

# Adenoma of the ampulla of Vater: putative precancerous lesion

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## Abstract

The histopathology of 12 patients with adenoma of the ampulla of Vater was examined to trace the adenoma-carcinoma sequence of the ampulla of Vater. Immunohistochemistry for carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 was also performed. Four large adenomas with mild dysplasia also had foci of moderate dysplasia while another one contained foci of severe dysplasia (intramucosal carcinoma). Immunohistochemically, adenomas of mild to moderate dysplasia had either linear CEA and CA19-9 immunoreactants at the apical portions, or fine granular immunoreactants in the cytoplasm of adenoma cells. In addition, adenomas of severe dysplasia (intramucosal carcinoma) showed a more diffuse or dense immunoreactivity for these two substances in the cytoplasm. These results are consistent with the adenoma-carcinoma sequence for the ampulla of Vater. The immunohistochemistry for CEA and CA19-9 was representative of the degree of dysplasia in the adenoma cells, but the relationship was not conclusive.

Adenoma of the ampulla of Vater is a rare neoplasm<sup>1</sup> and some authors have proposed it to be a premalignant lesion.<sup>2,3</sup> However, most of the papers were case reports and there has been no study with a large number of cases of the lesion. The exact clinicopathology of this disease has also been described in detail in only a few reports. We have reported the clinicopathology of 114 cases of neoplasms of ampulla of Vater, mainly carcinoma of ampulla of Vater.<sup>4</sup> In the report we briefly described five cases of adenoma of the ampulla of Vater. Since we experienced an additional seven cases of lesions, the clinico-

pathology of 12 cases of adenoma of ampulla of Vater will be reported in detail in order to trace the progressive changes in precancerous dysplasia of this lesion. Immunohistochemistry for carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 was also applied to this study.

## Materials and methods

A total of 12 patients with adenoma of the ampulla of Vater were selected from more than 400 patients with pancreatoduodenal tumours,<sup>4,7</sup> which were examined in 5 mm stepwise tissue sections. All the tissue sections were stained with haematoxylin and eosin and some representative tissue sections were also stained with periodic acid Schiff, alcian blue pH 2.5, and by Grimelius' procedure. They were submitted to immunohistochemistry for CEA and CA19-9.

The primary antibody CEA was a polyclonal rabbit antibody, which was obtained from Zymed Laboratories Inc, San Francisco, and generated against highly purified CEA isolated from liver metastasis of colon adenocarcinoma. Non-specific antibodies were removed by solid-phase immunoabsorption with normal human plasma and human red blood cells. Immunoelectrophoresis of the absorbed antiserum against parietal cell antibody extract of tumour tissue showed only a single precipitation arc. CA19-9 was a monoclonal mouse antibody and was obtained from Toray Fuji Bionics, Tokyo. The antibody (1116 NS19-9) was generated against a human colorectal carcinoma cell line (SW 1116) by a hybridoma technique. The avidin-biotin-peroxidase complex method was used and the avidin and biotin reagents were obtained from Vector Laboratories, Burlingame, California (Vectastain ABC kits, PK-4001 and PK-4002).

## Clinicopathological findings of 12 patients with adenoma of the ampulla of Vater

| No of cases | Age (years) | Sex | Chief complaints | Greatest diameter (cm) | Macroscopic type | Atypia                          | Prognosis          |         |
|-------------|-------------|-----|------------------|------------------------|------------------|---------------------------------|--------------------|---------|
|             |             |     |                  |                        |                  |                                 | Follow-up (months) | Outcome |
| 1†          | 57          | F   | Abdominal pain   | 2.5                    | EP               | Mild                            | 30                 | Well    |
| 2           | 72          | M   | †                | 2.2                    | EP               | Mild                            | 34                 | Well    |
| 3           | 70          | F   | Icterus          | 1.5                    | IP               | Mild                            | 52                 | Well    |
| 4           | 51          | F   | Abdominal pain   | 1.5                    | EP               | Mild                            | 88                 | Well    |
| 5           | 48          | M   | Abdominal pain   | 2.0                    | EP               | Mild                            | 96                 | Well    |
| 6           | 48          | M   | †                | 3.0                    | EP               | Mild                            | 8                  | Well    |
| 7           | 50          | F   | †                | 3.0                    | EP               | Mild                            | 2                  | Well    |
| 8           | 69          | M   | Abdominal pain   | 3.0                    | EP               | Moderate                        | 40                 | Well    |
| 9‡          | 64          | M   | Abdominal pain   | 3.0                    | IP               | Moderate                        | 17                 | Died    |
| 10‡         | 63          | F   | Fever            | 3.0                    | EP               | Moderate                        | 21                 | Died    |
| 11          | 71          | M   | Icterus          | 3.5                    | EP               | Moderate                        | 87                 | Well    |
| 12          | 58          | M   | Icterus          | 2.5                    | EP               | Severe (intramucosal carcinoma) | 32                 | Well    |

IP=intramural protruding form; EP=exposed protruding form.

\*Associated with early gastric carcinoma.

†A polypoid tumour of the ampulla of Vater was incidentally found by gastrointestinal series.

‡Two patients (cases 9 and 10) died from cardiac failure, not associated with metastasis.

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Figure 1: Intramural protruding type. Enlarged ampulla of Vater is covered by normal duodenal mucosa. Scale in cm.

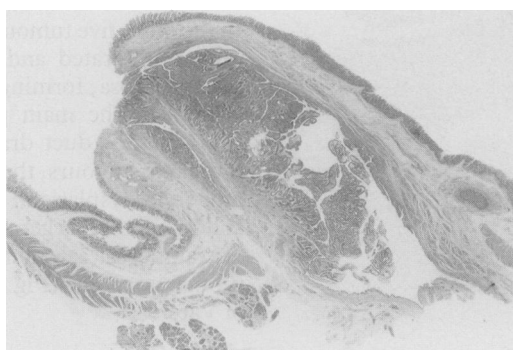


Figure 2: Intramural protruding type, papillary adenoma. Papillary proliferation of atypical cells mainly in the common channel, the bile duct and partly in the pancreatic duct. (Haematoxylin and eosin, original magnification  $\times 4$ .)



Figure 3: Exposed protruding type. Exposed adenoma is lobulated in surface.

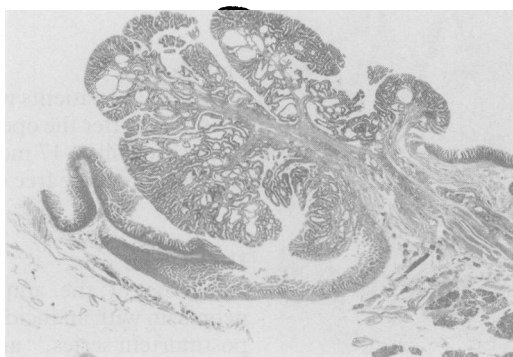


Figure 4: Exposed protruding type, papillotubular adenoma. Papillary or tubular structures of atypical cells, as in Figure 2. (Haematoxylin and eosin, original magnification  $\times 4$ .)

The localisation of antigens was visualised by placing the slides in 0.01% hydrogen peroxide and 0.05% diaminobenzidine in 0.05 M phosphate saline buffer, pH 7.2, for five minutes. All sections were counterstained with methyl green.

Clinical charts were available from all 12 patients. Follow up information was obtainable from all 12 patients and were up-dated on June 30, 1990.

## Results

### CLINICAL FINDINGS

The total of 12 patients with adenoma of ampulla of Vater ranged from 48 to 72 years of age with a mean of 59.7 years (Table). The patients consisted of seven men and five women, showing a male predominance of 1.4. Three developed icterus due to an obstruction of the bile duct by adenoma. Six patients complained of abdominal pain and/or fever probably caused by cholangitis. In the other three patients a polypoid tumour of the ampulla of Vater was incidentally found in upper gastrointestinal series. Preoperative serum CEA and CA19-9 levels were examined in five and three patients, respectively. All were within normal limits. Nine of the 12 patients had previously undergone pancreatoduodenectomy and the remaining three had received a transduodenal papillectomy.

### MACROSCOPIC FINDINGS

All 12 tumours were of a protruding type and consisted of two intramural types (Figs 1 and 2) and 10 exposed types (Figs 3 and 4). The 12 tumours ranged from 1.5 to 3.5 cm in the greatest diameter with a mean of 2.6 cm.

### MICROSCOPIC FINDINGS

All 12 tumours were composed of a papillary or tubular proliferation of atypical cells (Fig 5). They had tall or columnar epithelia with an eosinophilic or clear cytoplasm, containing goblet cells in 12 cases, argentaffin cells in 11 and Paneth cells in eight (Fig 6). Incomplete or complete brush borders were seen in a line along the luminal surface of atypical tubules or glands

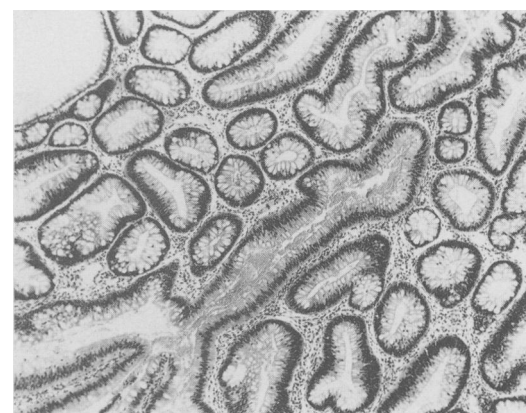


Figure 5: Tubular adenoma, with atypical tubules containing goblet cells. (Haematoxylin and eosin, original magnification  $\times 60$ .)

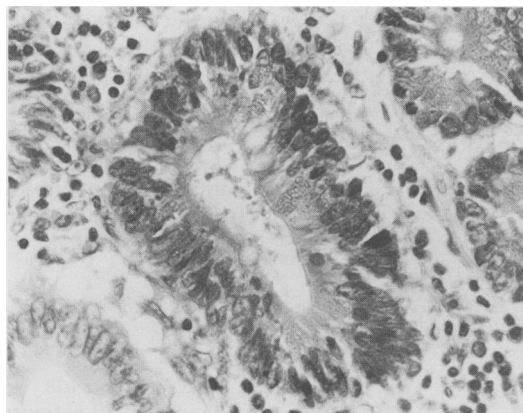


Figure 6: Atypical tubules are lined by columnar cells containing Paneth granules. (Haematoxylin and eosin, original magnification  $\times 600$ .)



Figure 10: CA19-9 immunoreactants are seen diffusely in the cytoplasm of adenoma cells. (ABC method, original magnification  $\times 240$ .)



Figure 7: Foci of moderate dysplasia in adenoma of mild dysplasia. (Haematoxylin and eosin, original magnification  $\times 77$ .)

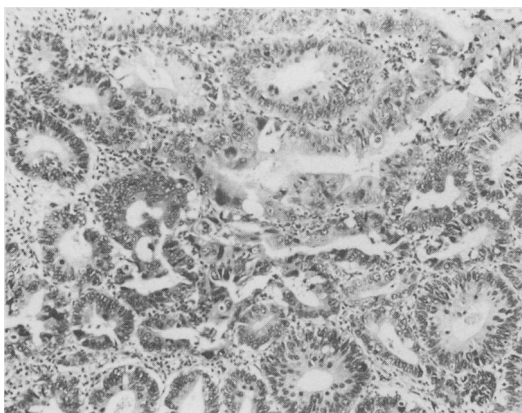


Figure 8: Foci of severe dysplasia (intramucosal carcinoma) in tubular adenoma. (Haematoxylin and eosin, original magnification  $\times 102$ .)

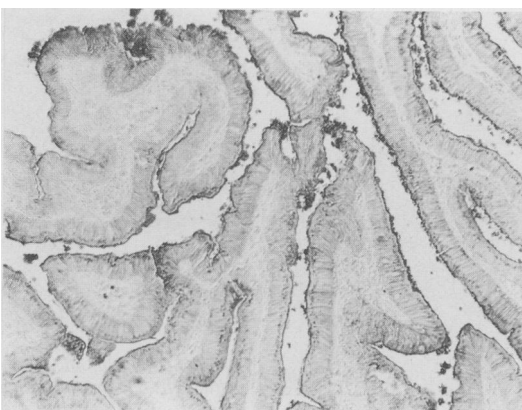


Figure 9: CEA immunoreactants are present in a linear at the apical portion of adenoma cells. (ABC method, original magnification  $\times 115$ .)

in all cases. In seven tumours, atypical epithelia proliferated intraluminally mainly in the common channel and intraduodenal bile duct, and focally in the intraduodenal pancreatic duct. In the other five tumours, tumour cells exophytically proliferated and extended onto the duodenal mucosa, forming a polyp surrounding the orifices of the main pancreatic duct, and the common bile duct drained into the polyps. In four large tumours, there were foci of epithelia of moderate dysplasia at the deep portions (Fig 7) and in another larger adenoma, severe dysplasia (intramucosal carcinoma) was encountered in a tubular adenoma (Fig 8) at the orifice of ampulla of Vater.

#### HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL STUDIES

Cytoplasm of tumour cells with goblet cell differentiation were positive for periodic acid Schiff and alcian blue. The incomplete or complete brush borders were positive for periodic acid Schiff at the luminal surface. Grimelius' positive cells were scattered at the basal layer of atypical tubules in 11 cases. The normal duodenal epithelia had linear immunoreactants of CEA and CA19-9 at the apical portions. Paneth cells, argentaffin cells and goblet cells were negative for CEA and CA19-9. CEA and CA19-9 immunoreactants were present in a line along the luminal surface while they were only weakly observed in the cytoplasm of adenoma of mild to moderate cellular atypia (Fig 9). In adenoma of severe dysplasia (intramucosal carcinoma), CEA and CA19-9 immunoreactants were present more densely and diffusely in the cytoplasm (Fig 10).

#### PROGNOSIS

Ten of the 12 patients were well from 2 months to 96 months after the operation. Two patients died of cardiac failure 17 months and 21 months after surgery, but were free of any metastasis.

#### Discussion

Adenoma of the ampulla of Vater is a rare neoplasm with an incidence of 0.04 and 0.12% in postmortem series,<sup>14</sup> and several different terms

have been applied to the probable adenoma, including polyp, papilloma<sup>3</sup> and adenomatous polyp.<sup>8</sup> Icterus has been observed in 69.2 to 100% of patients with carcinoma of the ampulla of Vater and a fluctuation of jaundice is characteristic of the carcinoma.<sup>4,6</sup> On the other hand, the clinical aspects of adenoma of Vater have not yet been described in a large series. In the present study of 12 cases of adenoma, only three patients developed icterus and none had any fluctuation of icterus. The difference of frequency of icterus may be due to the slow growing nature of adenoma of the ampulla of Vater.

Tasaka<sup>9</sup> reported a histological examination of a normal ampulla of Vater and said that goblet, Paneth and argentaffin cells were seen in 72.6%, 11.0% and 93.3%, respectively, of the ampulla of Vater in 73 cases of autopsy and surgical material. In the present study of 12 adenoma cases, goblet cells were found in 12, argentaffin cells in 11 and Paneth cells were encountered in eight. Most of the adenomas of the ampulla of Vater showed differentiation into intestinal epithelia.

The adenoma-carcinoma sequence is generally accepted in adenomas of the colon and rectum,<sup>10-13</sup> the basic evidence being the coexistence of adenoma and carcinoma in the same lesion. In adenoma of ampulla of Vater, the foci of in situ and invasive carcinoma were found in the adenoma lesion.<sup>14,15</sup> On the other hand, in our previous study residual adenoma was present at the periphery of carcinoma of the ampulla of Vater in 20 of 109 cases,<sup>4</sup> and the reported rate was 20 to 82%.<sup>16-21</sup> Such evidence supports the adenoma-carcinoma sequence of the ampulla of Vater.

The presence of CEA in colonic adenomas has been demonstrated by several authors.<sup>22,23</sup> The patterns of CEA distribution are similar to those in ampullary adenomas, with moderate staining along the glycocalyx borders and faint cytoplasmic staining of neoplastic cells.<sup>22</sup> Isaacson and LeVann<sup>23</sup> suggested that CEA might be a reliable indicator of malignant change within colonic adenoma. Our results of CEA and CA19-9 staining in adenoma of the ampulla of Vater was almost the same as those of colonic adenoma. Ampullary adenoma with severe atypia (intramucosal carcinoma) showed a staining similar to, but more intense than, that of the associated adenomas of moderate dysplasia. The staining of CEA and CA19-9 appeared representative of the degree of dysplasia in the adenoma cells. However, the relationship between staining and the degree of dysplasia was not conclusive. These differences in immunoreactivity for CEA and CA19-9 may be of diagnostic value in discriminating among the

different adenoma cells of moderate and severe dysplasia and early invasive carcinoma.

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