Review Article

Carcinoma in chronic calcific pancreatitis: review of literature

O. L. Naganath Babu, J. M. V. Amarjothi*, Villalan Ramasamy, Jeyasudhahar Jesudason

Department of Surgical Gastroenterology, Madras Medical College, Chennai, Tamil Nadu, India

Received: 10 March 2019

Revised: 04 June 2019

Accepted: 05 June 2019

*Correspondence:

Dr. J. M. V. Amarjothi,

E-mail: drmosesvikramamarjothi@hotmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Carcinoma occurring in 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.^{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.³ Another study describes the risk at 1.1% at 5 years and 1.7% at 10 years.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.

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

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.^{22,23} CA19-9>120 IU/ml.²⁴ 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 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.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

- Gold EB, Cameron JL. Chronic pancreatitis and pancreatic cancer. N Engl J Med. 1993;328(20):1485–6.
- Fernandez E, La Vecchia C, Porta M, Negri E, d'Avanzo B, Boyle P. Pancreatitis and the risk of pancreatic cancer. Pancreas. 1995;11(2):185–9.
- Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the risk of pancreatic cancer. International pancreatitis study group. N Engl J Med. 1993;328(20):1433–7.
- Farrow B, Sugiyama Y, Chen A, Uffort E, Nealon W, Mark Evers B. Inflammatory mechanisms contributing to pancreatic cancer development. Ann Surg. 2004;239(6):763–71.
- Balakrishnan V, Unnikrishnan AG, Thomas V, Choudhuri G, Veeraraju P, Singh SP, et al. Chronic pancreatitis. A prospective nationwide study of 1, 086 subjects from India. JOP. 2008;9(5):593–600.
- Augustine P, Ramesh H. Is tropical pancreatitis premalignant? Am J Gastroenterol. 1992;87(8):1005–8.
- Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1252–61.
- Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. European Registry of Hereditary, and C. Pancreatitis. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. 2004;2(3):252–61.
- Liao KF, Lai SW, Li CI, Chen WC. Diabetes mellitus correlates with increased risk of pancreatic cancer: a population-based cohort study in Taiwan. J Gastroenterol Hepatol. 2012;27(4):709–13.
- Hariharan M, Subhalal N, Anandakumar M, Chellam VG, Iype S. Chronic calcific pancreatitis of the tropics with carcinoma. In: Balakrishnan V (ed) Chronic pancreatitis and pancreatic diabetes in India. Bangalore: L.G. Creations; 2006: 147–154.
- Nouts A, Levy P, Voitot H, Bernades P. Diagnostic value of serum Ca 19-9 antigen in chronic pancreatitis and pancreatic adenocarcinoma. Gastroenterol Clin Bio. 1998;22(2):152–9.
- Perumal S, Palaniappan R, Pillai SA, Velayutham V, Sathyanesan J. Predictors of malignancy in chronic calcific pancreatitis with head mass. World J Gastrointest Surg. 2013;5(4):97–103.
- Bedi MM, Gandhi MD, Jacob G, Lekha V, Venugopal A, Ramesh H. CA 19-9 to differentiate benign and malignant masses in chronic pancreatitis: is there any benefit? Indian J Gastroenterol. 2009;28(1):24–32.
- Sivarman A, Muthukrishnan A, Senguttuvan NB, Suchak SA, Kannan U. Predictors of malignancy in pancreatic head mass: a prospective study. Pan Afr Med J. 2011;9:30.
- Sudhindran S, Krishnan P. Early detection of malignancy in tropical pancreatitis – is it possible? In: Balakrishnan V (ed). Chronic pancreatitis and pancreatic diabetes in India. Bangalore: L.G. Creations; 2006: 364–370.
- Liu J, Gao J, Du Y, Li Z, Ren Y, Gu J, et al. Combination of plasma microRNAs with serum CA19-9 for early detection of pancreatic cancer. Int J Cancer. 2012;131(3):683–91.
- Pancreatic Cancer Action, 2014. Available at: <http://pancreaticcanceraction.org/news/blood-test-differentiate-pancreatic-cancer-chronic-pancreatitis>. Accessed on 12 June 2017.
- Gold DV, Newsome G, Liu D, Goldenberg DM. Mapping PAM4 (clivatuzumab), a monoclonal antibody in clinical trials for early detection and therapy of pancreatic ductal adenocarcinoma, to MUC5AC mucin. Mol Cancer. 2013;12:143–57.

19. Newmarkers shed light on pancreatic cancer. Available at: <http://www.mayoclinic.org/medical-professionals/clinical-updates/digestive-diseases/newmarkers-shed-light-on-pancreatic-cancer>. Accessed on 12 June 2017.
20. Yamada Y, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N. Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. *Abdom Imaging.* 2010;35:163–71.
21. Rijkers AP, Valkema R, Duivenvoorden HJ, van Eijck CH. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. *Eur J Surg Oncol.* 2014;40:794–804.
22. Wapnick S, Hadas N, Purow E, Grosberg SJ. Mass in the head of the pancreas in cholestatic jaundice: carcinoma or pancreatitis? *Ann Surg.* 1979;190:587-91.
23. Frey CF, Suzuki M, Isaji S. Treatment of chronic pancreatitis complicated by obstruction of the common bile duct or duodenum. *World J Surg.* 1990;14:59-69.
24. Minghini A, Weireter LJ, Perry RR. Specificity of elevated CA 19-9 levels in chronic pancreatitis. *Surgery.* 1998;124:103-5.
25. Augustine P, Ramesh H. Is tropical pancreatitis premalignant? *Am J Gastroenterol.* 1992;87:1005-8.
26. Saruc M, Pour PM. Diabetes and its relationship to pancreatic carcinoma. *Pancreas* 2003;26:381-7.

Cite this article as: Babu OLN, Amarjothi JMV, Ramasamy V, Jesudason J. Carcinoma in chronic calcific pancreatitis: review of literature. *Int Surg J* 2019;6:2655-8.