# Extrapulmonary Small Cell Gastric Carcinoma

## *A Case Report and Review of the Literature*

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Extrapulmonary anaplastic small cell tumours (EPSCC) of the gastrointestinal tract are generally aggressive neoplasms with a poor prognosis. Recent work has demonstrated that EPSCC may be sensitive to the chemotherapeutic regimens employed to treat small cell lung cancer.

In this report we present the case of a patient with a primary anaplastic small cell gastric carcinoma treated with combination chemotherapy. Plasma calcitonin, somatostatin, gastrin releasing peptide, total enolase and non-muscle creatine kinase levels were measured before and, if elevated, after completion of induction chemotherapy. Doxorubicin, cyclophosphamide and etoposide treatment resulted in a complete remission which lasted for 11 months. Calcitonin levels, elevated prior to treatment, fell to within the normal range following completion of induction therapy. Extrapulmonary gastric small cell cancer is sensitive to cytotoxic chemotherapy. Like small cell lung cancer, these tumours may produce plasma/serum markers which may be useful in monitoring response to therapy.

*Case report.* A 54-year-old man presented with a 3-month history of severe epigastric pain in October 1992. The pain was waking the patient from his sleep, was aggravated by moving and eased by vomiting. The symptoms were associated with a weight loss of 16 kg. There was no history of dysphagia. He had stopped smoking cigarettes 14 years earlier. Physical examination revealed exquisite tenderness in the epigastrium. On the day following admission to hospital he had an episode of haematemesis.

At oesophago-gastroscopy examination a protruberant ulcerating lesion was noted in the gastric cardia below the oesophagogastric junction. The oesophegus appeared normal. Biopsies of the gastric mass (Figs 1a and b) revealed an infiltrating neoplasm composed of mitotically active small cells with hyperchromatic nuclei, inconspicuous nucleoli and scanty cytoplasm resembling small cell carcinoma of the lung. The cells were uniformly negative for common leukocyte antigen and weakly positive for keratin and neuron-specific enolase. Further biopsies were taken of the gastric antrum which revealed helicobacter pylori positive antral gastritis.

A full blood count, renal, liver and bone biochemistry were within normal limits. Bone marrow aspirate and bone biopsy showed no evidence of malignant infiltration. Radiology included a CXR and CT scan of the thorax, a CT brain scan and isotope bone scan all of which were normal. A CT examination of the abdomen revealed evidence of a tumour at the cardia of the stomach with submucosal extension to involve the lower oesophagus. A subsequent barium swallow confirmed these findings. A radiolabelled somatostatin analogue scan, using $^{111}$In-[DTPA-*D*-Phe$^1$]-octreotide as the radioligand, failed to localise either the primary tumour or show evidence of metastases.

Plasma and serum samples were obtained for analysis for the presence of a number of markers. Gastrin releasing peptide, somatostatin, total enolase and non-muscle creatine kinase levels were within normal limits. Calcitonin levels = 560 ng/l, were significantly elevated (normal range: 0–80 ng/l). In view of this, sections of tumour biopsy were stained for chromogranin (Fig. 2) and calcitonin, both of which were negative.

Following 6 cycles of ACE cytotoxic chemotherepy consisting of doxorubicin 50 mg/m$^2$, cyclophosphamide 750 mg/m$^2$ and etoposide 50 mg/m$^2$ on day 1, and oral etoposide 200 mg daily, days 2–5, the patient had a complete clinical remission with no evidence of disease found on biochemistry, at endoscopy or on chest x-ray, CT abdomen and isotope bone scan. Furthermore calcitonin levels = 50 ng/l had fallen to within the normal range.

Unfortunately in October 1993, 11 months after commencing chemotherapy, he developed a symptomatic relapse. Chest x-ray was again normal. Treatment with carboplatin 400 mg/m$^2$ and methotrexate 35 mg/m$^2$ for 1 cycle and cyclophosphamide 750 mg/m$^2$, doxorabicin 50 mg/m$^2$ and etoposide 100 mg/m$^2$ for 2 cycles failed to induce a response. In March 1994, repeat endoscopy and biopsy confirmed recurrence of disease with ulceration at the oesophego-gastric junction. Treatment with vincristine 2 mg i.v. on day 1, chlorambucil 10 mg daily days 1–10 and dexamethasone 20 mg daily days 1–4 again failed to induce a response. His condition worsened with progressive pain and weight loss and in April 1994 he was referred for palliative radiotherapy to his stomach and lower oesophagus. He died in September 1994, 22 months after diagnosis.

*Discussion.* Small cell lung cancer (SCLC) is a common, highly malignant disease which responds to both chemotherapy and

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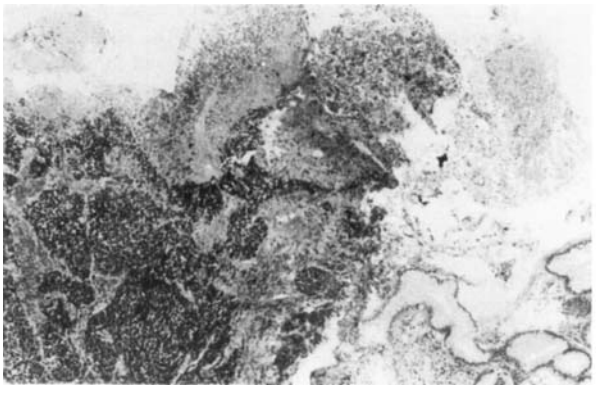
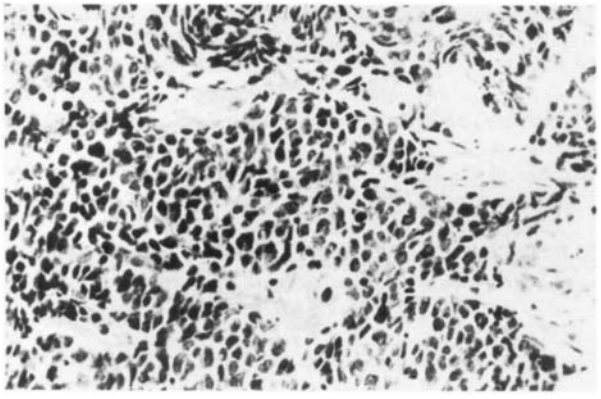


a)



b)

*Fig. 1.* a) Low power view of the small cell carcinoma invading gastric mucosa with surface ulceration (upper half of figure) and adjacent foveolar epithelium (bottom right), and b) a representative high power view showing the cytological characteristics of the neoplasm which is seen to be composed of mitotically active small cells with hyperchromatic nuclei, inconspicuous nucleoli and scanty cytoplasm.

radiotherapy (1). Unlike their pulmonary counterpart, extrapulmonary small cell tumours (EPSCC) are rare. It is estimated that in the region of 1 000 new cases of EPSCC present each year in the USA (2–4). Recent work has demonstrated that, like SCLC, chemotherapy is an effective treatment in EPSCC (2–6).

Small cell gastric carcinomas are extremely rare tumours. We have found 40 well-documented cases reported in the literature (2–20). The largest series studied included 17 cases (7). Patients present with epigastric pain, nausea, melaena, anorexia and weight loss. In a number of cases the tumour has been detected at routine medical check-up (7) while in one reported case the definitive diagnosis was made at autopsy (8). As with SCLC the majority of tumours will have metastasised at the time of presentation (7).

The tumour may arise in any part of the stomach from the cardia to the antrum. Initially the tumour may be polypoid. Later a crater-like ulceration develops due to rapid proliferation of disease. Pure small cell tumours account for 30–45% of the reported cases. The remainder are of mixed histology having undifferentiated, adenocarcinomatous and/or squamous cell elements (2–20).

As in SCLC the prognosis for untreated patients appears poor with survival being measured in weeks (9). In patients with limited disease confined to the stomach surgery alone appears effective

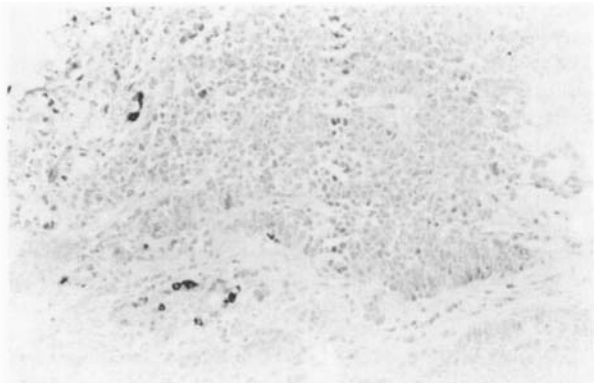


*Fig. 2.* Section of the tumour showing lack of staining for chromogranin. Darkly stained calls (to the left) are entrapped residual gastric mucosal neuroendocrine cells.

treatment with reported survival ranging from 9 months to patients being alive and well at 5-year follow-up (3, 10, 11). The majority of treated patients have received combined modality therapy with surgery followed by chemotherapy and, occasionally, subsequent radiotherapy. In the series of 17 cases reported by Matsui et al. (7), 14 patients had extensive disease. The median survival was 9 months. This is in keeping with other reports including 1 patient who received chemotherapy only and survived 10 months and another who had chemotherapy in the adjuvant setting and who survived 6 months (12–14).

Oesophageal small cell tumours are more frequent and account for approximately 2% of all oesophegeal cancers. They are associated with a poor prognosis having a median survival of 3–4.7 months (3–5). Recent studies have demonstrated that undifferentiated oesophageal small cell tumours are responsive to chemotherapy, which, some argue, should be the treatment of choice. (5). For this reason we chose to treat the patient with chemotherapy alone.

We did not perform a bronchoscopy to exclude a primary SCLC tumour. However the clinical presentation—epigastric pain and tenderness, the absence of respiratory symptoms and the results of the investigations (including the failure to detect any evidence of intra-thoracic disease on CT scan or serial chest x-rays) support the contention that the patient had a primary gastric small cell tumour.

This case lends further weight to the accumulating evidence that EPSCC of the gastrointestinal tract resembles SCLC in clinical behaviour. Approximately half of the cell lines established from small cell lung cancers synthesise calcitonin (21). Furthermore calcitonin has been shown to be of value as a tumour marker in SCLC in assessing response to chemotherapy (22). This is the first report to demonstrate elevated plasma calcitonin levels in a patient with small cell gastric carcinoma at the time of diagnosis. The calcitonin levels fell to normal following induction chemotherapy suggesting a similar role for this peptide, and indeed others, in EPSCC.

Despite negative staining for calcitonin or chromogranin it is assumed that the gastric carcinoma was the source of the peptide hormone, as there was no clinical evidence for other sources of the peptide such as SCLC, medullary carcinoma of the thyroid (23) or neuroendocrine carcinoma of the larynx (24). Support for this contention is given by the reduction of serum calcitonin levels after induction chemotherapy. It is likely that this tumour represents one of the well recognised group of small cell carcinomas that, while producing peptides, have immunohistochemically undetectable amounts of marker in individual cells (25). Further-

more, in SCLC cell lines, calcitonin mRNA expression may be detected in the absence of immunoreactive calcitonin (26).

Of interest was the lack of efficacy of radiolabelled somatostatin analogue imaging to detect the tumour in this case. In reported studies employing $^{111}$In-[DTPA-*D*-Phe$^1$]-octreotide as the radiolabel virtually all primary sites of SCLC disease have been successfully localised. However, a recognised drawback of this scintigraphic procedure is that of non-specific uptake of the radiolabel in the liver and spleen which can impair visualisation of lesions in these areas. The lack of visualisation of the tumour in this case may have been due to this non-specific uptake or due to an absence of somatostatin receptor expression by the disease (27, 28).

In summary, the described case of small cell gastric carcinoma, limited in stage at the time of diagnosis, had an excellent response to ACE chemotherapy resulting in a complete remission. Elevated calcitonin levels, detected at diagnosis, fell to normal with treatment. He remained without evidence of disease until relapse at 11 months and, with second line cytotoxic agents and subsequent palliative radiotherapy, survived a further 11 months.

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