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Intraductal Serrated Adenoma of the Pancreas. A Case Report

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Abstract. *Case Report: A 48-year-old male with known hypothyreosis consulted his physician for symptoms compatible with TIA (transient ischemic attacks). Computer tomography (CT) in December 2001 revealed an irregular, lobulated mass in the processus uncinatus of the pancreas head. A CT examination 14 months later revealed status quo. In July 2004, a new CT showed an increase in size of the expansive pancreatic mass. The patient was operated on in August 2004 with a preliminary diagnosis of incidentaloma of the pancreas. The pathological examination showed a 4 x 3.5 x 2.5 cm large tumour. Histology revealed an intraductal serrated adenoma. The epithelial fronds had sawtooth-like configurations. An area with early invasive carcinoma was found. The tumour had progressed slowly during the 2.7 years of surveillance. Serrated neoplasia in the duodenum may result in similar cases in the future.*

According to the WHO (1), ductal neoplasms and their variants comprise up to 90% of the exocrine neoplasms in the pancreas, and are the fifth cause of cancer death in Western countries. Cystic and papillary mucinous non-invasive neoplasms precede the development of ductal adenocarcinomas (2). Stirling (3) has divided non-invasive (benign) neoplasms of the exocrine pancreas into non-cystic (8 subgroups) and cystic (4 subgroups), while Solcia *et al.* (4) defined serous cystic tumours (*microcystic adenoma* or *glycogen-rich cystoadenoma*), serous cystadenoma, mucinous cystic tumours, pseudopapillary tumours and intraductal papillary-mucinous tumours. More recently, the WHO (1) has classified epithelial tumours of the exocrine pancreas into benign (4 subgroups, including intraductal papillary-mucinous neoplasm), borderline (*i.e.* with uncertain malignant potential, 3 subgroups), and malignant (non-invasive or invasive).

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Intraductal papillary mucinous neoplasm of the pancreas (IPMNP) arises in the main pancreatic duct or in its major branches (5). IPMNP is characterised by intraductal proliferation of neoplastic mucinous cells, which usually form papillae leading to ductal retention, cystic formation and finally to detectable clinical tumours (6-14). Recently, IPMNP has been subclassified into four groups (15): i) intestinal type, with finger-like projections indistinguishable from colonic villous adenoma, ii) pancreatobiliary type: complex arborized papillae lined by cuboidal cells, iii) null type, lined by tall columnar cells, and iv) unclassifiable.

For obvious reasons, the histogenesis of carcinomas of the exocrine pancreas is difficult to study. Because of the easy accessibility to both inspection and tissue sampling, it has been possible to monitor the evolution of the lesions preceding carcinomas in other organs such as the colon and rectum (16). In the colon and rectum, tubular, tubulovillous and villous adenomas were found to antedate sporadic and hereditary invasive carcinomas. A fourth histological phenotype, the serrated adenoma (17, 18), has received considerable attention.

Recently, in our investigation of a tumour of the head of the pancreas, an intraductal lesion was found and displayed the characteristics of a serrated neoplasia similar to those previously reported in the colon and rectum. Since no case of intraductular serrated adenoma of the pancreas is, to our knowledge, on record in the literature, and taking into account the current interest in this adenoma phenotype in other mucosae of the gastrointestinal tract, this case is of particular interest.

Case Report

The patient. A 48-year-old male with known hypothyreosis consulted for symptoms compatible with TIA (transient ischemic attacks). Laboratory analysis showed slightly elevated levels of Chromogranin A in the serum. A computer tomography (CT) in December 2001 revealed an irregular, lobulated lesion in the *processus uncinatus* of the head of pancreas, measuring 4 x 2 x 5 cm. The CT was repeated in January 2003, revealing *status quo*.

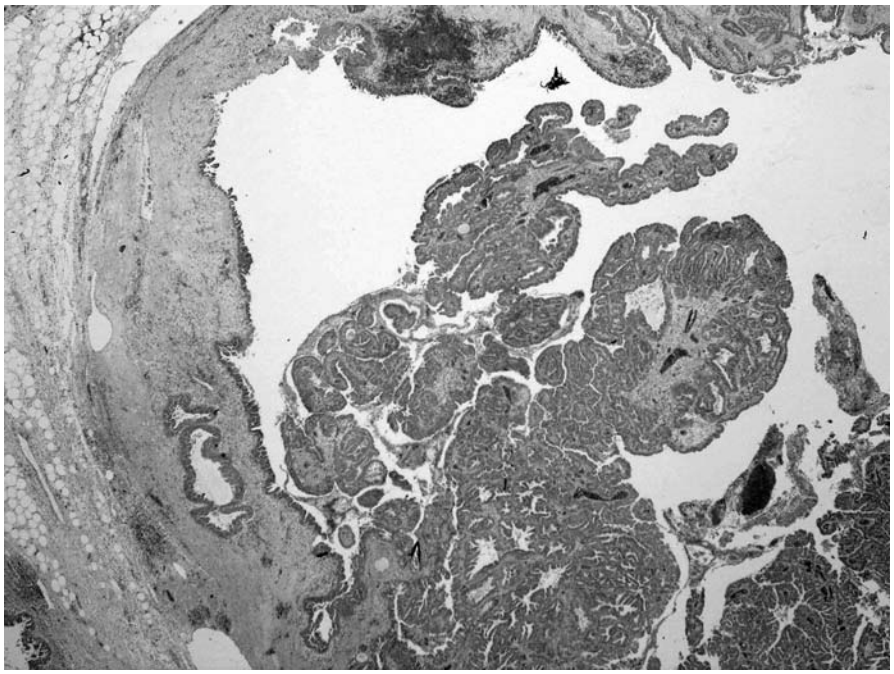

Figure 1. *Low-power view showing the intraductal lesion of the main pancreatic duct (H&E 2.5x).*

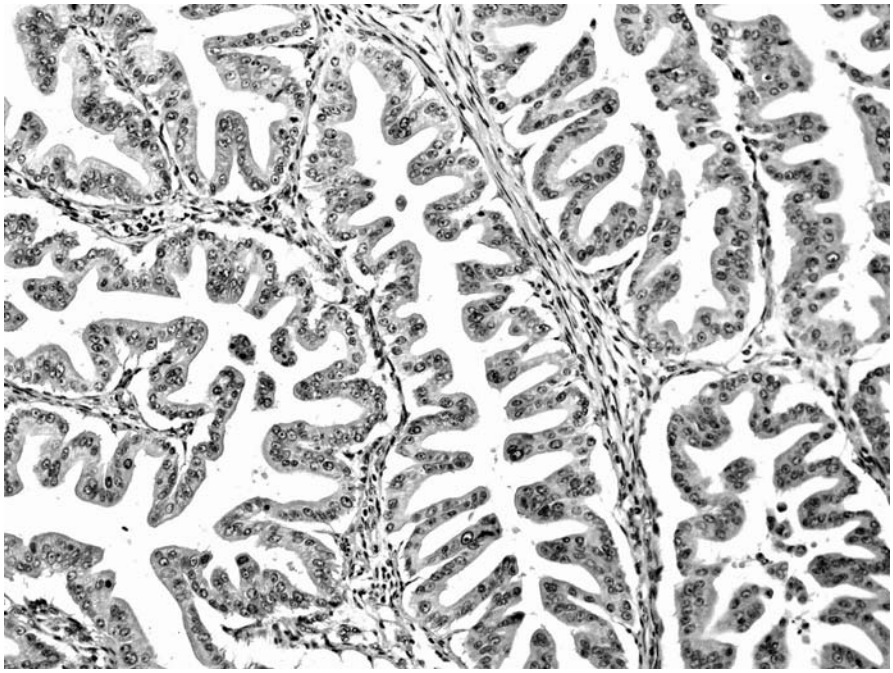

Figure 2. *Adenoma displaying serrated structures (H&E 20x).*

In April 2004, a CT-guided fine-needle aspiration yielded only blood, and in May 2004 the material was again unsatisfactory. A new CT examination in July 2004 showed an increased size of the expansive pancreatic process, measuring 5 x 3.5 x 7 cm. There was no lymph node enlargement or distal metastases. Intraoperative ultrasound showed no enlarged lymph nodes.

The patient was operated on in August 2004 with a preliminary diagnosis of incidentaloma of the *processus uncinatus* of the head of pancreas.

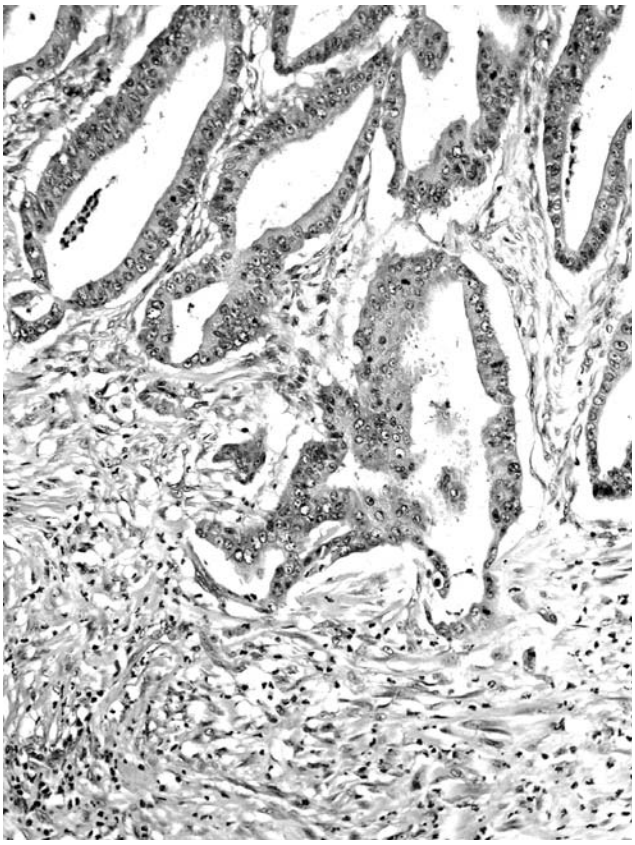

Figure 3. *Area with invasive carcinoma (H&E, 40x).*

Pathology. The surgical specimen consisted of a partial pancreatectomy with the head of the pancreas (7 x 5 x 4 cm), the gastric antrum (11 cm in length), the duodenum (28 cm in length) and the gallbladder (9 cm long without concreaments). At palpation, the head of the pancreas was hard. A transversal section showed a tumour-suspected mass measuring 4 x 3.5 x 2.5 cm surrounded by fatty-like tissue (in contrast to the "normal" pancreatic tissue at the free resection border). Two large tissue sections were taken from that area and tissue samples were taken from 12 other areas.

Histological examination revealed an intraductal adenomatous lesion (Figure 1) with sawtooth-like structural changes due to scalloped epithelial infolding (Figure 2). The epithelium of the serrated fronds showed high-grade dysplasia (HGD) and carcinoma *in situ* (*i.e.* intraepithelial carcinoma). The epithelium with HGD was lined with spindle or cigar-shaped, elongated, pleomorphic, hyperchromatic nuclei with irregular chromatin clumps. The nuclei were stratified up to the superficial half of the epithelium, and reached its luminal border. Areas with carcinoma *in situ* were characterized by large vesicular nuclei having irregular conspicuous nucleoli and an often-notched nuclear membrane. The nuclear polarity was disrupted and atypical mitoses were present. Structural glandular alterations such as budding or branching of the serrated crypts with epithelial septa, back-to-back glands, and cribriform growth of epithelial cells in clusters and sheets occurred. From areas with carcinoma *in situ,* deformed glands were seen invading the surrounding pancreatic tissue (Figure 3).

The following histochemical and immuno-histochemical reactions were done: PAS, Alcian blue pH 2.5, van Gieson, Grimelius, MUC2, cytokeratin 7, cytokeratin MNF 116. Ki67 (clone MIB1), insulin, chromogranin A, somatostatin, glucagon, pancreas polypeptide, synaptophysin, CEA, CD56, calciotonin, gastrin, p21 (WAF-1) and p53.

Immuno-histochemistry showed that the adenoma as well as the areas with invasion expressed cytokeratin 7 and broad spectrum cytokeratin MNF 116. Ki67 (clone MIB1) revealed that >60% of the neoplastic cells were proliferating. P53 was weakly-positive and only in some groups of cells. The tumour was negative for PAS, Alcian blue pH 2.5, MUC2, Grimelius, insulin, chromogranin A, somatostatin, glucagon, pancreas polypeptide, synaptophysin, CEA, CD56, calciotonin, and gastrin.

The fatty area seen at gross examination showed on histology fatty degeneration at the more proximal portion of the main duct. Sections taken 2 cm from the main tumour showed that the normal ductal epithelium had been replaced by serrated adenomatous structures. No lymph nodes were found. The tumour was considered to be locally radically excised. The histology of the gastric antrum, the duodenum and the gall bladder was normal.

Discussion

A case of intraductal serrated neoplasia of the pancreas (ISNP) with early invasive carcinoma is presented. Following the recommendations of the Vienna classification (19), areas with dark cigar-shaped "picket-fence" dysplastic nuclei reaching the superficial aspect of the epithelium were regarded as HGD, and areas with vesicular-shaped nuclei (with large nucleoli) reaching the upper border of the epithelium as carcinoma *in situ*. (*i.e.* intraepithelial carcinoma).

Cellular proliferation (Ki67) was intense in the dysplastic cells covering serrated indentations, and the cellular proliferation in this serrated adenoma mimics that of previously reported serrated adenomas of the colon (17, 18) and of other organs in the GI, such as in the stomach (20), the duodenum (21) and the appendix (22).

The p53 protein was not expressed. It should be pointed out that the preparation had been fixed in formalin for 2 days. The possibility that the relatively long period of fixation led to spurious results when sections were challenged with p53 cannot be rejected.

The finding that serrated adenomatous structures were found replacing the normal epithelium of the main duct 2 cm distal from the tumour border suggested that the serrated adenoma had grown laterally along the duct. The clinical follow-up indicates that the intraductal serrated tumour in this patient had progressed slowly during the 2.7 years of surveillance (33 months from the time of DT detection to surgical removal).

The ISNP reported here differs from other IPMNPs (15) inasmuch as in ISNP the fronds showed serrated indentations, and no mucin production could be demonstrated in PAS, and Alcian blue (pH 2.5) histochemical stains or in MUC2 immunostain.

In conclusion, the first case, to our knowledge, of intraductal serrated adenoma of the pancreas is reported. Increased awareness of the existence of serrated neoplasias in the pancreas may result in similar cases being reported in the future.

References

1 Klöppel G, Hruban R, Longnecker D, Adler G, Kern S and Partanen T: Ductal adenocarcinoma of the pancreas. *In:* Tumours of the Exocrine Pancreas. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. Chapter 10, Hamilton SR and Aaltonen LA (eds.). IARC Press, Lyon, pp. 221-230, 2000.

2 Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C and Warshaw AL: Cystic neoplasms of the pancreas. N Engl J Med *351*: 1218-1226, 2004.

3 Stirling GA: The exocrine pancreas: neoplasms. *In:* Liver, Biliary Tract and Exocrine Pancreas. Wight DGD (ed.). Systemic Pathology, Vol 11, third edition Churchill Livingstone Edinburgh, pp. 665-717, 1994.

4 Solcia E, Capella C and Klöppel G: Atlas of Tumor Pathology. Tumors of the Pancreas. Armed Forces Institute of Pathology, Washington, DC, Third Series, fascicle 20, pp. 25-144, 1997.

5 Volkan Adsay NV, Merati K, Basturk O, Iacobuzio-Donahue C, Levi E, Cheng JD, Sarkar FH, Hruban RH and Klimstra DS: Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an "intestinal" pathway of carcinogenesis in the pancreas. Am J Surg Pathol *28*: 839-848, 2004.

6 Albores-Saavedra J, Sheahan K, O'Riain C and Shukla D: Intraductal tubular adenoma, pyloric type, of the pancreas: additional observations on a new type of pancreatic neoplasm. Am J Surg Pathol *28*: 233-238, 2004.

7 Biankin AV, Kench JG, Biankin SA, Lee CS, Morey AL, Dijkman FP, Coleman MJ, Sutherland RL and Henshall SM: Pancreatic intraepithelial neoplasia in association with intraductal papillary mucinous neoplasms of the pancreas: implications for disease progression and recurrence. Am J Surg Pathol *28*: 1184-1192, 2004.

8 Jinfeng M, Kimura W, Sakurai F, Moriya T, Takeshita A and Hirai I: Histopathological study of intraductal papillary mucinous tumour of the pancreas: special reference to the roles of Survivin and p53 in tumorigenesis of IPMT. Int J Gastrointest Cancer *32*: 73-81, 2002.

9 Kubosawa H, Uehara T, Watanabe Y, Urashima T, Matsubara H, Asano T and Ochiai T: Intraductal papillary-mucinous tumours of the pancreas. Hepatogastroenterology *51*: 1489-1494, 2004.

10 Maire F, Couvelard A, Hammel P, Ponsot P, Palazzo L, Aubert A, Degott C, Dancour A, Felce-Dachez M, O'Toole D, Levy P and Ruszniewski P: Intraductal papillary mucinous tumours of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. Gastrointest Endosc *58*: 701-706, 2003.

11 Prasad SR, Sahani D, Nasser S, Farrell J, Fernandez-Del Castillo C, Hahn PF, Mueller PR and Saini S: Intraductal papillary mucinous tumours of the pancreas. Abdom Imaging *28*: 357-365, 2003.

12 Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA and Lillemoe KD: Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg *239*: 788-797, 2004.

13 Tanaka M: Intraductal papillary mucinous neoplasms of the pancreas: diagnosis and treatment. Pancreas *28*: 282-288, 2004.

14 Longnecker D, Adler G, Hruban R and Klöppel G: Intraductal papillary-mucinous neoplasms of the pancreas. *In:* Tumours of the Exocrine Pancreas. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. Chapter 10, Hamilton SR and Aaltonen LA (eds.). IARC Press, Lyon, pp. 237-240, 2000.

15 Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, Biankin SA, Compton C, Fukushima N, Furukawa T, Goggins M, Kato Y, Kloppel G, Longnecker DS, Luttges J, Maitra A, Offerhaus GJ, Shimizu M and Yonezawa S: An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol *28*: 977-987, 2004.

16 Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S and Simmang C: Gastrointestinal Consortium Panel. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. Gastroenterology *124*: 544-560, 2003.

17 Rubio CA, Nesi G and Kato Y: Serrated and microtubular adenomas of the colon and rectum. An 8-year histological survey. Anticancer Res *23*: 1693-1696, 2003.

18 Torlakovic E and Snover DC: Serrated adenomatous polyposis in humans. Gastroenterology *110*: 748-755, 1996.

19 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H and Yamabe H: The Vienna classification of gastrointestinal epithelial neoplasia. Gut *47*: 251-255, 2000.

20 Rubio CA and Lagergren J: Serrated adenomas of the cardia. Anticancer Res *24*: 2113-2116, 2004.

21 Rubio CA: Serrated adenoma of the duodenum. J Clin Pathol *57*: 1219-1221, 2004.

22 Rubio CA: Serrated adenomas of the appendix. J Clin Pathol *57*: 946-949, 2004.

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