RESEARCH COMMUNICATION

Primary Gastrointestinal Malignancies in Childhood and Adolescence - an Asian Perspective

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Abstract

Introduction: Primary gastrointestinal (GI) malignancies are a rarity in childhood and adolescence, with limited information from Asian populations. This study was conducted with the objective of identifying the existence of malignant GI tumors in the young population of Pakistan and to determine high risk geographical areas of the country. Methodology: Pediatric and adolescence (≤14 years; ≤19 years) gastrointestinal malignancies, ICD-10 categories C15-20 registered at the surgical pathology department of the Aga Khan University Hospital during 1st March 2004 to 30th April 2006 were included in the cross-sectional study. Results:Sixty cases in ≤19 year age group were studied. The mean age was 16.2 years (SD±4.56). Carcinoma comprised 47 cases (78.3%; 32 boys and 15 girls.) and lymphoma 13 cases (21.7%; 12 boys and 1 girl). All cases presented as advanced malignancies. Categorization of carcinoma by site was colon (85.1%), stomach (6.4%) and esophagus (8.5%). Lymphoid malignancies were diffuse large B-cell lymphoma (30.8%), Burkitt lymphoma (46.1%) and Burkitt-like lymphoma (23.1%). The mean age at presentation was 11.1 years (SD± 4.6). Conclusion: This study has identified a substantial number of GI malignancies in the ≤19 year Pakistani population, involvement of esophagus, male predominance, preponderance of carcinoma versus lymphoma and a high signet ring cell and mucinous colo-rectal carcinoma. It has identified Baluchistan as a high risk region for esophageal cancer and diffuse large B-cell lymphoma and NWFP for Burkitt and Burkitt-like lymphoma. Most findings in the present study did not concur with published western data, indicating the need to study cancer in the Asian population.

Key Words: Gastrointestinal malignancies - childhood - pediatric - adolescence - Karachi - Pakistan.

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Introduction

Primary gastrointestinal (GI) malignancies are rare in childhood (0-14 years) and adolescence (15-19 years) Dhams, 1992). Childhood malignant tumors are justifiably a frequent cause of concern to parents and physicians because they rank second only to trauma as a cause of mortality in children. The rarity of the disease, non-specific early symptoms and a variable clinical presentation often prevent an early diagnosis when possibility of surgical cures exist (Robison, 1997).

The reason for the rarity of GI neoplasm in the younger population is probably the dose and time dependent relationship of carcinogenesis to environmental and life-style risk factors, not prevalent in children e.g. alcohol and tobacco. A moderate intake of tobacco over a long period carries a higher risk than a high intake during a shorter period, whereas the reverse is true for alcohol (Carr et al., 1994).

Pakistan is a low to moderate resource country in Central Asia (30 00 N, 70 00 E). The population has a diverse ethnicity, the country being strategically situated between India on the east, Iran and Afghanistan on the west and north-west, and China in the north (World Factbook, 2007; World Health Report 2007).

The Aga Khan University Hospital (AKUH) is a tertiary care hospital located in Karachi, the southern-most city of Pakistan. The laboratory receives an average of over thirty five thousand surgical pathology cases per annum, approximately half from Karachi and the other half from various parts of Pakistan, the latter through 100 collection centers established in the country. Each of these centers cater to multiple hospitals, clinics and healthcare facilities in its immediate environment, thus providing a sample data, which has been of immense value in determining the geographical variation of malignancies in Pakistan.

The objective of this study is to identify the existence of malignant GI tumors in the young population of Pakistan, correlate the frequency with that reported in literature and to determine if possible the high risk geographical areas of the country.

Materials and Methods

Epidemiological data and pathology slides of all histologically verified incident GI malignancies, ICD-10 (International Classification of Diseases 10th Revision)

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categories C15-20, registered at the histopathology department of AKUH during 1st March 2004 to 30th April 2006 were reviewed. The selection criteria were topography and age. The topographic range included esophagus (ICD 10 category C15), stomach (ICD 10 category C16), small intestine (ICD 10 category C17), colon (ICD 10 category C18) and rectum (ICD 10 category C20). The age groups included were pediatric or childhood ages (0-14 years) and adolescence (15-19 years). The adolescent age group was selected as 15-19 though WHO indicates it as 10-19 years (http://www.un.org.in/Jinit/who.pdf) to make it comparable with cancer registry definitions.

Information regarding surgical pathology cases was extracted by the hospital 'Information System Department (ISD)'. The reported epidemiological cancer data were rechecked, and residency status re-ascertained. Cases were categorized by tumor site, age and sex of the patient. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, topography, morphology, grading and staging. The data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition). Manual and computerized validity check for the cancer data were performed to ensure reliability and to avoid duplication of the data.

The specimens as per laboratory routine were initially fixed overnight in 10% buffered formalin, grossed and adequate representative sections taken according to the standardized guidelines. All surgical specimens were initially evaluated on Hematoxylin and Eosin (H&E) stained sections. Special stains and immuno-histochemical stains were performed both for confirmation of diagnosis and typing of tumors. Special stains viz. Periodic Acid-Schiff (PAS) and Alcian Blue were carried out to demonstrate acidic mucin in cases of carcinoma. The panel of immuno-histochemical stains included Keratin CAM 5.2 (by Becton Dickinson) and LCA, PANB (CD20, CD79), CD 30, CD15, PAN T (UCHL), Ki -67 (by DAKO). The membranous positivity of all these antibodies was interpreted as positive. Nuclear positivity of Ki -67 was considered as positive. TNM staging was done for all specimens, Dukes Colin staging was additionally done for colonic carcinoma. Lymphomas were classified according to WHO/Real classification of lymphoid neoplasm.

The data were computerized and analyzed using SPSS version 15.0. Relative frequencies of different malignant gastrointestinal tumors, the mean ages and standard deviation, male- female ratios, tumor site, histological type, grade, clinical presentation and residential status of patients were evaluated.

Results

The current cross sectional study is based on the epidemiological, histopathological and immuno-histochemical review of pediatric and adolescence (≤14 years; ≤19 years) GI malignancies. The total number of surgical pathology cases received in the histopathology section during the study period was 65,000. Out of these, 2350 cases were GI malignancies inclusive of all ages. A total of 60 (2.5%) cases occurred in patients 0-19 years of age out of which 18 cases (0.76%) were from the pediatric age group. The mean age of patients (inclusive of all ages) was 16.2 years, standard deviation (SD) ± 4.56. The male to female ratio was 3:1 (table 1).

Carcinoma comprised 47 (78.3%) cases whereas lymphoma comprised 13 (21.7%) cases. The carcinoma: lymphoma ratio was 4:1. Categorization of carcinoma by site was colon (40 cases, 85.1%), stomach (3 cases, 6.4%) and esophagus (4 cases, 8.5%); 32 cases were diagnosed in boys and 15 in girls (table 2). The mean age at presentation was 17 years (range 9 -20 years; 95% CI 16 – 18; SD± 2.9). The male to female ratio was 2:1. The predominant presenting symptoms were abdominal pain with generalized weakness (15%) and bleeding per rectum (20%). The clinical and surgical findings were intestinal obstruction and/or growth, abdominal distention and dysphagia. History was not available in approximately 8% of the cases.

Esophageal cancers were morphologically sub-categorized as squamous cell carcinoma (SCC), ICD morphological category M-8070.3 (3 cases; 75%) and

Table 1. Mean Age at Presentation by Site and Morphology

Site	n (%)	Mean age in years (CI)		SD	Range (years)
Esophagus	4 (8.5)	17.8	(13.2; 22.3)	2.9	14;20
Male	3	18.0	(9.4; 26.6)	3.5	14;20
Female	1	17.0	(-)	-	-
Stomach	3 (6.4)				
Male	1 (33.3)	20.0	(-)	-	-
Female	2 (66.7)				
Colon	40 (85.1)	17.3	(16.4; 18.3)	3.0	9; 20
Male	28 (70.0)	17.5	(16.4; 18.6)	2.8	10,20
Female	12 (30.0)	16.9	(14.6; 19.2)	3.6	9;20
Morphology	**n (%) (CI)**	**Mean age in years (years)**		**SD**	**Range**
Burkitt L.	10 (87.0)	9.4	(6.3; 12.5)	3.7	6;17
Male	9 (90.0)	9.7	(6.1; 13.2)	3.9	6;17
Female	1 (10.0)	7.0	(-)	-	-
DBCL (male)	3 (13.0)	13.8	(7.8; 19.8)	4.8	7;20

CI- Confidence interval; SD- Std. Deviation

Table 2. Morphological Distribution of Epithelial Malignancies by Site

Morphology	Number (n)	Relative frequency (%)
Esophagus- total 4 cases		
Squamous Cell Carcinoma	3	75.0
Adenocarcinoma, NOS	1	25.0
Stomach- total 3 cases		
Signet Ring Cell Carcinoma	2	66.7
Adenocarcinoma, NOS	1	33.3
Colon- total 40 cases		
Signet Ring Cell Carcinoma	22	55
Adenocarcinoma, NOS	12	30
Well differentiated	2	16.6
Moderately differentiated	5	41.7
Poorly differentiated	5	41.7
Mucinous carcinoma	6	15

adenocarcinoma (M-8140.3) 1 case (25%). The SCC cases were moderately differentiated and adenocarcinoma was poorly differentiated. The morphological sub-categorization of gastric carcinoma was 2 (66.7%) cases of signet ring cell carcinoma (M-8490.3) and 1 (33.3%) case of adenocarcinoma. Colonic cancers were further sub-categorized as signet ring cell (poorly differentiated) carcinoma 22 (55%) cases, highlighted by PAS Alcian blue, mucinous carcinoma (M-8480.3), 6 (15%) cases and adenocarcinoma 12 (30%) cases. Adenocarcinoma, was graded as well differentiated (2 cases), moderately differentiated (5 cases) and poorly differentiated (5 cases). The morphological categorization of lymphoid malignancies was diffuse large B-cell lymphoma (DBCL, M-9680.3) 4 cases (30.8%), Burkitt lymphoma and Burkitt-like lymphoma (M-9687.3) 6 cases (46.1%) and 3 cases (23.1%) respectively. Of the lymphoma cases 12 were boys and 1 was a girl. The mean age at presentation was 11.1 years (range 6-20 years; 95% CI 8.3 – 13.8; SD± 4.6). There was a difference in the mean ages of the DBCL and Burkitt lymphoma. (table 1) The male to female ratio was 12:1. All DBCL and Burkitt-like lymphoma were observed in males. One case of Burkitt lymphoma was observed in a female child, the rest were observed in males. The distribution of lymphoma by site was 9 (69.2%) cases in the small bowel and 4 (30.8%) cases in the large bowel. The predominant presenting symptom for lymphoma was a large palpable abdominal mass, observed in all cases with associated recurrent abdominal pain and fever. A third of the patients presented with complications of intestinal obstruction, ileal perforation or intussusception. All cases of carcinoma and lymphoma presented as advanced malignancies. Approximately three-fourth the patients presented as stage III disease and another one-fourth with stage IV disease.

The residential status varied with each topographic sub-category. All cases of esophageal carcinoma hailed from Baluchistan and all gastric carcinoma from Karachi. Approximately 62.5% of colonic cancers were from Karachi, 3 (7.5%) cases each from Larkana, Hyderabad, Quetta, 2 (5.0%) cases each from Sukker and Peshawar and 1 (2.5%) case each from Rahim Yar Khan and Gotki. Two (66.7%) cases of Burkitt-like lymphoma were reported from Peshawar and 1 (33.3%) case from Abbotabad. Two (33.3%) cases of Burkitt lymphoma were reported from Peshawar, whereas a case (16.7%) each was registered from Karachi, Quetta, Faisalabad and Multan. Two of the DBCL were reported from Quetta a city in the Baluchistan Plateau, whereas a case each was reported from Karachi and Larkana (table 3).

Discussion

The present study has highlighted the existence of a substantial number of GI malignancies in children (0-14 years) and adolescents (15-19 years) in the Pakistani population. The highlights of our findings are a higher frequency of GI malignancies, a higher frequency of gastric and colonic malignancies, involvement of a rare site i.e. esophagus in both children and adolescents, a male predominance, a preponderance of carcinoma versus lymphoma and a high proportion of signet ring and mucinous colo-rectal carcinoma. The current study has identified 2 high risk regions in Pakistan viz. Quetta in Baluchistan for esophageal cancer and diffuse large B-cell lymphoma and Peshawar in NWFP for Burkitt and Burkitt-like lymphoma. The overall dismal picture of developing countries i.e. late presentation and advanced malignancy was observed for all cases.

Gastro-intestinal malignancies are rare in the young. The commonest pediatric GI malignancy reported in literature is lymphoma of the small and large bowel (Longino and Martin, 1958; Pickett et al., 1967; Bethel et al., 1997). Amongst the GI malignancies, only colorectal cancers have a well defined incidence in those below 19 years, esophageal and gastric malignancies are uncommon in this age. Gastric neoplasms are rare to the extent that a review of records of Mayo Clinic from 1935 to 1973 revealed no case below 16 year of age (Dhams BB, 1992). The tumor registry at the Children's Hospital, Columbus, registered 55 cases of primary intestinal malignancy out of a total of 4,547 tumor registrants (1.2%) over a 44 year period (Bethel et al., 1997).

Our data though based on a small sample size, indicates an increased risk of GI malignancies in the young population of Pakistan which may not be uniformly distributed in the country. It is our observation that Karachi is probably not a high risk region for GI malignancies in the young especially not for esophageal cancers and lymphoma. The ten year record of the Karachi Cancer Registry (KCR) supports our observation (Bhurgri et al., 2002; Bhurgri et al., 2007). Other published hospital studies from Karachi also give credence to our reasoning (Shah et al., 2000; Mehdi, 1988).

Table 3. Geographical Distribution of Malignancies.

Provinces	Sindh					Punjab			Baluch	NWFP	
Cities	Karachi	Larkana,	Hyderabad	Sukker	Gotki	RYK	Faisalabad	Multan	Quetta	Peshawar	Abbotabad
Carcinoma											
Esophagus (n=4)	-	-	-	-	-	-	-	-	4	-	-
Stomach (n=3)	3	-	-	-	-	-	-	-	-	-	-
Colon (n=40)	25	3	3	2	1	1	-	-	3	2	-
Lymphoma											
Burkitt-like (n=3)	-	-	-	-	-	-	-	-	-	2	1
Burkitt (n=5)	1	-	-	-	-	-	1	1	1	2	-
DBCL (n=4)	1	1	-	-	-	-	-	-	2	-	-

n=total number of cases.

The current data identifies the involvement of a rare cancer site i.e. esophagus in both children and adolescents. We registered 4 cases of esophageal carcinoma, one in the pediatric and 3 in the adolescent age groups. The pediatric age group case was reported from Quetta, Baluchistan. The 3 adolescent patients were cases from Baluchistan, who had come to Karachi for treatment and thus not reflected in the KCR data. The Baluchistan Plateau of Pakistan has been established as a high risk region for esophageal cancer and is an extension of the Asian esophageal belt (Bhurgri et al., 2003; Bhurgri, 2004). Case reports of esophageal cancer in the young are also documented from areas of India and Iran which are a part of the Asian cancer esophagus belt (Shahi et al., 1989; Kumar et al., 1992; Gangopadhyay et al., 1997). This occurrence is in contrast to published western data which report no case in the pediatric population (Pickett and Briggs, 1967).

In the high incidence esophageal cancer regions risk factors important in the carcinogenesis of squamous cell carcinoma (SCC) include deficiency of trace elements, consumption of pickled moldy foods, nitrosamines and thermal injury leading to chronic esophagitis and cancer (Bhurgri Y et al., 2003). These factors may not be the primary risk factors for carcinogenesis in the younger age groups and it would be well worthwhile to focus on other etiological risk factors e.g. an early exposure to biological agents like 'Human Papilloma Virus (HPV), the DNA has been consistently detected in 20 to 40% of SCC in high risk areas of China (Parkin et al., 1999). This region has also been documented as a high radioactivity area therefore the effect of ionizing radiation needs to be studied further (Amanullah et al., 2003).There were no gastric malignancies in the pediatric age group in the present study; however we registered cases in both genders in the adolescents. The frequency is higher then reported by KCR (Bhurgri et al., 2003; Bhurgri, 2004).

Colonic carcinoma in our study is higher then reported elsewhere. Skinner et al in 1994 cited a frequency of 10% over 20 years whereas Bethel et al cited a frequency of 56.4% in 44 years. A large majority (55%) of colonic carcinomas in our study were poorly differentiated tumors presenting at an advanced stage. These cases would have a poor prognosis unless diagnosed early. This can only be possible if childhood cases of bowel disorders prior to malignant transformation are identified and receive a more rigorous diagnostic evaluation, treatment and follow-up then adult cases.

Adult risk factors for colorectal carcinoma viz. high calorie food rich in animal fat, sedentary life style, smoking, alcohol, chronic inflammatory bowel disease, Crohn's disease, irradiation etc. cannot be justified in the younger age groups. Neither can protective factors viz. vegetable consumption, prolonged use of non –steroidal anti-inflammatory drugs, estrogen replacement therapy and physical activity (Gyde et al., 1988; Kvist et al., 1989; Gillen et al., 1994; Tsunoda et al., 1997).

Contrary to published western studies, our data identifies a morphological dissent (Pickett and Briggs , 1967). There is a preponderance of carcinoma in both genders, and a high mucinous and signet ring cell component. As the AKU laboratory is a referral centre for lymphoma we expected a lymphoma bias, however we observed a reverse pattern. The carcinoma: lymphoma ratio in our study was 4:1 whereas published western data show a 1:2 to 1:3 ratio (Bethel et al., 1997; Skinner et al., 1994, (Gyde et al., 1988; Kvist et al., 1989; Gillen et al., 1994; Tsunoda et al., 1997). Inverse associations and preponderance of mucinous morphology are also documented by other Asian authors (Karnak et al., 1999; Chen et al., 2001). A higher incidence for gastric adenocarcinoma and squamous cell carcinoma of esophagus in blacks has been reported by SEER, as an indication of a genetic predisposition (Thomas and Sobin, 1995).

Lymphoid neoplasms in our study were mainly high grade lymphoma i.e. diffuse large B cell and Burkitt and Burkitt-like lymphoma. Western literature, also reports a high incidence of Burkitt lymphoma but lower incidence of DBCL. Burkitt lymphoma was reported in the youngest age group, followed by the Burkitt-like and DBCL. We did not observe any case of MALT lymphoma, probably because of the advanced disease in our population.

Most findings in the present study did not concur with western data, but were supported by Asian studies (Karnak et al., 1999; Chen et al., 2001). A few observations in our study were however compatible all published data, these are the vague presenting complaints of recurrent abdominal pain, male predominance, and the advanced stage of the disease at the time of diagnosis (Skinner et al., 1994; Bethel et al., 1997; Karnak et al., 1999; Chen et al., 2001).

Conclusion

The current study identified the existence of a relatively high frequency of malignant GI tumors in the young population of Pakistan, despite the possibility of referral bias. The cause maybe a genetic predisposition, earlier individual exposures to risk factors or a dose related response, which is reflected as an earlier age at presentation for these malignancies. Awareness in the primary physicians needs to be raised to ensure early detection of tumors and identification of bowel disorders which could progress to malignancy.

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