

Chapter 29

**Early detection of malignancy in tropical
pancreatitis – is it possible?**

Sudhindran S, Prasad Krishnan

Summary

Carcinoma of the pancreas is an important cause of death in Kerala. This has been attributed to the high frequency of tropical calcific pancreatitis (TCP) in this part of India. We describe our experience with imaging, biochemical markers as well as the clinical profile of our subjects with pancreatic cancer arising in the setting of previous TCP. In our series, we found that none of the standard investigative modalities were useful in the early detection of cancer in TCP patients. Indeed, despite the prior knowledge of the diagnosis of TCP, which alerts us to the possible development of malignancy in these patients, the timely recognition of malignancy in TCP might prove to be very difficult, as is the case with de novo pancreatic cancers. In future, the increased use of imaging tools such as multi-slice CT scanners and MRI scanners might lead the way towards an earlier and a more precise diagnosis.

Introduction

Carcinoma of pancreas is a leading cause of cancer death in Kerala. This may be partly due to the high frequency of tropical calcific pancreatitis (TCP) in this region, which has now been more or less documented as a premalignant condition¹⁻³. Nonetheless, malignancy developing in patients with established TCP is detected at an advanced and incurable stage, that "curative" resection is often not possible. Although overall survival in carcinoma of pancreas may be abysmal, the only realistic approach to long-term survival is complete resection. Accordingly, patients with TCP, a known predisposing factor for pancreatic carcinoma, would be among the first to benefit from early detection of this cancer. The current methods for detection of pancreatic malignancies include biochemical markers such as CA 19-9 and radiological imaging techniques, which are regrettably suboptimal in de novo pancreatic cancers. We looked at the utility of these modalities in the detection of carcinomas occurring in patients with TCP.

Methods

Over a 6 year period from 1999, 61 patients with tropical pancreatitis underwent surgery at Amrita Institute of Medical sciences, Kochi, Kerala.

The indications for surgery was intractable pain (n=46), obstructive jaundice (n=7), gastric outlet obstruction (n=3), leaking pseudocyst (n=1) and suspicion of malignancy (n=4). Over a mean follow up of 30 months (range 4 to 56 months) histologically proven malignancy was detected in 9 patients in this group. The value of serum CA 19-9, occurrence of obstructive jaundice, endoscopic retrograde cholangio pancreatography (ERCP) findings and CT findings were reviewed in patients with and without malignancy (9 and 52 patients respectively) to distinguish any disparity between the two groups that would facilitate early detection of cancer in TCP. Patients with clinically obvious metastatic disease such as presence of supraclavicular or Sister Joseph nodes, peritoneal carcinomatosis on rectal examination, ascites, or radiologic evidence of liver metastasis were excluded from analysis (n=5 patients).

Results

Predictive value of CA 19-9

The mean value of CA 19-9 in patients with proven malignancy was 1086 ± 846 (range 101 to 1948) as compared to 136 ± 257 (range 3 to 1408) in those without malignancy. This difference however was not statistically significant (Mann-Whitney U test). The highest value for CA 19-9 that occurred in the benign group was 1408 and was associated with benign biliary stricture and cholangitis. It appears that very high values of CA 19-9, for instance, in excess of 1500, particularly in the absence of jaundice may have a high positive predictive value for malignancy. Below this level, the negative predictive value was much less dependable in this group of patients to rule out malignancy.

Occurrence of obstructive jaundice

Occurrence of obstructive jaundice in patients with known TCP may indicate benign biliary stricture or development of malignancy in the pancreatic head region. In our study 7 patients had developed obstructive jaundice, out of which 3 had malignancies (2 carcinoma of head of pancreas and 1 cholangio carcinoma). The other four patients had benign biliary stricture, due to inflammatory mass in the head of the pancreas. Repeated attempt at endoscopic stenting was unsuccessful

in relieving the jaundice in all four patients with benign strictures and eventually they underwent surgical decompression (whipple-1, Frey's procedure with hepaticojejunostomy-3 patients). Over a mean follow up of 18 months none of these four patients has developed any features to suggest occurrence of malignancy.

The 3 patients with malignant obstructive jaundice were, in fact suspected to have malignancy on CT imaging and 2 had preoperative diagnosis of carcinoma established by CT guided Fine Needle Aspiration Cytology (FNAC). The third patient had malignancy confirmed on frozen section biopsy at surgery. This patient underwent a "curative" resection (Whipple's procedure), whilst the remaining two merely had palliative biliary and gastric bypass, owing to advanced local disease with adjacent vascular invasion. All three have died (within 2 to 14 months), one with liver metastases and the others with malignant cachexia. The longest survivor lived 14 months following the Whipple's procedure.

ERCP findings

ERCP was performed in 31 out of the 61 patients in this study group. The primary indication for ERCP were obstructive jaundice (n=7), suspicion of malignancy (n=4) and in preparation for endotherapy for pancreatic stones in the residual 20 patients. Out of the seven patients with obstructive jaundice, 4 patients had smooth, tapering terminal bile duct strictures appearing "radiologically" benign and underwent initial biliary stenting and subsequent surgical drainage procedure (described above). Remaining three patients had irregular biliary stricture, highly suggestive of malignancy and all three were later histologically proven to have carcinomas (2 adenocarcinoma of pancreatic head and 1 cholangiocarcinoma).

In four patients, where ERCP was done for suspicion of malignancy, there was non visualization of part of the main pancreatic duct. All four were operated and malignancy was detected only in one patient where the ERCP had shown total main pancreatic duct block at the head region without the presence of stones. The other 3 had pancreatic duct blocks due to calculi and had excellent symptomatic relief following duct drainage procedure (Frey's procedure)

On the whole, ERCP findings per se were not entirely diagnostic of malignancies in TCP. Nonetheless, total blockage of pancreatic duct (in the absence of a contributory stone) and irregular bile duct stricture appeared to surface as strong indicators for malignancy in TCP, in this analysis.

CT scan findings

Of the 9 patients with malignancy out of the total 61 in our study group, CT had hinted unresectable pancreatic malignancy in 6 patients. The criteria for advanced malignancy were existence of tumor with peripancreatic extension to contiguous structures such as duodenum or bile duct, vascular encasement or invasion (such as to superior mesenteric vessels or inferior vena cava), and local lymphadenopathy. The remaining 3 patients with proven malignancy did have CT evidence of a pancreatic head mass but were deemed to be more likely to be of inflammatory origin rather than a malignant tumour. This was primarily due to the existence of extensive intraductal calcification, predominantly in the head region, making CT distinction of malignancy particularly demanding in this group. Splenic vein thrombosis was observed in 7 patients in our series and was not a sign of malignancy. This probably occurred following an acute exacerbation of chronic pancreatitis.

In the benign group of patients (n=52), CT had shown head mass in 11 patients. The radiologic features which tended to differentiate these from a carcinoma were presence peripancreatic inflammatory changes, the occurrence of unhindered ductal dilatation all the way to the tail region, calcification in the mass and absence of perivascular involvement. Nonetheless, the differential diagnosis by the radiologist in these 11 cases included malignancy. All have been operated and hitherto followed for a mean of 17 months (4 to 51 months) with no signs of malignancy emerging to date.

Discussion

We found that, regardless of the tests used, whether biochemical or radiological, distinguishing between an inflammatory and neoplastic mass in TCP was challenging. CA 19-9, the only widely used tumor

marker, is of limited value as a screening tool, because approximately 10% to 15% of individuals do not secrete CA 19-9 due to their Lewis antigen status⁴. Additionally, CA 19-9 levels may be within the normal range while the cancer is still at a small and asymptomatic stage and often is elevated in benign biliary or pancreatic conditions, such as acute cholangitis or chronic pancreatitis^{5,6}. In our study too, the value of CA 19-9 inclined to be of significance only in cases where it was above 1500 units. Indeed, in two benign cases with obstructive jaundice and cholangitis, values in the region of 1000 were observed. There is a growing field of research to discover new biomarkers of pancreatic cancer. A better knowledge of the most frequent genetic alterations, and the most frequently up-regulated proteins specifically found in pancreatic cancer would hopefully provide the basis for developing sensitive tumour markers for this malignancy.

Development of obstructive jaundice in patients with TCP, though often signaled a malignant transformation, was not a definite omen of pancreatic cancer in our series. Benign biliary stricture occurred with equivalent regularity and almost consistently required surgical decompression of the bile duct. Neither the depth of jaundice nor levels of alkaline phosphatase were contributory in this regard.

Among the imaging modalities, CT scan was much more valuable at predicting malignancy than ERCP. We were unable to characterize an ERCP finding that could reliably imply the presence of malignancy. Perhaps the only sign that may be of possible benefit in this respect maybe total blockade of the main pancreatic duct in the absence of an incriminating stone (or duct penetrating sign)⁷. CT scan, on the other hand showed several signs to distinguish malignant head masses in TCP; involvement of fat planes around the vascular structures, particularly the superior mesenteric artery, peripancreatic extension of the mass to contiguous structures such as duodenum, local lymphadenopathy and absence of peripancreatic inflammatory changes or calcification in the mass. Regrettably, existence of these signs indicates inoperability in the great majority of cases and do not aid us in the early detection of this dreadful ailment.

Thus, none of the standard investigative modalities that we studied were

useful in the early delineation of cancer in TCP patients. As a matter of fact, timely recognition of malignancy in TCP, despite its reputation as a pre malignant entity, may prove to be much more difficult than denovo pancreatic cancers. State-of-the art- techniques such as multi-slice CT scanners and MRI scanners may ultimately lead us to the light at the end of the tunnel.

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The Indian Pancreatitis Study Group has a mission - to study the etiology of pancreatitis in india. This might also help gain insights into the pathogenesis of the disease elsewhere. We wish to use the knowledge thus obtained to bring down the incidence of pancreatitis and to prevent it wherever possible. Hard task, but we shall do it.

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