



A 70-year-old male with chronic diarrhoea and flushing

Case report

A 63-year-old male was referred to the pulmonary oncology unit in March 1998 due to abnormalities found on chest radiography (figure 1), which was performed after an auto-limited "flu-like syndrome". Subsequently, a computed tomography (CT) scan was performed (figure 2).



Figure 1
Chest radiography.

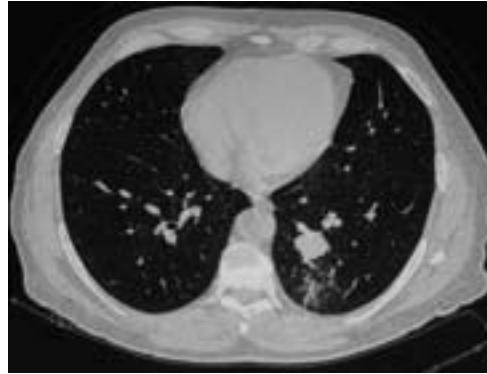


Figure 2
CT scan of the chest.

Task 1
Interpret the chest radiograph.

Task 2
Interpret the CT scan.

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Answer 1

The chest radiography shows opacity at the left base adjacent to the cardiac silhouette.

Answer 2

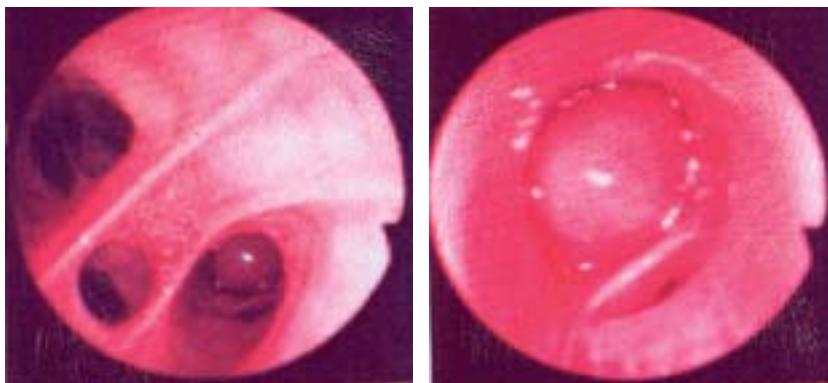
The CT scan of the chest shows an ill-defined pulmonary nodule on the postero-basal segment of the lower left lobe, with mediastinal adenopathy (not visible in this slice).

The patient's previous medical history was remarkable for hypertension. He had a 40-pack-year smoking history, but had ceased smoking 4 years previously. There was no history of significant alcohol intake.

At this point, the patient was asymptomatic and denied any respiratory symptoms, anorexia, recent weight loss, dyspepsia or changes in bowel habits. A physical examination was normal, with normal pulmonary auscultation, soft and flat abdomen without tenderness or rigidity, and the liver and spleen were not palpable.

Clinical investigations

On flexible fibreoptic bronchoscopy, the lumen of the posterior basal left lower bronchus was totally obstructed by an endobronchial formation covered with a smooth and shiny mucosa (figure 3). Histopathological results revealed an atypical carcinoid tumour.

**Figure 3**

Findings on flexible bronchoscopy. An endobronchial formation with a smooth and shiny mucosa was found, which totally occluded the posterior basal left lower bronchus.

Echography and CT scan of the abdomen showed two liver nodules, measuring 6 and 5 cm in the left and right lobe, respectively. A liver CT scan-guided biopsy was performed, which confirmed the presence of hepatic metastases of a neuroendocrine tumour.

The patient underwent octreotide scintigraphy, which revealed hyperfixation on the base of the left lung and in two localised liver areas. Primary carcinoid tumour of the gastrointestinal

tract, skin and skeletal metastatic carcinoid tumors, and carcinoid-related heart disease were excluded.

Levels of 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA) and cromogranin A were all within normal limits. Subsequently, the multidisciplinary team decided to maintain clinical vigilance and follow-up.

On February 1999, almost 1 year after diagnosis, the patient experienced his first auto-limited carcinoid syndrome episode, with pronounced flushing and watery diarrhoea, without wheezing or any repercussions on the hydro-electrolyte balance.

The patient continued to have sporadic auto-limited symptoms. Four months later, he was admitted for flushes and diarrhoea, which had resulted in dehydration, severe hypokalaemia (1.7 mEq L^{-1}), pre-renal insufficiency and severe metabolic acidosis. At this stage, therapy with somatostatin analogues was initiated (octreotide 0.05 mg *b.i.d. s.c.*) with a partial and temporary clinical response.

Despite therapy, the patient continued to experience carcinoid syndrome episodes with a progressive increase in frequency and severity for ~ 1 year, which was concomitant with progressive increases in octreotide doses to the maximum dose level.

Laboratory follow-up results showed elevated levels of 5-HT and 5-HIAA. Imaging re-evaluation of the carcinoid lesions demonstrated stability of the pulmonary tumour and a progressive increase in the number and dimensions of hepatic metastases.

Task 3

At this point, what is the best therapeutic approach?

Answer 3

Due to clinical worsening and frequent monthly admissions, ^{131}I -metaiodobenzylguanidine (^{131}I -MIBG) scintigraphy was performed. This revealed only a low uptake in the left hepatic lobe, which is predictive of a low clinical response to treatment with higher doses of ^{131}I -MIBG.

Between June and December 2000, reasonable control of carcinoid syndrome symptoms was achieved using double therapy of somatostatin analogues (octreotide *q.i.d.* and lanreotide monthly).

From January 2001 onwards, severe carcinoid crises often occurred, requiring monthly admissions. The hepatic metastatic lesions continued to grow, but there was stability of the pulmonary tumour, as demonstrated by CT scan of the chest, ultrasound and magnetic resonance imaging (MRI) of the liver.

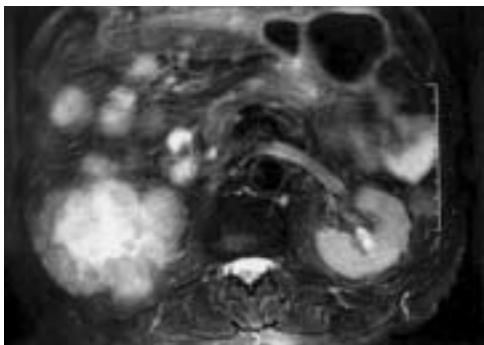


Figure 4
MRI of the liver.

At this point, octreotide scintigraphy was repeated, showing a higher fixation on lung and hepatic lesions as compared with the 1998 scan, suggesting a higher metabolic rate with excessive release of vasoactive peptides into the circulation but without any other localisation of disease.

A trial with therapeutic ^{131}I -MIBG was initiated, but there was no clinical response after two sessions.

Systemic chemotherapy with a combination of streptozotocin and 5-fluorouracil was given over 6 weeks, whilst maintaining a maximum dose of octreotide analogues (octreotide 0.1 mg *q.i.d.*). For the following 2 years, a good clinical response with a reduction of frequency and severity of carcinoid syndrome and no significant toxicity was achieved.

The multidisciplinary team continued to

explore and discuss future therapeutic approaches in this patient. The patient had an atypical high-grade malignant carcinoid pulmonary tumour with continuously growing liver metastases, with no other secondary localisation of disease and apparent stability of the pulmonary lesion. Temporary control of carcinoid syndrome symptoms was successfully achieved with multiple therapeutic approaches, including octreotide analogues in monotherapy and combination therapy, therapeutic ^{131}I - MIBG, and, later on, combination chemotherapy.

Subsequently, the patient was recommended for hepatic transplant, as he was generally in good health, with no laboratory evidence of organ failure during asymptomatic phases.

The transplantation team concurred that there was indication for hepatic transplant after surgical resection of the primary tumour if carcinoid syndrome symptoms were impairing the patient's quality of life, or in the presence of end-stage hepatic failure with confirmed exclusion of extrahepatic disease.

An inferior left lobectomy was performed in April 2003 without complications. The histopathological results confirmed the diagnosis of high-grade atypical carcinoid tumour without lymph node involvement.

In order to definitively exclude the presence of extrahepatic disease, a positron emission tomography (PET) scan was performed after lung surgery, which confirmed extensive liver involvement.

The patient was admitted to hospital again in December 2004 as a result of uncontrolled watery profuse diarrhoea, dehydration, severe hypokalaemia, metabolic acidosis and acute renal failure.

At this point, the patient was experiencing therapy failure due to persistent carcinoid symptoms, despite usual carcinoid tumour therapy (with octreotide analogues and chemotherapy), supportive care with antidiarrhoeal medication, continuous in-patient clinical monitoring, endovenous hydration, and ionic and acid-base disturbance correction. The persistence of carcinoid syndrome and consequent long-term hospitalisation resulted in a severe impairment of the patient's quality of life.

The patient was admitted on to the hepatic transplant list in April 2005 and the transplant was performed in September 2005. No significant complications occurred in the immediate post-surgical period, and the patient was discharged 2 months after transplant with no clinical signs of carcinoid tumour.

Please see page 322 for a review on pulmonary carcinoid tumours, including references.

Discussion

In this patient, the diagnosis of atypical carcinoid tumour was incidental, performed at an asymptomatic stage with hepatic metastatic disease, but without evidence of tumour hormonal production. The close monitoring of tumour size, extension of hepatic metastases and hormonal activity, and screening for other localisations of metastatic disease or complications of carcinoid disease permitted early and adequate adjustment of successive therapeutic options.

The carcinoid tumour was strictly localised to the lung and liver. There was stability of the pulmonary carcinoid tumour with progressive growth of hepatic metastasis, which was responsible for increasing the severity and frequency of carcinoid syndrome. Despite extensive hepatic disease with very few spared areas of normal hepatic parenchyma, the patient did not have hepatic insufficiency.

Reasonable control of carcinoid syndrome symptoms was successfully achieved with first-line somatostatin analogue therapy (first, with octreotide and, subsequently, with an octreotide and lanreotide combination), and then with streptozotocin and 5-fluorouracil-based

chemotherapy. Therapy with ^{131}I -MIBG was unsuccessful.

In the 9 months that preceded hepatic transplant, there was a significant deterioration of quality of life, with permanent hospital admission and uncontrolled carcinoid syndrome symptoms. The patient always maintained a good status performance, which was a determinant in the multidisciplinary team's decision for liver transplantation, after resection of primary pulmonary carcinoid tumour. Exclusion of other metastatic localisations of carcinoid disease and carcinoid-related heart disease was also assured. The balance between risks and long-term benefits of transplantation was evaluated. An improvement in survival and quality of life is the first goal to achieve, which should be evident during patient post-transplant follow-up.

Different therapeutic options and diagnostic procedures in this patient were always made based on a multidisciplinary approach that focused on patient-specific conditions.

In addition, data from literature considering the different diagnostic and treatment modalities in metastatic carcinoid disease were considered.