Neuroendocrine Pancreatic Carcinoma After Initial Diagnosis of Acute Postpartal Coeliac Disease in a 37-Year Old Woman – Fatal Coincidence or Result of a Neglected Disease?

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Abstract. *An acute presentation after pregnancy of coeliac disease (CD) in the puerperium is a rare condition which has been described mostly in primigravidae in patients highly suspicious of latent CD. We report the case of a 37-year-old woman who was referred to our Hospital because of refractory watery diarrhea and malnutrition syndrome. Endoscopy of the upper gastrointestinal tract revealed the classic visual features of CD and in addition, some duodenal ulcers negative for Helicobacter pylori, which seems to be another clinical feature in patients with CD. The diagnosis of acute onset of fulminant postpartal CD (Marsh score stage 3c) was confirmed histologically. Remarkably, simultaneous well-differentiated neuroendocrine non-functioning pancreatic neuroendocrine carcinoma (PNET) was diagnosed on radiological abdominal imaging which was performed since serum gastrin was remarkably high, treated by distal pancreatectomy and splenectomy. This report is, to our knowledge, the first description of the two entities, CD and PNET occurring together. Since results of antral histological studies showed diffuse hyperplasia of G-cells, probably in response to hypergastrinaemia, enterochromaffin cell carcinogenesis might have served as a possible link between both diseases.*

Coeliac disease (CD) is a common disorder affecting ca. 1% of the population in the USA and Western Europe, and which remains frequently undiagnosed since not every patient is equally symptomatically affected (1). Here, we report the unusual case of acute fulminant CD diagnosed initially in a female patient during early puerperium which was complicated by the simultaneous diagnosis of a large tumor in the pancreatic tail.

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Key Words: Coeliac disease, pancreatic neuroendocrine carcinoma, puerperium.

Case Report

In October 2011, a previously healthy 37-year-old Caucasian female was referred to our Hospital because of refractory watery diarrhoea of unknown origin at up to 20 times a day and strong recurrent abdominal pain of five weeks duration. Remarkably, symptoms arose only two weeks after the uneventful vaginal delivery of her first healthy child. Furthermore, she reported intense fatigue and a weight loss of ca. 4 kg within the last five weeks due to ongoing dehydration, resulting in termination of lactation. Laboratory findings revealed mild hypertransaminasaemia (aspartate aminotransferase, 58 IU/l; alanine aminotransferase, 42 IU/l; normal range, <35 IU/l), hypoalbuminaemia (2.6 g/l; normal range, 3.0-5.0 g/l), hypokalaemia (3.0 mmol/L; normal range, 3.5-5.0 mmol/l) and an elevated spontaneous International Normalised Ratio (INR) of 1.5. Further blood tests revealed mild hypochromic microcytic anaemia (haemoglobine 10.5 g/dl; normal range, 12.0-16.0 g/dl; MCV 82.5 fl; normal range, 85.0-95.0 fl) and low ferritin (6 μg/l; normal range, >50 μg/l). Other routine biochemistry was normal. Physical examination showed no major abnormality. Endomysial antibodies and tissue transglutaminase IgA antibodies were highly positive (>300 E/ml; normal range, <15 E/ml). When asked about possible suspicious symptoms of CD in the past, our patient described her digestive system in her own words ‘as unproblematic like that of a vulture’. Furthermore, she denied any problems during her pregnancy or abortions before.

Endoscopy of the upper gastrointestinal tract showed the classic visual features seen in CD including ‘cobblestone’ or ‘fissured’ appearance of the mucosa (surface lining) as

well as 'scallopping' or notches in the folds (Figure 1a). Additionally, we also found ulcerative reflux oesophagitis and some deep ulcers in the duodenal mucosa not related to *Helicobacter pylori* (HP; Figure 1b) ruled-out by histological examination and HP serology, while the patient denied any intake of non-steroidal anti-inflammatory drugs (NSAIDs). Histological examination, showing total villous atrophy, crypt hyperplasia, and infiltration of the surface epithelium with lymphocytes, confirmed the diagnosis of acute onset of fulminant postpartal CD (Marsh score stage 3c; Figure 2). Extensive differential diagnostic work-up was negative (including stool cultures and colonoscopy).

A gluten-free diet was initiated, and prompt complete recovery occurred, with disappearance of diarrhoea, increase in body weight and a rapid tendency towards normalisation of laboratory parameters. Serum gastrin was assessed because there was no obvious condition for HP-negative peptic ulcer disease in our patient to exclude potential Zollinger-Ellison syndrome. Since serum gastrin was remarkably high (541 pg/ml; normal range, <125 pg/ml), radiological abdominal imaging was performed demonstrating a large well-defined, heterogeneously enhancing mass of approximately 4×3×3 cm involving the pancreatic tail consistent with a neuroendocrine tumor (Figure 3). The mass was compressing the splenic vein. Since tumor marker chromogranin A was elevated (2336 μg/l; normal range, <98 μg/l) emphasizing the diagnosis of malignant neuroendocrine carcinoma, the decision was made to perform distal pancreatectomy and splenectomy. The postoperative tumor classification was pT3pN1 (1/37 lymph nodes positive) M0 L1 V1 Pn1 R0. Pathology classified the tumor as well-differentiated non-functioning pancreatic neuroendocrine carcinoma (PNET, G2) with angioinvasion, reacting positively to specific markers including chromogranin-A and synaptophysin (Figure 4). The number of cells positive for Ki-67 as a specific marker for proliferation was 12%. These findings were confirmed by a reference pathologist (Professor Dr. Günther Klöppel, Department of Pathology, Klinikum Rechts der Isar, Technical University of Munich). Currently, three months after surgery, the patient is in good health, under a gluten-free diet, without any signs of relapse of tumor or CD. Serum gastrin (38 pg/ml) and serum chromogranin A (142 μg/l) have decreased remarkably in the meantime.

Discussion

In this case report, we present a 37-year-old female patient in whom the initial diagnosis of fulminant CD was made under three remarkable conditions: i) as an acute presentation in the puerperium beginning two weeks after delivery; ii) in the presence of multiple HP-negative ulcers in the duodenum which is not a typical feature of CD; and iii) accompanied by coincidental diagnosis of a non-functioning, malignant PNET. This report is, to our knowledge, the first description of the two entities CD and PNET occurring together, and the results of our histological studies also suggest that there is a possible link between both diseases. Previous studies have raised concerns about reduced fertility and increased adverse pregnancy-related events in women with CD (2). CD has been linked to unfavourable outcomes of pregnancy due to malabsorption of folic acid and other nutrients (3). Screening studies demonstrated that CD appears to be a relatively common disorder during pregnancy which seems to be neglected compared with many other diseases for which pregnant women are routinely screened (4). However, reports about acute presentation of CD after a pregnancy in the puerperium are rare. PubMed and MEDLINE databases were searched for key words combining the terms 'coeliac disease' and 'childbirth', 'nativity', 'puerperium', 'postnatal presentation' and 'postpartum'. The relevant published articles were selected and then searched for further references. Our literature search found only 14 different case series and case reports including a total of 34 female patients with acute onset of postnatal presentation of CD (5-19). The majority of affected women, similarly to our case, were primigravidae and the beginning of clinical presentation was usually not later than 12 weeks after delivery. Differently from our case, most patients had reported typical symptoms suggestive of CD before (5-19). Among various triggering factors including surgical procedures, gluten overloading and viral infections, pregnancy and puerperium have been implicated in initiating or unmasking 'latent' CD. Most authors assumed a possible correlation between extreme hormonal variations, maternal exposure to foetal antigens, changes in immunoreactivity and autoimmune activation during the postpartum period and the acute onset of CD. Therefore, CD should always be considered when postpartal women develop refractory diarrhoea, especially in the presence of any concomitant findings such as anaemia, weight loss, elevated liver enzymes and hypoalbuminaemia (10, 15). Remarkably, endoscopy of the upper gastrointestinal tract of our patient revealed (apart from the classic visual features seen in CD, Figure a) ulcerative reflux oesophagitis and some deep ulcers in the duodenal mucosa (Figure 1b) which were not related to HP infection (ruled- out by histological examination and HP serology) nor to NSAID use. Although this does not represent typical clinical feature of CD, non-HP and non-NSAID-related peptic disease have been described before in patients with CD (20, 21). Levine *et al*. discuss gluten-induced damage which may cause crypt 'exhaustion' resulting in mucosal breakdown and ulceration and postulate that CD should be ruled-out carefully in all patients with unexplained peptic disease (20, 21). In our patient, we found an elevation of serum gastrin far above the normal range. The most frequent conditions of hypergastrinemia in Man are Zollinger-

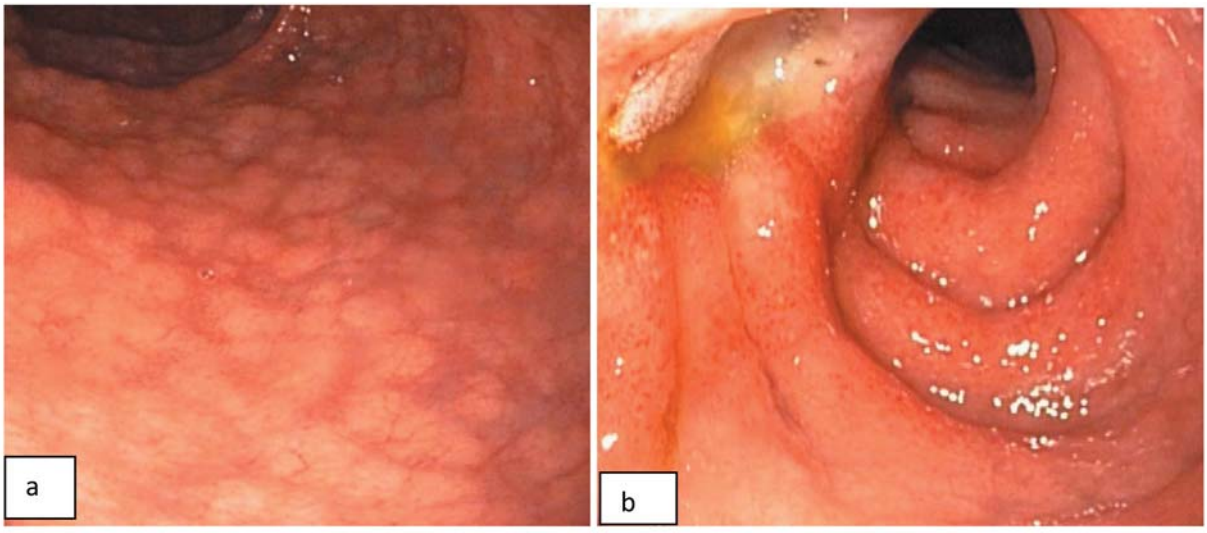

Figure 1. *a: Endoscopic images demonstrating the classic visual features seen in coeliac disease including "cobblestone" and "fissured" appearance of the mucosa (surface lining), as well as "scallopping" or notches in the folds. b: Deep ulcer in the duodenal mucosa not related to Helicobacter pylori.*

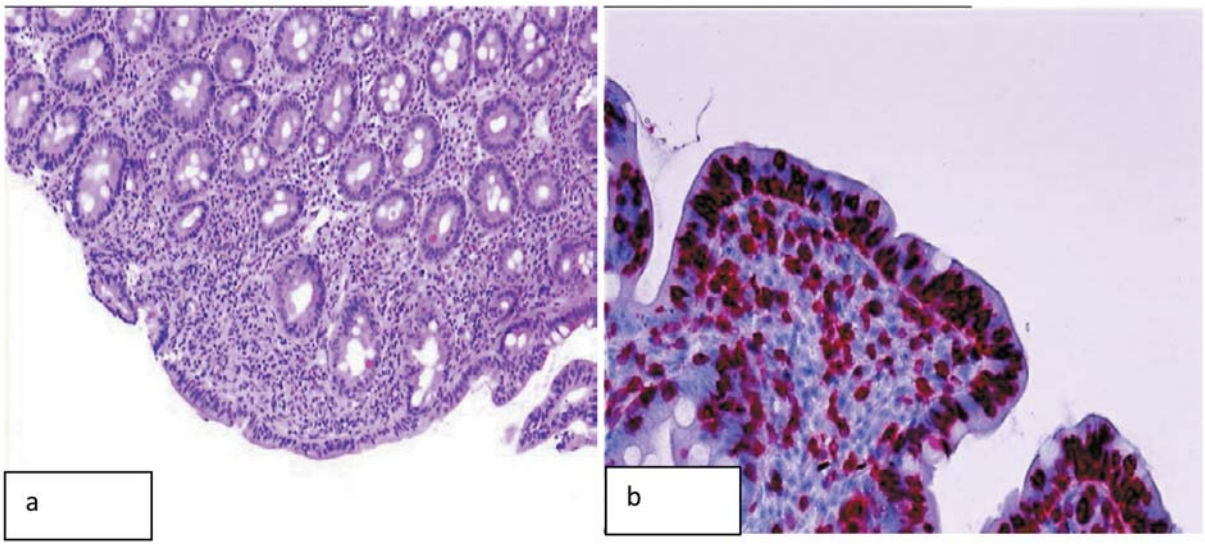

Figure 2. *Classic lesion of coeliac disease (including total villous atrophy, crypt hyperplasia, and infiltration of the surface epithelium with lymphocytes), Marsh score stage 3 c. a, Haematoxilin/eosin (HE, magnification ×10); b, CD3 staining (magnification ×20).*

Ellison syndrome with autonomous gastrin hypersecretion by tumour cells and reactive hypergastrinaemia in type A autoimmune chronic atrophic gastritis with achlorhydria, causing unrestrained gastrin release from gastrin-producing antral G-cells. Other conditions with moderate hypergastrinaemia include treatment with proton pump inhibitors, gastric outlet obstruction, previous vagotomy, chronic renal failure and postoperative short bowel syndrome (22). However, all these entities were excluded in our patient. Interestingly, conditions which lead to small intestinal resection may trigger raised gastrin concentrations secondary to reduced degradation, since the small bowel represents the major site of gastrin catabolism (23). Other authors postulate the absence of an inhibitor in the small intestine which might cause hypergastrinaemia in patients with short bowel syndrome, gastrointestinal-inhibitory polypeptide, cholecystokinin and secretin (24). Since malabsorption in CD, due to villous atrophy in the upper small intestine, may functionally-mimic short bowel syndrome, this might cause hypergastrinaemia which could have possibly induced the

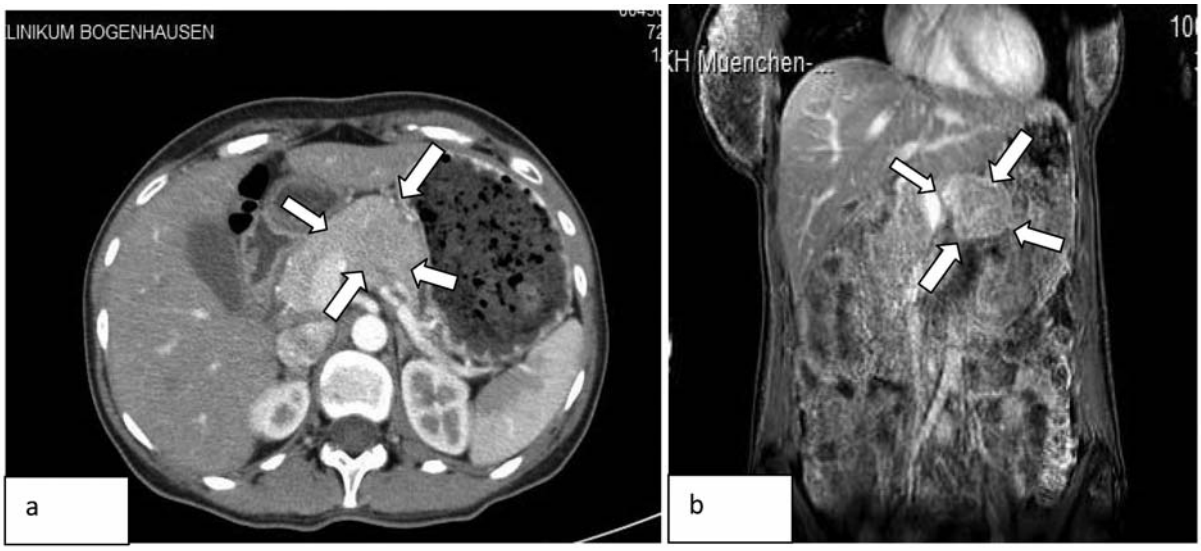

Figure 3. *Radiological abdominal imaging demonstrating a large well-defined, heterogeneously enhancing mass involving the pancreatic tail (arrows) consistent with a neuroendocrine tumor. a: Computed Tomography; b: Magnetic Resonance Imaging.*

formation of duodenal ulcers in our patient. However, this remains a hypothesis. The most striking feature of the present case is the association of a non-functioning, malignant PNET with CD. While the increased incidence of enteropathy-associated T-cell lymphoma and small bowel adenocarcinoma is long established, there seems to be obviously also an association between other forms of cancer in patients with CD, like primary liver cancer, papillary cancer of thyroid and melanoma (25-31). Since the time interval between onset of CD and cancer development is usually long, carcinogenesis in patients with CD seems to be a multi-step process requiring the accumulation of several carcinogenetic mutations (26). However, only four cases of neuroendocrine tumors have been reported before, all of them primarily located in the ileum (32-35). Intake of gluten may stimulate proliferation of enterochromaffin cells which might lead to cancerous transformation (36). Neuroendocrine malignancies of the pancreas are rare, with an estimated incidence of one case per 100,000 people (37). Furthermore, cancer diagnosed during pregnancy is an even more rare occurrence, with an incidence of ca. 0.1% of all pregnancies, with the most common tumours being breast, cervical, thyroid, leukemia, lymphoma, and ovarian cancer (38). Therefore, the existence of the two entities CD and PNET at the same time remains intriguing. PNET during pregnancy was reported only once in two female patients in their second trimester of pregnancy. Both successfully underwent surgical resection of the pancreatic tumour without any damage to the foetus (39). Histological examination of antral biopsies of the present case revealed diffuse hyperplasia of G-cells which might be another explanation for increased serum gastrin which we observed in our patient. It has become apparent that rat (ECL) cells, in response to hypergastrinaemia, exhibit hypertrophy within days, hyperplasia within weeks and carcinoids after months through a sequence of diffuse linear micronodular hyperplasia to ECL carcinoids (40). Therefore, there is a possible causative connection between hypergastrinaemia and ECL cell carcinogenesis. The question of whether the simultaneous occurrence of a rare tumor such as PNET in our patient, who also suffered from a relatively common disease such as CD, is an accidental coincidence or a pathophysiological principle cannot be definitely answered. However, since a strict gluten-free diet seems to be the only preventive strategy to avoid carcinogenesis, it might be possible that neuroendocrine malignancies in patients with CD are possibly the result of neglected 'latent' disease. Therefore, systematic analysis of neuroendocrine cancer incidence in large cohorts of patients with CD compared to that recently performed would be a preferable approach (41).

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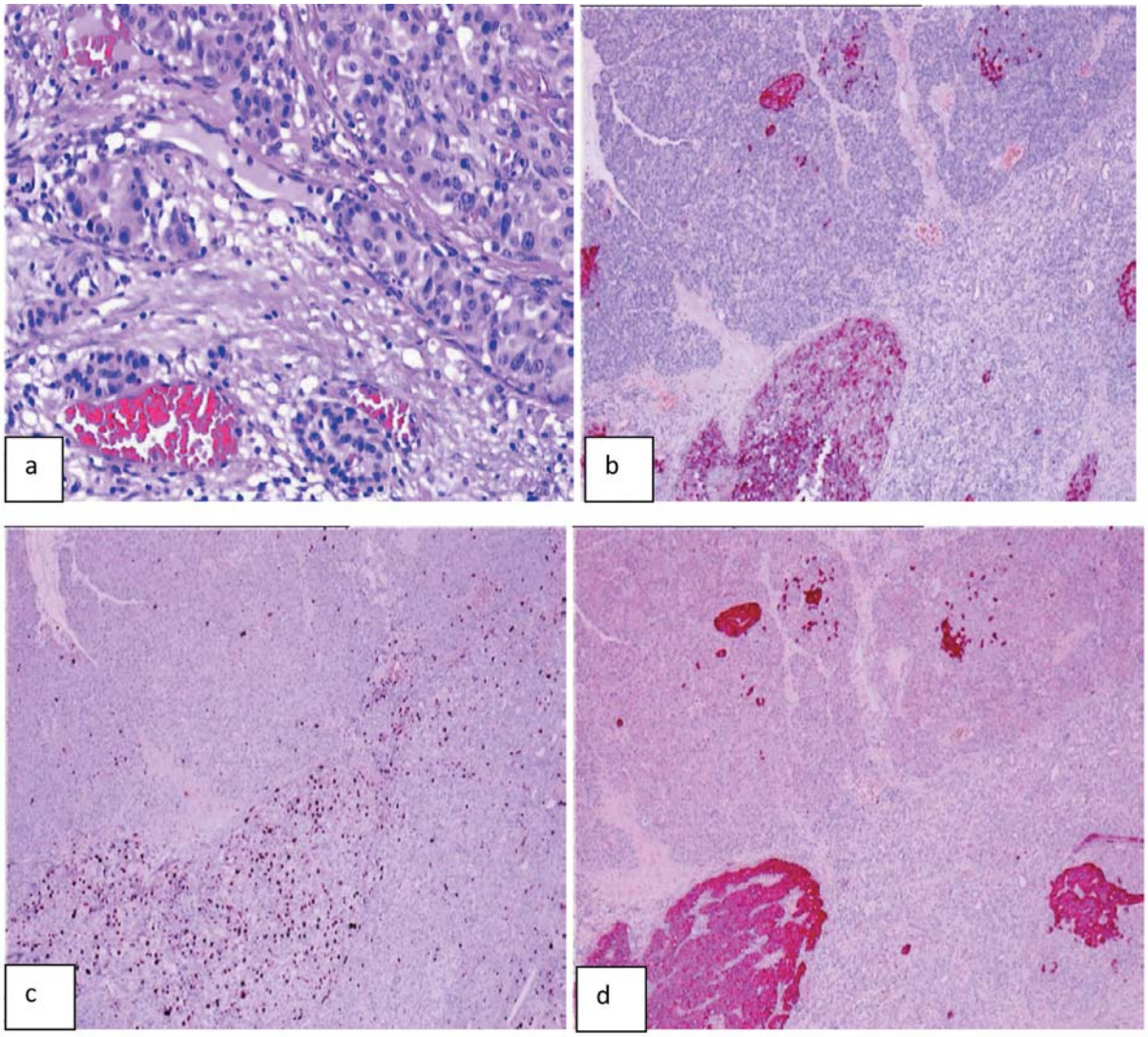

Figure 4. *Well-differentiated non-functioning pancreatic neuroendocrine carcinoma (G2) with angioinvasion (a, Haematoxilin/eosin strain, magnification ×20) and incorporation of pancreatic tissue showing chromogranin-A (b, magnification ×5) and synaptophysin (c, magnification ×5) positivity in tumor cells. d, immunostaining positive for Ki67 [12% (magnification ×5).*

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Received December 3, 2013
Revised February 3, 2014
Accepted February 4, 2014