Biologic Agents Of Oncogenic Importance

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INTRODUCTION

According to Stedmans medical dictionary, infection is the invasion of the body with organisms that have the potential to cause disease. Infections are very common in our environment principally because of the poor hygienic conditions occasioned by the poor socioeconomic situations of a third world country like ours.

The role of some infectious agents in the aetiology of neoplastic diseases has now been established. Several authors have reported that there is a putative association of some infectious agents with the development of human cancers. The Significant difference in the clinicopathological manifestations of some of the neoplastic conditions noted between Africans and Caucasians may be due to the heavy infection load of our patients. Research efforts in this direction will be worth while; the knowledge gained from such efforts will be beneficial to policy planners.

Viruses are the most widely studied of the oncogenic organisms: viruses such as hepatitis B and C, Epstein Barr virus (EBV), Human papilloma viruses and Human T-cell Leukaemia Virus type 1 (HTLV-1) are all well known aetiological factors in a wide variety of neoplastic conditions. Other groups of organisms have also been noted to cause cancer; bacteria such as Helicobacter pylori have been associated with gastric cancer and some form of gastric lymphomas. High prevalence of intrahepatic bile duct carcinoma in South-East Asia is linked to infestation with liver flukes: *Clonorchis sinensis* in Hong Kong and *Opisthorchis viverrini* in Thailand.

Schistosoma Sp. has been associated with bladder cancer and colorectal carcinoma.

Inflammation and Cancer

The infectious agents elicit specific inflammatory reaction. The link between inflammation and cancer was first suggested by Rudolf Virchow in 1863 when he noted the presence of leukocytes in neoplastic tissues. He hypothesized that, at sites of inflammation cancers are apt to develop. Okada et al have reported the conversion of human colonic adenoma cells to adenocarcinoma cells by foreign body-induced chronic inflammation in nude mice, thus indicating the contribution of chronic inflammation directly to tumour progression.

VIRAL AGENTS OF HUMAN CANCER.

A large number of DNA viruses and very few RNA viruses have been implicated in human neoplasia.

DNA VIRUSES

The DNA viruses implicated in human cancer are found predominantly in the hepadnavirus, herpesvirus, and papovavirus families[6].

Epstein Barr virus (EBV)

EBV is an herpesvirus which is a known aetiological factor in neoplastic disease conditions such as:-

(i) Endemic Burkitt Lymphoma; EBV genome had been found in over 90% of African (Endemic) Burkitt lymphoma and 100% of patients with Endemic Burkitt lymphoma have elevated antibody titres against the viral capsid antigen.

(ii) Undifferentiated Nasopharyngeal carcinoma (NPC)- EBV-DNA had been detected in cases of NPC seen in different part of the world.

(iii) Hodgkin's disease (HD),
EBV genomes and EBV- specific RNA transcripts had been identified in few subtypes of Hodgkin's disease. They are identifiable in Reed Sternberg (RS) cells in 40% of cases of Nodular sclerosing HD and about 70% of cases of Mixed cellulanty HD.

(iv) B cell lymphomas in immodeficient patients especially post transplant and patient with Acquired Immune Deficiency Syndrome.

(B) HHV 8 (Human Herpes Virus type 8)/Kaposi

Sarcoma Herpesvirus (KSHV) Also a member of herpes viridae. The virus had proven causative role in:
(i) AIDS associated Kaposi's sarcoma (KS) skin lesion. The genomic sequence of this virus had been detected in all Kaposi's sarcoma lesion (including those of HIV negative patients).
(ii) Body cavity based B-cell lymphomas /Primary Effusion Lymphoma.
The DNA of HHV-8 is also found in this rare lymphoma usually in HIV infected patients.
(iii) Castleman's disease which is a lympho proliferative disorder.
(C) Human Papilloma Virus (HPV) a member of papovavirus family. The virus had proven causative role in these important human malignances.
(i) Squamous cell carcinoma of cervix and anogenital region.
The DNA sequence of the 'high-risk HPV especially type 16 an 18 and less commonly types 31, 33, 35, 45 and 51 had been detected in over 90% of invasive squamous cervical cancers and their precursors (the cervical dysplasia and carcinoma in-situ) with HPV 16 accounting for over half of the cases followed by 18, 45 and 31.
Also, some types especially type 6 and 11 (low risk types) are associated with genital warts with low malignant potential.
(ii) Oral and laryngeal cancers There has been linkage of the virus to causation of oral and laryngeal tumors.
(iii) Skin cancers in patients with epidermodysplasia verruciformis
(D) SV 40 (Simian virus 40)
This virus has been associated with brain tumors; osteosarcomas and mesotheliomas.
(E) Hepatitis B virus this is a member of hepadnavirus family. Chronic infection with this virus is associated with high risk of hepatocellular carcinoma and the epidemiological evidences are compelling. It causes chronic liver cell damage with accompany regenerative hyperplasia, thus expanding the pool of cells at risk for subsequent genetic changes.

RNA viruses and associated cancers:
All the known RNA containing tumor viruses are classified as retroviruses, with the exception of HCV which resembles a flavivirus
(A) HTLV-1:- This is the only currently accepted human tumor viruses from the retrovirus family (except for HIV which predisposes to cancer directly by damaging the host immune system. The virus has been associated with induction of Adult T-cell leukaemia which is a form of T-cell leukaemia/lymphoma endemic in certain parts of Japan and the Caribbean basin and also found sporadically elsewhere.
(B) Hepatitis C virus {HCV}:This is a flavivirus which had been strongly linked to the pathogenesis of primary liver cell cancer. The epidemiological evidences are compelling. Prolonged chronic infection (compare HBV) is mandatory for eventual formation of hepatoma. In regions of the world where regular screening of blood for HBV is the rule, infection with HCV and subsequent hepatoma represented the commonest cause of hepatoma.

BACTERIA AGENTS OF CANCER
(A) Helicobacter pylori: this is a micro aerophilic gram negative bacterium that is transmitted by feco-oral route. There is much evidence linking the gastric infection of the organism with gastric carcinomas and gastric lymphomas (the link is particularly strong in gastric lymphomas).
The lymphomas arise usually in mucosa associated lymphoid tissues (MALT) thus, they are called MALTomas. Chronic infection by the organism leads to proliferation by B cells. Continuous proliferation leads to acquisition of genetic mutation such as t(11:18) translocation this leads to an uncontrolled growth by the lymphoid cells.
(B) Enteric Bacteria: There is increasing evidence supporting the role of bacterial inflammation in the pathogenesis of Colorectal Carcinoma, with evidence indicating that commensal colonic bacteria are important in influencing this process'. The role of the colonic microbial flora in the development of Colorectal Carcinoma is a multifactorial one that can affect the various stages of the neoplastic process. It may be that induction of mucosal inflammation, production of mutagens and reactive metabolites and alterations in carbohydrate expression are all processes that act in concert to set the colonic mucosa on the first step of the adenoma - carcinoma sequence.[133]

PARASITIC AGENTS OF CANCER

Schistosoma specie *S. haematobium* is a fluke (trematode) acquired by skin penetration of a developmental form (carcaria) from a contaminated water. It is associated with bladder carcinoma usually following a chronic infection over a long period. The eggs are deposited in bladder wall where they incite chronic inflammatory response which induces progressive mucosa squamous metaplasia and dysplasia and subsequent cancer. 70% of the malignancy induced is squamous cell carcinoma, while the transitional cell carcinoma of the bladder is 30%. Schistosoma-associated bladder cancer occurs in

younger age group compare to non-schistosoma bladder cancer.

The possible relationship between colorectal carcinoma and schistosomiasis was suggested by several studies. Helmstadter et al pointed out that chronic intestinal Schistosomiasis is a potentially precancerous condition. Investigators believe that the mechanism of schistosomal injury is due to endogenous production of toxins by the ova rather than a direct carcinogenic action of the ova. However, Matsuda et al believe that schistosomal ova have some direct carcinogenic effect.

The ova of all the different schistosomal species have been found to be associated with colorectal cancer. However, in the majority of the cases *Schistosoma japonicum* was the culprit, followed by *S. mansoni* and *S. haematobium.* The risk of cancer development in schistosomiasis is related to the site of involvement. It has been estimated that the relative risk of cancer development in rectal schistosomiasis is 8.3, while it is not significantly increased in colonic schistosomiasis (1.20).

(C) *Opistorchis viverrini* and *clonorchis sinensis* are bile duct flukes acquired by ingestion of developmental stage (metacercaria). They are putatively associated with biliary tract carcinoma following prolonged chronic infection. The epidemiological link for the causative roles of these parasites in cancer is highly compelling. It is thought that they induce chronic inflammation in bileduct epithelium with epithelial hyperplasia and formation of glands lined with columnar epithelial cells beneath epithelial lining and in severe cases adenocarcinomatous hyperplasia, periductal fibrosis and goblet cell metaplasia.

MECHANISM OF ONCOGENESIS FROM INFECTION.

These organisms are usually not complete carcinogens but they play different roles in carcinogenesis. Variable cofactors are involved and the organisms may be initiating or promoting factor in the multistep process of carcinogenesis. Cervical cancer and liver cancer which contribute significantly to the world-wide cancer burden have viral infections as of proven aetiological role. Virtually all infections implicated in carcinogenesis require prolonged duration of infection in form of chronic infection or long termpersistence before eventually resulting in human cancer.

Viral carcinogeses represent the best studied. The transforming retroviruses usually carry cellular genes, (protoncogenes) they share the unusual characteristic of reverse transcription in their life cycle, soon after infection the viral RNA genome is transcribed by a virion associated enzyme, the reverse transcriptase into a double-stranded DNA copy which is then integrated into the chromosomal DNA of the cell with the help of the viral integrate enzyme. The integrated copy (provirus) is similar to a cellular gene (proto/oncogene) except that transcription is usually controlled by sequence in the viral long terminal repeat. These viral oncogenes have usually been mutated in some way during their acquisition from the cell and once incorporated into the viral genome, an oncogene is freed from normal cellular constraints and is expressed constitutively in transduced cells under the control of the viral long terminal repeat.

Also there is possibility of transducing retrovirus to infect a cell type that does not normally express the proto-oncogene and lacks controls to regulate it, this combination of events, over expression or inappropriate expression of a modified growth related gene, leads to malignant transformation of the target cells.

The DNA tumor viruses usually target Tumor Suppressor proteins {TSP}; their oncogenes are of viral, not cellular, origin. These viral oncoproteins binds to cellular TSP {P53 and pRb}. The TSP exert central power over cell growth control (inhibit cell growth), and the viral influence is to circumvent that control.

Retinoblastoma gene product pRb normally binds transcription factors E2F in early G1 in the cell cycle: when Rb is phosphorylated by cyclin dependent kinases, E2F is released and functions to activate expression of growth stimulatory genes required for the cell to initiate DNA synthesis.

Wild type p53 is believed to guard the integrity of the cellular genome by inhibiting cell cycle progression or inducing apoptosis in response to aberrant proliferation signals, DNA damage or cellular stress. DNA oncogproteins abrogate p53 check on cell cycle progression. By abrogating the check effect of the TSP, initated cells are free to continue in cell cycle with eventual capacity for malignant transformation. Genetic alteration in p53 is the most common mutation in human cancers occurring in over 50% of tumors.

Oncogenes and TSG are a major focus of human cancer studies today:

Mechanism of oncogenesis in infection with hepatitis B and C, *Schistosoma haemotobium, opistorhis vIverrini, clornochis sinensis* and *Helicobacter pylori* is thought to require chronic infection with eventual metaplasia, dysplasia and subsequent malignant transformation. Little is documented about the molecular basis of the parasitic infections and oncogenesis.

PREVENTION, TREATMENT; CONTROL

(1) Antiviral Vaccines for cancer control.

Vaccines are the most effective preventive approach against viral infections, and vaccines against cancer viruses have the potential of reducing the global cancer rate. Both prophylactic and therapeutic vaccine strategies can be considered.

Prophylactic vaccines induce antibodies that are able to neutralize a virus before it infects a cell and establish an infection; therapeutic vaccines are designed to reduce or eradicate an existing infection or disease. The HBV vaccine has been used for >15 years to prevent transmission of virus to newborn and establishment of life long persistent infections.

Because of worldwide burden of HPVrelated diseases, Papilloma virus vaccines are under development. Therapeutic vaccines targeted against HPV oncoproteins E6 and E7 are under development.

Even if cofactors in addition to viral functions are necessary for tumour development, prevention of infection by the virus would greatly reduce the overall frequency of oncogenesis.

(2) Early detection of Helicobacter pylori associated gastritis, and gastric lymphoma and treatment with anti-*Helicobater pylori* regimen leads to commendable regression of tumor and resolution of gastritis.

(3) Prevention of parasitic infections bearing in mind the mode of transmission reduces the acquisition of most of these parasites which usually induce chronicity.

Also adequate treatment of these chronic parasitic infections once diagnosed will go a long way in reducing the global burden of cancers from treatable infections.

We can all work together to reduce the global burden of cancers which have origin or contributions from infections as infections are usually preventable, treatable and controllable. All we need to do is to get "AWARE" and 'ACTION ORIENTED'.

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