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Case report

Primary duodenal carcinoma arising in a non-vaterian tubulo-villous adenoma

A case report with immunocytochemical analysis and review of the literature

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Summary. Primary duodenal carcinoma and duodenal adenoma are rare tumours. Duodenal carcinoma makes up about 0.3% of all malignant tumours of the gastrointestinal tract (Alwmark et al. 1980; Spira et al. 1977). The present paper describes a duodenal carcinoma arising in a mixed tubulo-villous non-Vaterian adenoma in a 68 year old male. Immunocytochemical analysis revealed evidence of neuroendocrine differentiation in both adenoma and carcinoma. In a review of the literature a correlation between the size of adenoma and the probability of concomitant carcinoma is demonstrated. Duodenal adenoma measuring more than 4 cm in diameter should be considered potentially malignant.

Key words: Duodenal tubulo-villous adenoma – Adenocarcinoma – Immunohistochemistry – Diameter of adenoma

Case report

A 68-year-old man was admitted to the Cantonal Hospital Basel in April, 1988, because of a painful swelling of the left testicle, which was due to an old encapsulated pyaemic abscess. Anaemia and occult bleeding prompted esophago-gastro-duodenoscopy, which demonstrated a polypoid tumour of the third part of the duodenum, partially obstructing the intestinal lumen. Multiple biopsies were consistent with tubulo-villous adenoma with foci of moderate dysplasia. Upper gastrointestinal tract x-ray examinations and hypotonic duodenography revealed a 10 cm filling defect with partial obstruction of the lumen in the third and fourth parts of the duodenum (Fig. 1).

An ulcer was detected in the center of the tumour. CT-scan of the abdomen showed no evidence for organ or lymph node metastases. The third and fourth part of the duodenum were resected and an end-to-end duodeno-jejuno-anastomosis was performed. Because a metastasis was detected in the left lobe of the liver by intraoperative frozen section, the duodenopancreatectomy was not performed. The postoperative course was complicated and the patient died in cardiovascular failure on day 30 after surgery. An autopsy was performed within 3 h after death.

Pathology

The surgical specimen consisted of a 25 cm segment of the duodenum and jejunum. A greyish polypoid tumour measuring 6.5 cm in diameter

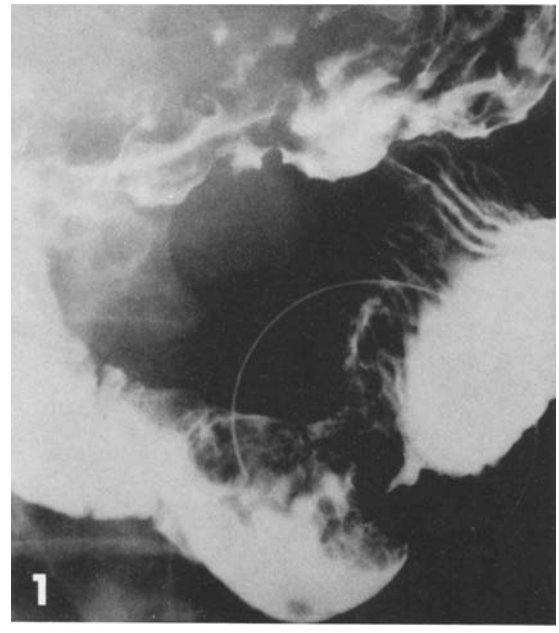

Fig. 1. Upper gastrointestinal tract X-ray showing a large filling defect in the third and fourth portion of the duodenum

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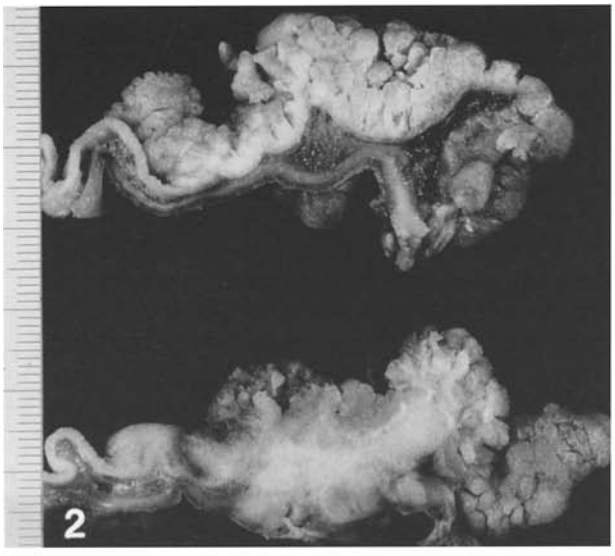
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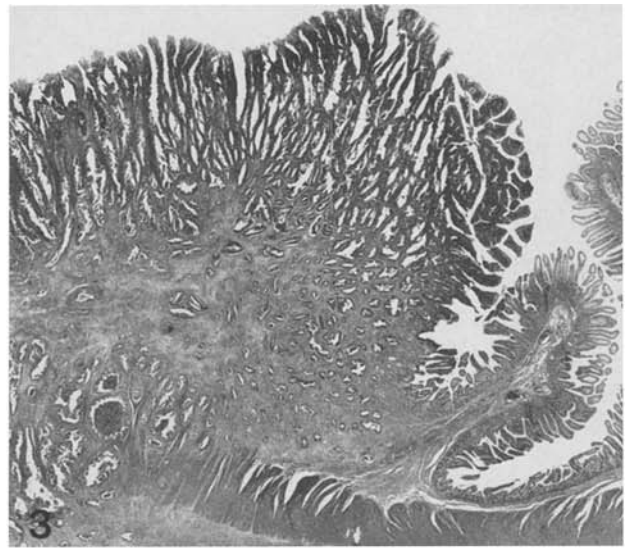
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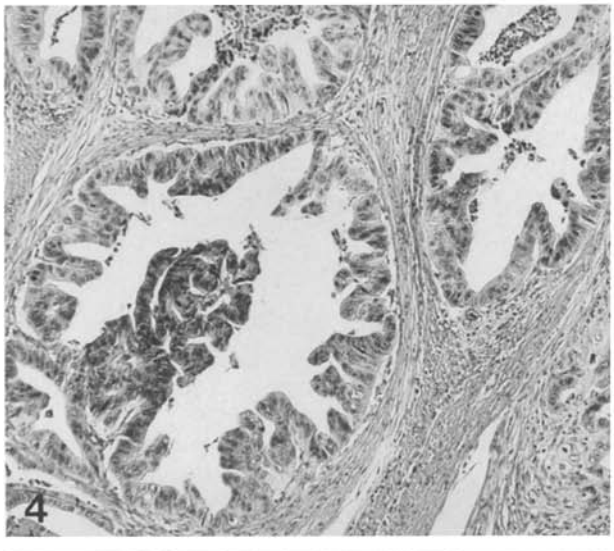
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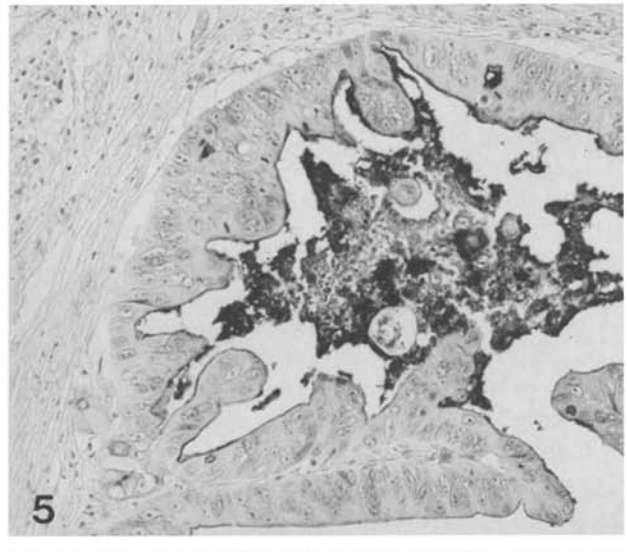
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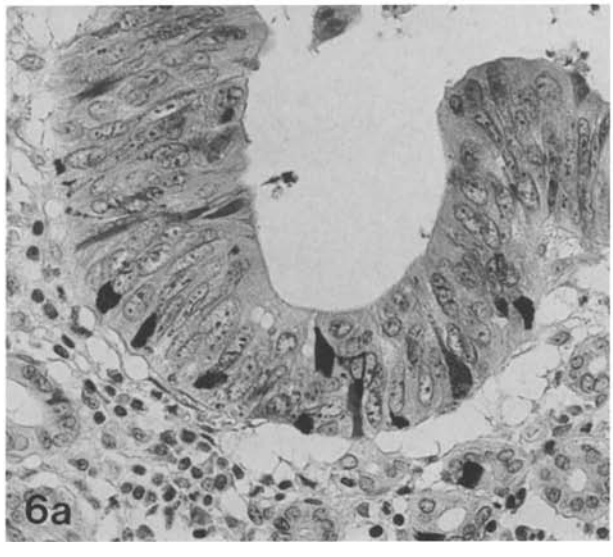
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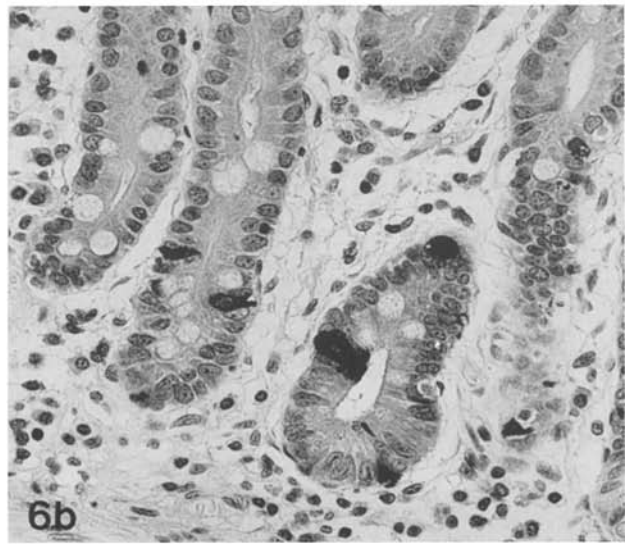
6b

was seen at its duodenal end, which projected into the gut lumen. On section the tumour was firm and white and was infiltrating the duodenal wall (Fig. 2). Histological examination revealed a mixed tubulo-villous adenoma with foci of moderate dysplasia. Furthermore a moderately well differentiated, papillary adenocarcinoma was found in the depth of ulcerated adenoma, which had infiltrated all layers of the duodenal wall reaching the surrounding adipose tissue and small veins (Figs. 3, 4). Paneth-like cells with granular eosinophilic cytoplasm were found to be scattered throughout the carcinoma.

At autopsy the adenocarcinoma was found to have infiltrated the head of the pancreas partly. Histologically verified metastases were present in the right lung, in the right adrenal gland, in regional lymph nodes and in the liver.

Material and methods

For immunocytochemical analysis two sections of the specimen were selected, each comprising unaltered mucosa, parts of the tubulo-villous adenoma and the carcinoma. The tissues were fixed in phosphate-buffered formaline (4%, pH 7.4) and embedded in paraplast. Histologic sections (4–5 μm) were stained with haematoxylin-eosin, PAS and van Gieson's stain. The immunoreactions were performed on deparaffinized, pronase-treated sections using the avidin-biotin-complex (ABC)-method. The following primary antisera were used: Alpha-fetoprotein (polyclonal, 1:1000, Behring, Marburg, FRG), Alpha-human chorionic gonadotropin (monoclonal, 1:1000, Sera lab, Crawley Down, Sussex, GB), b-12 (Mucin-associated glycoprotein) (monoclonal, 1:10000, Hoffmann-La Roche, Basel, CH), Carcinoembryonic antigen (CEA) (monoclonal, prediluted, Amersham, Buckinghamshire, GB), Chromogranin A (monoclonal, 1:1500, Hybritech, San Diego, CA, USA), Gastrin (polyclonal, 1:10000, J. Girard, Children's Hospital, Basel, CH), Neuron-specific enolase (NSE) (monoclonal, 1:1000, Sanbio, Uden, NL), Neurotensin (NT), polyclonal 1:10000, Immuno-Nuclear Corporation, MN, USA), Pancreatic polypeptide (PP) (polyclonal, 1:60000, R.E. Chance Eli Lilly 2 Comp, Indianapolis, USA), Serotonin (5-HT) (polyclonal, 1:20000 Immuno-Nuclear Corporation, MN, USA), Somatostatin (SOM) (polyclonal, 1:7500, J. Girard, Children's Hospital, Basel, CH), Substance P (SUBP) (monoclonal, 1:1000, Sera lab, Crawley Down, Sussex, GB), Synaptophysin (SYN) (monoclonal, 1:250, Progen Biotechnik, Heidelberg, FRG), Vasoactive intestinal polypeptide (VIP) (polyclonal, 1:2000, Amersham, Buckinghamshire, GB). The control of specificity of the antisera and the tissues used as positives controls are described in detail elsewhere (Heitz et al. 1982).

Results

Carcinoembryonic antigen and the epitope of monoclonal antibody b-12 disclosed a similar pattern of reaction in adenoma and carcinoma. Tubular parts of the carcinoma showed immunoreactive luminal surface of the cells and luminal secretory products (Fig. 5). The mucosal villi were negative for CEA. Neuroendocrine differentiation markers such as synaptophysin and chromogranin A were visualized in individual cells of adenoma, carcinoma and normal mucosa (Fig. 6a, 6b). The other neuroendocrine markers and gastrointestinal hormones were not found.

Discussion

Duodenal carcinomas and adenomas that did not originate from the papilla of Vater and whose diameter was exactly documented were taken into consideration in our literature review. 21 records from the literature fulfilled these conditions (Batra et al. 1983; Braga et al. 1986; Dwyer et al. 1975; Everett et al. 1981; Perzin et al. 1981) and for evaluation our case was added. There were 6 females and 5 males with primary duodenal carcinoma arising in an adenoma; their average age was 62 years (range: 41–73). 6 females and 5 males presented with an adenoma of the duodenum (average age of 55 years; range: 31–75). There were no typical clinical symptoms distinguishing patients with carcinoma from patients with duodenal adenoma. More discriminative between carcinoma and adenoma was the analysis of tumour diameter (Fig. 7). The median diameter of adenomas was 3 cm

Fig. 2. Section through the adenomatous parts with intact duodenal wall (*above*). Carcinoma destroying all layers of the gut wall is shown on the section *below*

Fig. 3. Adenocarcinoma adjacent to tubulo-villous adenoma, infiltrates lamina muscularis propria (×6.5). Haematoxylin-eosin

Fig. 4. Papillary forming parts projected into the lumina of a moderately well differentiated adenocarcinoma (×88). Haematoxylin-eosin

Fig. 5. Positive immunoreaction of CEA on the luminal cell membrane of adenocarcinoma and in luminal secretion (×175). Formaldehyde fixation, paraffin-embedded material, ABC-method, counterstained with haematoxylin

Fig. 6. Focal strong immunostaining of chromogranin A in individual intermingled cells in tubular forming parts of carcinoma and in some cells of normal mucosa (×350). Formaldehyde fixation, paraffin-embedded tissue, ABC-method, counterstained with haematoxylin

Fig. 7

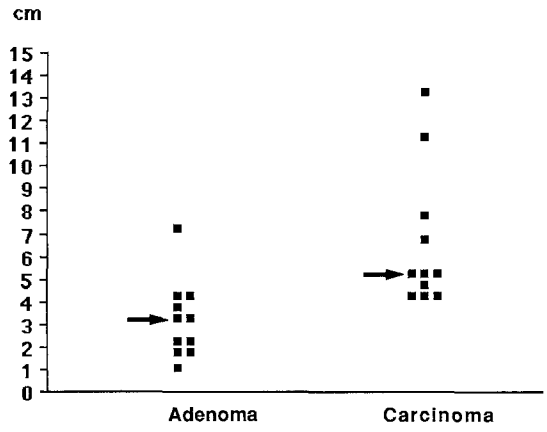

Fig. 7. Correlation between diameter of adenomas and carcinomas. The median values are indicated by *arrows*

(range: 0.8–7 cm), that of carcinomas 5 cm (range: 4–13 cm). The tumour diameters were found to be significantly different in the two groups ($p < 0.005$, non-parametric Mann-Whitney-*U*-test).

Primary duodenal carcinoma is a rare tumour making up only 0.3% of all malignant tumours of the gastrointestinal tract (Alwmark et al. 1980; Spira et al. 1977). Duodenal carcinoma and duodenal adenoma arise preferentially in the 6–7th decade of life (Alwmark et al. 1980; Galandiuk et al. 1988; Komorowski et al. 1981; Spira et al. 1977). However Perzin et al. (1981) reported two patients with duodenal adenoma at the age of 31 years.

An aboral distribution gradient (duodenal, jejunal, ileal) was repeatedly reported (Williamson et al. (1983), Reiner (1976)). The preferential localization of tumours in the duodenum, which forms only 25 cm (6%) of the entire small intestine (3.0–3.5 m), is explained by a higher concentration of carcinogens in bile excreted into the duodenum and lower concentration in the remainder of the small intestine due to bile dilution (Williamson et al. 1983).

Tumours are classified supra- peri- or infraampullary according their location (Alwmark et al. 1980; Cortese et al. 1972; Ryan et al. 1986). Since jaundice is the leading symptom of ampullary tumour, thus allowing for earlier clinical diagnosis, this is not the case in infra- or supraampullary tumours. Since the probability of invasive carcinoma increases with diameter of the adenoma (Delpy et al. 1983; Perzin et al. 1981), tumours with a diameter greater than 4 cm should be considered potentially malignant.

In contrast to Isaacson et al. (1978) we could not visualize CEA immunocytochemically on villi of the normal mucosa. CEA belongs to a family of closely related glycoproteins having several epitopes in common (Klöppel et al. 1987). The existence of several subtypes of CEA and CEA-related antigens makes it difficult to compare our immunohistochemical results with other authors. The mucinous property of the present carcinoma is confirmed by the positive immunoreactivity of monoclonal antibody b-12 within tumour cells. The monoclonal antibody b-12 recognizes a high molecular mucin-like epitope (Stähli et al. 1985; Stähli et al. in press), which is expressed in breast carcinomas and highly differentiated adenocarcinomas (Zenklusen et al. 1988). The weak immunoreactivity of synaptophysin, a calcium-binding membrane protein of presynaptic vesicles in neurons and in neuroendocrine cells (Rehm et al. 1986) is difficult to interpret. The intensive, focal expression of chromogranin A, a major soluble protein of the secretory granules of the adrenal medulla (Wilson et al. 1984) in Paneth-like cells in the tumour without co-expression of neuron-specific enolase (NSE) is puzzling. In previous work (Bremer et al. 1968; Malmed et al. 1965) Paneth cells have been described in villous adenomas of the duodenum. They may represent non-neoplastic Paneth cells integrated into the carcinoma, or an abortive differentiation of tumour cells, originating from a common, pluripotent stem cell of duodenal mucosa. We favor the latter hypothesis since these Paneth-like cells are clearly interposed between individual carcinoma cells. The carcinoma in the center of a mixed tubulo-villous adenoma of the duodenum, the proof of Paneth-like cells in the carcinoma and adenoma led us to suppose that the reported carcinoma is a true primary adenocarcinoma arising in a mixed tubulo-villous adenoma of the duodenum.

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