Composite glandular-carcinoid tumour of the terminal ileum

N M Varghese, A M Zaitoun, S M Thomas, A Senapati, A Theodossi

Abstract

Aims—To investigate a female patient with a tumour mass of the terminal ileum, to define the nature of the tumour, and to correlate its morphology and behaviour with similar types of tumours of the large intestine and stomach.

Methods—Tissues obtained at colonoscopy, from hemicolec tomy specimens, and from liver and peritoneal biopsy specimens were studied macroscopically, microscopically, histochemically, and immunohistochemically for epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), neuron specific enolase (NSE), and S100 protein.

Results—Macroscopic examination showed a tumour of the terminal ileum protruding into the caecum. Microscopically the tumour showed two components, one adenoma with moderate dysplasia and the other carcinoid tumour. The adenomatous component stained positively for EMA and CEA and negatively for NSE. The carcinoid component stained positively for NSE and negatively for EMA and CEA. Histochemically the carcinoid area was argyrophil positive and argentaffin negative. Only the carcinoid had metastasised, to the liver, peritoneum, and the lymph nodes, at the time of diagnosis.

Conclusion—the morphological, histochemical, and immunohistochemical findings confirm the diagnosis of a composite adenoma-carcinoid tumour of the terminal ileum.

Pathological examination

Specimens from the initial biopsy of the tumour, the tumour mass, liver, and peritoneal deposits were fixed in 10% buffered formaldehyde and processed routinely in paraffin wax. Blocks were cut at 5 μm thickness and stained with haematoxylin and eosin, diastase/periodic acid-Schiff, Grimelius (argyrophil), and Fontana-Masson (argentaffin) stains. Representative blocks from the primary tumour and metastatic deposits were also selected for immunohistochemical analysis and 4 μm sections were stained for carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), neuron specific enolase (NSE), and S100 protein by the avidin-biotin-peroxidase complex technique. Positive and negative controls were used to verify the specificity of the immunoreagents.
primary antibodies were obtained from Dako Limited, High Wycombe, Buckinghamshire, England.

Results
The surgical specimen consisted of 60 cm of terminal ileum, together with appendix, caecum, and a portion of the ascending colon. On section, a pedunculated polypoid tumour (4 × 3·5 × 2·3 cm) of the terminal ileum was seen, arising proximal to the ileocaecal valve and protruding through it into the caecum. The cut sections of the tumour looked light brown in colour. Histological examination showed a tubular adenoma with most of the central area occupied by carcinoid tumour cells. The adenomatous component was argyrophil positive and argentaffin negative. Immunohistochemical staining in the carcinoid areas was positive for neuron specific enolase (fig 1A) and negative for carcinoembryonic antigen. Immunohistochemical staining of the adenomatous areas was positive for CEA (fig 1B) and negative for NSE. Transition zones between the carcinoid and adenomatous components were seen. Carcinoid tumour had invaded the polyp stalk, muscle layers, serosal and subserosal tissues, and tumour thrombi was seen in adjacent blood vessels and lymphatics. Both lines of resection were free of tumour. Sections from the appendix, caecum, and ascending colon were normal. Sections from the liver, peritoneal nodules, and two of 13 lymph nodes examined showed metastatic carcinoid tumour of similar morphology and immunoreactivity to the ileal tumour.

Discussion
Composite adenoma/adenocarcinoma-carcinoid tumours of the gastrointestinal tract have aroused considerable interest.135 There are no reports of their occurrence in the small bowel. The feature of a benign glandular component in a composite tumour has only been previously reported on two cases.7

The clinical diagnosis of a polypoid tumour in the present case was made at colonoscopy. The negative barium enema may be explained by intermittent prolapse of the ileal polyp into the caecum. This clinical presentation is similar to "pure" ileal carcinoid tumours, which usually present with small intestinal obstruction or intussusception.

The case discussed is unique in that it is a true adenoma of the terminal ileum exhibiting moderate dysplasia, which is extremely rare in this part of the bowel.1 It is also unique for its morphological spectrum of adenomatous and carcinoid elements, which appear as separate components yet have occasional transitional zones between them. The morphology of metastatic elements in composite glandular endocrine cell tumours are similar to those of the primary tumour.5-10 Only the carcinoid element of this tumour behaved in a malignant fashion and a similar pattern of metastasis has been reported by Lyss et al.11 The histochemical and immunohistochemical findings confirm the diagnosis of the carcinoid elements within the primary tumour and in the metastatic deposits. The term composite glandular-carcinoid tumour is therefore an appropriate name for this neoplasm in our case. This is also supported by the absence of endocrine cell hyperplasia within the adenomatous component of this tumour and also within the adjacent normal mucosa of the caecum, terminal ileum, and appendix.

The advent of immunohistochemistry and
**Composite glandular-carcinoid tumour of the terminal ileum**

**Morphological spectrum and clinical behaviour with metastases of composite glandular-endocrine cell tumours of the gastrointestinal tract**

<table>
<thead>
<tr>
<th>Tumour and site</th>
<th>Description and components</th>
<th>Behaviour</th>
<th>Site of metastases</th>
<th>Metastatic components</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell carcinoma of the rectum and colon</td>
<td>Undifferentiated tumour cells with features of both carcinoid and squamous cell carcinoma</td>
<td>Highly malignant</td>
<td>Liver, lymph nodes and ovary</td>
<td>As primary</td>
<td>10</td>
</tr>
<tr>
<td>Small cell undifferentiated carcinoma of colon</td>
<td>Undifferentiated cells showing features of both carcinoid and carcinoid</td>
<td>Highly malignant</td>
<td>Liver and lymph nodes</td>
<td>As primary</td>
<td>8</td>
</tr>
<tr>
<td>Undifferentiated (stem cell) carcinoma of the colon</td>
<td>Undifferentiated malignant cells admixed with foci of neuroendocrine and squamous cells</td>
<td>Highly malignant</td>
<td>Liver and lymph nodes</td>
<td>As primary</td>
<td>9</td>
</tr>
<tr>
<td>Undifferentiated carcinoma of the colon</td>
<td>Undifferentiated small cell tumour with features of both carcinoid and squamous cell carcinoma</td>
<td>Malignant</td>
<td>Liver, adrenal gland, lymph nodes</td>
<td>As primary</td>
<td>5</td>
</tr>
<tr>
<td>Composite carcinoid — adenocarcinoma of stomach</td>
<td>Two separate components of carcinoid and adenocarcinoma invading the wall of the stomach No transitional zones between the two components</td>
<td>Malignant</td>
<td>No metastases</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Composite argentaffinoma-adenocarcinoma of the colon</td>
<td>Two separate components of carcinoid and adenocarcinoma with transitional zones</td>
<td>Malignant</td>
<td>Liver and lymphatic</td>
<td>As primary</td>
<td>6</td>
</tr>
<tr>
<td>Adenocarcinoid tumour of the colon arising in pre-existing ulcerative colitis</td>
<td>Microinvasive carcinoma with signet ring cell</td>
<td>Malignant</td>
<td>Lymph nodes, peritoneal and mesenteric deposits</td>
<td>Carcinoid</td>
<td>11</td>
</tr>
<tr>
<td>Mixed adenocarcinoma carcinoid of the large bowel in pre-existing Crohn’s disease</td>
<td>Two separate elements of adenocarcinoma with carcinoid</td>
<td>Malignant</td>
<td>No metastases</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Composite glandular carcinoid tumour of the terminal ileum</td>
<td>Two separate elements of benign adenoma with malignant carcinoid and transitional zones</td>
<td>Malignant</td>
<td>Liver, peritoneal deposits, and regional lymph nodes</td>
<td>Carcinoid</td>
<td>Current case</td>
</tr>
<tr>
<td>Composite tumour of the rectum</td>
<td>Tubulovillous adenoma with separate carcinoid element invading the stalk</td>
<td>Locally malignant</td>
<td>No metastases</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Composite glandular — carcinoid of the colon and rectum</td>
<td>Two separate elements of tubulovillous adenoma with carcinoid including transitional zones</td>
<td>Benign</td>
<td>No metastases</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Electron microscopy has, by supplementing routine methods, aided the diagnosis, morphological subtyping, and thereby the prognosis of mixed glandular-endocrine tumours. In general, composite glandular-carcinoid tumours have a poorer prognosis than pure carcinoids. A review of reports in English on composite glandular-endocrine cell tumours, helps to elucidate the morphological features and the clinical behaviour of these tumours (table). These vary from benign tumours to locally invasive and highly malignant metastasising tumours. It should be noted, however, that all cases of malignant composite tumours so far described have that metastatised, have been those in which the carcinoid has been associated with adenocarcinoma, unlike the present case where it is associated with an adenoma.

The histogenesis of composite adenocarcinoma-carcinoid tumours has not been fully explained. The collagen tumour theory suggests that the composite tumour represents two different carcinomas that grew together. In the common origin theory, composite tumours arise from bidirectional differentiation of a common stem cell. The presence of transitional zones where the adenocarcinoma and carcinoid areas meet together is thought to favour the common origin theory.

Such transitional zones were clearly seen in our case. As emphasised in earlier studies, further documentation is required to achieve a more complete clinical and pathological understanding of these enigmatic tumours.

We thank Dr I C Talbot, Department of Pathology, St Mark’s Hospital, London, for reviewing both the biopsy of the tumour and the manuscript.