Carcinoma in chronic calcific pancreatitis: review of literature

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ABSTRACT

Carcinoma occurring the setting of chronic calcific pancreatitis (CCP) are usually multifocal, poorly differentiated, advanced on presentation and associated with poor overall survival. Hence it is imperative that these patients should be identified in the early stages of malignant progression where by curative resection can then be employed. If not, only palliative approaches are feasible in advanced stages. We wish to present our experience of pancreatic carcinoma in the setting of CCP along with a review of literature.

Keywords: CCP, Pancreatic cancer, Malignancy, CA 19-9

INTRODUCTION

Chronic calcific pancreatitis (CCP) is associated with chronic inflammation and fibrosis of the pancreas. Carcinoma can occur as a rare complication of CCP due to the nature of chronic inflammation. It is very rare occurring in 0.1-0.5% of CCP cases where curative surgery is usually not feasible.\textsuperscript{1,2}

Our study database of CCP patients showed a few patients with malignancy. The main features of our analysis are as follows. The mean age of all the patients in this subset was 37 years (range: 26-46 years) with slight female predisposition (2:3). All the patients were with previous history of diabetes (3 years -15 years) and had history of long term abdominal pain with a mean of 6 years (2-18 years). The etiology was alcohol induced in 2 (40%) and unknown in 3 (60%). On CECT, all patients had head mass (mean 5 cm) with ductal and parenchymal calcification. The CBD was dilated in all patients with mean of 14 mm (12-18 mm) with mean serum bilirubin of 4.6 mg% (range- 0.8-18 mg%). The MPD was also dilated with mean diameter of 12.2 mm (8-19 mm). CA 19-9 levels were done in all patients with increased levels in 3 (60%) with levels ranging from (20-10, 998 IU/ml) (N<37 IU/ml). Two patients were diagnosed preoperatively (one with liver metastasis and one with peritoneal/omental/liver metastasis) and as they had features of gastric outlet obstruction (GOO), palliative gastro jejunostomy (PGJ) was done. Three patients were diagnosed only post operatively after head coring with pathology showing foci of adenocarcinoma. Incidentally, the frozen section done intraoperatively was negative in all these patients who also had normal CA19-9 levels. Hence after head coring, these patients were given palliative chemotherapy with mean survival of 6 months.

INCIDENCE

The actual incidence of malignancy in chronic calcific pancreatitis depends on the etiology of the chronic calcific pancreatitis. The cumulative risk of pancreatic cancer in patients with chronic calcific pancreatitis with alcoholic etiology was 1.8% at 10 years and 4% at 20 years.\textsuperscript{3} Another study describes the risk at 1.1% at 5 years and 1.7% at 10 years.\textsuperscript{4} An Indian study of 1086 patients describes the risk at 4%, where the most common etiology was idiopathic followed by alcoholic...
pancreatitis.\(^5\) In another study, the incidence of carcinoma among patients with head mass and tropical pancreatitis, a distinct subset of chronic pancreatitis, was higher at 8.3\%.\(^6\) Carcinoma in this subset is characterized by younger age of onset and earlier exocrine, endocrine deficiency.

### Table 1: The features of patients with CCP and carcinoma.

<table>
<thead>
<tr>
<th>SL No</th>
<th>Sex</th>
<th>Age</th>
<th>Etiology</th>
<th>Pain duration (yrs)</th>
<th>DM duration (yrs)</th>
<th>CBD diameter (cm)</th>
<th>Main pancreatic duct diameter (cm)</th>
<th>Serum Bilirubin (mg/dl)</th>
<th>CA19-9 (IU/ml)</th>
<th>Diagnosis</th>
<th>Surgery</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>31</td>
<td>Unknown</td>
<td>0.4</td>
<td>15</td>
<td>1.4</td>
<td>1</td>
<td>2.2</td>
<td>10998</td>
<td>P</td>
<td>PGJ</td>
<td>2</td>
</tr>
<tr>
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<td>46</td>
<td>Unknown</td>
<td>0.1</td>
<td>3</td>
<td>1.4</td>
<td>1.9</td>
<td>0.8</td>
<td>31.6</td>
<td>P</td>
<td>FP+PG</td>
<td>8</td>
</tr>
<tr>
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<td>F</td>
<td>42</td>
<td>Unknown</td>
<td>15</td>
<td>5</td>
<td>1.8</td>
<td>1.2</td>
<td>18</td>
<td>4120</td>
<td>I</td>
<td>PGJ</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>40</td>
<td>Ethanol</td>
<td>4</td>
<td>8</td>
<td>1.4</td>
<td>0.8</td>
<td>1.2</td>
<td>37</td>
<td>I</td>
<td>FP</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>26</td>
<td>Ethanol</td>
<td>2</td>
<td>3</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>20</td>
<td>I</td>
<td>FP</td>
<td>8</td>
</tr>
</tbody>
</table>

CA19-9=Carbohydrate antigen, F=Female, FP=Freys procedure, M=Male, P-Preoperative, I-Intraoperative/postoperative.

### ETIOLOGY

Hereditary pancreatitis, an autosomal dominant disorder involving the PRSS1 gene is associated with 40-55\% life time risk of pancreatic cancer.\(^7\) Idiopathic pancreatitis, which is due to SPINK1 gene mutation is also associated with increased risk. The role of smoking in the causation of pancreatic cancer is well known. The EUROPAC study shows hereditary pancreatitis is associated with increased risk of pancreatic cancer from a risk of 1.5\% at 20 years after symptom onset to 44\% at 70 years from symptom onset.\(^8\) The exact role of alcohol in the causation mechanism of cancer is unknown but is associated with increased risk. The role of diabetes mellitus as a risk factor or a confounding factor in causation of pancreatic cancer in CCP patients is unclear.\(^9\)

### CLINICAL FEATURES

Clinical features of CCP and early cancer in the setting of CCP are difficult to differentiate as both are associated with weight loss and anorexia. It is to be noted that early pancreatic cancer in CCP and denovo pancreatic cancer is also difficult to differentiate. However, pancreatic cancer in CCP with tropical pancreatitis is associated with more pain, weight loss, worsening of exocrine deficiency, more local invasion and peritoneal metastasis whereas de novo pancreatic cancer is associated with weight loss and increased liver metastasis.\(^10\)

### INVESTIGATIONS

#### Tumour markers

As clinical investigations and conventional markers like CA19-9 are ineffective to clearly delineate pancreatic malignancy in the setting of CCP, newer bio markers are in the process of investigation.

CA 19-9 is the most commonly used marker of malignancy in CCP patients but its utility is severely limited by cholangitis and pancreatitis which are associated with increase in levels.\(^11\) In a study, CA 19-9 > 127 ng% was the single most important predictor of malignancy which along with CBD diameter of >14.5 mm, main pancreatic duct diameter >11.5 mm, serum bilirubin >5.8 mg% was associated with high sensitivity and specificity.\(^12\)

In another study, CA 19-9 levels more than 300 IU/ml was 100\% specific for malignancy in CCP.\(^13\) Another study revealed the combination of significant weight loss (>10\%), serum bilirubin >3 mg%, and CA 19-9 >35 IU/ml was associated with a 100\% positive predictive value of malignancy.\(^14\) It was noted that an increased CA 19-9 value was more predictive of malignancy in non jaundiced than jaundiced patients. In another study, CA 19-9 levels >1500 IU/ml in the absence of jaundice were associated with malignancy.\(^15\)

Newer markers like plasma micro RNA and K Ras mutations are now introduced to diagnose pancreatic cancer accurately but it is not yet validated in large trials.\(^16\)\(^19\)

#### Radiological investigations

The most common radiological investigation used to differentiate malignancy and CCP is CECT. Though it is extremely difficult to differentiate CCP and malignancy in background of CCP, CCP is associated with delayed contrast enhancement whereas malignancy in the setting of CCP has a characteristic peak enhancement and wash out.\(^20\)

EUS has been used primarily to biopsy suspicious lesions but it is associated with low sensitivity for diagnosis of malignancy.

PET CT is not yet clinically used to differentiate malignancy from the background of CCP in normal clinical setting and its utility is confined to cases with equivocal findings on CT or EUS.\(^21\)
TREATMENT

The role of biopsy in the setting of suspected carcinoma in the setting of CCP is unclear as a negative biopsy does not rule out malignancy. Biopsy can be offered in selective subgroups of patients like those with age more than 55, elevated serum bilirubin, CA19-9 >120 IU/ml,34 sudden abdominal pain, weight loss, and worsening diabetes.25,26 Patients with preoperative suspicion of malignancy in the background of CCP should be offered resection, mostly Whipple’s Pancreatoduodenectomy as the masses are located in the head. CCP patients with alcoholic aetiology tend to respond to the treatment better than patients with tropical pancreatitis.12

Intraoperatively, in suspicion of pancreatic carcinoma in CCP, frozen section can be done and if negative, a Freys procedure can be followed.12 However it is to be noted that a frozen section in no way excludes malignancy and one could still have malignancy on the final histopathology report. The prognosis in such settings are usually poor.

CONCLUSION

Pancreatic cancer in the setting of chronic pancreatitis is a rare complication. Numerous markers (clinical and biochemical) have been tried to accurately diagnose it in the setting of chronic pancreatitis. In our study, pancreatic cancer in the setting in the setting of CCP was associated with young age, diabetes, increased serum bilirubin, pancreatic ductal dilation, pancreatic calcification, and raised CA 19-9 levels. An accurate diagnosis is a must as only a radical pancreatic resection would suffice in the unlikely occurrence of malignancy in the setting of CCP.

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REFERENCES


