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CASE REPORT

# Watery diarrhoea: an unusual manifestation of breast cancer

**N. al Saudi[1*], E. Maartense[1], J. Scherpenisse[2], A.W.F.M. van Leeuwen[3]**

Departments of [1]Internal Medicine, [2]Gastroenterology and [3]Pathology, Renier de Graaf Gasthuis, Delft, the Netherlands, [*]corresponding author

## ABSTRACT

**Analysis of an 83-year-old male presenting with diarrhoea showed secretory diarrhoea. Serum levels of gastrin and pancreatic polypeptide were elevated. Somatostatin-receptor scintigraphy revealed a hot spot in the left thoracic wall and subsequently, breast adenocarcinoma with neuroendocrine differentiation was diagnosed. Postoperatively, the patient made an uneventful recovery. The relationship between the clinical picture, the results of pathological examination and hormonal analysis is discussed and put into perspective.**

## KEYWORDS

Breast cancer, gastrin, neuroendocrine tumour, pancreatic polypeptide, watery diarrhoea

## INTRODUCTION

Several neoplastic disorders can cause chronic watery diarrhoea attributable to hormonal-mediated response. These include pancreatic endocrine tumours, carcinoid syndromes and medullary thyroid cancer. These disorders are not usually considered to be part of the differential diagnosis of chronic diarrhoea because of their rarity among all other causes of diarrhoea. We describe a patient with severe watery diarrhoea for whom a neuroendocrine tumour of the breast was the most probable explanation. To the best of our knowledge, this association has not been described before.

## CASE REPORT

An 83-year-old man presented with a three-week history of progressive diarrhoea. Apart from gastric outlet obstruction due to peptic ulcer disease, treated with esomeprazole 40 mg daily, his medical history was unremarkable. The diarrhoea was massive and watery (up to three litres daily). He had a weight loss of 5 kg. Treatment with loperamide and ciprofloxacin gave no relief.

Physical examination revealed no abnormalities apart from slight dehydration. The results of laboratory examination are shown in *table 1*. The patient was treated with parenteral fluids and supplementation of potassium. Stool examination for bacterial pathogens, parasites and toxins showed no pathogenic micro-organisms. Biochemical analysis of the stools showed elevated sodium and potassium excretion: sodium 68 mmol/l (normal <10 mmol/l), potassium 62 mmol/l (normal 5-15 mmol/l). The calculated osmotic gap (290- 2x {Na+K}) was 30 mOsmol/kg, suggestive of secretory diarrhoea. Upper gastrointestinal endoscopy showed gastric retention due to

**Table 1.** *Laboratory values on admission*

| | Value | Normal range |
|---|---|---|
| Haemoglobin (mmol/l) | 8.7 | 8.4-10.9 |
| Thrombocytes (x $10^9$/l) | 362 | 150-400 |
| Leucocytes (x $10^9$/l) | 8.3 | 3.5-11.0 |
| Sodium (mmol/l) | 138 | 137-145 |
| Potassium (mmol/l) | 2.7 | 3.6-5.0 |
| Chloride (mmol/l) | 108 | 97-107 |
| Bicarbonate (mmol/l) | 18 | 22-30 |
| Urea (mmol/l) | 3.3 | 2.5-7.0 |
| Creatinine (µmol/l) | 92 | 70-130 |
| Glucose (mmol/l) | 5.9 | 3.5-6.0 |
| Lactate dehydrogenase (U/l) | 349 | 200-450 |
| Albumin (g/l) | 38 | 35-50 |
| Total protein (g/l) | 69 | 60-80 |
| C-reactive protein (mg/l) | <1 | 0-10 |
| Thyroid-stimulating hormone (mU/l) | 1.70 | 0.3-5.0 |

pyloric stenosis, but no signs of active ulcer disease and the mucosa of the stomach appeared normal. Colonoscopy was normal. Determination of serum peptides showed elevated levels of gastrin and pancreatic polypeptide (PP), 1290 ng/l (normal <150) and 197 pmol/l (normal <100), respectively, while vasoactive intestinal polypeptide (VIP) measured <5 ng/l (normal <20). The elevated levels of gastrin and PP in the serum were suggestive of a neuroendocrine tumour. Treatment with octreotide established a relief in the severity of the diarrhoea. Computed tomography (CT) scan of the abdomen revealed no abnormalities. Somatostatin-receptor scintigraphy with indium-labelled octreotide showed an increased uptake in the left thoracic wall. Combining the data of the scintigraphy and CT scan confirmed the localisation of a tumour mass in the left breast (*figure 1*). Subsequent mammography revealed an irregular lump just behind the nipple. An ultrasound-guided biopsy of the left breast mass was performed. Cytological examination confirmed an adenocarcinoma in the left breast. The patient underwent mastectomy and axillary lymph node dissection. Pathological examination showed a ductal adenocarcinoma. Immunohistochemical phenotyping of the tumour confirmed the diagnosis of an adenocarcinoma with neuroendocrine differentiation (*figure 2 A-D*). Postoperatively, the diarrhoea disappeared

**Figure 1.** *Computer tomography of the thorax fused with somatostatin scintigraphy reveals a hot spot in the left thoracic wall suggesting a neuroendocrine tumour*

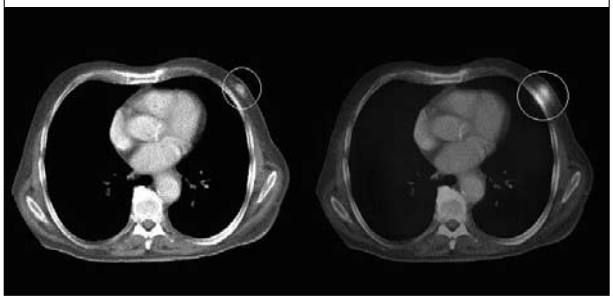
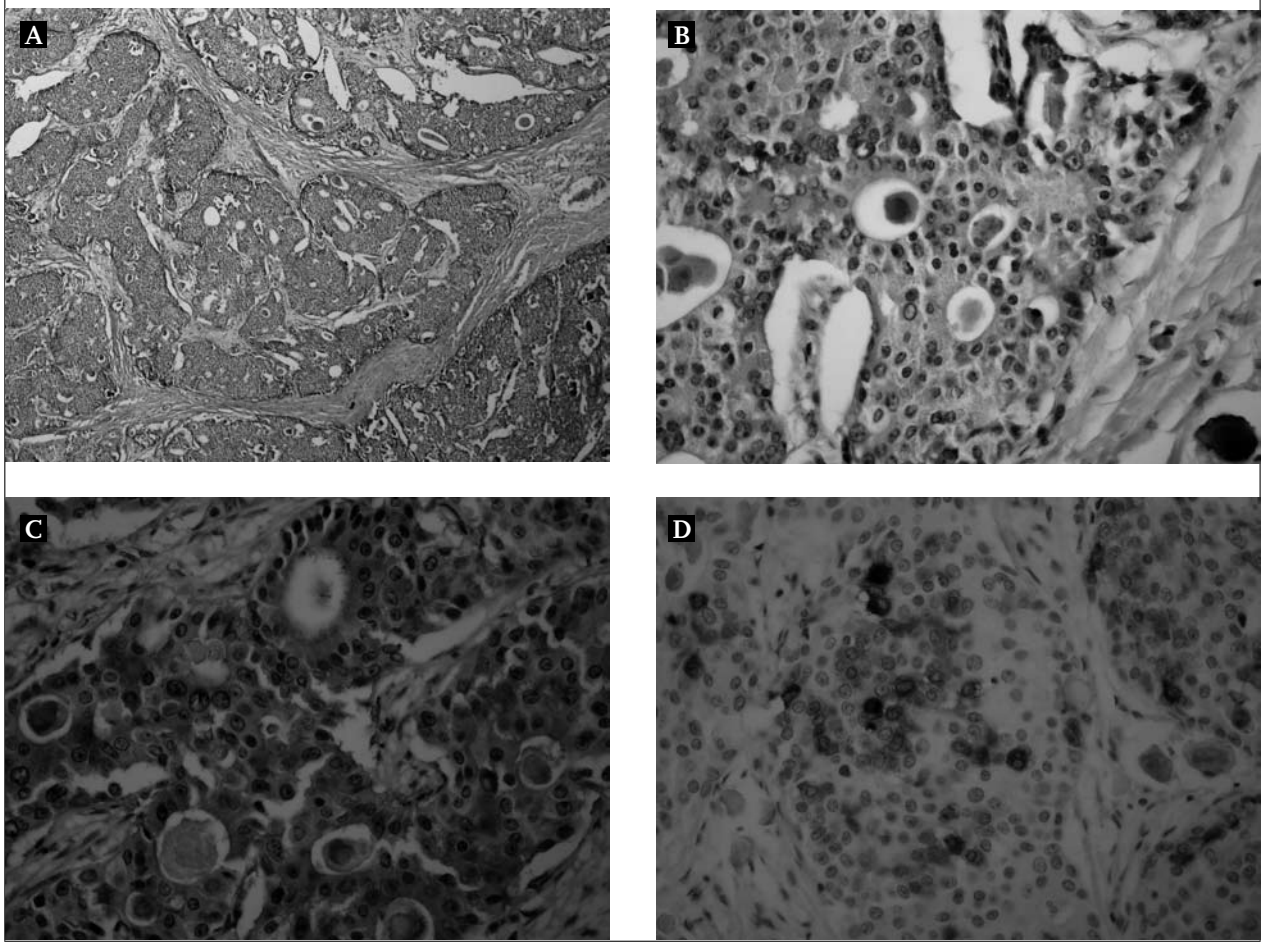


**Figure 2.** *(A) Tumour shows both solid and trabecular growth, and also forms glandular structures (H&E 5x); (B) Tumour cells are large with a rather monotonous enlarged nucleus with a prominent nucleolus. Mitotic figures are sparse (H&E 40x); (C) Tumour cells show neuron-specific enolase reactivity in the cytoplasm (40x); (D) Clusters of tumour cells show positivity for synaptophysin (40x)*



and the patient had an uneventful recovery. As an outpatient he remained asymptomatic during a follow-up of 12 months. Hormonal analysis, eight weeks after surgery, showed a normal level of PP (62 pmol/l). Serum gastrin level remained high at 997 ng/l.

## DISCUSSION

Feyrter and Hartmann were the first to describe two patients with breast cancers with carcinoid growth patterns.[1] Neuroendocrine differentiation can be identified in up to 30% of breast cancers.[2] Neuron-specific enolase (NSE) is a well-known marker to demonstrate neuroendocrine differentiation and the same is true for chromogranin and synaptophysin.[2] However, NSE-positive breast tumours are not always immunoreactive for peptide hormones and usually, neuropeptide immunostaining is only found in single cells or small groups of cells (most frequently for gastrin and PP).[3] The clinical meaning of a hormonal content is unknown, possibly related to local growth regulation and only very rarely associated with clinical signs and symptoms (known for norepinephrine and adrenocorticotropin).[2] There is no consensus with respect to the definition of neuroendocrine differentiated breast cancer. Some investigators consider tumours with even a minimal population of neuroendocrine cells (1-2%) to be neuroendocrine tumours,[4,5] while others only classify a tumour as neuroendocrine when the majority of tumour cells display neuroendocrine characteristics.[6] The described case showed activity of NSE in all tumour cells, while the positivity for synaptophysin was demonstrated in clusters of malignant cells.

The elevated levels of PP and gastrin supported the idea of a causal relationship between the diarrhoea and the tumour. Functionally active gastrointestinal neuroendocrine tumours have the ability to secrete multiple peptides into the plasma, thereby causing a chronic diarrhoea syndrome.[7,8] For many years it had been supposed that measurement of plasma peptide could be the way to diagnose such tumours with diarrhoea as first manifestation.[7,8] However, the diagnostic value of fasting plasma peptide concentrations to detect tumours in patients with chronic diarrhoea is questionable, as described by Schiller *et al.*[9] In their series of patients with chronic diarrhoea, none of whom had a neuroendocrine tumour, 45% showed elevated plasma peptide levels.

A serum gastrin level of more than 1000 ng/l is almost always due to Zollinger-Ellison syndrome.[10] Chromogranin A is another useful test in the diagnostic workup for suspected gastrinoma.[11] However, chromogranin A was not measured in the underlying case. The probability of Zollinger-Ellison syndrome was not supported by the findings on gastrointestinal endoscopy, lacking active ulcer disease and lacking prominent gastric folds.[12] Furthermore, high gastrin levels, in the absence of gastrinoma, can be ascribed to the chronic use of proton pump inhibitors (PPI), chronic diarrhoea and to gastric outlet obstruction,[10] as were present in the described case, although usually, with the long-term use of PPI, gastrin levels do not exceed 400 ng/l.[13] Finally, serum gastrin remained unchanged after the mastectomy and the chronic diarrhoea disappeared postoperatively. Therefore, an underlying gastrinoma was not a plausible explanation in this case. The highly elevated gastrin was most probably caused by PPI use combined with gastric outlet obstruction.[13]

Pancreatic polypeptide, besides chromogranin A, is considered to be a general marker for endocrine digestive tumours.[14] Also, a direct relationship between elevated PP due to PPoma and watery diarrhoea has been described.[15,16] However, in the underlying case the diarrhoea as such is the most probable explanation of the elevated serum PP level, supported by the failure to detect PP in the tumour by additional immunohistochemical examination and by the normalisation of serum PP postoperatively when the diarrhoea had disappeared.

Therefore, in the underlying case we were not able to determine which plasma peptide was responsible for the chronic diarrhoea. Nevertheless, the clinical picture and course strongly support the relationship between the tumour and chronic debilitating diarrhoea.

The present report supports the diarrhoeogenic potentials of neuroendocrine cells originating from a malignancy outside the gut or pancreas, more specifically from a male with breast cancer.

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