

Adenocarcinoid of the Vermiform Appendix

Birgitta Olsson and Otto Ljungberg

Department of Pathology, University of Lund, General Hospital, Malmö, Sweden

Summary. Four cases of adenocarcinoid of the appendix were studied. Two tumours were found among 28 cases primarily diagnosed as appendiceal carcinoids. They showed characteristic histological structures with features of both a conventional carcinoid tumour and a mucinproducing adenocarcinoma with goblet cells. All tumours were small and ill-defined; three were associated with fibrous obliteration of the appendiceal lumen. All were diagnosed incidentally by the pathologist in appendices removed “en passant” or because of acute appendicitis. Three of the tumours appeared well differentiated with a low degree of malignancy similar to that of the conventional carcinoid tumour. In one case however, the tumour was less differentiated with atypical foci and a high mitotic count and had metastasised to peritoneum and both ovaries.

Key words: Adenocarcinoid – Goblet cell carcinoid – Mucinous carcinoid tumour – Vermiform appendix.

Introduction

Recently an unusual composite appendiceal neoplasm has been defined, which possesses features of both carcinoid and adenocarcinoma and which contains both argentaffin cells and mucin producing cells. Various names have been suggested for this tumour, such as “mucinous carcinoid tumour” (Klein, 1974) and “goblet cell carcinoid” (Subbaswamy et al., 1974). Warkel et al. (1978) recognised two histological variants, i.e., a more common goblet cell-type and a rare tubular type which were considered to comprise subgroups of a distinctive entity and they proposed the name “adenocarcinoid” to designate the whole group.

We had the opportunity of studying two tumours of this particular type. This prompted us to search for additional cases in the files of the department.

Offprint requests to: Dr. Otto Ljungberg, Department of Pathology, Malmö General Hospital, S-21401 Malmö, Sweden

Two additional examples of the tumour were found among 28 appendiceal carcinoids surgically removed during the period 1978–1979. The purpose of this report is to describe the clinico-pathological features of the four tumours.

Materials and Methods

The tissue specimens were fixed in 10% formalin and embedded in paraffin. Sections were stained with haematoxylin-erythrosin, some were also studied with the method of Masson-Hamperl (Romeis, 1948) and the diazo-coupling method (Pearse, 1960) for the demonstration of argentaffin material and serotonin respectively. Grimelius silver nitrate procedure (Grimelius, 1968) was used for demonstration of argyrophilia. The presence of mucin was evaluated by the PAS stain.

Case Reports

Case 1. A 54-year-old woman was admitted for pain in the abdomen. A mass was found in the left iliac fossa, which was diagnosed as an ovarian tumour. She underwent a bilateral oophorectomy and the vermiform appendix, which was judged as normal by the surgeon, was removed "en passant". The left-sided ovarian tumour was found to be a large benign fibroma and in the right ovary a small benign serous cystadenoma was also detected. The lumen of the appendix was obliterated and no tumour could be seen macroscopically. The postoperative course was uneventful and the patient is well 2 years after the operation.

Case 2¹. A 40-year-old woman presented with pain in the right iliac fossa. Appendectomy was carried out for "acute appendicitis". There were no signs of acute inflammation but the apical part of the appendix was thickened, the lumen obliterated and its wall was diffusely thickened and firm. No defined tumour was found macroscopically. On microscopical examination the appendix was found to be involved by a diffusely growing malignant tumour. Since it was apparently not radically removed, the patient underwent a subsequent ileo-coecal resection. Residual tumour was found in the coecal wall, at the site of the base of the appendix.

Six months later the patient presented again with abdominal pain and a palpable mass in the right iliac fossa. At laparotomy, a generalised peritoneal carcinomatosis and some ascites was found. The left ovary was involved by a round, multicystic tumour (10 × 10 × 6 cm). The right ovary was somewhat enlarged (4 × 4 × 3 cm), its surface was covered by multiple small tumour nodules and there was a firm, multi-nodular tumour infiltrate in the ovarian stroma. Both ovaries and some of the peritoneal tumours were removed.

After an additional period of 3 months, the patient began to suffer from recurrent attacks of ileus and a fourth laparotomy had to be performed. There was extensive peritoneal carcinomatosis with wide-spread fibrous adhesions, especially in the lower part of the abdomen. An ileo-transversostomy was done. Postoperatively, the patient was given cytostaticum therapy with a temporary improvement of the clinical condition, but 12 months after the first operation there have been recurrent abdominal pain and episodes of sub-acute obstruction.

Case 3. A 20-year-old woman presented with symptoms of acute appendicitis. Appendix was removed. Its apical part was enlarged, showed thickened walls and the lumen contained pus. The patient is well 3 years after operation.

Case 4. A 26-year-old woman underwent appendectomy for "acute appendicitis". The appendix was uniformly thickened. There were signs of acute inflammation. In addition the lumen was partly obliterated by fibrous tissue, but no defined tumour was seen macroscopically. The postoperative course was uneventful and the patient is in good health 3 years after the operation.

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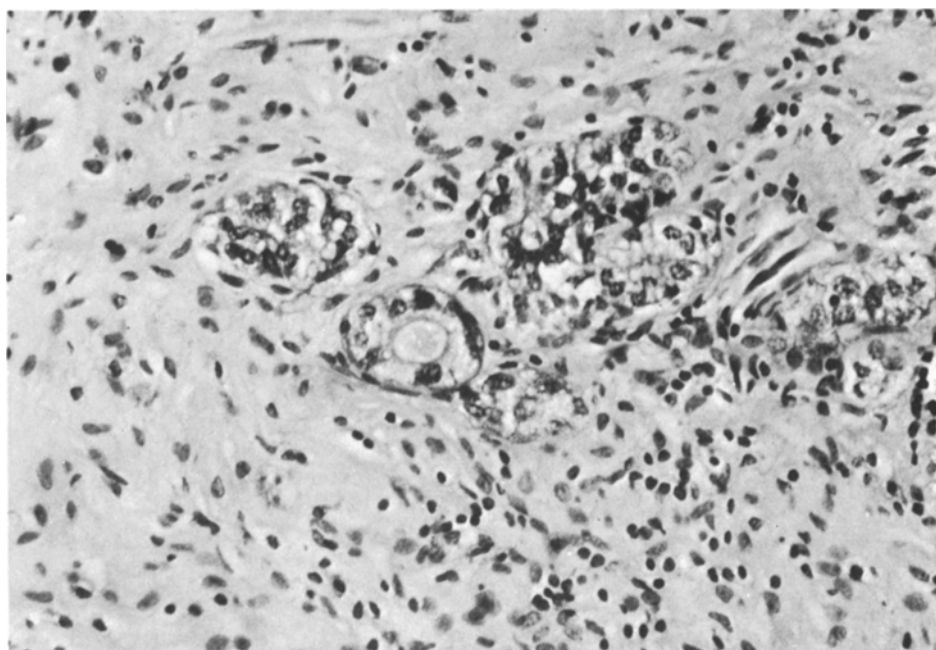


Fig. 1. Solid nests and tubular tumour structures growing in fibrous tissue which had completely obliterated the lumen of appendix. Case 1. Haematoxylin-erythrosin. $\times 255$

Microscopical Findings

All four appendices were involved by diffusely infiltrating tumour structures. These were growing in a large amount of fibrous tissue, which had partially obliterated the lumen in cases 1, 2 and 4. In cases 2 and 3 the major part of the tumour was situated in the apex of the appendix. In the remaining two cases the site of the major part of the tumour could not be determined. Acute appendicitis was also present in cases 3 and 4. The tumours showed great tendency to grow diffusely into the wall of the appendix (Fig. 2), but only in case 2 had the invasion penetrated through the serosal layer and infiltrated the base of the appendix. The general architecture of the tumours was similar in all cases. The tumours formed rounded and polyhedric solid nests and tubules of rather light, sometimes finely vacuolated cells with eosinophil cytoplasmic granules (Fig. 1). These granulated cells were diazo-positive, argentaffin and argyrophil (Figs. 3 and 4). Some nests also contained a varying number of mucin-producing, PAS-positive cells with clear cytoplasm and sometimes eccentrically located nuclei, mimicking goblet cells (Fig. 5). Small lumina were seen in some nests, surrounded by PAS-positive cells. There was a gradual transition towards formation of pure tubular and glandular structures, some of which contained mucin-producing cells with an admixture of a varying number of argentaffin and argyrophil cells: Some solid nests exclusively contained mucin-producing cells; this feature was most prominent in case 2 (Fig. 6).

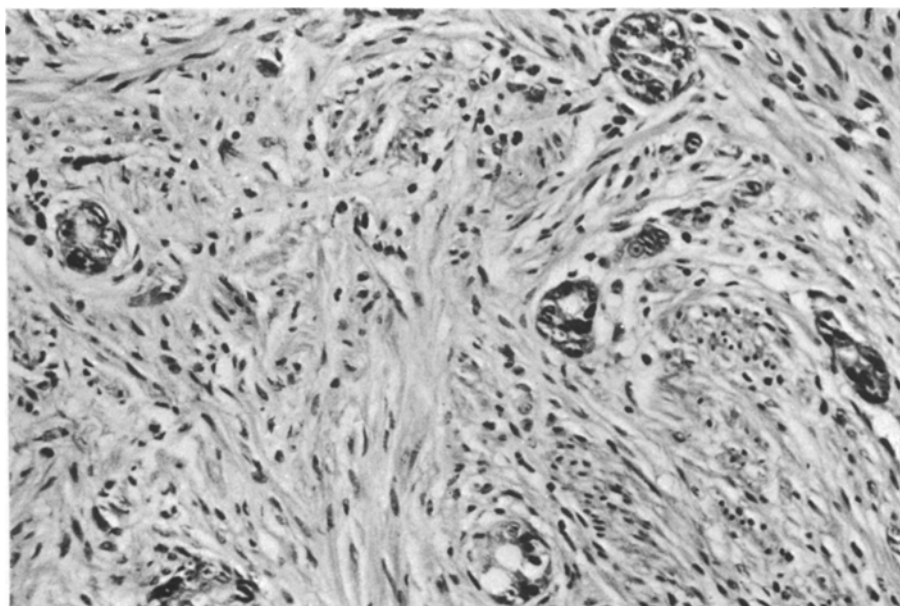


Fig. 2. Nests and tubules of tumour cells infiltrating the muscular layer of appendix. There is remarkably little destruction of the tissue. Case 1. Haematoxylin-erythrosin. $\times 100$

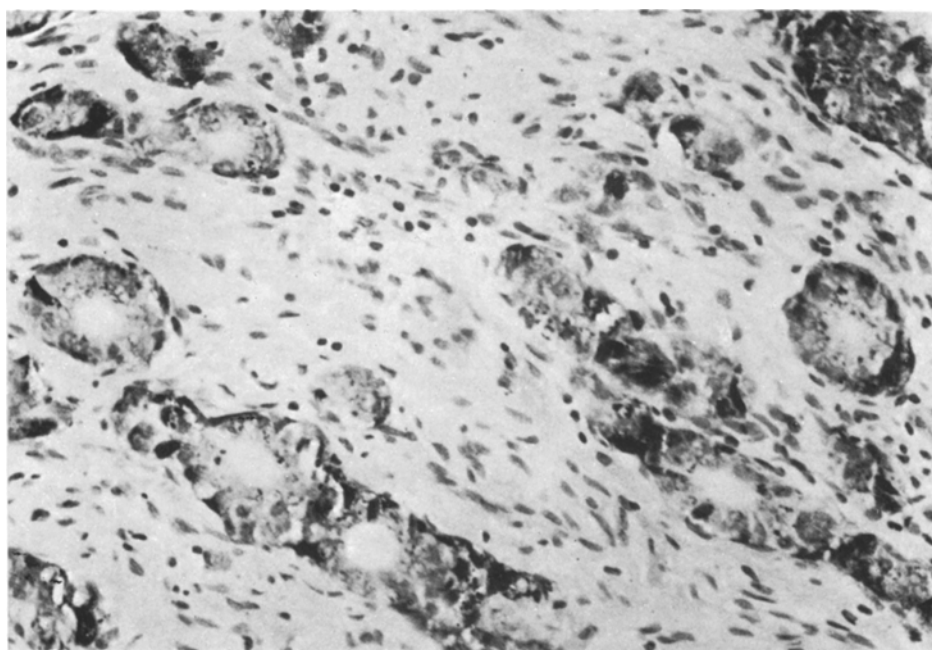


Fig. 3. Many cells show argentaffin cytoplasmic granules. The strongest reaction is present in peripheral parts of the acini and glandular structures. Case 1. Masson Hamperl. $\times 255$

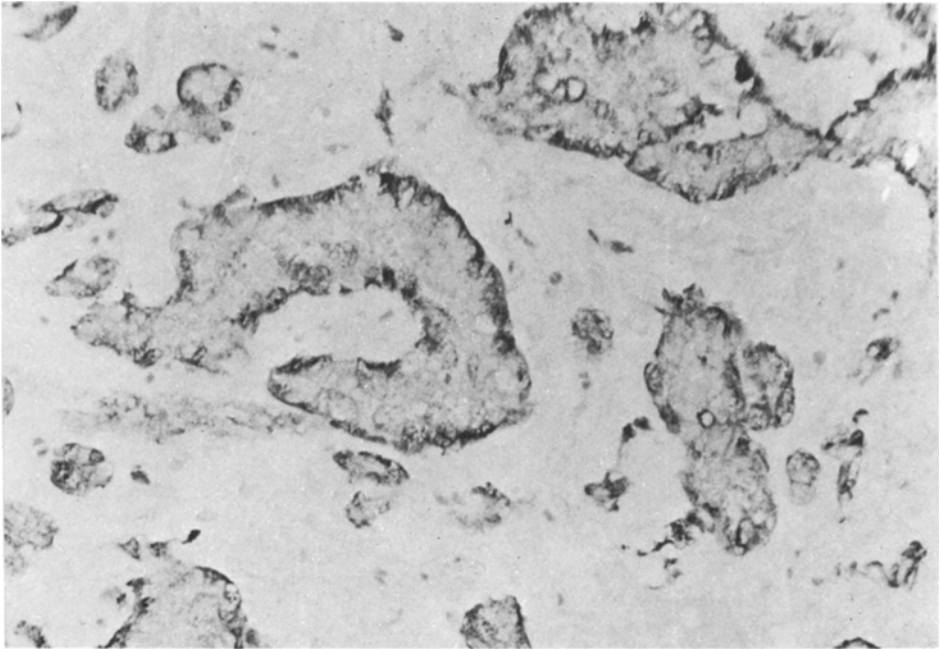


Fig. 4. Numerous argyrophil cells located in marginal parts of the nests. Case 1. Grimelius silver nitrate procedure. $\times 255$

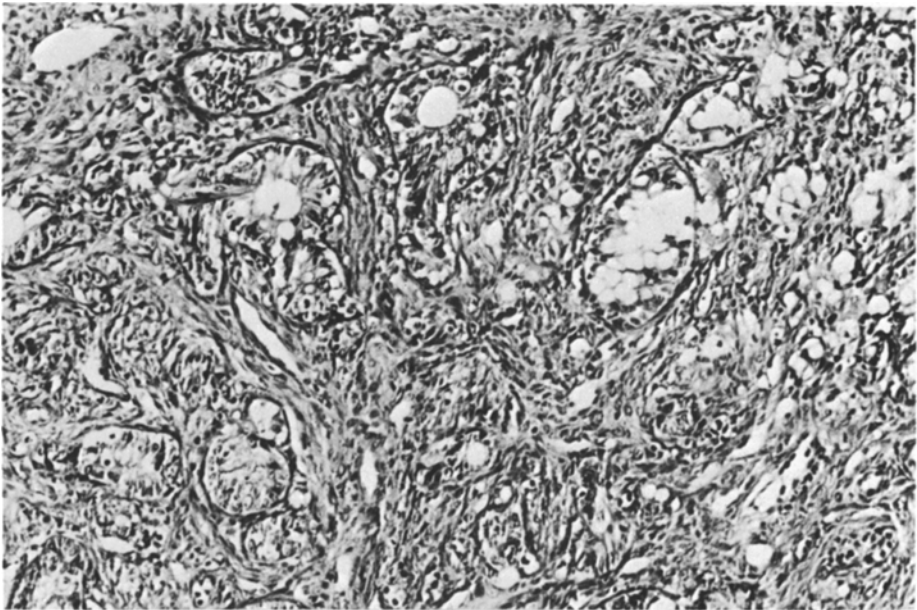


Fig. 5. Ovarian metastasis of adenocarcinoid in Case 2. Solid and glandular structures with varying number of mucin producing goblet cells. Haematoxylin-erythrosin. $\times 100$

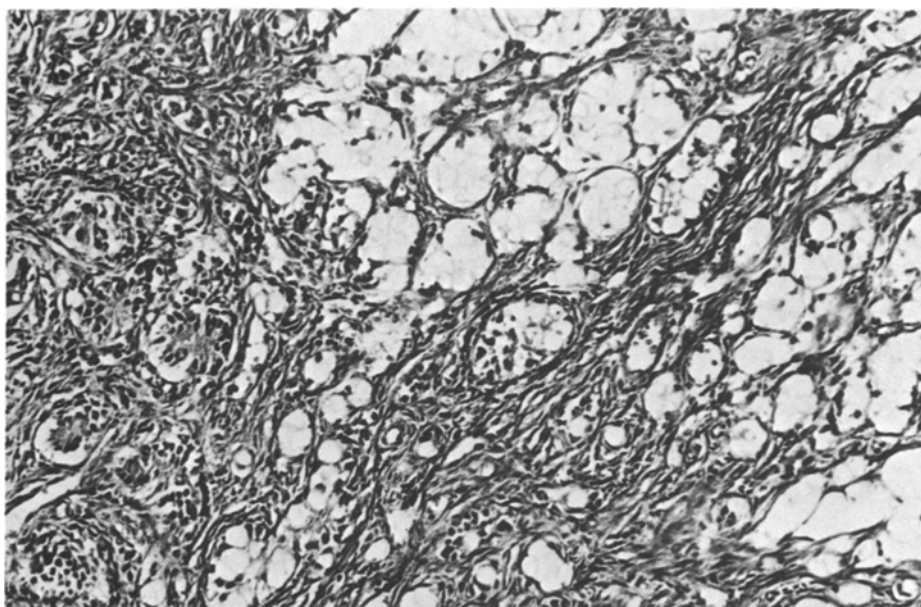


Fig. 6. Same case as in Fig. 5. Area of the tumour containing small, solid nests which are exclusively built up of goblet cells. Haematoxylin-erythrosin. $\times 100$

Three of the tumours (Cases 1, 3 and 4) appeared well differentiated. The cells were regular and monomorphic with rather uniform nuclei and mitoses were very inconspicuous. In case 2, however, the tumour cells showed a greater degree of atypia with nuclear polymorphism and numerous mitoses (Fig. 7). The multicystic tumour in the left ovary in this case was a papillary cystadenocarcinoma of a low degree of differentiation (Figs. 8 and 9). The cysts were lined by fibrous and papillary structures composed of cells which were more basophil and polymorphic than those of the adenocarcinoid, and showed more numerous mitotic figures. It contained occasional argyrophil cells but no goblet cells. Structurally, it differed markedly from the appendiceal tumour and was considered to be of ovarian origin. The superficial parts of the residual ovarian stroma and the major part of the right ovary, however, also contained metastatic infiltrates of the appendiceal tumour, growing diffusely or in ill-defined nodules with the same pattern as in a Krukenberg tumour. Similarly, the peritoneal metastases were of the adenocarcinoid type containing both serotonin and mucin producing cells. In some parts the metastases contained glandular structures and small solid nests which were exclusively composed of mucin producing goblet cells (Fig. 6).

Discussion

The tumour under discussion has been documented in several previous reports (Jablokow et al., 1965; Steinberg et al., 1967). Recently it has received new interest, which has mainly concerned its proper classification, i.e., whether

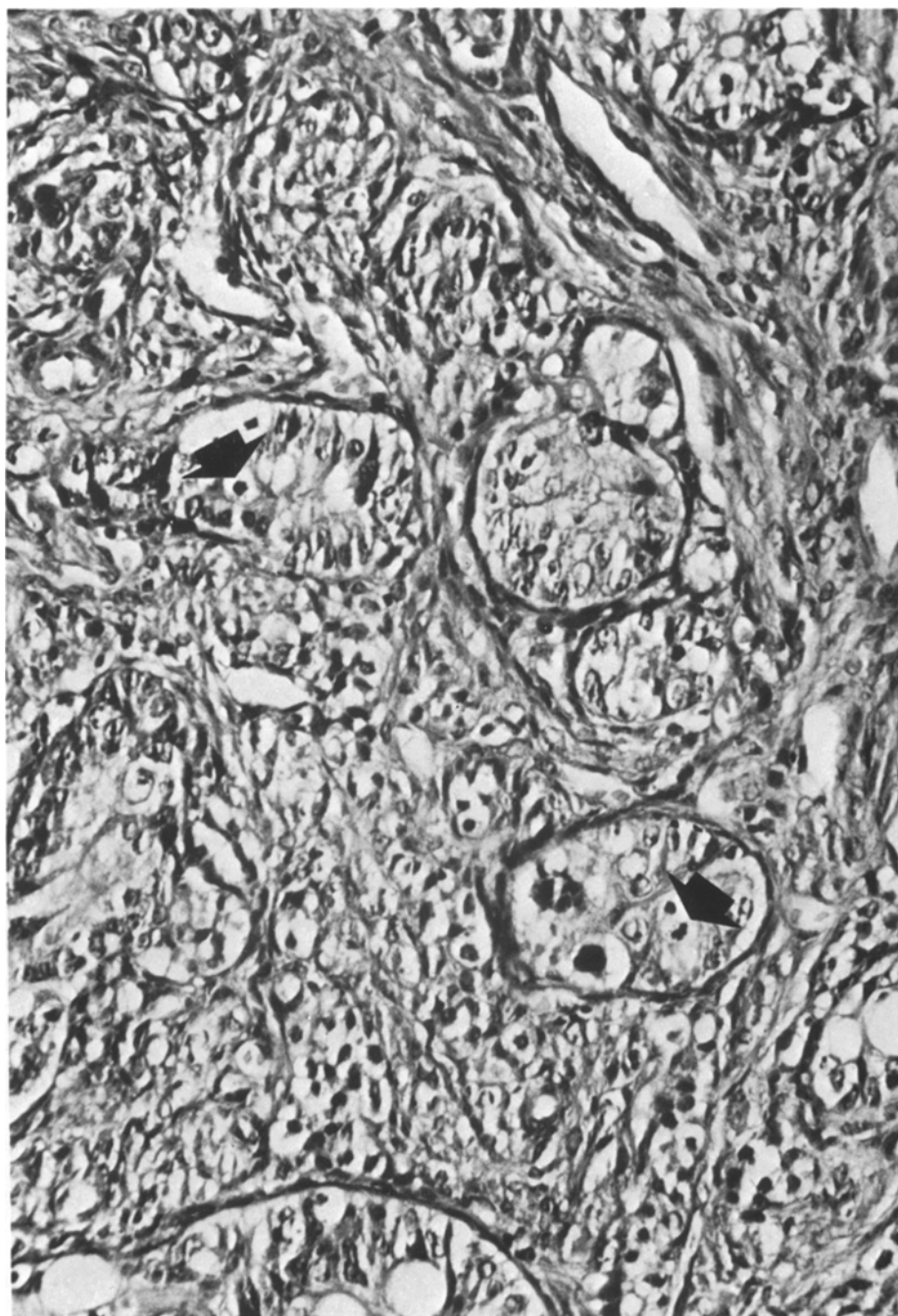


Fig. 7. Adenocarcinoid structures in Case 2, composed of rather polymorphic tumour cells with mitotic figures (*arrows*). Haematoxylin-erythrosin. $\times 255$

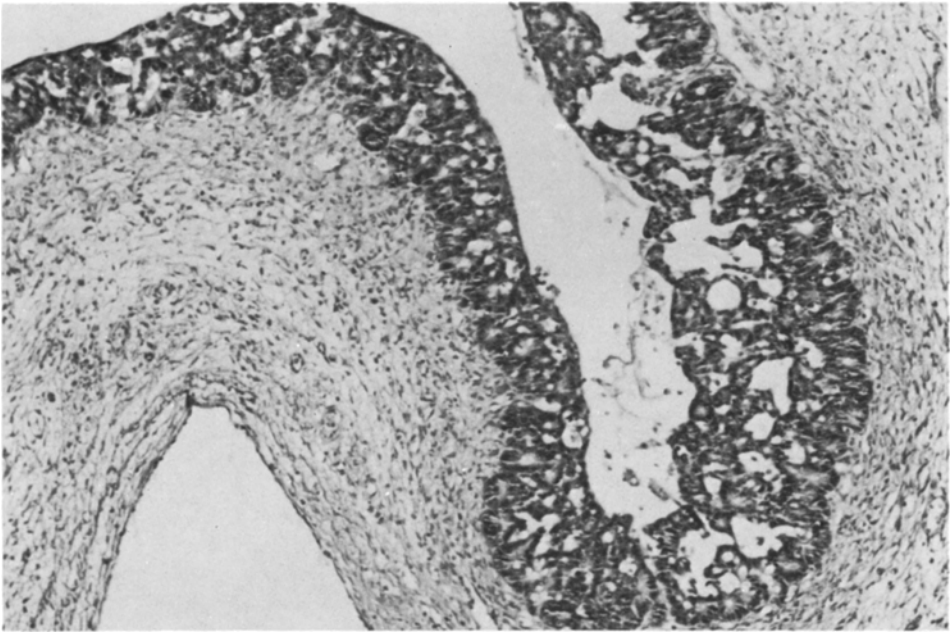


Fig. 8. Ovarian cystadenocarcinoma in Case 2. Part of a cyst lined by cribriform structures of basophil polymorphic tumour cells. Haematoxylin-erythrosin. $\times 100$

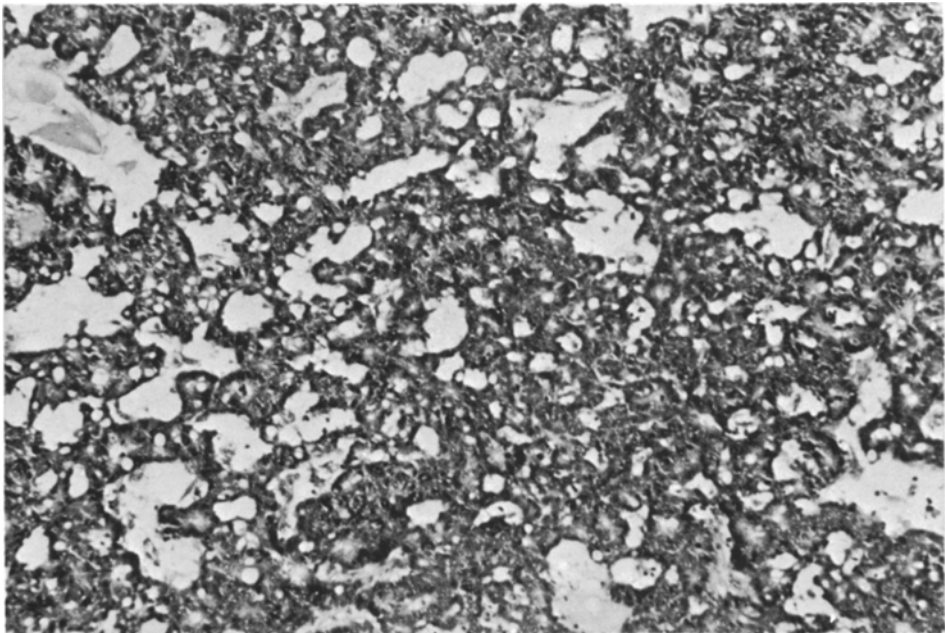


Fig. 9. Same tumour as in Fig. 8, with solid area composed of cribriform tumour structures shown for comparison with the adenocarcinoid in Fig. 7. Haematoxylin-erythrosin. $\times 100$

it should be regarded as a form of carcinoid or a variant of appendiceal adenocarcinoma. It has a structural resemblance to adenocarcinoma due to formation of abundant mucin and goblet cell and glandular arrangements. On the other hand, it also develops a spectrum of morphological structures towards solid nests which contain argentaffin, diazo-positive and argyrophil cytoplasmic granules which are similar to those in the classical mid-gut carcinoid in its ordinary form (Cooper et al., 1978). Its mode of growth with concentration of the tumour elements within the basal part of the mucosal lamina propria is more compatible with a carcinoid than with an adenocarcinoma. This also applies to its pattern of invasion, growing diffusely through the layers of the wall without causing necrosis or much tissue destruction. In three of the cases described here, the tumour structures were concentrated in the fibrous tissue which had completely obliterated the lumen of the appendix. It is not possible to determine whether this fibrous change had antedated the tumour and might have played a causal role in the development of the tumour or was merely a secondary phenomenon.

It is known that carcinoids of the conventional type may contain small amounts of mucin. Whitehead and Cosgrove (1979) reported the presence of small amounts of mucins in 11 of 16 usual carcinoids, located in lumina of more or less well differentiated acinar structures and, more rarely, as droplets in the cytoplasm of tumour cells. This finding raises the question whether we are dealing with a continuous spectrum of carcinoid subtypes, defined merely on the basis of quantitative differences with respect to their endocrine and exocrine characteristics or whether there exists a more fundamental biological difference between the carcinoid and the adenocarcinoid. This question is critical for the elucidation of the histogenesis of the tumour.

One group of authors favours the hypothesis of a single cell type as the progenitor cell of the neoplasm. Reports have appeared, describing the goblet cells and the argentaffin cells of adenocarcinoid tumours as two extremes of a spectrum with intermediate forms in between (Rosai et al., 1968; Abt et al., 1976). Ratzenhofer (1977) has described a combined endocrine-exocrine cell type in the gastro-intestinal tract harbouring both endocrine secretory granules and mucous and zymogen granules. He has coined the term "amphicrine cell" for this cell type which he regards as being of entodermal origin and progenitor cell for the adenocarcinoid. This may be consistent with the view proposed by Creutzfeldt (1977) that gastro-intestinal endocrine cells are secretory cells capable of carrying out a spectrum of different secretory functions which include endocrine, paracrine and/or exocrine mechanisms (cf. Heitz, 1977; Auböck, 1977). Recently, however, Cooper et al. (1978), in an ultrastructural study, could not verify these previous observations of transitional cells forms and suggest that the neoplasm is built up of two separate classes of cells which have different histogenesis and embryogenesis (i.e., ento- and ectodermal origin).

A third theory suggests that the overall organization of the tumour structures with argentaffin cells lying in the basal part of the tubular structures, interposed between mucinous glandular cells, may be an attempt to form normal glandular crypts (Warkel et al., 1978). This suggests a simultaneous and integrated neoplastic proliferation of histogenetically different components of a highly organized tumour.

Adenocarcinoid of the appendix has generally been considered to have a rather innocent clinical behaviour, similar to that of the conventional appendiceal carcinoid, and appendectomy has been advocated as sufficient treatment (Klein, 1974; Haqqani et al., 1977). In one of our cases, the tumour showed extensive local growth and had metastasised to peritoneum and both ovaries. Histopathologically, this tumour appeared less differentiated, containing atypical cells with a high mitotic activity. This indicated that in some cases, the behaviour of the tumour is more aggressive. This is compatible with the findings of Warkel et al. (1978) and suggests a more extensive surgical treatment for such cases.

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Addendum

After submitting the manuscript, sections from the tumours in cases 3 and 4 have been examined for immunoreactivity for the following peptide hormones: glucagon, gastrin, human pancreatic polypeptide, insulin, motilin, somatostatin, substance P, β -endorphin and leu-enkephalin. The indirect immunofluorescence method or the peroxidase-antiperoxidase (PAP) procedure was used.

None of these hormones was found in the two tumours.