

Review

## Goblet Cell Carcinoids of the Appendix

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### INTRODUCTION

Carcinoid tumours are rare, but are the most common gastrointestinal neuroendocrine tumours. We review the diagnosis, pathology and management of goblet cell carcinoid of the appendix using an illustrative case history.

### ILLUSTRATIVE CASE HISTORY

A 21-year-old man was admitted with a 24-hour history of right iliac fossa abdominal pain associated with nausea and vomiting. There was no history of diarrhoea or weight loss, and no family history of inflammatory bowel disease. He described a one-year history of right iliac fossa pain, colicky in nature, lasting for three to four days at a time and recurring every three months. This was his second hospital admission, the first episode settling with conservative management. On retrospective questioning he denied any symptoms suggestive of carcinoid syndrome.

On examination he was afebrile with rebound tenderness in the right iliac fossa. Blood investigations revealed a white cell count of  $19.3 \times 10^9/L$  and a C-reactive protein of 260mg/L. Abdominal sonography was performed in view of the recurrent nature of the pain and the possibility of Crohn's disease. This showed multiple fluid filled loops of bowel in the right iliac fossa but no direct visualisation of the appendix and no thickened loops of small bowel. Following a short period of observation we proceeded to appendectomy, which confirmed an acutely inflamed appendix with purulent free fluid in the pelvis. There were no post-operative complications.

Histopathology confirmed acute appendicitis. In addition, within the tip of the appendix there was a 4mm tumour composed of small glandular acini and individual cells with eosinophilic and

focally granular cytoplasm (*figs 1 and 2*). The tumour extended through the muscularis propria of the appendix into serosal fat, reaching 1.5mm from the serosal surface. The tumour was positive with the epithelial markers CAM 5.2, CEA and neuroendocrine marker Neuron Specific Enolase. The tumour cells failed to stain with the neuroendocrine marker Chromogranin. Overall the histological and immunohistochemical features were those of a goblet cell carcinoid tumour of the appendix tip with co-existing acute appendicitis.

Post-operatively a plasma neuroendocrine profile, including plasma Chromogranin A, and urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) and 5-hydroxytryptophan (5-HT) were within normal limits. A CT scan of abdomen and pelvis and an octreotide radioisotope scan did not reveal any metastatic disease (*Fig 3*). Despite our patient having a tumour size of less than 1 cm, it was felt that in view of the presence of mesoappendiceal extension and his younger than average age at presentation, a right hemicolectomy was justified to decrease his risk of delayed local and distant recurrence, and to study the regional lymph nodes. He proceeded to a laparoscopic right hemicolectomy, the pathology of which did not reveal any residual disease and at twelve month follow up he remains disease free.

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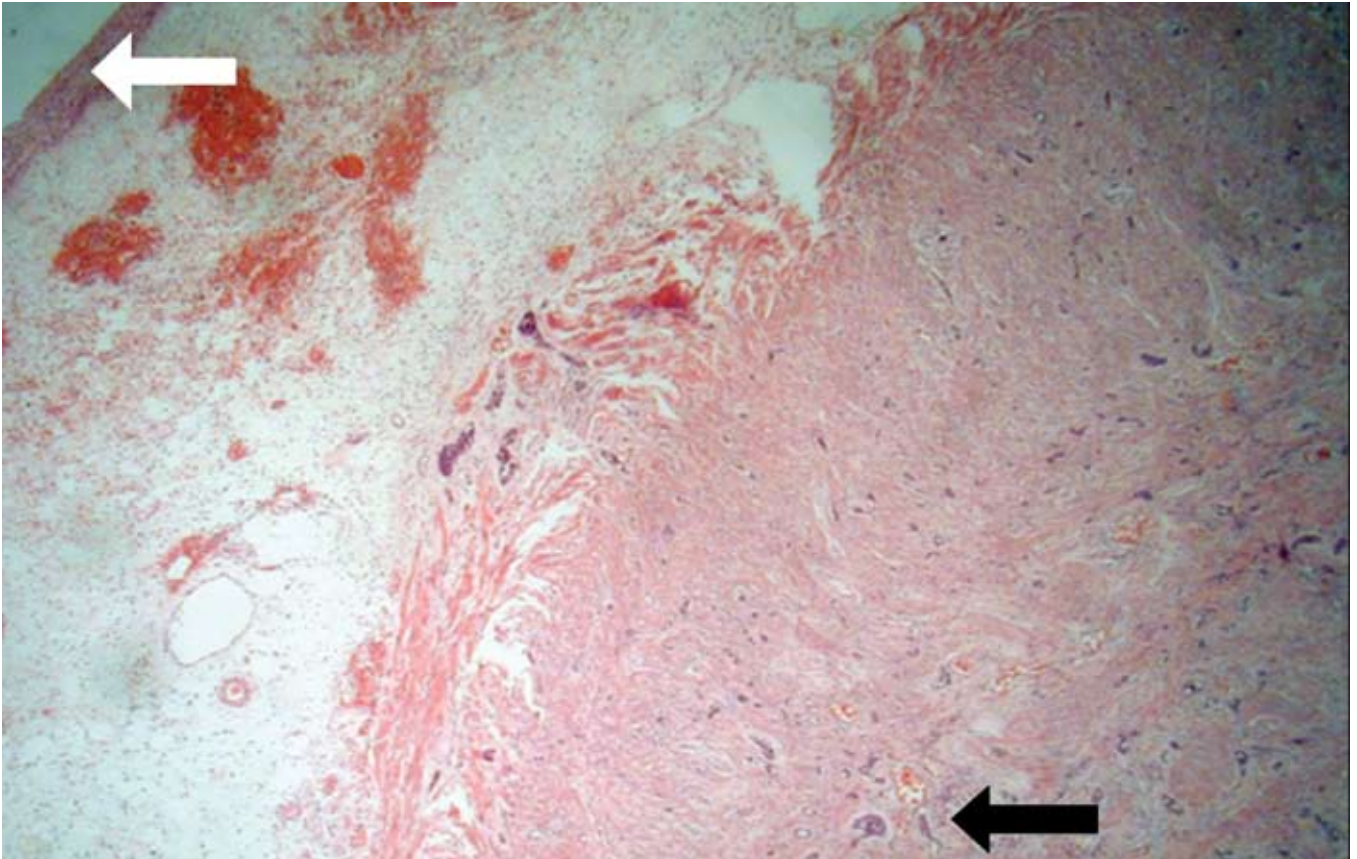


Fig 1. Haematoxylin-eosin slide showing tumour infiltrating wall (dark arrow) and a serosal reaction (white arrow).

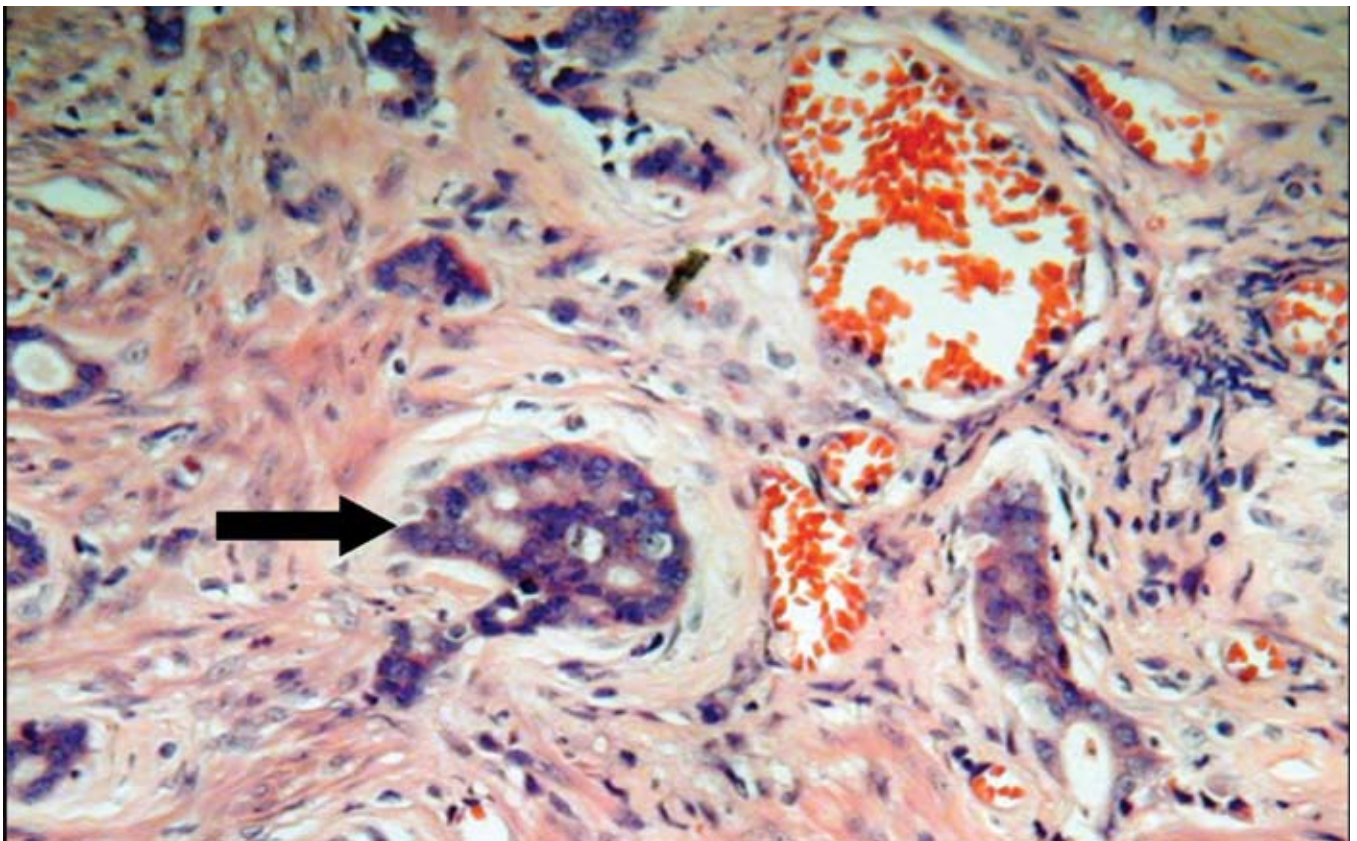


Fig 2. Haematoxylin-eosin slide showing tumour cells infiltrating through the muscularis propria (black arrow).

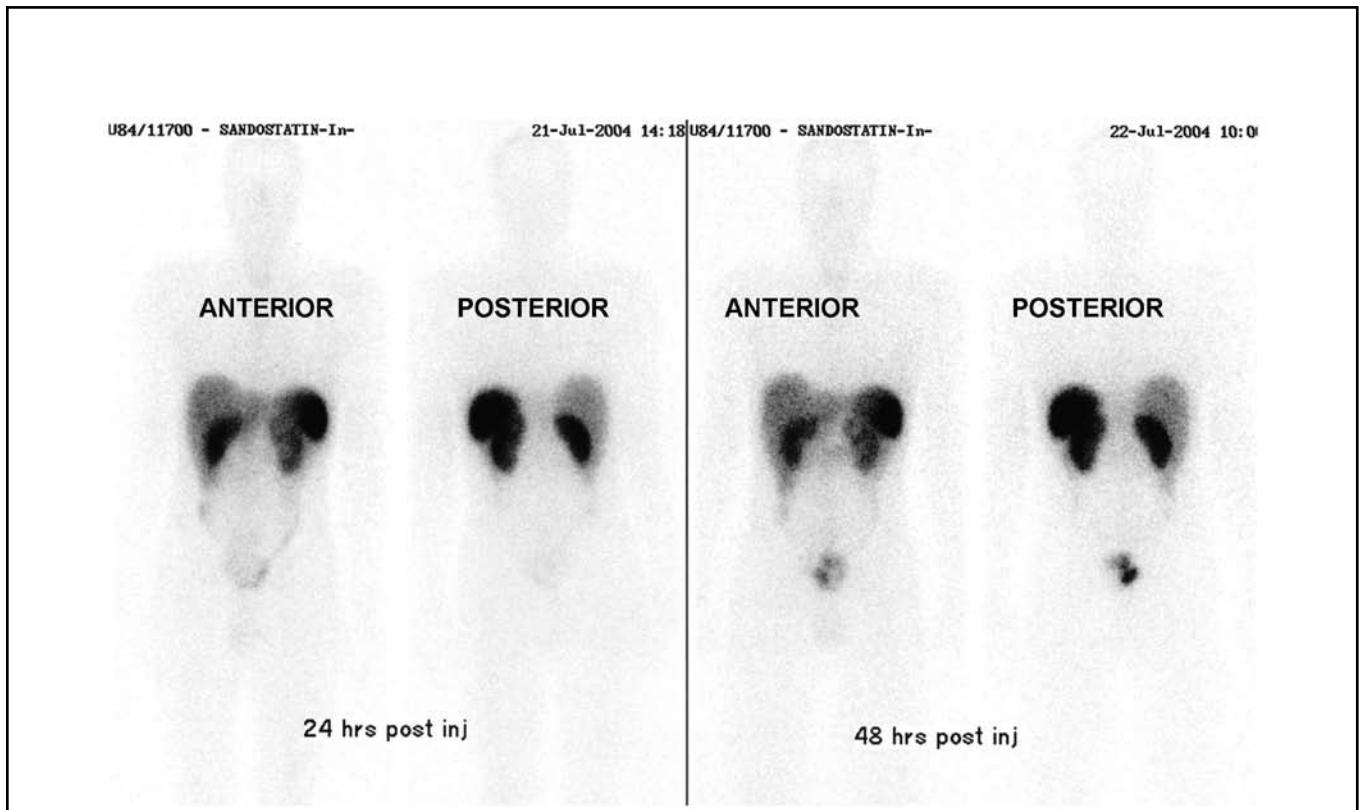


Fig 3. The normal octreotide scan of the patient looking for evidence of metastatic disease. Normal uptake is seen in the liver, kidneys and spleen, 24 and 48 hours post injection of radioisotope.

## EPIDEMIOLOGY

Carcinoid tumours are rare, but are the most common neuroendocrine tumours.<sup>1,2</sup> In a series of 13,715 carcinoids reported to the Surveillance, Epidemiology, and End Results programme of the National Cancer Institute, the majority were located in the gastrointestinal tract (67.5%) and in the bronchopulmonary system (25.3%).<sup>3</sup> Carcinoid tumours are the most common neoplasms arising in the appendix, accounting for about 85 per cent of all appendiceal tumours seen in surgical pathology. The prevalence of appendiceal carcinoid is between 0.3% and 0.9% in patients undergoing appendicectomy. The recent study of McCusker *et al*,<sup>4</sup> reported 227 goblet cell carcinoids (13.8%) among 1645 appendiceal malignancies, along with 613 cases (37%) of mucinous adenocarcinoma, the most frequent diagnosis. These epidemiological studies suggest an average diagnostic age of between 38 and 49 years for malignant lesions, although goblet cell carcinoids tend to present at a later age of about 52 years.

Data from the Northern Ireland Neuroendocrine Database (*Table 1*) includes 517 carcinoid tumours

of the appendix, midgut and lung diagnosed since 1975. 114 of these were appendiceal carcinoids, 16 of which were goblet cell in nature. The age at diagnosis and the presence of metastatic disease is shown in the table below. The mean age at diagnosis was 54.75 years  $\pm$ 4.57 SEM. Four of the 16 patients have since died. The only patient with hepatic metastases died from recurrent goblet cell carcinoid tumour, ten years following her appendicectomy and subsequent right hemicolectomy.

## MALIGNANT CHANGE

Tumour characteristics of all appendiceal carcinoids that predict aggressive behaviour include tumour size, histological subtype and mesoappendiceal involvement. Moertel *et al*<sup>5</sup> first indicated in 1968 that metastatic disease from lesions smaller than 2cm was unlikely and consequently considered that the risk of metastatic disease in tumours less than 2 cm was sufficiently low to treat them by appendicectomy alone. In one study mesoappendiceal extension correlated with nodal metastases and tumour size.<sup>6</sup> In a series of 92 appendiceal carcinoids they reported two patients with 1cm tumours with nodal spread, both of

TABLE I

*Patients diagnosed with appendiceal carcinoid from the Northern Ireland Neuroendocrine Database*

<i>Patient</i>	<i>Age at Diagnosis</i>	<i>Metastases</i>
1	78	No
2	73	Yes - mesentery
3	39	No
4	56	No
5	62	Yes - small bowel
6	46	No
7	15	No
8	65	No
9	22	No
10	74	No
11	59	No
12	60	No
13	47	No
14	67	Yes - hepatic
15	43	No
16	70	No

which had mesoappendiceal involvement. Serosal involvement is present in about 70% of malignant carcinoid tumours but this has been shown to be unrelated to outcome in several studies.

### DIAGNOSIS

The diagnosis of goblet cell carcinoid of the appendix is essentially made on histological examination after surgery, which is one of the clinical hallmarks of appendiceal carcinoids. This neoplasm has also been described as an adenocarcinoid, crypt cell carcinoma and goblet cell carcinoma. The preferred term, goblet cell carcinoma, was first coined in 1974 by Subbuswamy *et al.*<sup>7</sup> As the nomenclature implies, these tumours possess morphological features suggestive of both carcinoid and glandular differentiation. Appendiceal carcinoids are usually divided into three histological patterns; the typical argentaffin enterochromaffin (EC)-cell carcinoid, the non-argentaffin L-cell carcinoid and the more recently described goblet cell carcinoid. The goblet cell carcinoids show striking differences in histology from the other two varieties but more importantly, they are biologically more aggressive lesions.<sup>8</sup>

Goblet cell carcinoids behave differently biologically and their outcome is similarly different. In the study by McCusker *et al.*<sup>4</sup> only 17% of 227 patients with goblet cell carcinoma had positive lymph nodes, but in 65% there was spread through the serosa, invasion of the mesoappendix, or involvement of peritoneum or adjacent organs. Serosal involvement and mesoappendiceal extension are therefore more predictive of outcome than lymph node status in goblet cell carcinoids. In the Surveillance, Epidemiology, and End Results programme of the National Cancer Institute, patients with malignant

carcinoid had a better overall survival rate of more than 80% at 10 years compared with goblet cell carcinoids which had a 60% 10 year survival rate. The survival rate for goblet cell carcinomas was not significantly worse than that for malignant carcinoid when adjusted for age and extent of disease at presentation.<sup>4</sup>

### INVESTIGATION

Most patients do not require any further procedure or investigations relating to an appendiceal carcinoid. Those patients with tumours larger than 2cm, incomplete resections, metastatic disease or goblet cell carcinoids require estimation of plasma Chromogranin A concentration and 24-hour urinary levels of 5-hydroxyindolacetic acid along with CT scanning and octreotide scintigraphy.<sup>11</sup> In-labelled octreotide scintigraphy is the most sensitive imaging modality in the diagnosis and staging of metastatic disease. The isotope scans are performed more than eight weeks after initial surgery to avoid false positives and therefore any unnecessary further surgery.<sup>9</sup>

Chromogranin A is a secretory protein present in vesicles of neuroendocrine cells and its ubiquitous presence in these cell types makes it a suitable circulating marker of neuroendocrine neoplasms, the levels being raised in 80-100% of patients with these neoplasms.<sup>10</sup> It is currently the most important blood marker available for carcinoid tumours, with levels corresponding to tumour load and levels above 5000 µg/l predicting a poor outcome.<sup>11</sup>

### PROGNOSIS AND SURGICAL MANAGEMENT

Patients with appendiceal carcinoids have a good prognosis overall with the vast majority cured by

TABLE II

#### *Indications for right hemicolectomy*

1. All lesions larger than 2cm in diameter
2. Histological evidence of mesoappendiceal extension
3. Tumours at the base of the appendix with positive margins or involvement of the caecum
4. High-grade malignant carcinoids
5. Goblet cell carcinoids.<sup>13</sup>

simple appendicectomy as the definitive procedure. In at least 70% of the cases encountered by most general surgeons, patients with a tumour less than 1 cm will almost certainly have no future problem from the lesion. Patients with goblet cell carcinoid tumours however fall into a different category, as these tumours are more aggressive than classic appendiceal carcinoids. They are characterized histologically by wide invasion of the mesoappendix, and clinically by delayed local recurrence and distant metastases. As the vast majority of these tumours are detected post-operatively, management centres on the need for re-operation as a right hemicolectomy is often curative.<sup>12</sup> In patients with goblet cell carcinoids relative indications that may favour further surgery are: (1) angioinvasion as an isolated finding, (2) tumours at the base of the appendix with clear margins, greater than 1cm but less than 2cm in diameter and (3) mucin-producing tumours.<sup>13</sup>

### CONCLUSIONS

When considering appendiceal carcinoids as a whole, acceptable indications for a right hemicolectomy are shown in Table II. Careful diagnosis and management of goblet cell carcinoid tumours will hopefully improve prognosis in patients with this rare entity.

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### CONFLICT OF INTEREST

The authors have no conflict of interest.

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