

ESTIMATING DISEASE BURDEN ASSOCIATED WITH ONCOGENIC VIRUSES

Kanwal Baloch¹, Ameer Afzal Memon², Ikram Din Ujjan³, Furqan Ahmed Bhatti⁴

¹⁻⁴ Department of Pathology, Liaquat University of Medical and Health Sciences, Jamshoro, Sindh-Pakistan.

Address for Correspondence:

Dr. Kanwal Baloch

Assistant Professor,
Department of Pathology,
Liaquat University of Medical
and Health Sciences, Jamshoro,
Sindh-Pakistan.
Email: kanwal.baloch@lumhs.
edu.pk

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ABSTRACT

Objective: To determine the frequency of different pathological conditions associated with oncogenic viruses and estimate overall disease burden in our patient population.

Methodology: A retrospective study was conducted from August 2013 till December 2013 at the Department of Pathology, Liaquat University of Medical and Health Sciences, Jamshoro. Biopsy samples received at the Department of Pathology were histologically assessed by H&E staining and reported. Patients diagnosed with tumor virus-related conditions, both inflammatory and malignant, were included in this study. Patient's age, gender and presenting complaints were also noted.

Results: A total of 2723 patients attended the Diagnostic Research Laboratory during this period. Of these, 174 patients presented with cervical lesions such as chronic cervicitis (159 cases), cervical polyp (09 cases) and squamous cell carcinoma of cervix (06 cases). Chronic hepatitis was diagnosed in majority of liver samples (43 out of 45) while remaining 2 were labeled as hepatocellular carcinoma. There were 07 patients diagnosed with Hodgkin's lymphoma while 02 had nasopharyngeal carcinoma.

Conclusion: The current data on variety of conditions especially cervical lesions suggest a high frequency of oncogenic viruses associated diseases in our population.

Key words: Oncogenic viruses, Cervical cancer, Hepatocellular carcinoma

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INTRODUCTION

Viruses are group of microorganism which cause a number of human illnesses ranging from a mild sore throat and flu to a life threatening condition like Acquired immunodeficiency syndrome (AIDS). Since the introduction of Avian Rous sarcoma virus as an oncogenic agent, several other viruses have been implicated in malignant transformation¹. Oncogenic human viruses pose a significant health burden and are responsible for approximately 10.8% of human malignancies worldwide². Human tumor viruses carry oncogenes which when incorporated into host cell are usually responsible for transformation of target cells by expression of oncoproteins and alteration in cellular machinery³. International Agency for Research on Cancer (IARC) has classified seven human viruses as Group 1 human carcinogens⁴. These include Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma herpes virus (KSHV), human immunodeficiency virus, type-1 (HIV-1), human T cell lymphotropic virus, type-1 (HTLV-1), and human papilloma virus (HPV).

HPV is a non enveloped DNA virus belonging to Papillomaviridae family⁵. There are around 170 different HPV types that infect the mucosa of genitals, upper respiratory tract and skin⁶. Among 18 high risk HPV types worldwide, HPV types 16 and 18 are most common and highly oncogenic and are associated with the development of carcinoma cervix, whereas types 6 and 11 are associated with benign conditions such as papilloma or warts⁷.

Both HBV and HCV viruses have been associated with the development of chronic hepatitis, cirrhosis and hepatocellular carcinoma which is the 5th most common cancer among males and 7th among females globally⁸. The exact mode of oncogenesis is not known but is related to controlling cell cycle progression, cellular migration and proliferation, and most importantly evasion from apoptosis and host immune system⁹. Worldwide, around 350 million people are chronically infected with HBV¹⁰. It is a double stranded circular DNA virus with approximately 10 genotypes designated A to J based on its genetic variability¹¹. HCV infects about 130 to 170 million people worldwide¹². It is a single stranded linear

RNA virus with high genomic variability. It has 6 main genotypes and several subtypes. Genotype 1, 2, and 3 are most prevalent worldwide, and genotype 3a is most common in Pakistan¹³.

EBV is a DNA enveloped virus belonging to Herpes virus family. It causes several conditions such as infectious mononucleosis, nasopharyngeal carcinoma, Burkitt's Lymphoma and Hodgkin's disease. EBV is most common gamma herpes virus associated with the development of lymphoid as well as non lymphoid tumors in adults worldwide¹⁴. Kaposi sarcoma (KS) is a multifocal systemic disease which is caused by KSHV 8 in association with HIV infection¹⁵. HTLV-1 is a delta retrovirus which after the clinical latency of several decades leads to development of adult T cell leukemia/lymphoma¹⁶. In Pakistan, epidemiological data is insufficient to indicate exact burden of diseases associated with tumor viruses. To overcome this, we aimed to determine disease frequency associated with major tumor viruses in our population. Knowing exact disease status will in turn help healthcare professionals in establishing effective treatment and diagnostic guidelines and undertake preventive measures.

METHODOLOGY

We performed a descriptive study at Department of Pathology, Liaquat University of Medical and Health Sciences, Jamshoro. This study was ethically approved and retrospective analysis of histopathological data was performed from August 2013 till December 2013. Biopsy samples received at the Diagnostic Research Laboratory, Department of Pathology were histologically assessed by Hematoxyline and Eosin (H&E) staining and findings were reported. Briefly, biopsy samples were fixed in 10% formaldehyde, processed in an automatic tissue processor for 17 hours before being embedded

in paraffin wax. Sections of 3-4 micron thickness were obtained on rotatory microtome and stained by H&E for microscopic analysis. Special stains like PAS and Giemsa's stains were used in selected cases. For cervical lesions, PAP smear was done. Patients diagnosed with a condition associated with IARC Group 1 carcinogen virus, both inflammatory and malignant, were included in this study. Demographic data including patient's age and gender, and presenting complaints as well as site of biopsy were also noted. All information was recorded on a pre-designed structured proforma. Descriptive statistical analysis (frequency, percentage, ratio, range and mean/SD) was employed for variables of interest. Data storage, processing and analysis was done utilizing SPSS version 21.0. Data was presented in the form of graphs and tables.

RESULTS

During study period, a total of 2723 patients' biopsy samples were received at the Diagnostic and Research Laboratory, LUMHS Jamshoro. Majority of these patients were females with a male to female ratio of 1:4.8 as shown in figure 1. Overall, the mean age of presentation was 42 years with age range of 18-70 years for females and 07-70 years for males. Interestingly, males presented at a younger age when compared to females as given in table 1. Evaluation of these lesions showed that a large number of biopsy samples had lesions diagnosed with Group 1 oncogenic virus family related diseases (Table 2).

Histological assessment of biopsy samples showed that there were total of 202 inflammatory cases where as 26 samples were diagnosed as benign and malignant tumors (Figure 2). In a total of 174 patients presented, cervical lesions (associated with HPV) were diagnosed

Figure 1: Gender distribution of all cases

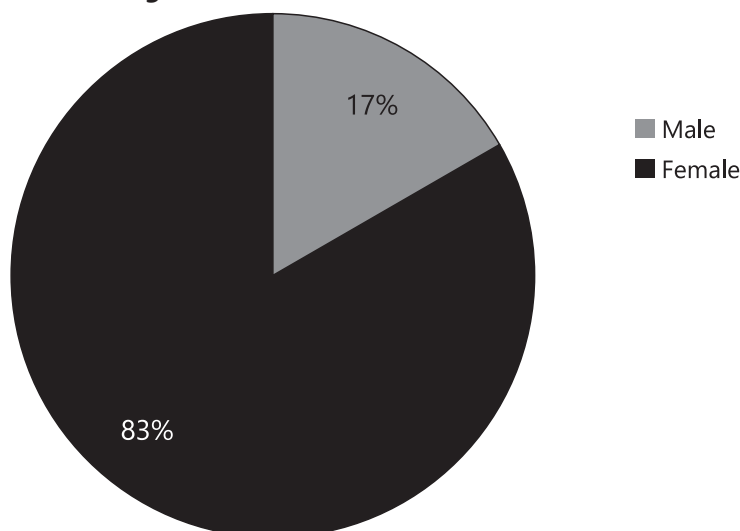
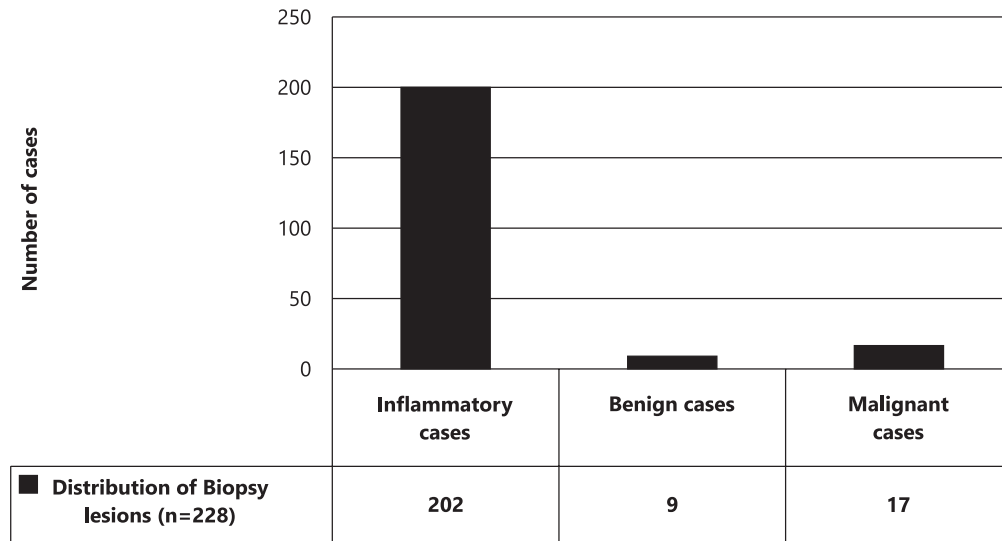


Figure 2: Distribution of benign, malignant or inflammatory lesions in biopsy samples**Table 1: Age of presentation and presences of benign, malignant or inflammatory lesion according to gender**

	Male	Female
Mean Age of presentation	36.28 ± 15.56 years	43.26 ± 9.59 years
Age range	07-70 years	18-70 years
Benign cases	00	09
Malignant cases	09	08
Inflammatory cases	30	172

Table 2: Frequency of various lesions associated with tumor viruses

Virus	Associated lesions	No of ccases
HPV (n=174)	Chronic Cervicitis	159
	Cervical Polyp	09
	Squamous Cell Carcinoma of Cervix	06
Viral Hepatitis (HCV and HBV) (n=45)	Chronic Hepatitis	43
	Hepatocellular Carcinoma	02
EBV (n=09)	Hodgkin's Lymphoma	07
	Nasopharyngeal Carcinoma	02

as chronic cervicitis, cervical polyp and squamous cell carcinoma of cervix. Chronic hepatitis (HBV and HCV) was diagnosed in majority of liver samples while only 02 were labeled as hepatocellular carcinoma. 07 patients had Hodgkin's lymphoma and 02 were diagnosed with nasopharyngeal carcinoma, both related to EBV infection (Table 2).

DISCUSSION

Viruses are a group of important human pathogens but are least considered in diagnosis of chronic conditions (benign, malignant or inflammatory). Limited knowledge regarding exact disease burden and inad-

equate screening methods predisposes our population to increased risk of developing chronic conditions associated with these pathogens.

Worldwide, cervical cancer is the fourth most common cause of cancer mortality in women of child bearing age and accounts for half of newly diagnosed cases¹⁷. HPV is thought to be a leading cause of both benign and malignant conditions of the cervix¹⁸. Chronic cervicitis significantly increases the risk of cervical dysplasia and cervical cancer. In this study, majority of cases diagnosed were females of reproductive age who mainly presented with cervical lesions. This indicates a

dire need to have effective screening method in place for HPV (preferably by a PAP smear) for women in high risk age group.

Chronic tissue inflammation induced by viruses is a major factor responsible for cellular damage and is thought to be a precursor of malignant change. Several viruses adapt this mechanism. This is particularly true for Hepatitis B and C virus where virus itself is not cytopathic. Chronic viral hepatitis progresses to liver fibrosis and hepatocellular carcinoma¹⁹. Data presented in this study showed that majority of the cases were diagnosed as having chronic inflammation (n=202) while remaining 09 were benign and 17 were malignant cases. Since hepatic inflammation is a strong risk factor for development of HCV related cirrhosis and end stage liver disease, an early diagnosis of these cases will prevent life threatening complications and liver cancer.

Role of EBV in malignancy of head and neck is being established worldwide suggesting increasing need of establishing early diagnosis of these lesions by maxillo-facial surgeons and oral specialists²⁰. Reportedly, a high antibody titer against EBV is a well known risk factor for development of nasopharyngeal carcinoma²⁰. Similarly, 30-50% of Hodgkin's lymphoma cases in European countries are attributed to EBV infection. Prevalence of EBV infection is higher in developing countries due to poor socioeconomic conditions²¹. In our patient population, there were seven diagnosed cases of Hodgkin's Lymphoma and two cases of nasopharyngeal carcinoma, both associated with EBV infection. This reiterates importance of effective screening tools and diagnostic methods for EBV. More importantly, latent EBV infection which occurs at a young age needs to be detected early.

CONCLUSION

Our study examined the presence of various diseases which are strongly linked to a particular viral infection. We have shown that virus associated conditions are quiet frequent in our population suggesting need to be identified by an efficient screening strategy.

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CONTRIBUTORS

KB conceived the idea, planned the study, and drafted the manuscript. AZM did statistical analysis and manuscript writing. IDU wrote and revised the manuscript. FAB helped acquisition of data. All authors contributed significantly to the submitted manuscript.