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Review Article

Signet ring cell cholangiocarcinoma in a patient previously operated for cholecystectomy: is there any connecting link?

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ABSTRACT

Cholangiocarcinoma are malefic tumours of bile duct. Signet ring cell carcinoma (SRCC) is rare entity. Several risk factors have been attributed to its ethology, the main overriding link between two being chronic inflammation of the bile system. Cholecystectomy has also been a proposed risk factor. This study was undertaken in Department of Pathology at LLRM Medical College, Meerut. A 49 years old female, operated for cholecystectomy 1.5 year back in same hospital, now presented with chief complains of jaundice and abdominal discomfort. The blood chemistry revealed increased total bilirubin (13.7 mg/dl), Alkaline phosphatase (877.6 IU/L), Carbohydrate Antigen (CA) 199(184 U/ml) and Carcinoembryonic antigen (CEA) (14.5 ng/ml). Computed Tomography (CT) showed a stricture in mid Common bile duct (CBD). Excision of stricture was done using retrocholic hepatico-jejunostomy. Tissue was submitted for histopathology. Histopathological assessment showed SRCC. The patient failed to turn up for further management but returned back after a span of time presenting with gross ascites and pallor ultimately leading to death within 12 weeks of diagnosis. This was the first case of SRCC to arise in a patient who had a previous history of cholecystectomy. Whether there is some connecting link between the two is still not clear. Further studies are warranted in this direction to establish cholecystectomy as an etiological factor for cholangiocarcinoma.

Keywords: Cholecystectomy, Connecting link, Malefic, Mid common bile duct, Signet ring cell cholangiocarcinoma, Stricture

INTRODUCTION

Cholangiocarcinoma are catastrophic tumours that arise from epithelial cells of bile ducts.[1] They are intrahepatic, perihilar and distal types.[2] Morphologically, most of them are well to moderately differentiated adenocarcinoma.[3] Others include, papillary, mucinous, squamous, small cell, mesenchymal and signet ring cell, latter being a rare variant.[4] The various risk factors are Alcohol, Obesity, Cigarette smoking, Primary sclerosing cholangitis, Clonorchis, Opistorchis infection, Caroli disease, Congenital choledochal cyst, Choledocholithiasis and Chronic intrahepatic lithiasis.[1,2,5,6]

Though increased risk of cholangiocarcinoma has been seen in previously cholecystectomized patients, its definite role still remains controversial.[5-7]

REVIEW OF LITERATURE

Signet ring cell carcinomas though common in sites like stomach is rare tumour of bile duct epithelium.[4]

Brief history

A 49 years old lady presented with history of yellowish discoloration of eyes and skin, along with abdominal

discomfort and fever for one month. Physical examination showed icteric sclera. However no palpable lump was noted. Rest of the histories were insignificant except for past medical history which revealed that this patient was operated for cholecystectomy 1.5 years back in same hospital. The blood chemistry revealed increased total bilirubin (13.7 mg/dl), Alkaline phosphatase (877.6 IU/L), CA19-9 (184 U/ml) and CEA levels (14.5 ng/ml). Serum urea, creatinine, electrolytes and blood sugar were within normal limits. Contrast Enhanced Computed Tomography (CECT) whole abdomen was done which revealed dilation of proximal CBD with irregular thickening and narrowing of mid CBD causing gross Intra hepatic biliary reflux disease (IHBRD) (Figure 1). Liver, stomach and colon were unremarkable.

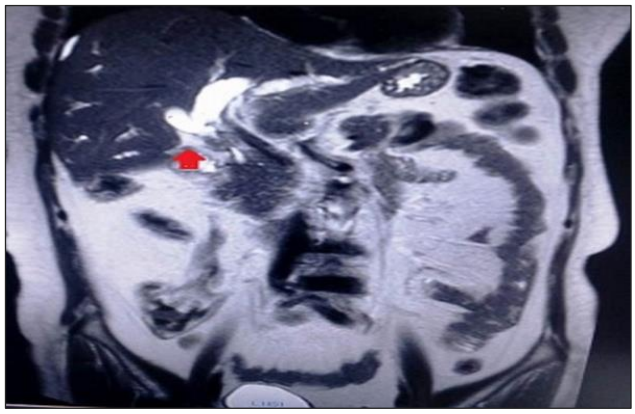

Figure 1: CT scan showing stricture of CBD.

Patient was managed operatively by excision of CBD stricture. Roux en Y Retrocholic Hepatico-jejunostomy with suprahepatic peritoneal drainage was done. Segment of excised stricture was sent for biopsy. Peritoneal washing was also sent for histopathological examination. Gross examination showed 0.8×0.7×0.3 centimeters of greyish white, irregular piece of tissue. Biopsy was processed and stained with H and E. Microscopy showed signet ring cells arranged in clusters, solid tubules, trabecular and vague glandular pattern (Figure 2).

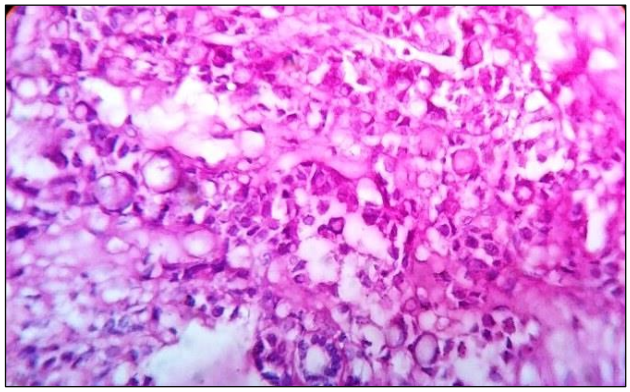

Figure 2: Histopathology showing signet ring cells (h and e stain, 400x).

These signet ring cells had eccentric nucleus and vacuolated cytoplasm ,comprising of >80% of the tumour cells Periodic acid Schiff (PAS) stain further revealed these cells (Figure 3).

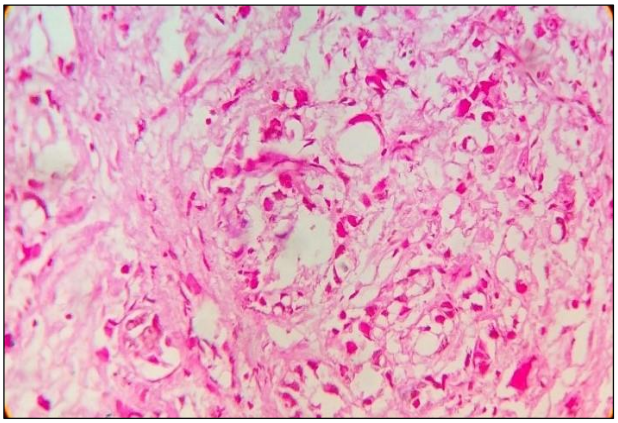

Figure 3: Signet ring cell morphology with eccentric nucleus (pas stain, 400x).

Extensive perineural invasion was noted (Figure 4).

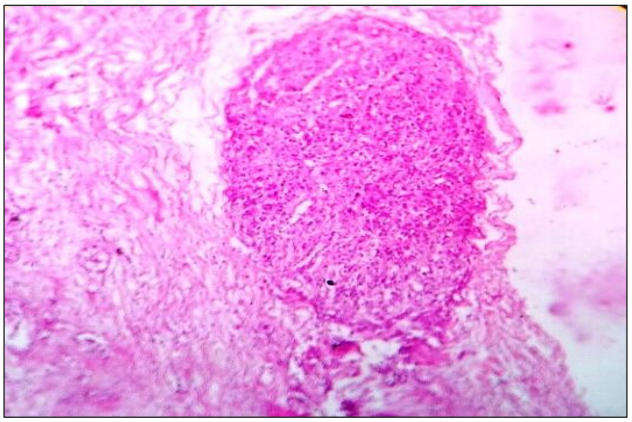

Figure 4: Histopathology showing perineural invasion (h and e stain, 100x).

Peritoneal fluid however did not reveal any atypical or malignant cells. Final diagnosis of signet ring cell cholangiocarcinoma was conferred. Further clinical and radiological examination was done to exclude primary from other sites including breast, Gastrointestinal tract, colon and ovaries, showed no evidence of malignancy at these sites. The patient was kept on palliative therapy and regular follow up. She however failed to turn up and presented again after few months with gross ascites, intense pallor and difficulty in breathing finally leading to death of the patient within 12 weeks of diagnosis.

Incidence

CC are most common biliary tract malignancy and the second most common primary hepatic malignancy arising in 5th to 6th decade of life with slight male

predominance.[2,8,9] Its incidence is reported to be highest in Hispanic and Asian populations (2•8-3•3 per 100 000) and lowest in non-Hispanic white people and black people (both 2•1 per 100 000).[10,11]

Table 1: Tabulated description of all the reported cases of signet ring cell carcinomas.

No.	Author	Year	Age/ sex	Race	Signs and symptoms	Type of lesion	Treatment	Mortality/ Morbidity	Other associated significant disease
1	Kita et al[3]	2014	73/M	Japanese	Obstructive jaundice	CT: stricture in lower bile duct	Pancreaticoduodenectomy with pylorus preservation	Disease free in 1 year follow up	
2	Lee et al[4]	2010	55/M	Korean	Jaundice and pruritus	Obstruction of distal CBD	PPPD [a] and Chemo radiotherapy	Disease free survival 1yr +	-
3	Ogata et al[11]	2010	42/F	Japanese	Obstructive jaundice	Stricture	Subtotal Stomach preserving pancreatic oduodenectomy	Disease free survival 6 months+	
4	Somer et al[13]	2012	66/F	N/A	Obstructive jaundice	ERCP[b]: Stenosis of left hepatic duct	Roux-en-Y cholangiojejunostomy	16 post-operative day	
5	Kwon et al[14]	2014	63/M	Korean	Epigastric pain and jaundice	ERCP :polypoid mass at distal CBD	Pylorus-preserving pancreatoduodenectomy	15 months	
6	Mizukami et al[15]	1999	74/M	Asian	Jaundice and fever	Multiple cystic lesions in liver, stricture of hepatic duct	None	3 weeks	-
7	Hiraki et al[16]	2007	78/F	Japanese	-	Stenosis of CBD	NA	3 months	-
8	Matsumoto et al[17]	2011	72/M	Japanese	Obstructive jaundice	Tumour with cystic component	Subtotal gastrectomy and chemotherapy	3 months	
9	Hua et al[18]	2015	52/M		Jaundice, pruritus	mass		6 months	
10	Chedid et al[19]	2015	66/F	Caucasian	fatigue, anorexia, jaundice, itching and pale stools	CT: tumour	Laparotomy ,biliary tree resection, en-bloc regional lymphadenectomy	15 months	Renal cell carcinoma
11	Shechter et al[20]	2017	69/M	Caucasian	Abdominal pain, jaundice	Mid CBD	Chemotherapy	3 weeks	
12	Welsh et al[21]	2016	55/F	Caucasian	Jaundice, Abdominal pain	Distal CBD	PPPD	4 months	-
13	Present study	2019	49/F	Caucasian	Jaundice, abdominal discomfort	Mid CBD		3 months	Cholecystectomy for chronic cholecystitis

aERCP: Endoscopic retrograde cholangiopancreatography
bPPPD: Pylorus preserving pancreaticoduodenectomy

On the basis of anatomical location within biliary tree, Cholangiocarcinoma have been classified into three major subgroups, intrahepatic (<10%) (iCCA), perihilar (pCCA) (50%), and distal (dCCA) (40%) subtypes, the latter two were previously grouped under extra hepatic carcinoma.[2,10,12] Among them, pCCA is the commonest. 2 Hilar cholangiocarcinoma's which involve the bifurcation of the hepatic duct are called klatskin tumours.[13] SRCC of extra hepatic bile duct is an extremely rare variant.[14] Extensive search of English literature in PubMed was done using key words SRCC and CBD and only 11 such well- documented cases have been studied and tabulated (Table 1).

All the clinic radiological details and demographic details are also summarized in Table 1.

DISCUSSION

SRCC have fatal outcome. Most of these tumours (70%) originate de novo for which no attributed risk factors have been identified. However studies have suggested that chronic inflammation and bile duct cell injury induced by obstruction to bile flow, provide a suitable platform for development of cholangiocarcinoma.[22]

Some major risk factors are primary sclerosing cholangitis, parasitic infestation opistorchis viverrini, Clonorchis sinensis), biliary duct cysts, Hepatitis B and C, cholelithiasis and other lifestyle related factors including Diabetes Mellitus, Obesity, alcohol consumption and tobacco chewing.[2,9,23] According to some studies the risk factor for intrahepatic and extra hepatic cholangiocarcinoma varies.[7,24]

Petrick et al, in their study noted that incidence of hypertension, dyslipidemia and Type II diabetes were prevalent in both ICC and ECC while Non-Alcoholic Fatty Liver Disease (NAFLD), obesity, Hepatitis C virus (HCV), lupus, Alcohol related disorders, nonspecific cirrhosis and hemochromatosis were more associated with ICC.[24] On the other hand cases of cholangitis, chronic pancreatitis, choledochal cyst, cholelithiasis and choledocholithiasis were more in ECC.

Many studies were undertaken in the past to study the relationship between cholecystectomy and other Gastrointestinal Tract (GIT) malignancies. It was seen that cholecystectomy increases the risk of colorectal, liver and pancreatic cancers.[25-28] Noguiera et al, reported that gall stones and cholecystectomy were associated with an increased risk of cancers occurring throughout GIT.[29] Similarly in a study of 99 patients; Kang et al, reported increased association of gall stones and cholecystectomy with stomach cancers.[30]

The relationship between intra and extra hepatic cholangiocarcinoma and cholecystectomy is still not clear due to sparse literature and controversial results. In the past studies cholecystectomy was seen to be associated with decreased risk of cholangiocarcinoma.[31]

However various other studies undertaken afterwards showed that cholecystectomy increases the risk of cholangiocarcinoma.[5,7] Welzel et al, found that cholecystectomy increased the risk of both ECC and ICC.[5] Tao et al, also conducted a study in China and found the same results.[32]

Met analysis study by Xiong et al, showed that risk of cholangiocarcinoma was associated with a 54% increase in previously cholecystectomized patient.[7] Also the risk was only for ECC and not for ICC. In this case also the patient had past history of cholecystectomy and later on developed ECC, the time duration being a gap of approximately 2 years.

Since there are a lot of controversial results in various studies it is still difficult to say that cholecystectomy increases the risk of development of cholangiocarcinoma. Further studies are warranted to validate this association There are various proposed possible mechanism behind this association, firstly it could be due to the gall stones itself rather than cholecystectomy which causes the cancer. Secondly cholecystectomy causes the accumulation of bile and secondary bile acids which further increases the tumorigenesis in hepatic tissue. As both cholangiocytes and hepatocytes differentiate from the same progenitor cells, it is proposed that secondary bile acids triggers tumorigenesis in cholangiocytes through the same mechanism.[7]

The patients of extra hepatic cholangiocarcinoma presents with jaundice, pruritus, pale stools, dark urine and loss of weight while intrahepatic cholangiocarcinoma presents as liver mass and pain.[1,14,33] In this case patient presented with jaundice and abdominal discomfort.

CEA levels can be increased in cholangiocarcinoma but CEA levels alone are unreliable due to low specificity. CA-19-9 is another serum biomarker used for diagnosing cholangiocarcinoma. It has a sensitivity of 67-89% and a specificity of 86%-98%, the levels being more than 100 U/ml.[2,10]

In this case the CEA and CA 19-9 levels were 14.5 ng/ml and 184 U/ml respectively. In the patients presenting with obstructive jaundice, ultrasound of the liver and biliary tract can be used as an initial test to identify the obstruction and ductal dilatation and in some cases, it is sufficient to diagnose cholangiocarcinoma.[33]

In suspected cases of malignant biliary obstruction, ERCP and EUS may provide tissue for definite diagnosis. EUS is however more superior to ERCP with a sensitivity of 66-90% and specificity of 90-100%.[20]

CT can find out the level of biliary obstruction or focal biliary dilatation when there are no stones.[22]

In this case CT revealed dilatation of proximal CBD with irregular thickening and narrowing of mid CBD causing gross intrahepatic biliary radicle dilatation. Signet ring cell carcinoma is poorly differentiated malignant neoplasm that is common in stomach and other organs like colon, prostate, and bladder.[19,20]

SRCC of the biliary system is a rare entity and most of them arise from the gall bladder.[4]

Signet ring cell carcinoma of extra hepatic bile duct is classified as a separate entity by World Health Organization, where predominant cells are those having intracytoplasmic mucin displacing the nucleus to periphery.[14] This shape is rendered by loss of function of the tumour suppressor gene CHD1, which further leads to loss of cell adhesion protein E-cadherin and lack of formation of normal glands. Thus mucin accumulates in large vacuoles and gives the appearance of signet ring cell.[20]

Other metastatic tumours especially primary from Gastric tumours has to be ruled out before making this diagnosis. In this case, no lesions were found in stomach, duodenum or colon, thus excluding the metastatic origin. Signet ring cell carcinoma undergoes rapid clinical deterioration with the survival period varying from 6 months to as less as 3 weeks.[20]

In this case also the survival period was short of 12 weeks.

CONCLUSION

Signet ring cell carcinomas are rare tumours of bile duct epithelium. This case is unique for several reasons. Firstly in this case, there was no mass lesion on CT, instead only a stricture of mid CBD was noted. Secondly this was the first case of signet ring cell cholangiocarcinoma to arise in a patient who had a previous history of cholecystectomy. Whether there is some connecting link between the two is still not clear. Further studies are warranted in this direction to establish cholecystectomy as an etiological factor for cholangiocarcinoma.

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