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Original Research Article

Etiological study of urinary bladder carcinoma in patients presenting to tertiary care centre

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ABSTRACT

Background: Urothelial carcinoma is the most common invasive cancer of the urinary tract. Lately, there has been an increased incidence of urothelial neoplasia due to exposure to a wide range of potentially carcinogenic substances. Studies of involved factors led to the concept of existence of a so-called malignization terrain, which claims that individual genetic predisposition and chronic exposure to carcinogens act synergistically leading to the appearance of urothelial carcinomas of the bladder. Aim of the research was to find out the common etiological factors of bladder cancer in this part of India.
Methods: The study included 100 patients of bladder carcinoma reporting to Sri Guru Ram Das Hospital, Amritsar from March 2018 to December 2019. A detailed history was taken to have the insight of various etiological factors of the disease. The data was entered in Microsoft excel spreadsheet and analysis was done using statistical package for social sciences (SPSS) version 21.0.
Results: The most common blood group associated with CA UB was A +ve (39%) followed by B +ve (29%). 89% of the cases of CA UB were non-smokers predominantly attributed to type of patients coming to our tertiary care institute which are from a rural background (73%) and are mostly Sikhs (80%) and Sikhs are traditionally non-smokers. 80% were farmers by occupation who have exposure to pesticides, insecticides, weedicides and herbicides routinely.
Conclusion: In our study majority of the patients turned out to be non-smokers and A +ve blood group in contrast to the strong predilection of smoking and bladder cancer.

Keywords: Carcinoma bladder, Etiology, Non-smoker

INTRODUCTION

Urothelial carcinoma of urinary bladder cancer is the fourth most common cancer in men and eighth most common malignancy in women in Western world.[1] In India, according to the recent reports of the National cancer registry programme, the overall incidence rate of the urinary bladder cancer is 2.25% (per 100,000 annually): 3.67% among males and 0.83% for females.[2] There are several risk factors connected to bladder carcinoma. The use of tobacco with its release of α-naphthalene and β-naphthalene into the urine is an important risk factor.[3] Another risk factor for development of bladder cancer is occupational exposure to aromatic amines (2-naphthylamine, 4-aminobiphenyl and benzidine) and 4,4'-methylenebis (2-chloroaniline), which can be found in the products of the chemical, dye and rubber industries as well as in hair dyes, paints, fungicides, cigarette smoke, plastics, metals and motor vehicle exhaust, drinking water contaminants and phenacetin-containing analgesics.[4] Among the various known risk factors, cigarette smoking is the most important and responsible for 48% cases of bladder cancer in men and 32% in female in USA.[5] Until now few of the studies conducted in western countries have concluded that incidence of NMIBC is highest in O blood group, but

similar studies in India have concluded that NMIBC is most common in B blood group.[6,7]

Bladder carcinoma represents a type of cancer which has many causes which are preventable and which vary in different parts of the world. It also presents with symptoms early on (hematuria) and if detected early on has a good prognosis. Many studies have been done on its etiology the world over which further show that different regions have a different etiological profile. So an etiological study at Sri Guru Ram Das institute of medical sciences and research, Amritsar was done to understand the disease etiology in our region with objective for early identification of high risk groups and also identifying remedial measures which would enable us to eradicate the preventable causes.

Aims and objective

To find out common causes of urinary bladder carcinoma in patients presenting to tertiary care centre in this part of world.

METHODS

This prospective comparative study was conducted at Department of Surgery of Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar on all newly diagnosed bladder cancer patients presenting from March 2018 to December 2019

Inclusion criteria

All patients with a diagnosis of bladder cancer presenting during the study period were included in the study.

Exclusion criteria

Patients unwilling or unable to give consent were excluded from the study.

Methodology

After obtaining ethical approval from the institutional ethics committee, all newly diagnosed patients with urinary bladder carcinoma from March 2018 to December 2019 were included for their etiological analysis.

Clinical details including history of hematuria, smoking, daily fluid intake, dietary history, symptoms of urinary tract infection (UTI), loss of weight/appetite, past medical history and blood tests including hemogram, renal function tests, liver function tests, imaging like ultrasonography of kidney, ureter, urinary bladder (USG KUB), contrast enhanced computed tomography of kidney, ureter, urinary bladder (CECT KUB) (if needed) and chest X-ray (CXR) was done in all the patients as per the standard protocol in the department of surgery. In addition, blood grouping of every patient was done and recorded.

All patients underwent treatment in the form of transurethral resection of bladder tumor as per the standard protocol in the department.

RESULTS

The mean age of presentation of carcinoma urinary bladder was 55.24 years. The male to female ratio was 5.66:1.

Table 1: Age distribution.

Age (years)	Number	Percentage
30-39	21	21.0
40-49	15	15.0
50-59	16	16.0
60-69	27	27.0
70-79	18	18.0
80-89	3	3.0
Total	100	100.0
Mean±SD	55.24±15.19	

As shown in the table, the mean age of presentation of carcinoma urinary bladder was 55.24 years (30-89 years) with the maximum number of patients being in the age group of 60-69 years followed by 30-39 years.

Table 2: Smoking history.

Smoker/non-smoker	Number	Percentage
Non-smoker	89	89.0
Smoker	11	11.0
Total	100	100.0

As shown in the table and figure 89% of the patients of carcinoma urinary bladder in our study were non-smokers.

Table 3: Distribution according to UTI history.

UTI history	Number	Percentage
Absent	73	73.0
Present	27	27.0
Total	100	100.0

As shown by the table, history of UTI was present in only 27% of the patients of carcinoma urinary bladder.

Table 4: Distribution according to blood group.

Blood group	Number	Percentage
A+	34	34.0
A-	2	2.0
AB+	7	7.0
B+	29	29.0
B-	2	2.0
O+	25	25.0
O-	1	1.0
Total	100	100.0

As shown by the table the maximum number of patients of carcinoma urinary bladder belonged to A+ blood group followed by B+ and the least number of patients belonged to O- blood group.

Table 5: Distribution according to occupation.

Occupation	Number	Percentage
Businessman (owner)	4	4.0
Farmer	59	59.0
Housewife	13	13.0
Labourer	15	15.0
Others	9	9.0
Total	100	100.0

As shown by the table, the maximum number of patients of carcinoma urinary bladder were farmers by occupation followed by labourers (mainly workers of dye, chemical, fertilizer industry and housewife in females' subset).

Table 6: Religion wise distribution.

Religion	Number	Percentage
Christian	2	2.0
Hindu	17	17.0
Muslim	1	1.0
Sikh	80	80.0
Total	100	100.0

As shown in the table the maximum number of patients of carcinoma urinary bladder were Sikhs followed by Hindus.

DISCUSSION

Bladder cancer is the ninth most common cancer in the world and one of the most common urological malignancies.[8] 100 patients with a primary diagnosis of carcinoma urinary bladder were included in our study. These included newly diagnosed cases as well as previously operated patients who were under follow up in the Department of Surgery, SGRDIMSR, Sri Amritsar. Etiological parameters of these patients were recorded and these patients were followed up for the duration of the study period. Median follow up of the patients included in the study was 18 months.

The median age of patients in our study was 55.24 years. The ratio of males to females is 5.66:1.

Cigarette smoking is the most important risk factor for bladder cancer on a population basis, additional factors play a role in modifying the risk posed by the smoking. History of tobacco smoking is present in 78.9% males and 25% females in the series. It depends on amount and duration as it is observed throughout the world.[9] There are populations with high smoking rates but low bladder cancer rates.[10] This suggests differences in the metabolism of smoking-related carcinogens. For example, individuals with N-acetyltransferase-2 slow acetylators as compared to rapid acetylators are known to have a higher risk of bladder cancer.[11] Exogenous agents (such as vitamins C and E intake) may modify the susceptibility to smoking induced bladder cancer as well. Familial bladder cancer is a fairly rare phenomenon compared with the familial occurrence of cancer in many other tumor sites. Numerous case reports describe familial clustering of urothelial carcinoma and early age of onset suggesting a genetic component.[12] Only a few epidemiologic studies specifically address familial bladder cancer, Goldgar et al.[13] We therefore tried to explore the relationship between blood group and TCC with familial background but it remains inconclusive due to small sample size for a familial type of TCC.

It has been estimated that occupational exposures may account for as much as 20% of all bladder cancer.[14] Exposure to α-naphthylamine, 4-aminobiphenyl (ABP), and benzidine, principally among workers in the textile dye and rubber industries are the only specific agents that have been unequivocally associated with bladder cancer.[15] In fact, many occupations have been marked as potentially high risk. The authors observed maximum number (50%) of bladder cancer among labourers and industry workers including employees of leather and textile factories, hair-dye handlers (barber) and shoe-makers. But the limited sample size does not give any significant epidemiological clue. Carcinogenesis in these cases thought to be a result of exposure to possible carcinogenic constituents of paints and solvents. The risk of bladder cancer among workers, especially in industries should therefore be monitored continuously. Though the present study did not find any occupational relationship since the subjects were not exposed to typical jobs. Study used data from the Agricultural Health Study, a prospective cohort study which includes 57,310 pesticide applicators with detailed information on pesticide use, to evaluate the association between pesticides and bladder cancer. Results found associations with bladder cancer risk for two imidazolinone herbicides, imazethapyr and imazaquin, which are aromatic amines. Ever use of imazaquin was associated with increased risk whereas the excess risk among users of imazethapyr was evident among never smokers. Study also observed increased risks overall and among never smokers for use of several chlorinated pesticides including chlorophenoxy herbicides and organochlorine insecticides. Several associations between specific pesticides and bladder cancer risk were observed, many of which were stronger among never smokers, suggesting that possible risk factors for bladder cancer may be more readily detectable in those unexposed to potent risk factors like tobacco smoke.[16]

A study was conducted by Sharma et al carried out in urinary bladder cancer (UBC) subjects and healthy control subjects with an aim to determine the role of GST and GSTT1 polymorphism and its implication on the organophosphate compounds (OPC) detoxification or bioaccumulation which may increase the risk of UBC in humans.[17] This study was also designed to identify the

"gene-environment interaction" specifically between gene polymorphism in xenobiotic metabolizing genetic enzyme (s) and blood OPC levels. The results demonstrated a significant increase in frequency of glutathione S-transferase GSTM1/GSTT1 (null) genotype in UBC cases without interfering the distribution of other GSTT1/GSTM1 genotypes. Findings indicate that "gene-environment interaction" may play a key role in increasing the risk for UBC in individuals who are genetically more susceptible due to presence of GSTM1/GSTT1 null deletion during their routine encounter with or exposure to OPCs.

A study in Costa Rica finds heavy pesticide use in rural counties is associated with an increased risk for bladder cancer in males (OR 1.71).[18]

People having non-vegetarian diet (3/4th of cases) and poor water intake (almost half of the cases) are the victims of TCC. This can be explained by their poor socio-economic status (82% of the study population) who cannot afford balanced diet lacking anti-oxidants like fruits and vegetables. High heavy metal level in water may be one of the risk factors which could be included in the study. Chronic UTI is associated with the development of bladder cancer, especially invasive squamous cell carcinoma.[19] We observed in 27% cases.

Genes for ABO blood group antigens are located on chromosome 9q34.[20] This area of chromosome 9 has been seen to be frequently affected by gene deletions in carcinoma urinary bladder. It has been seen that these deletions might lead to loss of ABO antigen expression in about 25% of the cases.[21] It has been hypothesized that loss of ABO antigen expression may cause resistance to immune mediated apoptosis, altered adhesion/aggregation. Moreover, single nucleotide polymorphisms of the ABO gene are associated with increased plasma levels of soluble ICAM-1 and TNF, leading to altered immune response and possibly cancer growth.

In the study by Chihara et al loss of heterozygosity of ABO gene or hypermethylation in the promoter region of the ABO gene showed significant reduction of A antigen expression in UBC, while the expression of the A antigen is maintained in concomitant dysplasia or normal urothelium, suggesting that loss of the ABO gene and/or its promoter hypermethylation is a specific marker for TCC.[22]

Most common blood group among patients with NMIBC in our study was A positive (34%). In a study by Biswas et al it was seen that urothelial cancer was most commonly seen in B blood group. However they did not comment on the statistical significance of that finding.[7]

The Rhesus factor gene is located on the short arm of chromosome 1, a region of tumor suppressor genes and the proto-oncogene L-Myc, which is down-regulated in UBC.[24] The Rhesus factor proteins are expressed on erythrocyte membranes as well as various epithelial tissues, facilitating the oxygenation of tissue and removal of deoxyribonucleic acid (DNA)-damaging agents.[25] Thus, the risk of development of various malignancies may be increased in Rhesus factor-negative patients, as shown in skin, esophageal, breast, lung and endometrial cancer.

Compared to the normal population, greater distribution in patients with NMIBC was seen in A positive, B positive, O positive and AB positive blood groups. No previous studies evaluating the role of RhD blood group in pathogenesis of bladder cancer are available. This observation of A positive blood group being significantly associated with bladder cancer, as seen in our study, warrants a further study at a molecular level.

CONCLUSION

The true natural history of bladder cancer is not yet fully known. Every effort has been made to explore epidemiological risk factors and for appropriate diagnosis. The study suggests that epidemiological survey should be incorporated in the evaluation of bladder cancer to formulate any disease control programme. However, large well designed prospective multicentre studies are needed to standardize the protocol.

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