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Pattern of biliary tract carcinoma at the University College Hospital, Ibadan

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Abstract

Background- Biliary tract carcinomas are uncommon but highly fatal malignancies. Most patients in our environment are diagnosed late and are not candidates for curative resection.

Objective- To determine the pattern and risk factors of biliary tract carcinoma in Ibadan.

Methodology- This was a retrospective study of histologically confirmed cases of biliary tract carcinoma diagnosed at the University College Hospital, Ibadan between January 1971 and December 2010. Data was obtained from the records of the Ibadan Cancer Registry, surgical day books and post-mortem records of the Department of Pathology. Histological classification based on the 2010 'WHO classification for tumours of the intrahepatic bile duct, gallbladder and extrahepatic bile duct' was done.

Results- There were 37 cases of biliary tract carcinoma accounting for 0.18% of cancers seen during the period of study. These comprised of 26 (70.3%) females and 11 (29.7%) males. 20 females and 4 males had gallbladder carcinoma, while 6 females and 7 males had cholangiocarcinoma (P=0.02). The age range was from 37 years to 75 years (mean = 52.5 ± 9.7 years). The peak occurrences of gallbladder carcinoma and cholangiocarcinoma were in the fifth and sixth decades of life respectively. The identified risk factors included female gender (83%), gallstones (33%), and dysplasia (42%).

Conclusion- The findings in this study agree with what has been described in the English literature in respect of gender distribution, histological types and some associated risk factors as well as in the fact of its being rare.

Keywords: *Biliary tract carcinoma, gallbladder carcinoma, cholangiocarcinoma, Pattern, Ibadan*

Résumé

Contexe- les carcinomes de la voie biliaire sont des tumeurs malignes rares mais hautement mortelles. La plupart des patients dans notre environnement sont diagnostiqués tardivement et ne sont pas candidats pour la résection curative.

Objective : Pour déterminer les modèles et les facteurs de risque du carcinome de la voie biliaire à Ibadan.

Méthodologie - Ceci fut une étude rétrospective de cas confirmés histologiquement du carcinome de la voie biliaire diagnostiqué au Collège Hospitalier Universitaire, Ibadan entre Janvier 1971 et Décembre 2010. Les données ont été obtenues à partir des dossiers du Registre de Cancer d'Ibadan, des livres de jour chirurgicaux et dossiers post-mortem provenant du Département de pathologie. La classification histologique basée sur 'La Classification 2010 de l'OMS pour les tumeurs de la voie intra-hépatique biliaire, la vésicule biliaire et de la voie extra-hépatique biliaire' a été faite.

Résultats : Il y avait 37 cas de carcinome de la voie biliaire comptant pour 0,18% des cancers observés au cours de la période d'étude. Ceux-ci comprenaient 26 (70,3%) femmes et 11 (29,7%) hommes. 20 femmes et 4 hommes avaient le carcinome de la vésicule biliaire, tandis que 6 femmes et 7 hommes avaient cholangiocarcinome (P = 0,02). La tranche d'âge était de 37 ans à 75 ans (âge moyen = 52,5 ± 9,7 ans). Les occurrences de pointe du carcinome de la vésicule biliaire et du cholangiocarcinome étaient respectivement dans les cinquième et sixième décennies de la vie. Les facteurs de risque identifiés comprenaient le sexe féminin (83%), les calculs biliaires (33%), et la dysplasie (42%).

Conclusion- Les résultats de cette étude sont en accord avec ce qui a été décrit dans la littérature anglaise à l'égard de la répartition par sexe, les types histologiques et certains facteurs de risque associés, ainsi que dans le fait de sa rareté.

Mots-clés: *carcinome de la voie biliaire, carcinome de la vésicule biliaire, cholangiocarcinome, Modèle, Ibadan*

Introduction

Biliary tract carcinoma is the second most common primary hepatobiliary cancer, after hepatocellular carcinoma, occurring relatively infrequently but as a highly lethal disease that is notoriously difficult to diagnose and treat. Commonly diagnosed in its late

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stages, the general prognosis for patients is dismal. Local invasion, extensive loco-regional lymph-node metastasis, distant metastases, vascular encasement and invasion often preclude resection, and neither radiation nor conventional chemotherapy significantly improve survival or quality of life thus giving survival rates of about 15% at 2 years after diagnosis. The median time from diagnosis to death for intrahepatic cholangiocarcinomas is 6 months, even after surgery [1-4].

Biliary tract carcinomas include carcinomas of the gallbladder (GBC) and those of the intra- and extrahepatic biliary tree (cholangiocarcinoma, CCC). Fifty to 60% of all CCCs are perihilar (Klatskin) tumours (involving the bifurcation of the hepatic duct), while the remainder are either distal tumours or intrahepatic [4]. Hilar cholangiocarcinomas, or Klatskin tumours, have a comparatively favourable mortality profile because of their anatomic location. While gallbladder carcinoma is a relatively uncommon neoplasm worldwide, it shows significant geographical variation in incidence. It is the most common type of biliary tract carcinoma and it occurs at a particularly high frequency in Chile, Japan and Northern India [1,5,6]. It is the fifth most common form of digestive tract malignancy in the United States of America and accounts for about 2,000 cases per year in the United States [1,6-10]. Gallbladder carcinomas have a strong female predominance and affect women two to six times more commonly than men with its incidence steadily increasing with age but occurring most frequently in the seventh decade of life [4,5,11-14].

Cholangiocarcinoma, on the contrary, accounts for 10-25% of all hepatobiliary malignancies and 3% of all gastrointestinal cancers worldwide. It is the second most common primary hepatic tumour after hepatocellular carcinoma [15-18]. The peak age for patients with the disease is the seventh and eight decades and the sex incidence shows a slight male preponderance [2,15]. The reported incidence in the USA is 1–2 cases per 100 000 (3,500 new cases per year) with no clear racial predisposition [15].

Studies of biliary tract carcinoma from various parts of Africa, including Libya, Egypt, Tanzania, Algeria and Nigeria consistently show a mean age of incidence in the sixth decade of life with a female preponderance [19-23]. A study of gallbladder carcinoma from South Africa showed a slightly higher mean age of incidence but still with a female preponderance at a ratio of 1.7:1 [24]. Literature on biliary tract (gallbladder and intra- and extrahepatic biliary tree) carcinomas is generally sparse in Nigeria as a whole and so this study has been undertaken in order to describe the pattern and risk factors of biliary tract carcinoma in Ibadan.

Materials and methods

We reviewed the available histopathology slides of cases of biliary tract carcinoma diagnosed in the Department of Pathology, University College Hospital, Ibadan over a 40 year-period (1971 to 2010). Where necessary, new haematoxylin and eosin (H&E) stained sections were obtained from archival formalin fixed paraffin embedded (FFPE) blocks. Ethical clearance for the study was obtained from the joint University of Ibadan-University College Hospital Ethical Review Committee. The demographics and clinical history of these cases were obtained from case notes, surgical daybooks, surgical pathology request forms, post-mortem records and Cancer Registry data. All cases were classified into histological subtypes according to the 2010 'WHO classification for tumours of the intrahepatic bile duct, gallbladder and extrahepatic bile duct' using histological features alone. The data obtained were subjected to statistical analysis using the Statistical Package for Social Sciences version 20. The continuous variables were compared using the student's T test while discrete variables were compared using the chi-squared test. The level of significance was set at $p \leq 0.05$.

Results

General

A total of thirty-seven (37) cases were histologically confirmed as biliary tract carcinoma (24 cases (64.9%) of gall bladder carcinomas and 13 cases (35.1%) of cholangiocarcinomas) and these were all included in this study. Biliary tract carcinomas accounted for 0.18% of all cancers diagnosed during the study period.

Age and gender distribution

The age range of the thirty-seven patients was from 37 years to 75 years with a mean age of 52.5 ±9.7 years. The mean age of female patients (51.3 ±9.4) years) was lower than that for male patients (55.6 ±10.3 years). $t = 1.3$, degrees of freedom = 34, $p = 0.19$.

The mean age of patients with gallbladder carcinoma (50 ±8.6 years; females 50.5 ±8.6 years and males 52.5 ±9.6 years) was lower than that of patients with cholangiocarcinoma (55.6 ±11.2 years; females 53.8 ±12.2 years and males 57.3 ±11 years), ($t = 1.6$, degrees of freedom = 34, $p = 0.13$).

There was no significant statistical difference in the gender age groups for both gallbladder carcinoma (p=0.72) and cholangiocarcinoma (p=0.61) cases. The limited number of cases available for analysis may be responsible for this statistical indifference but this can only be tested with a larger number of cases in the future.

Figure 1, shows that the peak occurrence of gallbladder carcinoma was in the fifth decade of life, while that of cholangiocarcinoma was in the sixth decade. Twenty-six patients (70.3%) were females and eleven (29.7%) were males giving an overall female to male ratio of 2.4:1 for biliary tract carcinomas.

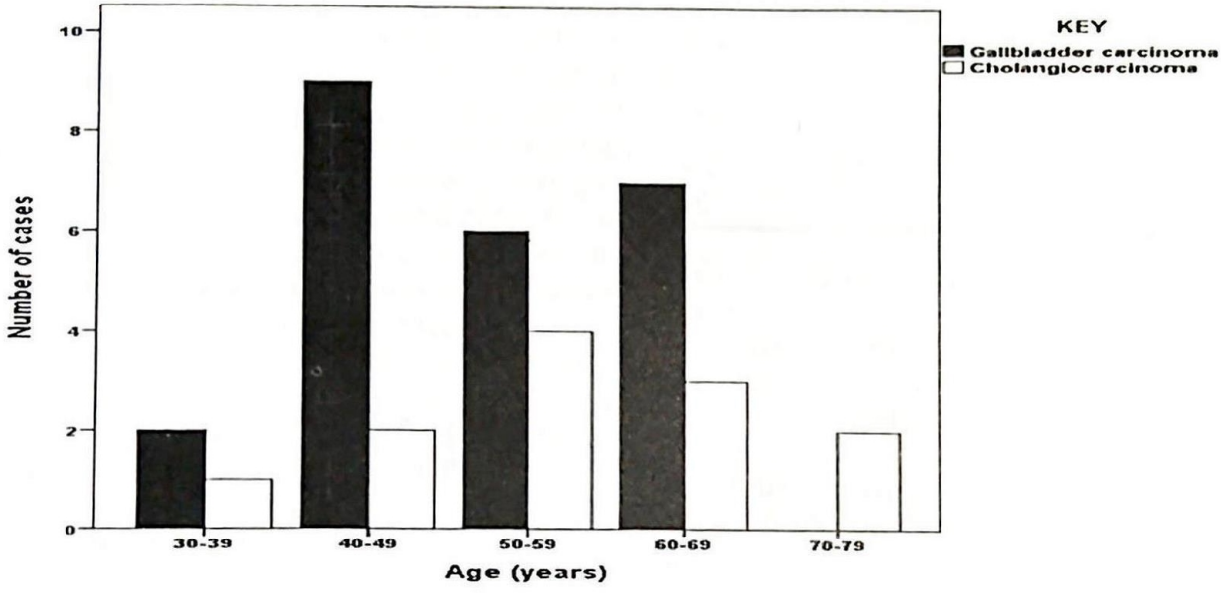

Fig. 1 - Age Distribution of Patients with Biliary Tract Carcinoma

With gallbladder carcinoma, there were twenty females and four males thus giving a female to male ratio of 5:1, while for cholangiocarcinoma there were six females and seven males giving a female to male ratio of 1:1.2. The difference in gender distribution for gallbladder carcinoma when compared to cholangiocarcinoma was statistically significant (χ^2 = 5.6, degrees of freedom = 1, p = 0.02).

Clinical presentation

Of the cases with available clinical data, the major symptoms of patients with gallbladder carcinoma were right hypochondrial pain, jaundice, weight loss, pruritus, anorexia and fever in descending order of frequency while the major symptoms of the patients diagnosed with cholangiocarcinoma were abdominal swelling, right hypochondrial pain, weight loss, jaundice, pruritus and ascites in descending order of frequency.

Gross morphology

The weights of cholecystectomy specimens ranged from 10 grams to 100 grams and they ranged in size from 3.5x1.5x0.5cm to 9.5x4.5x2.5cm. About fifty six percent of the specimens reviewed had thickened walls.

Four specimens contained stones, three of which were pigment stones and the remaining one was a compound stone. The stones ranged in diameter from 2cm to 3cm. Three other gallbladder specimens had stones lodged in their ducts and one had it in its Hartmann's pouch.

Specimens were described as having masses. The tumour masses in the gall bladders were either located in the fundus (4 cases) or within the lumina (4 cases). The fundic masses were described as fleshy (1), polypoid and fungating (1), hard irregular (1), and papillary (1). The luminal tumours were obliterative (2), greyish white friable (1) and spongy polypoid (1). One specimen also had whitish plaques in its wall. These masses ranged in dimension from 2x1.8x1cm to 8x6x5cm.

The majority of the specimens received as cases of cholangiocarcinoma were fragments of tissue ranging in dimension from 1x0.5x0.5cm to 3x0.2x0.2cm. Two of the specimens received were wedge biopsies of the liver which measured 1.6x1.0x 0.6cm and 1.0x1.0x0.2cm respectively.

Histological findings

The most common histological variant of gallbladder carcinoma was adenocarcinoma, biliary type which accounted for 13 (54.1%) of the 24 cases. The other

variant of adenocarcinoma was mucinous adenocarcinoma, which accounted for 2 (8.3%) cases. The other histological types were intracystic papillary neoplasm with an associated invasive carcinoma, 8 (33.3%) and adenosquamous carcinoma, which accounted for a single case (4.2%). The frequency of the histological variants of biliary tract carcinoma is shown in table 1.

Table 1: Frequency of the histological variants of biliary tract carcinoma

Histological variants	Frequency	%
Gallbladder carcinoma		
Adenocarcinoma, biliary type	13	35.1
Intracystic papillary neoplasm with an associated invasive carcinoma	8	21.6
Mucinous adenocarcinoma	2	5.4
Adenosquamous carcinoma	1	2.7
Cholangiocarcinoma		
Adenocarcinoma, NOS	13	35.1
Total	37	100

The cholangiocarcinomas were predominantly moderately to well differentiated adenocarcinomas composed of tubular glands, some of which contained variable amounts of mucin and the stroma surrounding the neoplastic glands showed variable degree of desmoplasia.

Of all the histological variants of gallbladder carcinoma there was a clear female preponderance except the single case of adenosquamous carcinoma whilst cases of cholangiocarcinoma were seen predominantly in males (Table 2).

Table 2: Gender distribution of the various histological variants of biliary tract carcinoma.

Histological Variants	Gender	
	Male	Female
Gallbladder carcinoma		
Adenocarcinoma, biliary type	3	10
Intracystic papillary neoplasm with an associated invasive carcinoma	0	8
Mucinous adenocarcinoma	0	2
Adenosquamous carcinoma	1	0
Cholangiocarcinoma		
Adenocarcinoma, NOS	7	6
Total	11	26

Discussion

The frequency of biliary tract carcinoma at 0.18% of cancers during the study period indicates that they are also uncommon in our environment. A previous study of cases seen between 1960 and 1971 in this hospital showed a relative ratio frequency (RRF) of 0.3% for biliary tract carcinomas [25].

In a subsequent report the majority of gallbladder carcinomas were found to have occurred in the sixth decade of life with a female to male ratio of 2:1, whereas this study shows the peak occurrence to be in the fifth decade and the female to male ratio to be 5:1 [26]. It would appear that the gender gap is widening while the age incidence is dropping. By comparison, gallbladder carcinoma cases accounted for about 0.3% of all cancer cases that were diagnosed at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria between January 1990 and December 2010, most cases occurring in the sixth decade and with a female to male ratio of 7:1 [27]. A similar study of 21 cases of gallbladder carcinoma over a 5-year period from the Nnamdi Azikiwe University Teaching Hospital, Anambra state, Nigeria showed the mean age of the patients to be in the sixth decade, the peak incidence being the 7th decade and the female to male ratio was 2.5:1 [28]. The incidence of gallbladder carcinoma in this study was 3.04%, while that at the University of Calabar Teaching Hospital, Calabar was 0.6% [19,28].

The incidence of gallbladder cancer is low in this environment as in certain other geographical locations including Singapore and the United States of America (2.5 per 100,000) [5,10,29,30].

Gallbladder carcinoma and cholangio carcinoma occurred with increasing incidence from the 3rd decade and were most common in the 5th and 6th decades of life respectively, as is the case in the English literature. The peak frequency of occurrence for gallbladder carcinoma was during the 7th decade while cholangiocarcinomas are usually diagnosed in the 7th and 8th decades of life with the majority of patients presenting after 65 years [2,4,6,14].

Biliary tract carcinomas appear to have occurred a decade earlier in this environment and there are probably many reasons for this, least of which is the life expectancy (male=52 years, female=54 years) that may be partly responsible for the age distribution pattern in this study compared to the developed parts of the world where the life expectancy is about three decades more [31].

The gender ratio of 5:1 of gallbladder carcinoma corroborates studies that have shown that gallbladder carcinoma affects women 2 to 6 times more commonly than men [1]. Interestingly, while previously thought not to be a sex hormone-mediated process, recent findings raise the possibility that gallbladder carcinogenesis may have estrogen- or progesterone-mediated features [12]. The female to male ratio of 1:1.2 for cholangiocarcinoma also

corroborates the fact that cholangiocarcinoma is slightly more common in males than females [3,10]

The difference in gender distribution for gallbladder carcinoma as compared to cholangiocarcinoma in this study was statistically significant. Our finding that the most common histological variant of gallbladder carcinoma was adenocarcinoma concurs with the findings in other studies from the literature, in which adenocarcinoma (well to moderately differentiated) was the most common histological variant of gallbladder carcinoma accounting for 80-95% of cases [6,14].

In this study, 33.3% of the gallbladder specimens contained stones. Gallstones are known risk factors associated with gallbladder carcinoma, it would seem they were positively associated with cases from our own centre too [1,5,10,14,29,32].

Gallbladder carcinoma usually produces asymmetric thickening of the gallbladder wall with infiltration of surrounding structure. It is therefore not surprising that 56.3% of the gallbladder specimens reviewed in this study had thickened walls.

However, none of the associated risk factors such as parasitic infestations, primary sclerosing cholangitis, biliary duct cysts, hepatolithiasis, toxins, inflammatory bowel disease, hepatitis B and C virus-related cirrhosis, diabetes, obesity, alcohol, smoking and host genetic polymorphisms for the development of cholangiocarcinoma could be identified with certainty in these patients aside from age because of inadequate clinical information [3,18,33]. Nevertheless, there were a few interesting findings amongst our patients; one patient had a history of a previous episode of febrile illness accompanied by jaundice and was noticed to have multiple tattoo marks on the body, three (3) other patients had hepatomegaly with dilation of the intrahepatic ducts that were diagnosed sonographically, four (4) had multinodular enlarged liver, and finally, there was a case of an enlarged cirrhotic liver which was diagnosed intra-operatively. Thus, the other possible deducible risk factors in this study include alcohol, hepatitis B virus and hepatitis C virus related cirrhosis.

Conclusion

The findings in this study of biliary tract carcinoma in Ibadan generally agree with what has been described in the English literature in respect of gender distribution, histological types and some associated risk factors as well as its rarity. There is some difference however in respect of the age distribution in that the peak occurrence of cholangiocarcinoma was in the sixth decade, while the peak occurrence of gallbladder carcinoma was in the fifth decade. There might be some genetic basis to predisposition yet unknown or heavy early environmental exposure to some carcinogens such as hepatitis B and C viruses and alcohol.

Some risk factors associated with biliary tract carcinoma such as female gender (83%), gallstones (33%) and dysplasia (42%), a premalignant lesion were found to be present in some of our patients.

The limitations encountered in this study included the fact that there was no extrahepatic biliary lesion seen since the surgical specimens reviewed for the cholangiocarcinoma cases were predominantly liver biopsy specimens. This rarity of extrahepatic biliary lesion could also be explained by the decline in autopsy rates. Metastatic carcinomas to the liver were also difficult to exclude in the cholangiocarcinoma cases reviewed.

We recommend adequate and detailed clinical information with essential laboratory and radiological investigations for suspected cases of biliary tract carcinoma in order to identify or exclude possible associated risk factors for future cases. There is also a need for extensive sampling of the gallbladder specimens for histological review in the future in order to identify and appreciate the spectrum of premalignant lesions that are associated with the carcinomas and this should determine the further course of action in our cases.

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