CASE REPORT

Metastatic small bowel neuroendocrine tumour with bilateral carcinoid heart disease

V Jahagirdar,¹ Ali Kamal,¹ R Steeds,² John Ayuk³¹Department of Diabetes and Endocrinology, Birmingham Heartlands Hospital, Birmingham, UK²Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK³Department of Endocrinology, Queen Elizabeth Hospital, Birmingham, UK

Correspondence to

Dr V Jahagirdar, drvidhya_uk@yahoo.co.uk

Accepted 16 January 2016

SUMMARY

A 63-year-old woman was admitted with a year's history of exertional breathlessness, anxiety attacks, syncopal episodes, diarrhoea, fatigue, reduced appetite, 2 stones weight loss, and flushing affecting her face and trunk. Investigations revealed raised urine 5-hydroxy indole acetic acid (5-HIAA) and chromogranin A. CT scan demonstrated extensive soft tissue encasing the major vessels intra-abdominally, and a retroperitoneal mass. ¹¹¹In-octreotide single-photon emission CT (SPECT CT) showed increased focal activity in the mediastinum, retroperitoneum and mesenteric lymph nodes. Para aortic lymph node biopsy confirmed the diagnosis of metastatic well-differentiated grade 1 gastrointestinal neuroendocrine tumour (NET). Extensive cardiac investigations confirmed severe mitral regurgitation, moderate aortic and tricuspid regurgitation, and mild pulmonary regurgitation. The patient's symptoms of flushing and diarrhoea were controlled with octreotide LAR, and she underwent mechanical aortic and mitral valve replacement. Following discharge from surgery, she went on to develop hydronephrosis and urosepsis, followed by infective endocarditis, resulting in recurrent admissions, and eventually passed away in her sleep nearly 14 months after her initial diagnosis.

BACKGROUND

Neuroendocrine tumours are rare tumours arising from enterochromaffin cells. Although rare, they are the most common small bowel tumour (37.4%). They often remain asymptomatic until they metastasise. Owing to the varied constellation of symptoms, diagnosis can be delayed for several years. In gastrointestinal neuroendocrine tumours (NETs), carcinoid syndrome generally occurs in the presence of hepatic metastases, but this case illustrates that, in the presence of significant retroperitoneal lymph node involvement, carcinoid syndrome can occur in the absence of liver metastasis, due to release of vasoactive amines directly into the systemic system. In addition, carcinoid heart disease generally involves the pulmonary and tricuspid valves, as serotonin is metabolised in the lungs to inactive 5-hydroxy indole acetic acid (5-HIAA). Left-sided heart valve involvement, as seen in this patient, occurs in <10% of cases of cardiac carcinoid disease.

CASE PRESENTATION

A 63-year-old woman with a history of primary hypothyroidism and depression presented to the acute medical unit following exertional breathlessness, anxiety attacks associated with syncope,

diarrhoea, fatigue and flushing affecting her face and upper body. She had lost around 2 stones in weight over the previous 12 months. Colonoscopy organised by her general practitioner 5 months earlier for ongoing diarrhoea revealed diverticular disease. Biopsy of the colonic mucosa was normal. The patient was taking levothyroxine, citalopram, bendroflumethiazine and omeprazole.

On examination she was cachectic. Cardiovascular, respiratory and abdominal examination was normal apart from mild pitting oedema of the ankles. Her blood pressure was 120/70 mm Hg. The typical episodic dry facial and truncal flushing of carcinoid syndrome was observed.

INVESTIGATIONS

Initial laboratory investigations showed normocytic anaemia with haemoglobin of 109 g/L (reference 115–160) and raised alkaline phosphatase (ALP) of 178 (reference 30–130 IU/L). The rest of her liver and renal parameters were normal. Twenty-four hour urinary 5-HIAA was modestly elevated at 116 µmol/24 h (reference <50). Chromogranin A was grossly elevated at 5817 pmol/L (reference <60).

Ultrasound scan of the abdomen revealed a suspicious hyperechoic area in the liver suggestive of metastasis or fatty liver. Multiphase CT of the thorax, abdomen and pelvis demonstrated an extensive soft tissue mass encasing the upper abdominal aorta, compressing the inferior vena cava, and extending down along the retroperitoneum and iliac vessels, with prominent mesenteric lymphadenopathy. There was obstruction of the right ureter, with moderate hydronephrosis (figure 1). The liver lesion identified on ultrasound was an area of altered perfusion rather than metastatic disease.

The patient underwent CT-guided biopsy of the para aortic lymph nodes. Histology showed tumour

Figure 1 CT of the abdomen and pelvis.

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To cite: Jahagirdar V, Kamal A, Steeds R, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213693

cells, which stained positive for synaptophysin and CDX2, with a Ki67 index <1%, indicating a well-differentiated grade 1 neuroendocrine tumour from a bowel primary. The patient was referred to the regional Neuroendocrine Tumour Centre. She underwent ^{111}In -octreotide single-photon emission CT (SPECT CT), which demonstrated marked tracer uptake bilaterally in the retroperitoneal lymph nodes and mild uptake in the left superior mediastinal and mesenteric lymph nodes. There was no increased uptake in the liver, lungs, bowel and bones (figures 2 and 3). She was started on octreotide long acting repeatable (LAR), 30 mg intramuscularly every 4 weeks.

As her N-terminal pro-brain natriuretic peptide (NTpro-BNP) was elevated at 3239 ng/L (reference <203 ng/L), further investigations were planned under the NET cardiology team. However, in the meantime, she deteriorated and was admitted with severe breathlessness. Transthoracic and then transoesophageal echocardiography revealed severe mitral regurgitation, moderate aortic and tricuspid regurgitation, and mild pulmonary regurgitation. Cardiac MRI (CMRI) confirmed dilation of the left ventricle, increased left ventricular mass and impaired biventricular function. Cardiac catheterisation demonstrated normal coronary arteries but with elevated pulmonary artery V wave due to mitral regurgitation. Following cardiac catheterisation, the patient developed transient renal dysfunction. Renogram confirmed a non-functioning right kidney and normal functioning left kidney.

TREATMENT

Once the diagnosis was confirmed, the patient was started on octreotide LAR 30 mg intramuscularly every 4 weeks, aiming to

Figure 2 ^{111}In -octreotide single-photon emission CT (SPECT CT) scan—axial view.

Figure 3 ^{111}In -octreotide single-photon emission CT (SPECT CT) scan—coronal view.

control symptoms and tumour progression. A ureteric stent was inserted in the right ureter, later replaced by a nephrostomy tube, resulting in resolution of the hydronephrosis and improvement in her renal function.

Owing to frailty, four-valve surgery was deemed too risky, and the patient subsequently underwent mechanical mitral and aortic valve replacement. Histology of the resected valves was characteristic of chronic carcinoid valvulopathy. Appropriate anticoagulation therapy was started and the octreotide LAR was switched to lanreotide autogel (ATG), which could be administered subcutaneously.

OUTCOME AND FOLLOW-UP

Treatment with somatostatin analogue injections resulted in normalisation of 5-HIAA to 35.4 $\mu\text{mol}/24\text{ h}$ (reference <45) and significant reduction of chromogranin A to 1382 pmol/L. The symptoms of carcinoid syndrome were well controlled on 3 weekly lanreotide ATG 120 mg subcutaneous injections.

The patient was readmitted and treated for *Klebsiella* urosepsis and vancomycin-resistant *Enterococcus* (VRE) septicaemia. She also required a prolonged course of antibiotics for infective endocarditis, and diuretics for heart failure. Unfortunately, she failed to respond to treatment and passed away in her sleep nearly 14 months after her initial diagnosis.

DISCUSSION

Neuroendocrine tumours are rare tumours arising from enterochromaffin cells, most commonly occurring in the lung and gastrointestinal tract. Although rare, there has been a significant increase in the incidence of NETs of the small intestine, colon, rectum and stomach in the past few decades.^{1 2} In the early stages, the symptoms of gastrointestinal NETs can be non-specific, including intermittent abdominal pain, nausea, vomiting or anaemia. These can be easily mistaken for other common gastrointestinal conditions, resulting in a significant delay in the diagnosis of NET. Gastrointestinal NETs are frequently metastatic at the time of diagnosis, and survival duration depends on the extent of spread at diagnosis and the degree of differentiation of the tumour.³ The mid-gut blood supply drains directly into the portal circulation, often leading to hepatic metastases.

Carcinoid syndrome occurs in about 20% of patients with well-differentiated NET of jejunum and ileum, less commonly in NETs of other origin and rarely in rectal NETs.³ The manifestations of carcinoid syndrome are dry flushing (flushing without sweating), bronchoconstriction, secretory diarrhoea, intermittent abdominal pain and carcinoid heart disease, caused by

vasoactive amines and peptides, including neurotransmitters such as serotonin and histamine, that are secreted by the NET cells. As the vasoactive amines are efficiently metabolised by the liver, carcinoid syndrome rarely occurs in the absence of hepatic metastases. Exceptions can occur, as in this case, if there is significant retroperitoneal or pelvic involvement with direct drainage of the vasoactive amines into the systemic circulation, bypassing the liver. Very few similar cases have been reported in the literature.^{4–6}

Mesenteric and retroperitoneal fibrosis can occur, and is due to the local fibrotic action of the vasoactive amines. Studies have demonstrated elevated levels of transforming growth factor β (TGF- β_1) and connective tissue growth factor (CTGF) in association with small intestinal NETs with mesenteric fibrosis.⁷ The fibrotic response can be significant enough to cause intestinal obstruction, mesenteric ischaemia or hydronephrosis.

Carcinoid heart disease (CHD) is a serious sequel of carcinoid syndrome, with a significant impact on outcome.⁸ High serotonin level and prolonged duration of exposure to serotonin appear to play an important role in the development of CHD⁹; substances other than serotonin, such as tachykinins, neurokinin A and substance P have also been linked to cardiac fibrosis.¹⁰ Serotonin-mediated upregulation of TGF- β_1 and increased collagen synthesis by heart valve interstitial cells lead to valve fibrosis and retraction, resulting in stenosis and/or regurgitation, affecting the heart valves. Pulmonary and tricuspid valves are most commonly affected as serotonin is inactivated in the lungs to 5-HIAA, generally sparing the left-sided valves. However, mitral and aortic valves may be affected in the presence of bronchial carcinoid, patent foramen ovale (PFO) or very high levels of circulating vasoactive amines.¹¹ This patient had significant retroperitoneal involvement with probable drainage of large quantities of vasoactive amines into the systemic circulation, which would explain the CHD in the absence of liver metastases; still, it is unusual for the left heart valves to be significantly more affected than the right heart valves.

NT-pro-BNP is significantly higher in patients with CHD. At a cut-off of 260 ng/L, the sensitivity and specificity for detection of CHD is 92% and 91%, respectively, making it an excellent screening tool for CHD.¹² Early diagnosis of CHD is essential to make management decisions for timely surgical intervention of carcinoid valvulopathy. Although significant functional improvement occurs in those who survive cardiac valvular surgery, it is associated with high peri-operative risk due to right ventricular dysfunction, carcinoid crisis, renal failure and sepsis.⁸

In this patient, a decision was made to intervene surgically only on the left-sided heart valves, and to manage the moderate tricuspid regurgitation and mild pulmonary regurgitation conservatively, as the patient's prognosis from the carcinoid tumour was felt to be worse than predicted due to the risk of urosepsis, given the ureteric stenting. In such cases, recurrent infection can be a major problem postoperatively, as was proven here.

Learning points

- Carcinoid syndrome can present with a constellation of symptoms mimicking common conditions. Detailed history-taking and appropriate investigations could lead to early diagnosis.
- Carcinoid syndrome can occur in the absence of liver metastasis in patients with bronchial or ovarian neuroendocrine tumours (NETs), or in those with mid-gut NETs with retroperitoneal involvement, as vaso-active amines are secreted directly into the systemic circulation, bypassing the portal circulation.
- Right heart valves are commonly involved in carcinoid heart disease. Left heart valves may be involved in the presence of patent foramen ovale, bronchial carcinoid or significantly elevated vasoactive amines.
- Early diagnosis and management of carcinoid valve disease and heart failure could improve survival.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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