Ductectatic-type Mucinous Cystadenoma and Cystadenocarcinoma of the Human Pancreas: A Novel Clinicopathological Entity

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A new type of mucinous cystic pancreatic neoplasm is described. The lesions, which have been recognized only recently with the progress of diagnostic techniques and have not previously been described in the literature, are characterized by multilocular cysts with papillary proliferation of the lining epithelium. They occur exclusively in the head and body, predominantly in males, and coexistence of well-differentiated adenocarcinoma as well as adenoma components is frequently encountered. These lesions are quite different from hitherto described mucinous cystic neoplasms of pancreas, not only in terms of gross features but also with regard to intrapancreatic location, and sex and age distributions. We propose to classify these lesions as a new pancreatic tumor entity: the ductectatic-type mucinous cystadenoma/cystadenocarcinoma.

Key words: Pancreas — Mucinous cystic neoplasm — Pancreatic neoplasm

Recent advances in diagnostic techniques, including endoscopic retrograde pancreatography (ERP), ultrasonography (US) and computed tomography (CT), have allowed detection of a considerable number of relatively small neoplastic and pseudoneoplastic lesions of the human pancreas, some of which have not previously been described in the literature. Included among such newcomers is the particular type of mucinous cystic neoplasm which we describe in the present paper.¹⁾ These lesions were first recognized in our laboratory and reported previously under the tentative designations, ductectatic-type mucinous cystadenoma and cystadenocarcinoma (collectively cystic neoplasm) (DMCN). Since our proposal for the recognition of these lesions as a new clinicopathological entity of human pancreatic neoplasm has found acceptance²⁻⁵⁾ we have extended our study and characterized these lesions in more detail.

MATERIALS AND METHODS

A total of 16 cases designated as ductectatic-type mucinous cystic neoplasms, accumulated in our Cancer Institute Hospital over the last 10 years, were used for the analysis. Since 1981, doctors belonging to the pancreas research group in our hospital have been conducting extensive clinical investigations, utilizing ERP, US and CT, for detecting pancreas cancers at an early stage. It was only after the commencement of this program that we encountered these particular pancreatic neoplastic lesions, which had never been described in the literature.

Material from six of the 16 cases was obtained by pancreatoduodenectomy, from 9 by distal pancreatectomy and from 1 by total extirpation of the pancreas.

The resected materials were sectioned totally at 5 mm intervals transversally across the main pancreatic duct. Precise examination was performed on cut sections and a tentative diagnosis of DMCN was made grossly. All the sections were then fixed in 10% formalin solution and subjected to microscopical observation.

RESULTS

Grossly, DMCN are characterized by multilocular loculi containing large amounts of thick mucin (Figs. 1a and 2a). The dilated structures mainly stem from side branches of the main pancreatic duct. The appearance of the cut section is reminiscent of bronchoectasis of the lung. The size of the present lesions ranged from 15 to 70 mm in greatest diameter with a mean value of 33 mm. Cases containing a carcinoma tended to be larger than pure adenomas, the average diameter being 50 mm and 30 mm, respectively. The boundaries of the lesions were found to be irregular, with a thin fibrous capsule, if any. Individual loculi within lesions measured from 2 mm to 35 mm and were usually not encapsulated.

Microscopically the loculi were observed to be commonly lined by tall, mucin-producing columnar cells similar to the lining cells of pancreatic ducts (Figs. 1c and 2c). The epithelial cells were usually arranged in single rows, but occasionally stratification or papillary projections were apparent (Figs. 1b and 2b). Neither marked nuclear atypia nor pleomorphism was evident

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Fig. 1. a. Gross features of a cystadenocarcinoma with adenoma component (Case 14), showing multiple loculi with various sizes. b. Histology of the adenocarcinoma component (single short arrow in Fig. 1a). Papillary growth pattern is visible. H&E, $\times 80$. c. Histology of the mucinous cystadenoma component (double arrow in Fig. 1a). H&E, $\times 80$.

in the proliferated cells. Mitotic figures were rarely encountered ($5/10^4$ cells). A histological diagnosis of ductectatic-type mucinous cystadenoma was applied to lesions of this character.

In three cases (No. 14–16), focal areas, surrounded by or mixed with adenoma components, showed remarkable

papillary growth of cells with distinct nuclear atypia and an increased mitotic rate ($48/10^4$ cells). In one case (No. 14) there was a site of probable early invasion. Our histological diagnosis of these lesions was of ductectatic-type mucinous cystadenocarcinomas with adenoma components. No metastases were observed.

Fig. 2. a. Gross features of a cystadenoma (Case 8) demonstrating multiple loculi with various sizes and septation. b. Low-power view of the histological section of Fig. 2a. H&E. c. A histological picture showing papillary proliferation of neoplastic cells. H&E, $\times 15$. d. Higher magnification of a site of Fig. 2c (arrow). Note proliferation of high columnar cells with minimal nuclear atypia and abundant intracytoplasmic mucin. H&E, $\times 170$.

Table I. Summary of Clinicopathological Features of Cases

Case No.	Age	Sex	Location	Size (mm)	Histological diagnosis
1	49	male	body	15	adenoma
2	50	male	head	15	adenoma
3	67	male	head	18	adenoma
4	75	male	body	20	adenoma
5	72	female	head	24	adenoma
6	72	male	head	25	adenoma
7	65	male	head	30	adenoma
8	66	male	head	30	adenoma
9	73	female	head	30	adenoma
10	60	male	body	30	adenoma
11	58	male	head	35	adenoma
12	55	male	head	50	adenoma
13	74	female	body	60	adenoma
14	68	male	head	35	adenocarcinoma with adenoma
15	72	female	body	45	adenocarcinoma with adenoma
16	76	female	head	70	adenocarcinoma with adenoma

The clinicopathological features of all 16 DMCNs are summarized in Table I. Age at the time of resection of DMCNs ranged from 49 to 76 years, the mean being 66. Almost three-quarters of the patients were older than 60 years. Eleven of the 16 patients (69%) were male. In 11 out of 16 cases (69%) the tumor was located in the head of the pancreas, the remaining 5 being found in the body.

DISCUSSION

The existence of cystic neoplasms or mucinous cystic neoplasms has long been described in the literature⁶⁻¹⁵⁾ and in standard textbooks.¹⁶⁻¹⁸⁾ The clinicopathological features of such lesions, however, while being similarly described in all the above reports, essentially differ from these of our present lesions. On the basis of Compagno and Oertel's data,¹⁹⁾ which cover the largest number of cases and are often cited in textbooks,^{16, 20)} the predominant differentiating features between classical mucinous cystadenoneoplasms appearing in the literature and DMCNs are comparatively summarized in Table II. Striking differences are evident in terms of age and sex distribution, intrapancreatic localization, size, presence of capsule and mode of compartmentalization.

The core image of the classical mucinous cystic neoplasm is a tumor comprised of a large, dominant loculus, with or without satellites, surrounded by a thick fibrous capsule, located in the pancreas tail and showing a distinct female predominance.^{16, 20)} In contrast, DMCNs are composed of multiple loculi, the majority develop in the head, and none was found in the tail. Since the intrapancreatic location and sex dependence are different and the DMCNs are generally much smaller than the classical lesions in spite of their manifestation at older

ages, it is clear that we are not looking at an early stage precursor relationship. If we consider the possibility that lesions belonging to the present DMCN entity may in fact have been mistakenly included in the classical series, in the absence of the concept of DMCN, the difference between the two types of lesions may actually be even more pronounced.

DMCNs demonstrate similarities to retention cysts in terms of intrapancreatic location and histogenetic connection to the main duct. However, since retention cysts are usually smaller and are lined by flattened epithelium they are in most cases easily distinguishable.

DMCNs should also be discriminated from intraductal papillary neoplasms in which adenoma or carcinoma cells spread diffusely or focally, replacing the mucosa of the main pancreatic duct.²⁰⁾ Although, in the latter lesions, the main ducts may be dilated considerably due to mucus retention, these are principally non-cystic lesions and distinctly different from the multilocular configuration of DMCNs derived from side branches. It should be mentioned, however, that since DMCNs and intraductal papillary neoplasms share very similar cytological and mucin histochemical²¹⁾ features together with site predilection (head to body),²²⁾ there is some basis to regard these two types of lesions as macro-morphological variants of essentially the same neoplastic category.²³⁾

As to the nature of DMCNs, some people have argued that what we call adenomas might rather be hyperplasias, and therefore not true neoplastic lesions. The presence of atypical elements and the recent finding of K-ras activation in adenomas at high frequency,²⁴⁾ however, support the conclusion of neoplastic nature.

Several investigators have reported the concurrent presence of seemingly benign columnar epithelium adjacent

Table II. Differential Predominant Features of Classical and Ductectatic Types of Mucinous Cystoneoplasm of Pancreas

	Classical type ^{a)}	Ductectatic type
Age	Middle (range 20–82, mean 49)	Old (range 49–76, mean 66)
Sex	Female (male:female=6:35)	Male (male:female=11:5)
Location	Tail (H:B:T=2:11:25) ^{b)}	Head (H:B:T=11:5:0) ^{b)}
Size (cm)	Large (range 2–19, mean 10.5)	Small (range 1.5–7.0, mean 3.3)
Capsule	Thick	Thin
Compartment	One dominant loculus	Multiple loculi

a) Compagno's series (ref. 19).

b) H, head; B, body; T, tail.

to obviously malignant epithelial structures in classic mucinous cystic neoplasms.^{6, 8, 9, 12, 19)} We also detected three cases in the present series in which overt carcinoma components coexisted within benign adenomas. This supports the view that cystadenomas may be forerunners of cystadenocarcinomas, malignant transformation occurring with time. Such an adenoma-carcinoma sequence was also indicated by our recent observation of K-ras activation with the same point mutation in both the adenoma and the carcinoma components of one and the same case.²⁴⁾

The 5-year survival rate after surgery of common invasive ductal carcinoma of the pancreas is about 1%, at best.¹⁶⁾ On the other hand, classical mucinous cystic neoplasms of the pancreas generally have a much better prognosis; according to Compagno and Oertel's report, the 5-year survival rate was 50%.¹⁹⁾ Although we do not have comparable data for DMCNs as yet, all the 16 patients operated for this disease are still surviving. DMCN may, therefore, have a far better prognosis than other mucinous cystic neoplasms, although the natural

history of ductectatic-type mucinous cystadenocarcinoma remains to be confirmed.

Among the operation material obtained in our hospital in the last 10 years, there were only 3 cases of classical-type mucinous cystic neoplasm (age, 35, 42, 46; sex, all female; location, all tail; size, 12.5, 16, and 16 cm). It is not clear why the number is so small as compared to other series. One possibility is that formerly investigations were carried out principally by autopsy, where only large cystic lesions might have attracted attention while smaller DMCN-type lesions were overlooked or neglected. With recent progress in imaging modalities, the chances of detecting cystic pancreatic lesions have been increasing rapidly. The present investigation contributes to our understanding of the nature of the various types of pancreatic neoplasms of clinical importance.

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