Histopathological Patterns in Pancreatic Neoplasms- A Descriptive Observational Study over a Period of Six Years at a Tertiary Care Centre in Kerala

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ABSTRACT

BACKGROUND

Pancreatic neoplasms consist of a broad spectrum of benign and malignant tumors, with pancreatic ductal adenocarcinoma accounting for 85% of malignant cases. The poor prognosis of pancreatic ductal adenocarcinoma may be due to its insidious growth often presenting late in the clinical disease process. It is estimated that at initial diagnosis of disease, approximately 50% of patients will have distant metastases, while only 10% will have tumours localized to the pancreas. Pancreatic ductal adenocarcinoma (PDAC) carries a dismal prognosis. It is important to identify prognostic subtypes of pancreatic carcinoma to predict clinical and therapeutic outcomes accurately. The purpose of this study is to assess the histopathological features and expression of the proliferation marker Ki-67 in pancreatic neoplasms, in a tertiary care hospital in Kerala over a span of 6 years.

METHODS

This is a descriptive observational study. All pancreatic neoplasms diagnosed in the Department of Pathology, Medical College, Kottayam during the period of 6 years from January 2011 to December 2016 were analysed. Age distribution, morphologic features and Ki-67 expression were studied using the registers, histopathology slides and immunohistochemistry slides in the department. The data was analysed using SPSS.

RESULTS

We received a total of 111 neoplastic lesions of pancreas. 95% were malignant and 5 % were benign. The age distribution ranged from 17 to 85 years. Males were more affected 55.9% (62 cases) than females 44.1% (49 cases). Epithelial neoplasms accounted for 94% of the cases. Ductal adenocarcinomas constituted 78% the total lesions and 82.1% of malignancies. Benign neoplasms included serous cystadenomas, mucinous cystadenomas and lymphangiomas.

CONCLUSIONS

Pancreatic adenocarcinomas constituted the majority of lesions. The most commonly affected age group was 5th to 6th decade, whereas certain studies showed a predominant involvement in 7th decade. Moreover, predominant types were well differentiated adenocarcinomas. Ki-67 expression was high in neoplasms with lymph node metastasis and low in better differentiated neoplasms. The gender predilection, lymph node involvement, lymphovascular invasion and perineural invasion were compatible with other studies.

KEY WORDS

Adenocarcinoma, Ki-67, Pancreatic, Neoplasms

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BACKGROUND

Neoplasia of the pancreas consists of a wide spectrum of benign and malignant tumours. Epithelial neoplasms constitute the majority of cases with others like mesenchymal, neuroendocrine and mixed types constituting the remaining types. Ductal adenocarcinomas are the most common among the malignancies comprising 85% the cases. It is one of the five leading causes of cancer deaths.¹ The American Cancer Society estimates approximately 39,400 fatalities to the disease.¹ Although rates of pancreatic cancer have slowly declined in the United States over the past 15–25 years, it is the fourth leading cause of cancer mortality, with a 5-year survival rate as low as 5%.² The poor prognosis of pancreatic ductal adenocarcinoma is mainly attributed to its insidious and inconspicuous growth often presenting late in the clinical disease process. It is estimated that at the time of initial diagnosis, a good percentage of patients will have distant metastases, though diagnosis at a stage where tumour is localized to the pancreas is of prognostic significance. Pancreatic ductal adenocarcinoma (PDAC) carries a dismal prognosis. There is a need to identify the subtypes of pancreatic carcinoma to predict clinical and therapeutic outcomes accurately and define novel therapeutic target. Studies have shown that Ki-67 expression was one of the most important determinants of long-term survival. IHC expression of Ki-67 has been shown to affect the prognosis. Ki-67 values may be high in ductal hyperplasia and dysplasias in pancreas which represent precursor lesions for pancreatic cancer. This study is being done to assess the histopathological features of pancreatic neoplasms, in a tertiary care hospital in Kerala over a span of 6 years. We have also studied the expression of the proliferation marker, Ki-67 in all possible cases. In addition to this, various neuroendocrine and mesenchymal neoplasms of pancreas have also been analysed.

METHODS

This is a descriptive observational study. All pancreatic neoplasms diagnosed in the Department of Pathology, Medical College, Kottayam during the period of 6 years from January 2011 to December 2016 were analysed. Sample size was 111 cases. Sample size was taken based on the convenience of the study. Age distribution, morphologic features and Ki-67 expression were studied using the registers, histopathology slides and IHC slides in the department. IHC studies was done in paraffin blocks of all newly diagnosed cases of pancreatic carcinoma and some of the previously diagnosed cases. The study was accepted by the Institutional ethics committee (IRB 40/2017).

Study Tools

1. Instruments to take bits of tissues to be studied.
2. Reagents for tissue processing.
3. Instruments for making paraffin blocks and cutting thin sections from it.
4. Glass slides and cover slips for mounting.
5. Microscope.
6. Eosin-Haematoxylin staining.

7. Mouse monoclonal antibody for Ki-67 and other reagents for immunohistochemical studies.
8. Proforma to record serial number, Biopsy number, Name, age, sex, clinical investigations, gross, histopathology and immunohistochemical features.

Study Procedure

Clinical details of each case will be recorded first. Gross examination of the specimen will be done. All specimens fixed in formalin and embedded in paraffin. 4 microns thick sections were taken and stained with H & E for routine histological examination. Immunohistochemical staining was performed using mouse monoclonal antibody for Ki-67 labelling index.

Inclusion Criteria

All pancreatectomies and small biopsies with diagnosis of pancreatic neoplasia received in the histopathology lab during the period of January 2011 to December 2016

Exclusion Criteria

Cases without proper data, inadequate specimen and cases with indefinite diagnosis were excluded.

Statistical Analysis

The data was entered in Microsoft excel and further statistical analysis done using SPSS.

RESULTS

Figure 1. Decade Wise Distribution of Pancreatic Neoplasms

Histological Type	No. of Cases	% of Cases
Adenocarcinoma	82	73.9
Adenocarcinoma with mucin secretion	6	5.4
Adenosquamous carcinoma	2	1.8
Carcinoma with neuroendocrine differentiation	2	1.8
Solid pseudopapillary tumour	4	3.6
Undifferentiated carcinoma	1	0.9
Acinar carcinoma	1	0.9
Carcinosarcoma	1	0.9
Secondary infiltration	3	2.7
Mucinous cystic neoplasms with atypia	3	2.7
Serous cystadenoma	2	1.8
Mucinous cystadenoma	1	0.9
Lymphangioma	2	1.8
Haemangioma	1	0.9
Total	111	

Table 1. Relative Frequencies of Pancreatic Neoplasms

Of the total 111 cases, 6 were benign neoplasms (5%) and 105 cases were malignant (95%). Males were more affected 55.9% (62 cases) than females 44.1% (49 cases). The age ranged from 17 to 85 years. Majority occurred in the 5th and

6th decade (51.4%). Decade wise distribution is shown in [Figure 1]. Epithelial neoplasms accounted for 94% of the cases. Thus, we had 104 epithelial and 3 mesenchymal neoplasms. There were two cases of endocrine and mixed types each. The different histopathologic types of neoplasms are shown in Table 1.

The benign neoplasms in our study were serous and mucinous cystadenomas, lymphangiomas and haemangiomas. Grossly serous cystadenomas are seen as well circumscribed growth and microscopy will show cystic spaces with serous lining. Figure [2a and inset] showing gross appearance of the same. 6 benign neoplasms, 3 mucinous neoplasms with atypia and 12 cases of malignancies diagnosed on biopsy were not included in further analysis. The age and sex predilection, tumour size and lymph node status were assessed in the malignant neoplasms only. (90 cases, 111-21, =90). Of the malignant neoplasms with epithelial component, majority (49 cases=51.6%) occurred in 5th and 6th decade. 50 cases (55%) in males and 40 in females (45 %). 44/90 (48%) showed lymph node involvement. 80% cases were solid on gross and 14% were predominantly cystic, remaining showed solid and cystic areas. Tumour size varied from 0.8 cms to 10 cms. The histopathological types of pancreatic epithelial malignancies are shown in the figure. [3] Adenocarcinomas accounted for the majority, 78% (70 cases). Gross appearance of a case of pancreatic adenocarcinoma is shown in Figure [2b]. Among adenocarcinomas, tumour size ranged from 0.8 to 6 cms. 37 cases were well differentiated. Perineural invasion was detected in 45.7% of cases and 42.8% of the adenocarcinomas showed lymph node metastasis. Fig [2b, c].

Since in some cases a proper categorization into pancreatic origin, ampullary origin, bile duct or intestinal origin was not possible, all adenocarcinomas involving the pancreas were included. Of the 70 cases of adenocarcinoma, 84% (59 cases) occurred in head of pancreas followed by the body 10% (7 cases) and tail 4% (3 cases) of pancreas. One was multifocal. 53% of the adenocarcinomas were well differentiated [Table 2]. 30/70 (42.8%) cases showed lymph node involvement and 22/70 (31%) showed lymphovascular invasion. Perineural invasion was seen in 32 cases (45.7%). In 40 cases margins of resection was free.

Adenocarcinomas	Total 70 Cases
Well differentiated	37
Moderately differentiated	15
Poorly differentiated	18

Table 2. Classification of Adenocarcinomas based on Degree of Differentiation

Ki67 could be done only in 20 cases and it showed high values in poorly differentiated type. [Figure 4a]. Moreover, all of them showed lymph node metastasis, lymphovascular invasion and perineural spread. Mucinous carcinomas accounted for 7% of cases in our study. 3 of them showed lymph node metastases. Microscopic image of mucin secreting adenocarcinoma pancreas and perineural invasion. Figure [2d and inset]. In our study neuroendocrine neoplasms accounted for 1.8% cases. One of the cases showed amyloid secretion and was seen to involve the spleen. [Figure 4 b]. Ki 67 expression and mitotic figures are important in grading and categorization of neuroendocrine tumours. [Figure 4 c, d inset]. Adenosquamous carcinomas

constitute a small subset of adenocarcinomas involving pancreas and in our study there were 2 cases. Acinar carcinoma constituted 1% of the cases only which was in a 44 year old male patient. Of the mesenchymal neoplasms, benign neoplasms like lymphangioma and hemangioma were seen in second and third decades. There was a single case of carcinosarcoma pancreas occurring in a 45-year-old male.

DISCUSSION

Diagnosis of pancreatic cancer can be challenging for the pathologist. The risks are high and sometimes the diagnoses are difficult. The life expectancy and the most appropriate management for a patient diagnosed with chronic pancreatitis differ significantly from the life expectancy and appropriate management for a patient diagnosed with pancreatic cancer. Yet, sometimes, it can be extremely difficult, if not impossible, to distinguish histologically between a benign reactive gland of chronic pancreatitis and an infiltrating gland of well-differentiated pancreatic cancer.³

Pancreatic neoplasms are mostly malignant. In our study 95% cases were malignant. Epithelial neoplasms constituted the majority accounting for 94% of the total cases and of these 78% were adenocarcinomas. The dismal prognosis in many pancreatic malignancies is thought to be due to late diagnosis. Benign neoplasms of pancreas accounted for 5% cases only and were mostly in younger decades.

Mucinous cystic neoplasms are non-invasive mucin secreting neoplasms that occur in the body and tail of pancreas.⁴ Intraductal papillary mucinous neoplasm (IPMN) may be associated with mild, moderate or severe dysplasia. Mucinous neoplasms with atypia constituted 2.7% of the cases in our study. Of the patients with IPMNs who undergo pancreatic resection, 30% will have associated invasive adenocarcinoma.^{5,6}

Infiltrating ductal adenocarcinoma of the pancreas (Pancreatic cancer) is one of the most lethal of all of the solid malignancies and the fourth leading cause of cancer death.¹ Worldwide it is estimated that 213,000 people will die from pancreatic cancer.² These numbers are expected to increase as the population ages. Of the different types of pancreatic cancer, pancreatic adenocarcinoma is the most common one, accounting for 85% of the cases and the term pancreatic cancer usually refers to this type only.⁷ Ryan et al has suggested that more than 50% cases of adenocarcinoma occurs after 70 years.⁸ However in our study the predominant age group affected was in 5th and 6th decade [Table 1] which is of concern. Associated risk factors are tobacco smoking, obesity, diabetes and some rare genetic conditions.⁸

The prognosis of Pancreatic ductal adenocarcinoma (PDAC) is poor.⁹ In many cases a differentiation between ductal adenocarcinoma pancreas and pancreatic involvement from periampullary adenocarcinoma can be difficult especially in poorly differentiated and advanced cases.¹⁰ A proper categorization regarding the site of origin of adenocarcinoma may seem to be possible conceptually, however practically it is quite challenging and prone to subjective variations. Hence in our study we included all cases of adenocarcinomas involving the pancreas.

Biankin et al evaluated 348 patients with pancreatic adenocarcinoma and demonstrated that tumour size (greater than 4.5 cm), resection margin involvement, and perineural invasion were independent prognostic factors.¹¹ In our study there were 70 cases of adenocarcinoma, 84% were located in the head of pancreas. Tumour size ranged from 0.8 to 6 cms. Perineural invasion was detected in 45.7% of the cases and 42.8% showed lymph node metastasis. Figure [2c]

Pancreatic Adenocarcinoma	% of Males Affected	Lymph Node Metastasis	Lymphovascular Invasion	Perineural Invasion
Qin et al ¹⁶	54.4%	49.7%	24%	60.5%
Jin he et al ¹⁸	53%	76%	40%	69%
Present study	53%	42.8%	31%	45.7%

Table 3. Comparison with Similar Studies

Figure 2. Gross and Microscopic Features of Pancreatic Neoplasms- 2a. Microscopy of Serous Cystadenoma Showing Cystic Spaces Lined by Clear Cells. H & E 100X. Inset- Gross Specimen of Serous Cystadenoma Pancreas Showing a Well Circumscribed Solid Lesion. 2b. Gross Specimen of Pancreatic Adenocarcinoma Showing an Infiltrating Grey White Growth. Inset Microscopy of Adenocarcinoma Pancreas Showing Cells Arranged in Glandular Pattern. H & E 100X. 2c. Lymph Node Metastasis from Pancreatic Adenocarcinoma. H & E 100 X. Inset - Photomicrograph of Perineural Invasion in Adenocarcinoma. H & E 400X 2d. Microscopy of Mucinous Carcinoma Pancreas Showing a Cystic Dilated Glandular Space Lined by Goblet cells. H & E 100X. Inset- Photomicrograph of Perineural Invasion in Mucinous Adenocarcinoma. H & E100X.

Figure 3. Distribution of Epithelial Malignancies

Ki-67 expression is thought to be the most important determinant of long-term survival. c-jun and Ki-67 are overexpressed in pancreatic carcinoma, but only Ki-67 is considered as a strong predictive factor.¹² Presence of any precursor lesions like pancreatic ductal hyperplasia or dysplasia have to be identified since these have also shown increased Ki-67 values.¹³ Early diagnosis of pancreatic

carcinoma is difficult and different subtypes have different prognosis. So, it becomes important to analyse various histological patterns for further sub classification of this group of tumours. Moreover, IHC expression of Ki-67 has been shown to affect the prognosis. Ki-67 antigen is a non-histone nucleoprotein selectively expressed by actively cycling cells. It reflects the proliferation and malignancy of tumour cells. It is demonstrable in paraffin-embedded material using the MIB-I monoclonal antibody 1.

Figure 4. Gross and Microscopic Features of Pancreatic Neoplasms- a. High Ki 67 Staining in Adenocarcinoma. H & E 400X. Inset- Low Ki 67 Staining in Adenocarcinoma. H & E 400X. b. Neuroendocrine Carcinoma Pancreas a Showing Cells Arranged in Gyriform Pattern. H & E 100X Inset- Perineural Invasion. H & E 400X c. Amyloid Deposition and Salt and Pepper Chromatin in Neuroendocrine Carcinoma. H & E 400X. Inset- Photomicrograph showing Ki 67 staining in neuroendocrine carcinoma. H & E 400X. d. Undifferentiated Carcinoma Pancreas Showing Giant Cells. H & E 400X. Inset- Photomicrograph Showing Ki 67 Staining in the Same. H & E 400X.

Zapata et al has demonstrated the use of SMAD4 staining in combination with CK19 and CA19-9 in pancreatic adenocarcinoma.¹⁴ Cao et al has also evaluated the role of SMAD4 expression in pancreatic neoplasms and demonstrated that whereas pancreatic adenocarcinomas show loss of SMAD4 protein in 55% of cases, loss of SMAD4 expression is absent in pancreatic non ductal neoplasms.¹⁵ These studies suggest that SMAD4 expression is useful in diagnosing pancreatic adenocarcinoma and it may be helpful in preoperative assessment when used on pancreatic aspirates. In our study Ki-67 expression was done in 20 cases of adenocarcinomas only and showed high values in 48% of cases and all of them showed lymph node metastasis. However, the remaining 52% of cases showed low expression only. In Quin et al's study the median Ki-67 level was 40%.¹⁶ In our study the Ki-67 values ranged from 18 to 65%. Pancreatic neoplasms which are of neuroendocrine origin constitute a very small percentage compared to epithelial neoplasms and they have a better prognosis. They may be functional or nonfunctional depending on whether they secrete hormones or not. Different types of neuroendocrine tumours can affect the pancreas and they are thought to be less aggressive than adenocarcinomas of pancreas.⁷ They can be either benign or malignant. They may or may not produce

hormones. The grading of neuroendocrine neoplasms is based on the mitotic rate and Ki-67 proliferation index.¹⁷

Limitations

Subcategorization of adenocarcinoma was not possible in all cases, especially in poorly differentiated cases and those diagnosed on biopsy; hence, whether all adenocarcinomas are of pancreatic ductal origin could not be definitely ascertained.

CONCLUSIONS

Epithelial neoplasms contributed to the majority (94%). Adenocarcinomas accounted for 73.9% of the total cases and 78% of the epithelial malignancies. The results of our analysis were comparable with those of other similar studies [Table 3].

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