Facial flushes and diarrhoea

V Crasset, E Delcourt

A 64-year-old woman presented with episodic abdominal pain, watery diarrhoea and facial flushes for two years. She reported 6 kg weight loss during this period. The frequency of the diarrhoea varied between two and eight times per day. Her symptoms of feeling warm occurred either spontaneously or precipitated by urinary voiding and defaecation. She reported no history of dyspnoea or bronchial asthma.

Laboratory tests revealed normal erythrocyte sedimentation rate and C-reactive protein. Four consecutive 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) measurements were within the normal range. Urinary norepinephrine, epinephrine, calcitonin, thyroid hormones, carcinoembryonic antigen, and neuron-specific enolase were normal. Chest X-ray, abdominal ultrasound, computed tomography (CT) scan, liver magnetic resonance imaging (MRI), liver technetium-99 colloidal scintigraphy, small bowel contrast, barium enema, oesophago-gastro-duodenoscopy and colonoscopy examinations failed to demonstrate any tumour, liver metastasis, enlarged para-aortic or mesenteric lymph nodes. No extra-abdominal tumours were found. Specific peptide concentrations, assessed by radioimmunoassay, were serum pancreastatin 290 pg/ml (normal <150 pg/ml), chromogranin A 4150 pg/ml (normal <500 pg/ml), and chromogranin B 320 pg/ml (normal <200 pg/ml). Figures 1 and 2 show [^{123}I]meta-iodo-benzyl-guanidine (MIBG) and [^{111}In]octreotide scintigraphies.

Figure 1 ^{123}I -MIBG abdomen scintiscan after 27 h delay

Figure 2 ^{111}In -Octreotide abdomen scintiscan, 29 h after injection

Department of
Cardiology, Erasme
Hospital, Route de
Lennik, 808, B-1070,
Brussels, Belgium
V Crasset

Department of
Nuclear Medicine,
CHUA Vesale, Route
de Gozée, 706,
B-6110 Montigny-
le-Tilleul, Belgium
E Delcourt

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Questions

- 1 What do the blood results and isotopic scanning suggest?
- 2 What is the most likely diagnosis and what further investigation is required to confirm this?
- 3 Explain the failure of 'classical investigations' to allow diagnosis.

Answers

QUESTION 1

Pancreastatin and chromogranins A and B are hormones secreted by almost every neuropeptide-producing endocrine cell. Pancreastatin is a minor form of the chromogranin A immunoreactive peptides. High levels of these peptides suggest the existence of a neuroendocrine tumour. Several neuroendocrine tumours possess the property of MIBG accumulation through a neuronal pump uptake process and present high-affinity binding sites for somatostatin. The ^{131}I -MIBG and ^{111}In -octreotide scans show four intra-abdominal hot spots, independently seen by the two methods, lying in the right lower iliac area.

QUESTION 2

The most likely diagnosis is abdominal neuroendocrine carcinoid tumour. Laparoscopy is the following step. In the reported case, laparoscopy confirmed a 1-cm wide tumour, located in the terminal ileum, with multiple peritoneal metastasis. On pathological examination, the Grimelius stain and chromogranin immunoreactivity were strongly positive, suggesting carcinoid tumour.

QUESTION 3

The clinical features of carcinoid syndrome occur late in the natural history of carcinoid tumours. These tumours are frequently underdiagnosed when the small intestine is affected. Small bowel carcinoids are observed in about 1.2% of autopsies, which is far more frequent than the clinical diagnosis rate.^{1,2} Because of slow progression and intramural localisation, patients often remain asymptomatic until lumen obstruction, bleeding or peritoneal spreading occurs.

Small bowel series and abdominal ultrasound usually fail to provide the diagnosis and small bowel barium studies are negative in more than half the patients.³ CT lacks sensitivity to detect the primary lesion but is reliable in assessing tumour spread within the abdomen,⁴ especially when there is mesenteric involvement. However, the CT appearance of mesenteric, lymph node or liver metastases is not specific. MRI is highly sensitive in detecting liver metastases but its value as a primary screening modality requires further evaluation.¹ The diagnosis of these endocrine tumours thus remains difficult, even with a combination of imaging techniques including

ultrasonography, arteriography, CT and selective portal venous sampling; explorative coeliotomy is required in about 20% of patients.⁵

One-third of gastrointestinal tract carcinoid tumours have evidence of distant metastases otherwise unexpected at the time of laparotomy, predominantly in the liver. Isotopic imaging with ^{131}I -MIBG is a sensitive screening procedure for the detection of ileocaecal carcinoid tumours, with a high specificity. In a meta-analysis, its sensitivity was 55% and its specificity above 95%.¹ Recently, Hanson found a sensitivity of 68% for carcinoid arising from the terminal ileum due to its high ability to accumulate MIBG through a neuronal pump uptake process.⁶

A large number of endocrine tumours present high-affinity binding sites for somatostatin. Therefore, radiolabelled octreotide, a somatostatin analogue, is useful in their detection. Several radiolabelled somatostatin analogues have been found to show good sensitivity with specificity (^{111}In -labelled [DPTA-D-Phe-1]-octreotide and ^{123}I -labelled Tyr3-octreotide).⁷ The use of radiolabelled MIBG and octreotide analogues offer complementary imaging techniques to demonstrate primary and metastatic carcinoid tumours.⁸ Compared to other imaging methods, isotopic scanning allows whole body examination, including detection of secondary spread. Furthermore, a high affinity of somatostatin receptors to radio-labelled octreotide may preclude a good response to octreotide palliative therapy.

When a carcinoid tumour is suspected, 24-hour urinary 5-HIAA has a sensitivity of 73% and a specificity of 100%. When carcinoid syndrome occurs (in less than 10% of carcinoid tumours), hepatic metastases are found in 95% and elevated urinary 5-HIAA in 88–99% of patients. Biochemical identification of carcinoid tumours involves not only estimation of urinary 5-HIAA but also a search for other markers such as chromogranin, substance P, neurotensin, serotonin, or b-human chorionic gonadotropin. After biochemical characterisation, a combination of several imaging techniques may provide the best chance of locating the tumour.

In the present case, long-acting somatostatin analogue treatment, gradually increased to a daily dose of 1.5 mg subcutaneously, allowed good control of diarrhoea and flushes.

Keywords: carcinoid tumour, carcinoid syndrome, isotope scanning

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