RESEARCH ARTICLE

Gastrointestinal, Liver and Biliary Tract Pathology: A Histopathological and Epidemiological Perspective from Pakistan with a Review of the Literature

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Abstract

   <u>Aim</u>: To present an epidemiological and histological perspective of diseases of the gastrointestinal tract (including liver and biliary tract) at the Section of Histopathology, Department of Pathology, AKUH, Karachi, Pakistan. <u>Materials and Methods</u>: All consecutive endoscopic biopsies and resections between October 1 and December 31, 2012 were included. <u>Results:</u> A total of 2,323 cases were included. Carcinoma was overwhelmingly the commonest diagnosis on esophageal biopsies (69.1%); chronic helicobacter gastritis (45.6%) followed by adenocarcinoma (23.5%) were the commonest diagnoses on gastric biopsies; adenocarcinoma (27.3%) followed by ulcerative colitis (13.1%) were the commonest diagnoses on colonic biopsies; acute appendicitis (59.1%) was the commonest diagnosis on appendicectomy specimens; chronic viral hepatitis (44.8%) followed by hepatocellular carcinoma (23.4%) were the commonest diagnoses on liver biopsies; chronic cholecystitis was the commonest diagnosis (over 89%) on cholecystectomy specimens. <u>Conclusions:</u> Squamous cell carcinoma comprised 88.8% of esophageal cancers. About 67% were in the lower third and 56.5% were moderately differentiated; mean ages 49.8 years for females and 55.8 years for males; 66% cases were from South West Pakistan. Over 67% patients with gastric adenocarcinoma were males; mean ages 59 and 44 years in males and females respectively, about 74% gastric carcinomas were poorly differentiated; and 62.2% were located in the antropyloric region. About 63% patients with colorectal adenocarcinoma were males; mean ages 46.1 and 50.5 years for males and females respectively; tumor grade was moderately differentiated in 54%; over 80% were located in the left colon. In 21.2% appendicectomies, no acute inflammation was found. Acute appendicitis was most common in young people. Hepatitis C (66.3%) was more common than hepatitis B (33.7%); about 78% cases of hepatocellular carcinoma occurred in males; females comprised 76.7% patients with chronic cholecystitis; and 77.8% patients with gall bladder carcinoma. All resection specimens showed advanced cancers. Most cancers occurred after the age of 50 years.

Keywords: Gastrointestinal tract - liver - biliary tract - histopathology - epidemiology - Pakistan

Introduction

   The Section of Histopathology at the Aga Khan University Hospital, Karachi is the largest and busiest center for Histopathology in Pakistan, a country with a population of over 170 million people. Our section is also Pakistan's premier referral center for Histopathology and we receive cases from the whole country as well as from neighbouring countries like Afghanistan, and places as far as Kenya. Our annual work load is around 50,000 surgical cases.

   Gastrointestinal pathology is one of the busiest components of our practice, and as awareness about gastrointestinal diseases increases among the general public as well as clinicians, the number of endoscopic biopsies (as well as resections) from gastrointestinal tract is increasing. Although definite statistics about exact number of gastrointestinal tract related specimens are not currently available, we feel that there is a consistent increase in the number of these cases. Diseases of the gastrointestinal tract, liver and biliary tract appear to be rampant in Pakistan and the aim of this study is to place these diseases in their proper perspective from the point of view of histopathological practice.

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Materials and Methods

All biopsies and resection specimens from gastrointestinal tract (esophagus, stomach, colon, appendix, liver and gall bladder) received in the Section of Histopathology, Department of Pathology and Microbiology, Aga Khan University Hospital, Karachi over a three month period from October 1 to December 31, 2012 were included in the study. Biopsies from small intestine are not included as these were already discussed in a separate study (Arshad and Ahmad, 2012) Findings on pancreatic biopsies and whipple resection will also hopefully be published soon in a separate study. All endoscopic and core biopsies were received in 10% buffered formalin and were submitted entirely for microscopic examination. Resection specimens were also received in formalin and representative sections were submitted according to standard College of American Pathologist (CAP) protocols (CAP, 2012) for microscopic examination. All slides were stained with routine Hematoxylin and Eosin (H&E) stain. Special stains such as Periodic Acid Schiff (PAS) ±diastase, PAS Alcian Blue ± diastase, reticulin, trichrome etc. were performed whenever required. Similarly, immunohistochemical stains such as Cytokeratin (CK) AE1/AE3, CK CAM 5.2, CK7, CK20, CDX2, Leucocyte common antigen (LCA), CD20 (PanB), CD3 (PanT), CD117, CD34, Heppar1, chromogranin, synaptophysin etc. were performed whenever required. The latest WHO classifications were used.(WHO, 2010) Resection specimens in malignant cases were reported strictly according to the latest College of American Pathologists (CAP) protocols (CAP, 2012) and staged according to the updated TNM classification (Edge et al., 2010).

All relevant data was recorded and analysed using commercially available SPSS 19.0 software package. Fisher exact and chi square tests were used to calculate p values for different variables. The p value equal to or less than 0.05 was considered significant.

Results

During the study period, a total of 311 esophageal biopsies were received. The breakup of histologic diagnosis is shown in Table 1.

Carcinoma was the single largest group comprising 215 (69.1%) cases. Squamous cell carcinoma was the commonest histologic type comprising 191 (88.8%) cases, which was statistically significant (p value: 000). Of the remaining 24 cases of carcinoma, 18 (8.4%) were adenocarcinoma (of lower esophagus/gastroesophageal junction). The remaining 6 cases of carcinoma included 2 cases (0.9%) of small cell carcinoma, 3 cases (1.4%) of adenosquamous carcinoma, and 1 case (0.5%) of large cell neuroendocrine carcinoma. Among the 191 cases of squamous cell carcinoma, 6 (3.1%) were diagnosed as basaloid variant of squamous cell carcinoma. Out of the 191 cases of squamous cell carcinoma, 105 (55%) were in females and 86 (45%) in males. Female to male ratio was 1.22:1. In females, age range was 19-82 years, with a mean age of 49.8 years and median age of 49 years. In

males, age range for squamous cell carcinoma was 18-85 years, with a mean and median age of 55.8 and 56 years respectively. Of the 191 cases of squamous cell carcinoma, 128 (67%) were in the lower third, 38 (19.9%) were in the middle third, and 9 (4.7%) were located in the upper third of the esophagus. This propensity for the lower third was statistically significant (p value 0.034). In 16 cases (8.4%), the exact location was not known. Of the 191 cases of squamous cell carcinoma, 39 (20.4%) were well differentiated, 108 (56.5%) were moderately differentiated, and 44 (23.1%) were poorly differentiated. As many as 126 out of 191 cases of squamous cell carcinoma (66%) were from South West Pakistan especially from Baluchistan along the Pakistan-Iran and Pakistan-Afghanistan border. The propensity for Baluchistan was also statistically significant (p value: 0.005). During the study period, 7 esophagectomy specimens were also received. During the study period, a total of 643 gastric biopsies were received. The breakup of histologic diagnoses is shown in Table 1.

Chronic Helicobacter gastritis was the largest group comprising 293 cases (45.6%). There was a male preponderance, 164 patients (56%) were males, while 129 (44%) were females. The age range for Helicobacter gastritis in males was 15 to 89 years, with mean age of 44 years and median age of 41 years. In females, age range was 11 to 80 years, with mean and median age of 41 and 46 years respectively.

The second largest group was gastric adenocarcinoma comprising 151 cases (23.5%). There were 102 males (67.6%) and 49 females (32.4%). Male to female ratio was 2.08:1. Age range for gastric carcinoma in males was 22-85 years, with mean age of 59 years and median age of 60 years. In females, age range was 18-76 years with mean and median age of 44 and 47 years respectively. This age difference between males and females was statistically significant (p value: 0.001). Gastric carcinoma was poorly differentiated (signet ring cell type) in 112 of the 151 cases (74.2%), and well to moderately differentiated in 39 cases (25.8%). The predominance of poorly differentiated gastric carcinoma was statistically significant (p value: 0.000). Neuroendocrine differentiation was seen in 7 out of 151 cases (4.6%). Carcinoma was located in the antropyloric region of the stomach in 94 cases (62.2%), and in the body and fundus in 57 cases (37.8%). However, this propensity for the antropyloric region was not statistically significant (p value: 0.498).

The third major histopathological diagnosis was chronic nonspecific gastritis rendered in 132 out of 643 cases (20.5%). These were cases in which no specific or definite cause of gastritis was found. During the study period, 14 gastrectomy specimens were also received. Of these, 9 (64.3%) were T3, 3 (21.4%) were T4 and 2 (14.3%) were T2. Similarly, 7 cases (50%) were N2, 4 (28.6%) were N3, 1 (7.1%) was N1 and 2 cases (14.3%) were N0. Vascular and/or perineural invasion was present in 9 (64.3%) out of 14 cases. In 5 cases (35.7%), one peripheral resection margin was positive. Tumor grade was poorly differentiated (signet ring type) in 9 out of 14 cases (64.3%), moderately differentiated in 3 cases (21.4%), and well differentiated in 2 cases (14.3%). During the study period, a total of 678 colonic endoscopic biopsies were

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received. The breakup of histologic diagnoses is shown in Table 1.

Carcinoma was the largest group comprising 185 cases or 27.3%. There was a male preponderance of 1.68:1. Out of 185 cases, 116 (62.7%) were males and 69 (37.3%) were females. The difference was statistically significant (p value: 0.020). The age range for colorectal carcinoma was 12-80 years in males, with a mean age of 46.1 and median age of 48 years, age range was 13-85 years in females, with a mean and median age of 50.5 and 49 years respectively. Out of 185 cases, 26 (14.1%) were well differentiated, 100 (54.0%) were moderately differentiated, and 59 (31.9%) were poorly differentiated. These 185 cases included 22 (11.9%) mucinous carcinomas, 13 (7.0%) signet ring carcinomas, and 5 (2.7%) cases with neuroendocrine differentiation. Out of 185 cases, 149 (80.5%) cases of carcinoma were located in the left colon while 36 (19.5%) were located in the right colon. This propensity for the left side of the colon was statistically significant (p value: 0.046).

The second largest group was that of ulcerative colitis (UC) comprising 89 cases (13.1%) closely followed by infectious colitis (12.4%). UC was almost equally distributed between males and females, there were 45 males and 44 females. Age range for UC was 10-66 years in males and 6 to 60 years in females. Mean and median age for UC were 40 and 41 years respectively for males and 40.7 and 42 years respectively for females.

Infectious colitis (excluding tuberculosis and amebiasis) was more common in males. Out of 84 cases, 55 (65.6%) occurred in males and 29 (34.4%) in females. Male to female ratio was 1.9:1. During the study period, 23 colonic resection specimens were also received. Of these, 16 (69.6%) were in the left colon (15 in the rectosigmoid region) and 7 (30.4%) were in the right colon. Out of 23 cases, 18 (78.3%) were T3, 4 (17.4%) were T4, and 1 case (4.3%) was T1. Similarly, 11 cases (47.8%) were N1, 6 (26.1%) N2 and 1 (4.3%) was N3, while 5 cases (21.7%) were No. Out of 23, 2 cases (8.7%) were M1. Vascular and/or perineural invasion was seen in 11 (47.8%) cases, while radial margin was positive in 8 (34.8%) out of 23 cases. Tumor grade was moderately differentiated in 12 cases (52.2%), poorly differentiated in 7 (30.4%) and well differentiated in 4 (17.4%) out of 23 cases. During the study period, a total of 132 appendix (appendicectomy) specimens were received. The breakup of histologic diagnoses is shown in Table 1.

Acute appendicitis was the commonest diagnosis rendered in 78 cases (59.1%). There were 48 males (61.5%) and 30 females (38.5%). Male to female ratio was 1.6:1. Age range for acute appendicitis in males was 2 to 65 years with mean and median age of 25.4 and 24 years respectively. Age range in females was 8 to 70 years with mean and median age of 31 and 27 years respectively.

Out of the 78 cases of Acute appendicitis, accompanying serositis was seen in 44 cases (56.4%). Perforation was seen in 9 cases (11.5%).

The second commonest diagnosis was 'no acute inflammation seen' in specimens resected for suspected 'acute appendicitis' clinically, rendered in 28 cases (21.2%).

Table 1. Breakup of histologic diagnoses.

S. No.	Esophageal Biopsies (n=311)			Gastric Biopsies (n=643)			Colonic biopsies (n=678)			Appendicectomy Specimens (n=132)			Liver Biopsies (n=192)			Cholecystectomy Specimens (n=323)		
	Histologic Diagnosis	No.	%	Histologic Diagnosis	No.	%	Histologic Diagnosis	No.	%	Histologic diagnosis	No.	%	Histologic diagnosis	No.	%	Histologic diagnosis	No.	%
1	Carcinoma	215	69.10	Chronic Helicobacter gastritis	293	45.60	Adenocarcinoma	185	27.30	Acute appendicitis	78	59.10	Chronic viral hepatitis	86	44.80	Chronic Cholecystitis	207	64.10
2	Esophagitis	26	8.40	Adenocarcinoma	151	23.50	Ulcerative colitis	89	13.10	No acute inflammation present	28	21.20	Hepatocellular carcinoma	45	23.40	Acute on chronic cholecystitis/empyema	82	25.40
3	Barrett Esophagus	20	6.40	Chronic nonspecific gastritis	132	20.50	Infectious colitis**	84	12.40	Mucinous neoplasms	11	8.30	Metastatic carcinoma	21	10.90	Adenocarcinoma	27	8.30
4	Hyperplasia	16	5.10	Perforated gastric ulcer	12	1.90	Nonspecific colitis	58	8.50	Enterobius	5	3.80	Storage disorders	7	3.60	Mucocele	2	0.60
5	Non neoplastic ulcer	13	4.20	Atrophic gastritis and intestinal metaplasia	12	1.90	Biopsies for evaluation of HD	58	8.50	Carcinoid tumor	4	3.00	Autoimmune hepatitis	5	2.60	Polyp	2	0.60
6	Candidiasis	11	3.50	Proton pump inhibitor (PPI) changes*	12	1.90	Juvenile retention polyp	49	7.20	Ganglion cells present or absent	3	2.30	NASH	4	2.10	Polyp, adenomatous	1	0.30
7	Leiomyoma	4	1.30	Gastric GIST	11	1.70	Adenomatous polyp	39	5.70	Adenocarcinoma	2	1.50	Extrahepatic Biliary Atresia	3	1.60	Angiosarcoma	1	0.30
8	CMV Esophagitis	3	1.00	Non-Hodgkin lymphoma	7	1.10	Solitary rectal ulcer	36	5.30	Tuberculosis	1	0.70	Cholangio carcinoma	3	1.60	Papillary hyperplasia	1	0.30
9	GIST	2	0.60	Hyperplastic polyp	4	0.60	Unremarkable	22	3.20				Congenital hepatic fibrosis	2	1.00			
10	Heterotopic gastric mucosa	1	0.30	Foveolar hyperplasia (chemical gastropathy)	3	0.50	Tuberculosis	16	2.40				Hemochromatosis	2	1.00			
11				Meckel's diverticulum	2		Hyperplastic polyp	10	1.50				PBC	2	1.00			
12				Adenomatous polyp	2	0.30	Amoebic colitis	5	0.70				Wilson's disease	2	1.00			
13				Cytomegalovirus (CMV) Gastritis	1	0.10	Ischemic colitis	5	0.70				Primary Sclerosing Cholangitis	2	1.00			
14				Parietal cell hyperplasia	1	0.10	Non-Hodgkin lymphoma	3	0.40				Hemangioma	1	0.50			
15							Peutz Jegher's polyp	3	0.40				Hepatoblastoma	1	0.50			
16							GIST	3	0.40				Angiosarcoma	1	0.50			
17							Inflammatory Myofibroblastic	2	0.30				Fibrolamellar carcinoma	1	0.50			
18							Crohn's Disease	2	0.30				ASH	1	0.50			
19							Melanosis Coli	2	0.30				Tuberculosis	1	0.50			
20							Microscopic Colitis (collagenous)	2	0.30									

*including 3 fundic gland polyps; **excluding tuberculosis and amebiasis; ***Hirschsprung Disease: HD, Gastrointestinal Stromal Tumor: GIST, Non-alcoholic steatohepatitis: NASH, Alcoholic Steatohepatitis: ASH, Primary Biliary Cirrhosis: PBC

Table 2. Age Incidence of Various Cancers (decade wise breakup)

Organ	Total no.	0-10	11-20	21-30	31-40	41-50	51-60	61-70	>70
1 Carcinoma esophagus	215	-	-	17 (7.9%)	39(18.1%)	63(29.3%)	47(21.9%)	30(13.9%)	19 (8.8%)
2 Carcinoma colorectum	185	-	12(6.5%)	32 (17.3%)	28(15.1%)	42(22.7%)	33(18.0%)	33(17.8%)	5 (2.7%)
3 Carcinoma stomach	151	-	2(1.3%)	5 (3.3%)	26(17.0%)	42(27.8%)	36(23.8%)	31(20.5%)	9 (6.0%)
4 Carcinoma liver (HCC)	45	-	-	1 (2.2%)	3 (6.7%)	9(20%)	21(46.7%)	6(13.3%)	5(11.1%)
5 Carcinoma Gall bladder	27	-	-	2 (7.4%)	1 (3.7%)	8(29.6%)	12(44.4%)	3(11.1%)	1 (3.0%)

Appendiceal mucinous neoplasms are now being increasingly diagnosed. Of the 11 cases diagnosed during the study period 9 (81.8%) were low grade with acellular extraappendiceal mucin and 2 (18.1%) were low grade with extraappendiceal mucin having neoplastic cells. Adenocarcinoma of appendix was seen in 2 out of 132 cases (1.5%). During the study period, a total of 192 core biopsies of the liver were received. The breakup of histologic diagnoses is shown in Table 1.

The most common reason for performing liver biopsies was for the evaluation (grading and staging) of chronic viral (Hepatitis B and C) hepatitis and such biopsies comprised almost 45% of all liver biopsies. Of the 86 such cases, 57 (66.3%) were due to Hepatitis C virus while 29 (33.7%) were due to Hepatitis B virus. So, Hepatitis C was much more common than Hepatitis B. the difference was statistically significant (p value: 0.003). Combined hepatitis B and D infection accounted for 9 out of 29 cases (31.3%). Out of 86 cases of chronic hepatitis, 55 (64.0%) occurred in males and 31 (36.0%) in females. Male to female ratio was 1.8:1. Age range for males was 10-65 years, mean and median ages were 36 and 38 years respectively. Age range for females was 14-62 years, mean and median ages were 40.2 and 40 years respectively. Out of 86 cases, 3 (3.5%) were histologically grade-I, 30 (34.9%) were grade-II, 51 (59.3%) were grade-III and 2 (2.3%) were grade-IV. Out of 86 cases of chronic viral hepatitis, 11 (12.8%) were histologically stage-I, 28 (32.5%) were stage-II, 20 (23.2%) were stage-III, and 27 (31.4%) were stage-IV. Concomitant steatosis was seen in 22 (25.6%) out of 86 cases. Of these 22 cases, steatosis was mild in 12 cases (54.5%), moderate in 8 (36.4%) and severe in 2 cases (9.1%).

Out of the 45 cases of primary hepatocellular carcinoma, 35 (77.8%) occurred in males and 10 (22.2%) in females. This difference was statistically significant (p value: 0.028). Male to female ratio was 3.5:1. Age range in males was 26-80 years with mean and median age of 54 and 53 years respectively. In females, age range was 30-73 years with mean and median age of 55 and 53 years respectively. During the study period, a total of 323 gall bladder (cholecystectomy) specimens were received. The breakup of histologic diagnoses is shown in Table 1.

Chronic cholecystitis followed by acute and chronic cholecystitis comprised the commonest histologic diagnosis accounting for 289 out of 323 cases or 89.5%. Gall stones were grossly present in 133 out of 289 (46%) patients with chronic or acute on chronic cholecystitis. Of these 133 patients, 102 (76.7%) were females, and 31 (23.3%) were males. Female to male ratio was 3.3:1. Age range in females was 23-76 years with mean and median age of 43 and 42 years respectively. Age range in males was 21-65 years with mean and median age of 51 and 49 years respectively.

A diagnosis of chronic cholecystitis was given in 207 out of 323 cases (64.1%). There were 163 females (78.7%) and 44 males (21.3%). Female to male ratio was 3.7:1. Age range for females was 22-76 years with mean and median age of 43 and 42 years respectively. Age range in males was 21-74 years with mean and median age of 51 and 53 years respectively. A diagnosis of acute on chronic cholecystitis was given in 82 out of 323 cases (25.4%). There were 56 females (68.3%) and 26 males (31.7%). Female to male ratio was 2.2:1. Xanthogranulomatous pattern of inflammation was seen in 9 out of 289 cases (3%). Cholelithiasis was seen in 52 out of 289 cases of chronic and acute on chronic cholecystitis (18%). So, out of a total of 289 cases of chronic and acute on chronic cholecystitis, 219 (75.8%) were females and 70 (24.2%) were males. The difference was statistically significant (p value: 0.000). During the study period, 27 cases of gall bladder adenocarcinoma were diagnosed comprising 8.3% of the total 323 cases. Of these 27 cases, 21 (77.8%) occurred in females, and 6 (22.2%) in males. This difference was statistically significant (p value: 0.009). Female to male ratio was 3.5:1. Age range in females was 30 to 50 years, with mean and median age of 49 and 50 years respectively. Out of 27 cases, 8 (29.6%) were well differentiated, 15 (55.5%) were moderately differentiated, and 4 (14.8%) were poorly differentiated. As many as 26 out of 27 cases (96.3%) were full thickness tumors; cystic duct margin was positive in 7 cases (25.9%). Inked Outer serosal/adventitial margin was also positive in 8 cases (29.6%). Vascular and/or perineural invasion was seen in 9 cases (33.3%). Adjacent organs or tissues like liver, pancreas, omentum etc. were involved by direct extension in 6 cases (22.2%). Perforation occurred in 5 out of 27 cases (18.5%). The decade wise breakup of cancers is shown in Table 2.

Discussion

Carcinoma was the commonest diagnosis rendered on esophageal biopsies (69.1%). Squamous cell carcinoma was the commonest histologic type (88.8% of all esophageal cancers) while adenocarcinoma was very uncommon. In our study, 66% of esophageal squamous cell carcinoma was from South-West Pakistan especially the province of Balochistan along Pakistan's border with Iran, China and Afghanistan. These areas are documented to have high recorded rates for esophageal squamous cell carcinoma in both males and females (Curado et al., 2007). In our study, esophageal carcinoma emerges as the commonest type of gastrointestinal tract malignancy, even

more common than colorectal carcinoma. Esophageal carcinoma remains among the top ten malignancies (in both males and females) that we see in our practice. Its incidence in Quetta (capital of Balochistan) is comparable to that in moderate-incidence zones for esophageal cancer (Bhurgri et al., 2003; 2004). It is ranked seventh and fifth in males and females respectively in Karachi (Bhurgri et al., 2003), and fourth among females in Hyderabad (Bhurgri et al., 2005). Esophageal carcinoma is the eighth most common cancer worldwide and the sixth most common cause of death from cancer (Herszenyi and Tulassay, 2010). Although incidence of esophageal cancer and mortality related to it have recently shown a reducing trend in some parts of the world (AIRTUM, 2009; Xie et al., 2012), this is not the case in Asia, even in developed countries like Japan and China (Lin et al., 2013) or other high risk Asian countries such as Iran (Bafandeh et al., 2006). We feel in our practice that the incidence is in fact increasing. However, in all high risk zones (including ours), the incidence of esophageal adenocarcinoma is extremely low (Bafandeh et al., 2006; Lin et al., 2013).

However, in the West, studies have demonstrated an increase in the incidence of esophageal adenocarcinoma (Herszenyi and Tulassay, 2010).

Over two thirds of esophageal squamous cell carcinoma in our study were located in the lower third of the esophagus. Some studies have shown the middle third to be the commonest location (Li et al., 2009). However, in two studies from Iran, a high incidence zone, lower third was the commonest location (Bafandeh et al., 2006; Safaee et al., 2012).

International data also show that incidence rates for esophageal squamous cell carcinoma are 2-10 times higher in males (Khursheed et al., 2007). However, in our study, it was much more common in females, almost 55% compared to 45% in males. In a previous study from Pakistan (Bhurgri et al., 2004), a similar trend was observed, while a study from Iran demonstrated an almost equal gender distribution (Bafandeh et al., 2006). Mean age in our study was also lower in females i.e. 50 years compared to 56 years in males. In Bafandeh et al. (2006) from Iran, mean age was 61 years (Bafandeh et al., 2006). None of the cases of esophageal cancers in our study occurred in patients 20 years of age or younger. However, 7.9% occurred in the age group 21-30 and another 18.1% occurred in the age group 31-40 years. Hence, 26% cases occurred in patients 40 years or younger. A previous study from Pakistan however found that 8.5% of all esophageal carcinomas occurred in patients 19 years of age or younger (Khursheed et al., 2007). Larger studies are required to get a clearer picture. Apart from genetic factors in high risk areas, environmental risk factors like cigarette smoking (Lin et al., 2013), areca nuts, low consumption of raw vegetables and fruits are all operative in Pakistan (Bhurgri et al., 2004). The incidence of Barrett esophagus in our biopsies was very low (6.4%) and none of the cases showed evidence of dysplasia. Bafandeh et al. (2006) also found a very low incidence of Barrett esophagus.

Chronic helicobacter gastritis was the commonest diagnosis rendered on gastric biopsies (45.6%). Over 55% patients were males. Mean ages were 44 and 41

years in males and females respectively. Developing Asian countries generally have higher prevalence rate while prevalence rates are lower in more developed and industrialized countries (Fock and Ang, 2010). There is convincing evidence that Helicobacter (*H pylori*) is an important causative factor for occurrence of non-cardiac gastric adenocarcinoma. In Asia, there are wide variations between different countries in the prevalence of *H pylori* infection. In most Asian countries, there is a strong link between *H pylori* infection and gastric carcinoma with the incidence rate of gastric adenocarcinoma tending to mirror the seroprevalence rate of *H pylori* infection. However, in some countries there is a paradox, with low incidence rates of gastric cancer in spite of high prevalence of *H pylori* infection (Fock and Ang, 2010; Miwa et al., 2002). In Japan, most infections are associated with strong virulence strains of *H pylori*. However, with strong measures to eradicate *H pylori* infections, the prevalence of *H pylori* infection in Japan is gradually decreasing (Shiota et al., 2013).

Pakistan also has a high prevalence of *H pylori* infection and the strong virulence strains of *H pylori* i.e. cagA and vacA are predominant (Khan et al., 2013). Owing to the high prevalence of *H pylori* infection in Asia and its strong association with gastric carcinoma, Asia-Pacific consensus guidelines for management of *H pylori* infection have been developed (Fock et al., 2009). In addition, a Gastric cancer consensus conference recommended population based screening and treatment of *H pylori* in especially high risk population settings (Talley et al., 2008).

Gastric adenocarcinoma was the second commonest diagnosis in gastric biopsies in our series (23.5%). Over 67% cases occurred in males. Mean ages were 59 and 44 years in males and females respectively. So, gastric carcinoma occurred at much younger age in females. Over 74% cases were poorly differentiated (signet ring type) on histological examination. Over 62% were located in the antropyloric region, and over 21% occurred in patients under 40 years of age. The high incidence of gastric adenocarcinoma is not surprising given the high prevalence of *H pylori* infection. Gastric adenocarcinoma is still the fourth commonest cancer and among the commonest causes of death from cancer especially in developing countries (Miwa et al., 2002). This is in spite of the fact that its incidence and mortality rates have significantly decreased in many developed countries (Roder 2002; Crew and Neugut, 2006). The incidence of gastric cancer remains particularly high in East Asia, Eastern Europe and in parts of Central and South America (Herszenyi and Tulassay, 2010). Gastric carcinoma still accounts for about 10% of all newly diagnosed cancers. Studies have estimated that an increased intake of fresh fruits and vegetables in diet, decreased intake of salted, smoked and chemically preserved food, effective use of antibiotics to treat *H pylori* infection and better living standards are extremely important in reducing the burden of gastric cancer and that this burden can be reduced by up to 50% simply by making the dietary changes outlined above (Roder, 2002). This study also showed a prevalence of gastric cancer in males. Another study on

epidemiology of gastric cancer demonstrated that distal gastric cancer predominates in developing countries, with high prevalence rates of *H pylori* infection and among lower socio-economic groups (Crew and Neugut, 2006). In Japan, where gastric cancer is extremely common, the age standardized rates have consistently declined and a large population of cancers are detected at an early age with better overall survival rates (Inoue and Tsugane, 2005). Like Japan, China too has high prevalence rates of *H pylori* infection and high incidence of gastric cancer. Compared to China, there has been a more rapid decline in *H pylori* infection especially in young people in Japan (Lin et al., 2011). Iran is a high risk area for gastric cancer and incidence rates for gastric cancer are increasing, and incidence rates are higher in men than in women (Haidari et al., 2012). Similarly, studies from Pakistan have also demonstrated a rising incidence of gastric cancer, with a male preponderance and mean ages of 51.9 years and 48.8 in males and females respectively. Majority of cases were poorly differentiated, distal cancer (Bhurgri et al., 2009). These findings are similar to findings in our current study. Another study from Pakistan showed that 6.4% of all gastric carcinomas occurred in patients 19 years of age or younger (Khursheed et al., 2007). The Asia-Pacific consensus guidelines on gastric cancer prevention recommended *H pylori* screening and eradication in high risk populations to reduce gastric cancer incidence. It must be mentioned here that a positive family history of gastric cancer is an important risk factor (Center et al., 2009).

As shown by our data on the 14 gastrectomy specimens, most cancers were advanced (over 85% were T3 or T4), and all cases except two were node positive.

Adenocarcinoma was the commonest diagnosis rendered on colonic biopsies (27.3%). Colorectal adenocarcinoma is one of the commonest cancers globally, and the highest incidence rates are found in North America, Australia, New Zealand and Europe; and it is a leading cause of cancer death in Western countries. "Western" risk factor such as obesity and physical inactivity are important. The lowest incidence rates are found in Asia, Africa and South America, all less developed and poorer regions of the world (Center et al., 2009). With an annual incidence of one million cases and annual mortality of more than 500,000, colorectal carcinoma is the second commonest cause of cancer mortality, accounts for 9% of the world's cancer burden and is considered a disease of the Western lifestyle (Herszenyi and Tulassay, 2010). In the West, however, incidence rates and mortality rates are showing a downward trend (AIRTUM, 2009; Center et al., 2009). A study from United States showed a shift in incidence from distal to proximal colon (Jubelirer et al., 2003). However, in Asia, even developed countries like Hong Kong (Xie et al., 2012) continue to show an upward trend in incidence. Studies from Thailand (Khuhaprema and Srivatanakul, 2008) and Iran (Abdifard et al., 2013) show upward trend in the incidence of colorectal cancer in both sexes. Our experience, and the other Asian studies mentioned above demonstrate that colorectal cancer incidence is not low in Asia, indeed it has emerged as one of the commonest cancers in this region. In Pakistan, it is consistently ranked among the top ten cancers in both

sexes (Bhurgri et al., 2005). Whereas in our study, most colonic carcinomas were left sided, a study from China (Ji et al., 1998) showed proximal colon as the more common location. This study also demonstrated increasing trend in the incidence of colorectal carcinoma.

Our cases showed a male preponderance (62.7%). Mean ages were 46.1 years and 50.5 years in males and females respectively. Almost 40% of our cases occurred in patients younger than 40 years old.

A male preponderance was also shown in other studies from Asia (Ji et al., 1998 ;Abdifard et al., 2013). However, a study from West showed that women have the same risk of developing colorectal cancer as men and have a 6% lifetime risk factor for developing colorectal cancer. (Osias et al., 2001) In one study from Europe (Efremidou et al., 2008), the mean ages were much higher (66 years in males and 64.7 years in females) than in our study. A recent study from Pakistan found an equal male to female ratio, 50% cases were diagnosed above 50 years of age, and cancers of the rectum presented at a relatively earlier age. This study had mean ages ranging from 43.7-51.2 years (Bhurgri et al., 2011). All the 23 resection specimens in our study showed advanced disease. Except for one case, all were T3 (78.9%) or T4 (15.8%). Similarly, almost 80% cases were lymph node positive. Almost 70% were located in the left colon. In endoscopic biopsies, over 80% were located in the left colon. In endoscopic biopsies, and resection specimens, 54% and 52.2% respectively were moderately differentiated.

Ulcerative colitis (UC) was the second commonest diagnosis in our biopsies (13.1%), it was almost equally distributed between males and females. Mean ages were 40 and 40.7 years for males and females respectively.

Studies have shown that both UC and Crohn's Disease (CD) are less common in Asia than in the West. However, the incidence of UC has been increasing rapidly although the incidence of CD is also increasing in some areas. Apart from genetic differences, environmental factors such as Westernization of diet, improved hygiene etc. have contributed to this increased incidence (Prideaux et al., 2012). Similarly increases in incidence of UC, and to a lower extent CD, have also been documented in South Asians including those who migrate to the West (Goh and Xiao, 2009). Other studies have also shown that the incidence and prevalence rates of inflammatory bowel disease (IBD) especially UC are low in Asia compared to Europe and North America but are increasing rapidly; and among Asians the disease is more common in South Asians (Indians, Pakistanis and Bangladeshis), and in Japan and the Middle East South Asians appear to be genetically predisposed (Ahuja and Tendon, 2010). With the increase in incidence and prevalence of IBD in developing countries, it is emerging as a truly global disease (Molodecky et al., 2012). Even today, the burden of IBD is not just increasing in the East but also in West (Kappelman et al., 2013). A number of environmental factors are implicated in UC and CD. These include protective factors such as smoking and appendectomy for UC; and risk factors such as infectious agents, bacterial flora of gut, oral contraceptives, antibiotics etc. especially in Crohn's disease (Jantchou et al., 2006; Carbonnel et

al., 2009). Childhood factors have also been shown to be involved in Crohn's disease (Gearry etal, 2010). However, Crohn's disease is extremely rare in our practice and only 2 (0.3%) cases were seen during the study period. IBD is especially common in Jews, the onset is more often in the second or third decade with another peak in the 60s and there is a slight preponderance of UC in men and CD in women (Karlinger et al., 2000). Recent studies have shown that the risk of colorectal cancer in CD is equivalent to the risk in UC while patients with CD are also at increased risk for small intestinal cancer (Burisch and Munkholm, 2013). Acute bacterial and viral infections giving rise to infectious colitis were common (over 12% of all biopsies). This is not surprising in a developing, poor country with overcrowding, poor hygienic and sanitary conditions etc. Similarly, Tuberculosis is extremely common in Pakistan and is seen in our practice in all body organs and tissues. The reasons for tuberculosis being the commonest chronic infectious disease in Pakistan are the same as outlined for acute bacterial infections i.e heavy population growth, rising poverty and poor socio economic conditions, malnutrition leading to decreased resistance, poor hygienic conditions etc. Tuberculosis is exacting a terrible burden on the Pakistani people in terms of both morbidity and mortality and it is especially common in young females and children of both sexes belonging to lower socioeconomic groups (Codlin et al., 2011). Similarly, intestinal tuberculosis remains quite common in Pakistan again due to poor hygiene and use of unpasteurized milk (Ahmed, 1996).

In the past, we hardly saw adenomatous polyps in our practice, but now with increasing awareness about these polyps among medical professionals in Pakistan and the presence of several good gastroenterologists in the country with busy practices, the frequency of colonic adenomatous polyps that we see in our practice is constantly increasing. However, we rarely see cases of microscopic colitis (lymphocytic or collagenous colitis) in our practice but this may also change in the near future.

In the appendix, acute appendicitis was the commonest diagnosis (59.1%). Acute appendicitis is considered to be predominantly a disease of the West (Luckman and Davis, 1991) but it is very common in our country. It may be more common than what our figures suggest since being a referral center, we get to see less of these specimens. Significantly, no acute inflammation was seen in 21.2% cases, especially those received from smaller towns in the country. Studies have shown that the accuracy of the diagnosis is around 80% (Gilmore et al., 1975). We are seeing mucinous neoplasms of the appendix more frequently now (over 8% in our series). We are using the WHO classification for these neoplasms. Most cases in our series and in our practice, qualify for low grade appendiceal mucinous neoplams (WHO, 2010).

Almost 45% liver biopsies showed changes of chronic viral hepatitis; either hepatitis C or B. Hepatitis C was more common than B (66.3% versus 33.7%). Both these infections are endemic in the Pakistani population: low socio economic status, intravenous drug abuse, sexual promiscuity and abuse, transfusion of infected blood, use of contaminated razors, towels etc. by roadside barbers,

lack of vaccination all contribute to making chronic Hepatitis B and C infection and resultant cirrhosis a tragedy of huge proportions in our country with terrible morbidity and mortality. Alcohol consumption is a less important factor. Mainly in the West but also in the more developed Asian countries, the incidence, morbidity and mortality from hepatitis B and C have shown a declining trend owing to implementation of an effective HBV vaccine program, mandatory screening of blood donors etc. However, intravenous drug abuse continues to be an important cause of Hepatitis B and C infection (London and Evans, 1996; Te and Jenson, 2010; Nelson et al., 2011; Kim et al., 2012; Poethko-Mullar et al., 2013). For some reason, Iran is a low endemic area for both Hepatitis B and C, while in Saudi Arabia, owing to extensive investment in health care the prevalence of both hepatitis B and C has declined significantly (Abdo et al., 2012; Zidan et al., 2012). Even then, these infections are still significant cause of morbidity and mortality and a considerable burden on Saudi Arabia's health care system. In developed countries like United States, African Americans bear a disproportionately large burden of these infections as they more often belong to low socioeconomic groups and are exposed to the various etiologic factors discussed above (Forde et al., 2013). However, poor countries in Asia, Africa, Latin America etc. continue to bear heavy burden of these infections (Ola et al., 2012).

Hepatocellular carcinoma (HCC) was the second commonest diagnosis rendered on liver biopsies (23.4%). As is well known, Hepatitis B and C infections are extremely important etiologic factors in the development of primary HCC (London and Evans, 1996; Olal et al., 2012; Zidan et al., 2012; Fares and Peron, 2013). HCC is the sixth commonest malignancy worldwide and among the top five cancers as a cause of cancer related mortality (Herszenyi and Tulassay, 2012; Fares and Peron, 2013). In several developed countries, the age-standardized incidence rate (ASIR) and mortality have shown declining trends (AIRTUM, 2009; Xie et al., 2012). However, the mortality worldwide remains high and is mostly due to late diagnosis at an advanced stage and even today very few patients, even in developed countries, are treated with a curative intent. The importance of a surveillance program (biannual liver ultrasonography in cirrhotic patients) may be critical (Fares and Peron, 2013), but the possibility of such a program to be implemented in Pakistan even ten years from now appears extremely remote. Owing to high burden of Hepatitis B and C infection, the prevalence of cirrhosis and HCC in Pakistan is very high (Bhurgri et al., 2005). Hardly any resections for liver carcinoma are performed in Pakistan and most patients only receive palliative care.

In our practice, the liver remains a common site for metastatic carcinoma (10.9%). NASH is also being reported now, although until the recent past, patients with NASH were not biopsied.

Chronic cholecystitis followed by acute/acute on chronic cholecystitis was the commonest diagnosis made on gall bladder specimens in our series and majority of cases were associated with gall stones. Chronic cholecystitis is the most common disease of

the gall bladder worldwide and the large majority of cholecystectomies are performed for chronic cholecystitis, and over 90% cases of chronic (and acute) cholecystitis are related to gall stones. Gall stones (cholelithiasis), chronic cholecystitis and acute cholecystitis are all more common in obese, middle aged females (Weedon, 1994; Bateson, 2000). Cholelithiasis is believed to affect approximately 10% adults over 40 years of age, while female-to-male ratio in the reproductive years is 4:1 (Schirmer et al., 2005). In our study also, the large majority of cases were diagnosed in middle aged females.

Carcinoma of gall bladder was the third commonest diagnosis on gall bladder specimens in our series. It was seen predominantly in females with mean age around 50 years and over 55% of our cases were moderately differentiated. The overwhelming majority (96.3%) involved the full thickness of the gall bladder wall. Carcinoma of the gall bladder is a relatively rare cancer with a wide variation in its geographical distribution. Its incidence has shown a declining trend in some parts of the world while high incidence rates are found in certain populations in Mexico, Central and South America, Eastern Europe and Asia (India, Pakistan, Korea and Japan). In Pakistan, it ranks among the commonest cancers in females and infact one of the highest incidence rates were reported from South Karachi, Pakistan. History of cholelithiasis has been shown to be the strongest risk factor for gall bladder carcinoma (Randi et al., 2006; AIRTUM, 2009; Horner et al., 2009). while consistent associations have also been found with obesity, multiparity, and chronic infections like Salmonella typhi and paratyphi, Helicobacter bilis and pylori etc (Randi et al., 2006). All the above factors are commonly present in our population.

Most gastrointestinal tract cancers in our series occurred after the age of 30 years, the notable exception being colorectal carcinoma (almost 25% cases occurred in patients younger than 30 years of age. Most of these cases had a signet ring or mucinous histological pattern). In our study, carcinoma of esophagus was most common in the fourth, fifth and sixth decades of life; carcinoma of colon (colorectum) was more evenly distributed in the third to seventh decades of life; gastric carcinoma was mostly seen in the fourth to seventh decades of life; hepatocellular carcinoma was most common in the fifth to seventh decades of life; while carcinoma of gall bladder was also most common in the fifth to seventh decades of life. International cancer statistics are similar to our findings (Curado et al., 2007; Ferley et al., 2010).

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