90% containing HPV 16.
- Survival advantage was seen in OC patients with HPV association albeit not coming to statistical significance as seen in American whites.

4. Epstein-Barr virus (EBV)

EBV was initially discovered from cell cultures of a high grade B-cell lymphoma *'Endemic (African) Burkitt Lymphoma (BL)'*, which is highly prevalent in paraequatorial Africa and New Guinea. The disease affects children and adolescents and has strong association with malaria. Endemic BL commonly involves extra-nodal sites particularly jaw. In rest of the world *'sporadic form of BL'* is seen having a weaker association with EBV and commonly affecting gastro-intestinal tract (GIT) particularly small intestine.

EBV associated other lymphomas include 'classic Hodgkin lymphoma (cHL)' particularly 'mixed cellularity' type (~60%), 'B-cell lymphoma in immunosuppressed', 'mature T-cell lymphoproliferative disorders' in particular 'Angioimmunoblastic T-cell lymphoma (AILT)', 'Angiocentric (Nasal) T-cell lymphoma'. Non-lymphoid associations include 'Nasopharyngeal carcinoma'.

4.1 EBV & mature T-cell non-Hodgkin lymphoma (T-NHL)

EBV association with certain subsets of T-NHL is now well established. In a study conducted by us in Pakistan (Noorali et al, 2003), mature T-NHL comprised 22.2% of total mature NHLs. These cases were characterised on the basis of morphology, immunohistochemistry and T-cell receptor (TCR) gene rearrangement studies. This study demonstrated frequent presence of EBV in mature T-NHL cases (55.4%) by *'PCR'* (Figure 7) and *'in-situ hybridization (ISH)'*. While analysing various subsets of mature T-NHL 'Peripheral T-cell lymphoma (PTCL) - unspecified' (n=88) showed 51.2% EBV positive cases. EBV can be differentiated according to size polymorphism depending on the number of

internal repeats in the Bam HI, E, K, N and Z regions. We also studied the extent of polymorphism in EBV genome by *'single stranded conformation polymorphism (SSCP)'* technique for '*Bam HI E, K, N and Z regions*'. Hypervariability in Bam HI, K and N regions was noticeably higher compared to *E or Z* regions. All in all no association was established between EBV variants differentiated on the basis sequence heterogeneity in *Bam HI, K, N, E and Z regions* in different subsets of T-NHL.

Mode of infection of T-cells by EBV is complex and poorly understood. Nazaruk et al, 1998 proposed that initially virus infects the B-cells and remains in the latent phase but under immunosuppressive conditions IL10 is secreted by EBV specific CD8+ T-cells activating B-cells. Subsequently reactivation of EBV lytic cycle occurs that may contribute to the development of EBV-associated T-cell lymphoproliferative disorders.

Fig. 7. Ethidium Bromide stained agarose gel showing PCR products of EBV-DNA amplified with primers specific for gp200 region.

4.2 EBV & angioimmunoblastic T-cell lymphoma (AILT)

AILT is an uncommon form of mature T-NHL characterised by systemic disease that occurs predominantly in middle-aged and elderly patients. The clinico-pathologic syndrome is characterised by fever, night sweats, weight loss, generalised lymphadenopathy, hepatomegaly and splenomegaly. Histologic examination of lymph nodes typically shows effacement of lymph nodes architecture, a polymorphous infiltrate including immunoblasts, lymphocytes, plasma cells, eosinophils, epithelioid histiocytes and a prominent arborizing postcapillary vasculature (Figure 8). In a study conducted by us a total of 13 well characterised cases of AILT based on morphology, IHC and TcR gene rearrangement studies were analysed for EBV by PCR and ISH (EBER). Association of EBV was seen in 11 out of 13 cases (84.6%) by PCR. By ISH (EBER), EBV was detected in 8 out of 9 cases (88.8%) cases. (Figure 8) So all in all strongest correlation of EBV was seen in this type of T-NHL. (Noorali et al, 2005).

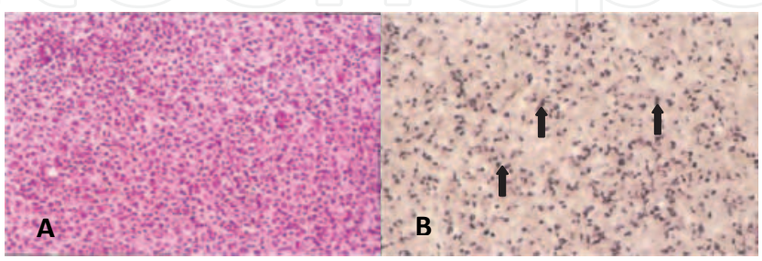

Fig. 8. I*n situ hybridization* photomicrograph of a lymph node showing the localisation of EBV in the nuclei of neoplastic lymphocytes indicated by blackish signal (↑) (B), H& E of the same (A).

4.3 EBV & Mycosis fungoides (MF)

MF is an indolent T-cell lymphoma of skin. In a study conducted by us a total of 14 well characterised cases of MF were analysed for EBV by PCR and ISH (EBER). EBV was identified in 3 out of 6 cases (50%) by PCR but all these were negative on ISH (EBER). This discrepancy is most likely caused by low copy number of infected cells in tissue sections not amplified as in PCR based studies (Noorali et al, 2002).

4.4 EBV & anaplastic large cell lymphoma (ALCL)

ALCL is a peculiar type of T-NHL. In a recent study by us (Syed et al, 2011) ALCL was turned out to be the most common T-NHL in the archives of the largest referral centre of Pakistan. This variant of T-NHL however has the weakest association with EBV (Noorali et al 2004).

5. HTLV-1 & T-NHL

HTLV1 is a RNA oncogenic virus which is associated with *'adult T-cell leukemia /lymphoma'* and is endemic in southern Japan and Caribbean basin. Like HIV which causes AIDS, HTLV1 also shows tropism for CD4+ T cells, hence this subset is the main victim for neoplastic transformation. In our local studies HTLV1 association was absent in mature T-lymphoproliferative disorders. This is in line with relatively low burden of HIV-AIDS in Pakistan so far (Noorali et al, 2004). (Figure 9)

Fig. 9. Agarose gel showing samples of mature T-NHL negative for HTLV-1 DNA by PCR.

6. Role of EBV detection by PCR, ISH & IHC in diagnostic pathology

The ability to amplify specific regions of DNA from paraffin-embedded tissue by PCR has a profound impact on diagnostic pathology. For routine histopathological diagnosis of various lymphoproliferative disorders EBV-ISH (EBV-encoded nuclear RNA -1(EBER-1) and IHC by using an antibody to 'Latent Membrane Protein-1 (LMP-1) are frequently used in diagnostic dilemmas. For instance in the differential diagnosis of cHL and ALCL, EBER or LMP-1 positivity in neoplastic cells will strongly favour cHL as EBV association with ALCL is very *weak*. (Figure 10)

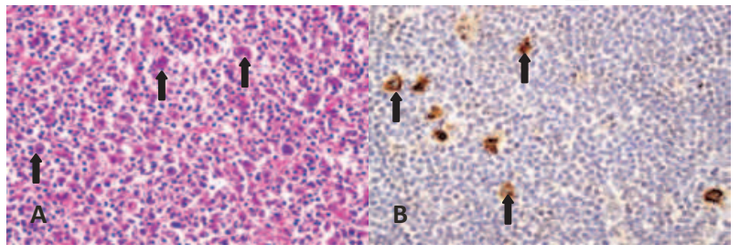

Fig. 10. Photomicrograph of a case of Hodgkin lymphoma (mixed cellularity, H&E, A ↑) stained with an antibody to LMP-1, note cytoplasmic staining of large Hodgkin cells (↑ B).

6.1 Conclusions

- EBV association with '*classic Hodgkin lymphoma*' is well established and is strongest with *'mixed cellularity variant'*
- Endemic (African) *'Burkitt lymphoma (BL)'* involving jaw is strongly associated with EBV while association with *'sporadic BL'* is relatively weak.
- EBV association with mature T-NHL is variable
- Strongest association of EBV is seen in AILT subtype while weakest association with ALCL subtypes.
- EBV immunohistochemistry using an antibody for LMP-1 and *'in situ hybridization (EBER)'* are commonly used in routine diagnostic pathology
- HTLV-1 association with 'adult T-cell leukemia/lymphoma' endemic in Japan & Caribbean is insignificant in our experience in Pakistan.

7. EBV & nasopharyngeal carcinoma

Nasopharyngeal carcinomas are particularly common in some parts of Africa and southern China. In former they constitute most frequent childhood cancer while in the later adults are mostly affected. Association of EBV with nasopharyngeal carcinoma is well established. In fact this association is literally 100%. EBV associated protein LMP-1 is expressed in most cases. (Figure 11)

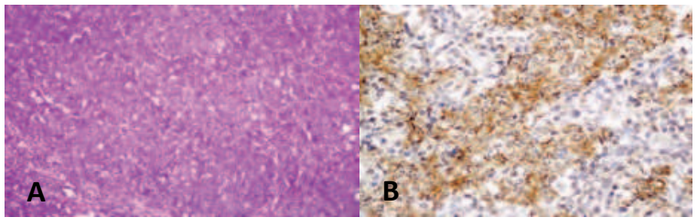

Fig. 11. Photomicrograph of a case of Nasopharyngeal carcinoma (H& E, A) stained with an antibody to LMP-1 (B), note cytoplasmic staining of neoplastic cells.

7.1 Conclusions

- EBV association in *'nasopharyngeal carcinoma'* is literally 100%

8. HHV8 & Kaposi sarcoma

Relatively recently in 1994 *'Human Herpesvirus-8 (HHV-8)* was identified in an AIDS patient with cutaneous *'Kaposi sarcoma (KS)'*. Later it was found that over 95% KS are associated with HHV-8. This virus is largely transmitted sexually. An antibody against HHV-8 shows positive reactivity in about 100% of cases and is a useful tool to confirm the diagnosis. Although *'Kaposi sarcoma'* is uncommon in our practice in Pakistan, it is highly prevalent in developing world with high AIDS incidence. (Figure 12) Four forms are recognized based primarily on population demographics and risk factors. These include a) *'Chronic KS'*, also called European KS b) *'Lymphoadenopathic KS'* also called African or endemic KS c) *'Transplant associated KS'* and d) *'AIDs-associated KS'*.

8.1 Conclusions

- HHV-8 association with KS is near 100%

- KS incidence in countries like Pakistan with relatively low burden of HIV carriers & AIDS is very low

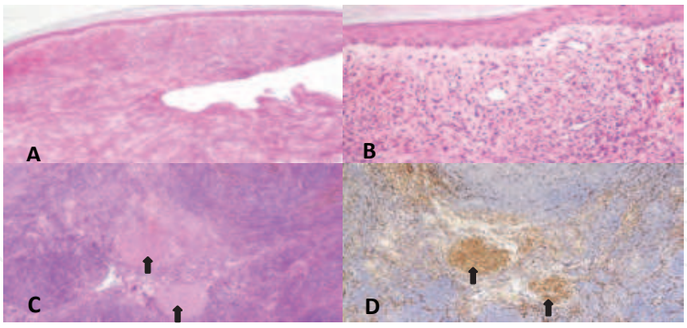

Fig. 12. Photomicrograph of Kaposi sarcoma resected from skin (H&E, A & B). Figure C shows lymph node metastases of the same (↑) highlighted on immunohistochemistry with CD31 (↑D).

9. *Helicobacter pylori* & gastric MALT lymphoma

'MALT lymphomas' were first described in 1983 by Peter Isaacson and Dennis Wright. They noted that primary low grade gastric B cell lymphomas recapitulate the histology of *'Mucosa Associated Lymphoid Tissue (MALT)'* exemplified by the Peyer patches and coined the term *'MALT lymphoma'*. These lymphomas are currently recognized as '*Extranodal marginal zone B cell lymphomas of MALT type'* according to the *'WHO Classification for Tumours of Haematopoietic and Lymphoid Tissues'* (Issaacson et al, 2008) (Figure 13). The stomach is the most reported and best studied site of *'MALT Lymphomas'*. An intimate relationship has been reported between the presence of '*Helicobacter pylori (HP)'* in the stomach and the development of '*MALT Lymphoma'* (Figure 13). In fact the pathogenesis of gastric '*MALT Lymphoma'* is believed to be caused by repeated antigenic stimulation of the immune system in the stomach by HP. The role of HP in the pathogenesis of *'gastric MALTomas'* can be illustrated by the fact that 75% of the patients who have gastric MALToma undergo remission if treated with antibiotics to eradicate HP (Ono et al, 2008). About half the people in the world have HP colonized in their gastrointestinal tract. Of these most remain asymptomatic. Despite the fact that, a high prevalence of HP is reported from Pakistan (Pervez et al, 2011), the prevalence of *'gastric MALTomas'* is very low in our experience. Seroprevalence of HP infection in the Pakistani population has been reported as high as 58%. This correlates with the *'Asian enigma'* described by various authors where less developed Asian countries like Pakistan, India, Bangladesh and Thailand have lower rates of gastric carcinoma compared to well developed countries like Japan and China, despite a higher prevalence of HP infection in the population. HP has been established to have a role in the aetiology of gastric carcinoma and its paradoxical high prevalence in areas with few cases of gastric carcinoma has long puzzled researchers. Available evidences do not support difference in HP strains as the sole explanation for this enigma.

9.1 Conclusions

- Helicobacter Pylori (HP) association with gastric adenocarcinoma & MALT lymphoma is well established.

- In Pakistan though prevalence of HP is very high, associated gastric adenocarcinoma & MALT lymphoma is low.

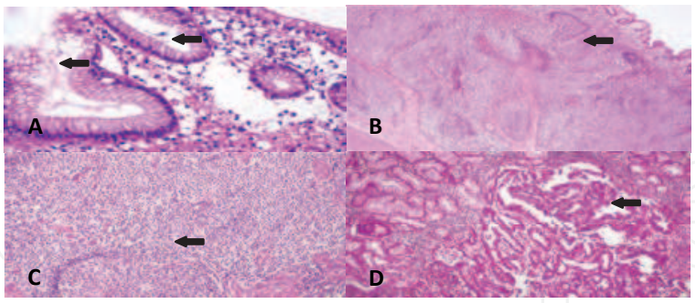

Fig. 13. Photomicrograph of gastric biopsy showing abundant '*Helicobacter pylori*' organisms on epithelial surface (←A), Figure B & C shows gastric MALT lymphoma arising from the marginal zone of lymphoid follicle ←. Figure D shows well differentiated adenocarcinoma of stomach (intestinal type ←).

10. Immunoproliferative small intestinal disease (IPSID) & *Campylobacter jejuni*

Immunoproliferative small intestinal disease (IPSID) is a special variant of, *'Extranodal marginal zone B cell lymphoma'*, which affects the small intestine. In early to mid 1960s it was referred to as *'Mediterranean lymphomas'*, during late 1960s the term *'a-heavy chain disease'* was also used for patients with similar clinico-pathological presentations. Later it was realized that both *'Mediterranean lymphomas'* and *'a-heavy chain disease'* represented a spectrum of the same disease which presents in different stages i.e., benign, intermediate and overtly malignant (stage A, B & C) and the disease was named IPSID (Fine & Stone 2000). IPSID is predominantly found in patients of *'Mediterranean origin'*; however a few cases of IPSID are also diagnosed in the subcontinent (Pervez et al, 2011). IPSID involves the production of truncated alpha heavy chains which may appear in the serum and other body fluids. It can be treated with broad spectrum antibiotics at its early stages.

It is postulated that IPSID occurs in patients with repeated intestinal infections. Recent studies suggest association with *Campylobacter jejuni* (Lecuit et al, 2004). It is postulated that this results in continuous chronic antigenic stimulation of IgA secreting lymphoid tissue common in small intestine with a resultant clonal proliferation of IgA secreting lymphoid cells. Subsequently most cases lose the ability to synthesize light chain. In early stages it may be very difficult to differentiate IPSID, from chronic inflammatory process by the reporting pathologists. In such circumstances it may be impossible to diagnose without the help of clonal studies for IgH chain gene rearrangement (Figure 14). The other close mimicry includes '*Coeliac disease*' as both IPSID and '*Coeliac disease*' are characterised by lympho-plasmacytic infiltrate and villous atrophy. In these cases demographics are important; also gluten free diet will lead to improvement of '*Coeliac disease*' cases. Intra-intraepithelial lymphocytosis with surface epithelial damage shall also favour Coeliac disease. As some cases of IPSID particularly if untreated may transform into aggressive lymphomas like '*Diffuse large B-cell lymphoma*' *(DLBCL)*, recognition of subtle features and follow-up is of paramount importance, particularly in endemic regions.

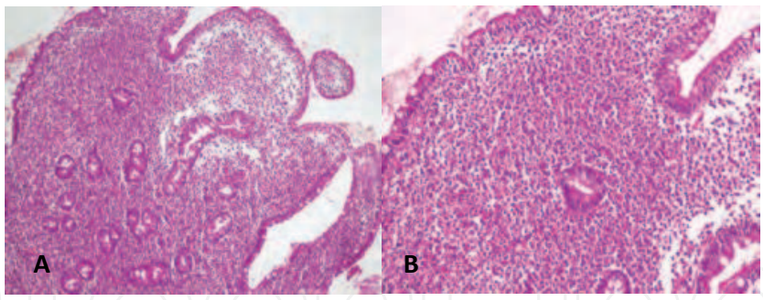

Fig. 14. Photomicrograph of duodenal biopsy from an IPSID patient diagnosed at stage A. Note flattening of mucosa with loss of villous architecture. Lamina propria shows diffuse sheets of plasma cells (H&E A & B).

10.1 Conclusions

- IPSID is a special variant of *'Extranodal marginal zone B-cell lymhoma'* predominantly found in Mediterranean region with sporadic cases in sub-continent.
- Recent studies suggest association with *'Compylobacter jejuni'*.
- In early stages treatment with broad spectrum antibiotics like tetracycline is curative.

11. Hepatitis B virus (HBV), Hepatitis C virus (HCV) & Hepatocellular carcinoma (HCC)

Developing countries bear major burden of 'Hepatitis B & C' for the obvious reasons i.e., insufficient or no screening of transfused blood, multiple use of contaminated needles, drug abuse and overall poor safety standards (Jafri et al, 2006). Pakistan for instance carries a very high burden of hepatitis B & C. There are estimated 7-9 million carriers of hepatitis B with a carrier rate of 3-5% (Ali et al, 2011). Genotype D (63.71%) is the most prevalent genotype in Pakistani population (Ali et al, 2011). The overall anti-HCV prevalence rate is 14-15% in general population of Pakistan (Idrees et al, 2009). Though hepatitis C is a major culprit for the reasons including increased potential to cause '*chronic liver disease*' and '*no vaccination*'; hepatitis B is still highly prevalent as well. A large proportion of population is still not vaccinated for hepatitis B, though now it is included in EPI (Extended Program of Immunization) program by the government and all newborns do get it.

In a recent study from Pakistan out of 161 subjects with HCC, chronic HCV infection was identified as a major risk factor (63.44% of tested HCC patients) for the development of HCC (Idrees et a, 2009). The time from HCV infection to the clinical appearance of cancer ranged from 10-50 years. In this population with HCC among various genotypes of HCV, genotype 3a was predominant (40.96%), followed by 3b in 15.66%, 1a in 9.63% and 1b in 2.40%.

On the face of such a high burden of Hepatitis B & C, hepatocellular carcinoma (HCC) is one of the common malignancies in our practice arising in a background of liver cirrhosis (Figure 15). Besides several other environmental factors are also playing their role in the causation of HCC. In Karachi, a port city of about 15 million inhabitants with hot and humid climate, it is reported that in wholesale markets selling food commodities without proper packing and preservation, a very high content of *'aspergillus flavus'* is isolated which is a known cause of HCC. Unfortunately HCC is a bad cancer and in our experience life expectancy at the time of diagnosis is not more than six months.

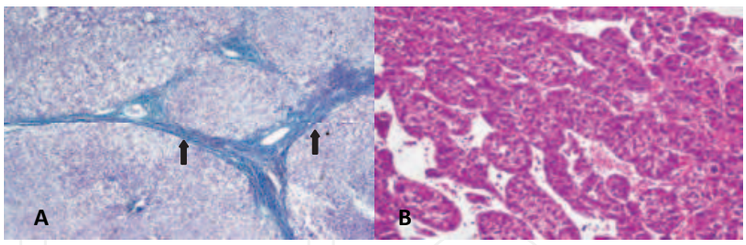

Fig. 15. Photomicrograph of a liver biopsy in a patient infected with Hepatitis C. Note fibrous band dividing the liver parenchyma into varying size nodules (↑A, Trichrome). Figure B shows a well differentiated hepatocellular carcinoma (HCC) arising in this patient (H&E).

11.1 Conclusions

- Hepatitis B & C are highly prevalent in the developing countries like Pakistan
- In Pakistan Hepatitis B carrier rate is 3-5% while anti-HCV prevalence rate is up to 15%.
- HCC is s common cancer in Pakistan mostly arising in a background of liver cirrhosis secondary to Hepatitis B & C.
- Over 60% of HCC are associated with HCV in Pakistan.

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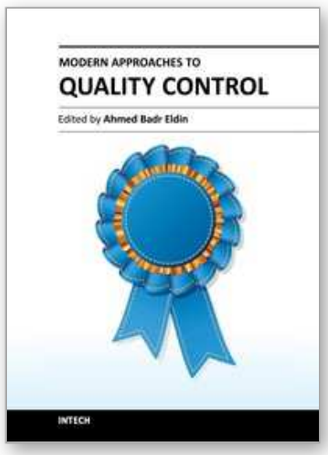

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