

# Duodenal carcinoid: a rare cause of melaena in a cirrhotic patient

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## ABSTRACT

Small intestinal neuroendocrine tumours are relatively rare. Laboratory tests and diagnostic imaging are of help in diagnosis. Surgical resection is the standard approach. Metastatic disease has a poor prognosis. These are indolent tumours and hence role of chemotherapy is limited. Radionuclide and biological therapies are emerging. We report a 29-year-old man presenting with melaena and diagnosed as having a neuroendocrine tumour of the duodenum together with liver cirrhosis. Standard Whipple's procedure was done and he is doing well at follow-up.

**Keywords:** carcinoid tumour, chromogranin A, carcinoid crisis, duodenal carcinoma, neuroendocrine tumour

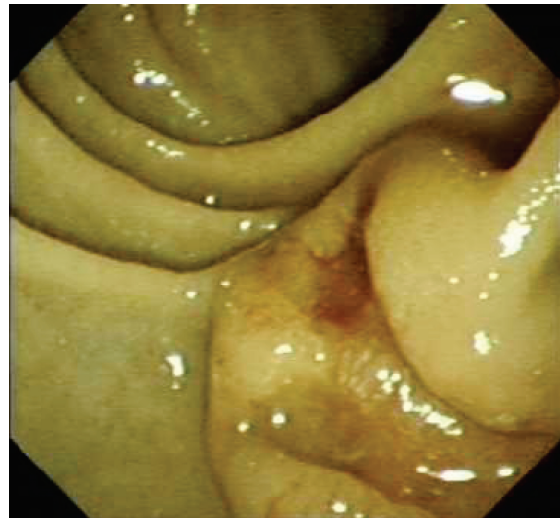
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## INTRODUCTION

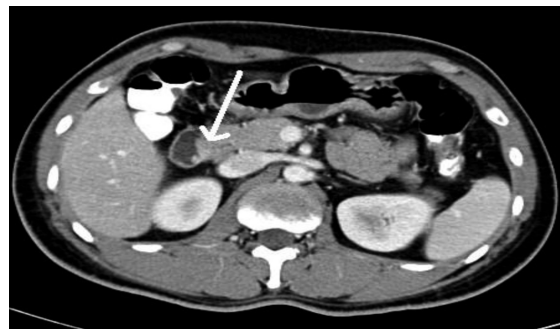
Carcinoid tumour arises from the enterochromaffin (EC) or Kulchitsky cells located in the crypts of Lieberkühn. EC cells are a part of neuroendocrine system and located diffusely. Otto Lubrasch first characterised carcinoid tumour from small bowel autopsy of two patients in 1888.<sup>(1)</sup> Tumours of small intestine are uncommon and they present with vague clinical features. Adenocarcinoma is the commonest malignancy of the small bowel, and duodenal carcinoids are rare. We report a young man presenting with melaena and who was diagnosed to have a neuroendocrine tumour of duodenum together with liver cirrhosis.

## CASE REPORT

A 29-year-old Chinese man was admitted with complaints of passing black tarry stools of three days' duration, giddiness of two days' duration and nausea of one day's duration. On further questioning, he gave a history of passing black tarry stools for the past one year. He did not have any other significant past history. Abdominal examination was unremarkable and digital rectal examination confirmed the presence of melaena. His blood tests showed a haemoglobin level of 11.8 g/dL with a hypochromic microcytic picture, normal



**Fig. 1** Endoscopic photograph shows an ulcerated duodenal mass.



**Fig. 2** Axial CT image shows a duodenal tumour (arrow)

electrolytes, glucose, renal and liver functions. He underwent upper gastrointestinal endoscopy (OGD) with a biopsy, which showed a 2.5–3.0 cm ulcerated duodenal mass 0.5 cm proximal to the major papilla (Fig. 1). Computed tomography (CT) of the abdomen showed an eccentric soft tissue mass in the medial wall of the second part of duodenum which could not be separated from the pancreas (Fig. 2). CT of the thorax, CA 19-9, carcinoembryonic antigen (CEA), colonoscopy, phaeochromocytoma screen, urinary 5-hydroxy-indole acetic acid (5-HIAA), 24-hour urinary cortisol, serum cortisol, serum adrenocorticotrophic hormone (ACTH) and thyroid function tests were all normal.

The endoscopic biopsy showed a neuroendocrine tumour with low mitotic activity and Ki-67 expression. The tumour cells expressed both AE1/3 and chromogranin antibodies. The cells were negative

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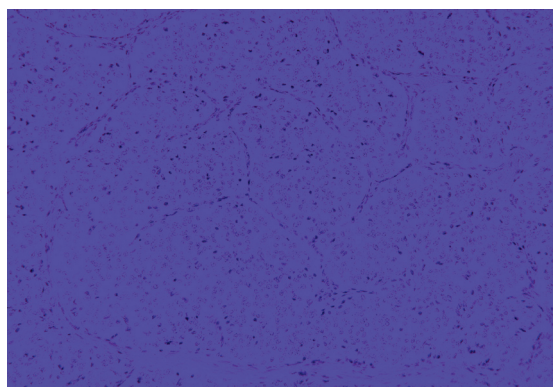
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**Fig. 3** Specimen photograph shows the duodenal neuroendocrine tumour (carcinoid) (Courtesy of Dr Amanda Charlton, Consultant Pathologist, National University Hospital, Singapore).



**Fig. 4** Photomicrograph shows that the carcinoid tumour is composed of solid nests of uniform cuboidal cells, separated by fine fibrovascular septae [Haematoxylin & eosin,  $\times 40$ ]. (Courtesy of Dr Amanda Charlton, Consultant Pathologist, National University Hospital, Singapore).

for gastrin and somatostatin. His pulmonary function tests and two-dimensional echocardiography done as a preoperative assessment were normal. He underwent a standard Whipple's procedure. Intraoperative frozen section biopsy of portocaval, right gastric and celiac lymph nodes were negative for tumour. Intraoperative ultrasonography showed hypoechoic liver nodules and his liver showed early cirrhotic changes. A liver biopsy was taken. Postoperative hepatitis screening revealed HBsAg and anti-HBc reactive with a viral load of  $1.78 \times 10^2$  copies/ml. His alphafoetoprotein level was normal, and he was anti-HBe and anti-HCV non-reactive. Liver biopsy showed cirrhotic changes. Histology showed 2.5 cm submucosal duodenal carcinoid tumour (Figs. 3 & 4) of insular pattern with low mitotic activity and no necrosis. The tumour did not penetrate the duodenal wall and the pancreas was normal. There were three out of four metastatic lymph nodes in the subserosa of the duodenum. Immunostains show that the carcinoid cells were negative for gastrin, insulin and somatostatin. The final diagnosis was a duodenal carcinoid tumour with regional lymph node metastases. His postoperative recovery was uneventful and he was discharged on the 11th postoperative day. He was doing well at 15 months follow-up.

## DISCUSSION

Oberndorfer was the first to coin the name '*Karzinoid*' almost a century ago, and Masson in 1928 identified that EC cells demonstrate amine precursor uptake and decarboxylation (APUD) characteristics. Carcinoids account for 0.5%–1.2% of all malignancies and nearly two-thirds of carcinoids are found in the gastrointestinal tract.<sup>(2)</sup> The epidemiology of carcinoid tumours has evolved in the past decades. The incidence of appendiceal carcinoids is decreasing

and the appendix is no more the commonest site to harbour carcinoids. Increasing use of the upper and lower gastrointestinal endoscopies along with decreasing rates of incidental appendectomy for other diseases are perhaps contributory to this trend. Carcinoids are less aggressive than adenocarcinoma and they appear yellowish in colour due to their high lipid content. On electron microscopy, carcinoid tumour contains membrane-bound electron-dense neurosecretory granules.

Carcinoids produce a variety of substances, such as amines, peptides, tachykinins and prostaglandins. Serotonin is the most commonly secreted substance. Increased serotonin production is due to 5-hydroxylation of dietary tryptophan. Serotonin is subsequently metabolised to 5-HIAA by monoamine oxidase. Abnormal tryptophan metabolism may result in deficiency of nicotinic acid with resultant pellagra. Chromogranin, neuron specific enolase and synaptophysin are the markers of neuroendocrine tissue. Carcinoid tumours can be classified based on different embryonic divisions of the gut, or according to growth patterns into insular, trabecular, glandular, undifferentiated or mixed. These classification systems are confusing due to the heterogeneity of subgroups in biological and clinical characteristics. In 2000, the World Health Organisation (WHO) developed a revised classification system incorporating site of origin and histological features.<sup>(3)</sup> The term, neuroendocrine tumour, is now preferred over the term, carcinoid, and these tumours are divided into three subcategories: (a) well-differentiated neuroendocrine tumour; (b) well-differentiated neuroendocrine carcinoma; and (c) poorly-differentiated neuroendocrine carcinoma. These tumours are further subdivided based on organ of origin.

Although the small intestine represents 75%

of the length and 90% of the surface area of the alimentary tract, small bowel malignancies account for only 2% of all gastrointestinal neoplasms.<sup>(4)</sup> The unique microenvironment of the small intestine has been postulated as being protective against cancer.<sup>(5)</sup> Carcinoids constitute 29%–40% of all small bowel malignancies.<sup>(4,5)</sup> Adenocarcinoma is the commonest small bowel tumour and it occurs commonly in the proximal small bowel. Carcinoids are common in the distal small bowel and occur more commonly in the sixth or seventh decade of life. Carcinoid tumours are rarely found in the duodenum, and represent 3.4%–11.9% of all duodenal neoplasms and 0.7%–1.8% of all primary small bowel neoplasms.<sup>(4,5)</sup> The incidence is increased in the presence of other cancers (commonly, gastrointestinal and gynaecological), and multiple synchronous tumours are present in around 30% of patients. Small bowel malignancies may present with vague abdominal pain, occult bleeding, palpable abdominal mass, anorexia, weight loss, diarrhoea, bowel perforation or bleeding. Patients may be asymptomatic and the diagnosis incidentally made.

Carcinoid tumours may produce intense desmoplastic reaction and mesenteric fibrosis with resultant intestinal obstruction and mesenteric ischaemia. Small bowel perforation is comparatively more common in lymphoma and sarcoma. Carcinoid syndrome is a rare presentation and usually implies hepatic metastases. Episodic flushing, wheezing, diarrhoea and eventual right side valvular heart disease characterise the carcinoid syndrome. Midgut carcinoids are classically associated with carcinoid syndrome due to high serotonin content. Foregut carcinoid presents with features of overproduction of ACTH or growth hormone releasing hormone. Carcinoid crisis is characterised by profound flushing, extreme changes in blood pressure, bronchoconstriction, arrhythmias and confusion or stupor lasting many hours or even days. Carcinoid crisis can occur in patients with extensive disease, during induction of anaesthesia, after chemotherapy, after hepatic arterial embolisation or during surgery.<sup>(6)</sup> Somatostatin analogues should be given before general anaesthesia, surgery and hepatic artery embolisation to prevent a carcinoid crisis.<sup>(7)</sup>

24-hour urinary levels of 5-HIAA have a sensitivity of 70% and specificity of 88%–100% for the diagnosis of carcinoid tumours and levels correlate with tumour burden.<sup>(8,9)</sup> A variety of fruits, vegetables, nuts and medicines can affect the urinary levels of 5-HIAA. Platelet serotonin levels are more sensitive than urinary 5-HIAA levels and are not affected by consuming serotonin-rich foods.<sup>(8,10)</sup> Chromogranin A (CGA) is a more sensitive tumour marker for carcinoid

tumour.<sup>(11)</sup> False-positive results with CGA can occur with liver or kidney failure, inflammatory bowel disease, atrophic gastritis or the chronic use of proton pump inhibitors.<sup>(11)</sup> CGA is more sensitive for foregut and hindgut carcinoids, because midgut carcinoids tend to produce serotonin and hence excrete 5-HIAA in the urine. CGA levels reflect tumour burden, correlate with the response, may be used for monitoring for recurrence after surgery and may also have a prognostic value.<sup>(8,11)</sup> CT can identify retroperitoneal disease, hepatic metastases and mesenteric calcifications associated with carcinoid tumours. OGD can visualise the proximal small intestinal carcinoid and a tissue diagnosis can be achieved with biopsy. Endoscopic ultrasonography may help in the evaluation of duodenal and pancreatic carcinoids.

More than 80% of carcinoid tumours express surface somatostatin receptors and hence somatostatin receptor scintigraphy (SRS) is very useful in the localisation of carcinoid tumours.<sup>(12)</sup> Octreotide is an analogue of somatostatin, and hence, octreoscan can also be used for localising carcinoids. In patients with carcinoid syndrome, the detection of metastatic lesions with SRS predicts a response to treatment with somatostatin analogues. <sup>131</sup>I or <sup>123</sup>I radiolabelled metaiodobenzylguanidine (MIBG) scintigraphy can also help localise carcinoid tumours. MIBG is less sensitive than octreoscan and is only rarely used for metastatic disease.<sup>(13)</sup> Carcinoid tumours are slowly growing and standard positron emission tomography scans are not useful in the diagnosis, as they rely on high glucose uptake in metabolically-hyperactive cells. Recently, <sup>11</sup>C-labelled 5-hydroxytryptophan (5-HTP) is used to localise carcinoid tumours.<sup>(14)</sup> Barium studies are nonspecific for filling defects and tumours can be missed.

Surgical resection is the standard treatment approach for carcinoid tumours. Metastasis to mesenteric lymph node is common at presentation and the resection should be *en bloc* to include mesenteric lymphnodes. Complete resection results in improvement of symptoms and survival. Since the incidence of multicentric disease is 20%–40% and of a second primary malignancy is 20%–30%, the entire bowel should be inspected.<sup>(15)</sup> Prophylactic cholecystectomy should be strongly considered during laparotomy for carcinoid tumours. This is because these patients can develop cholelithiasis due to somatostatin analogues. Surgical debulking has shown to improve quality of life and prolong survival in advanced metastatic disease causing intestinal obstruction and ischaemia due to desmoplastic reaction. The five-year overall survival rates for small bowel carcinoid tumours with localised/

regional disease is 65%, but falls to 36% when distant metastases are present.<sup>(2)</sup> Tumour size, increased depth of invasion, small bowel location, high plasma CGA levels, regional lymph node spread, hepatic metastases, age > 50 years, male gender, increased expression of Ki-67 and p53, specific histological growth patterns and positive antibody staining of tumour cells for CEA are all helpful in predicting prognosis. Patients with hepatic metastases can present with carcinoid syndrome. Hepatic resection has shown to improve survival.

Liver transplantation is also feasible with encouraging results in a highly select group of patients. However, there is significant transplant-related morbidity and risk of early tumour recurrence. Liver transplantation is however limited to few centres with restricted donor availability. Hepatic artery embolisation and local ablative therapies are an effective means of tackling hepatic metastases when surgery is not feasible. Hepatic artery embolisation has demonstrable biochemical and tumour response rates. Chemoembolisation with agents such as 5-fluorouracil, decarbazine, doxorubicin, cisplatin, mitomycin C or streptozotocin have been studied with variable response rates.<sup>(8)</sup> Carcinoid crisis may be precipitated and typical postembolisation syndrome consists of high fever, severe pain, nausea, fatigue and transient transaminitis. Somatostatin exerts a cytostatic effect on carcinoid tumour cells and inhibits symptoms such as flushing and diarrhoea. Lanreotide is the longest acting analogue, with effects lasting for 10–14 days.

Recently, radiolabelled somatostatin analogues have also been tried for treatment purposes, and such modalities are still experimental. The analogues include yttrium-90, lutetium-177 and indium-111 labelled octreotide. Interferon alpha (IFN- $\alpha$ ), interferon gamma (IFN- $\gamma$ ) and human leucocyte interferon have shown encouraging results.<sup>(8)</sup> Biochemotherapy with a combination of IFN- $\alpha$  and various chemotherapeutic agents have been discouraging, as some of the newer forms of chemotherapeutic agents. Human monoclonal antibody, bevacizumab, and multitargeted tyrosine kinase inhibitor, sunitinib, are under experimental

trials. These agents act on angiogenesis by interfering with the vascular endothelial growth factor/receptor. External beam radiotherapy is for palliation of metastatic disease. Radiation therapy can achieve symptomatic palliation for patients with metastatic/unresectable malignant carcinoid tumours, and is well-tolerated. In conclusion, small bowel neoplasms can present as melaena and duodenal carcinoid is a rare variety of small bowel neoplasm. This case also illustrates that Whipple's operation can be offered in appropriately selected patients with cirrhosis.

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