

Fulminant ectopic Cushing syndrome in a patient with metastatic neuroendocrine carcinoma and Crohn's disease

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Abstract

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have been rarely reported in patients with Crohn's disease, being usually small and incidentally detected in areas uninvolved by the inflammatory process. We describe the case of a young female patient with Crohn's disease and a fulminant Cushing's syndrome induced by the ectopic secretion of adrenocorticotrophic hormone (ACTH) by an aggressive gastrointestinal neuroendocrine carcinoma (NEC). Despite a multi-therapeutic approach, including the administration of multiple courses of chemotherapy, hypo-cortisolemic agents, somatostatin analogues, as well as the performance of bilateral adrenal vein embolization followed by bilateral adrenalectomy, patient's condition progressively deteriorated and she died nine months after the diagnosis of NEC due to liver failure. The available literature addressing the possible connection between Crohn's disease and NEC is discussed in detail.

INTRODUCTION

Crohn's disease (CD) belongs to the inflammatory bowel diseases group; it may involve any part of the gastrointestinal tract (Kasser *et al.* 2010), most frequently the ileum. CD may develop at any age, most frequently between 15 and 30 years of age. The clinical course of the disease varies from mild to fulminant, with either prolonged remissions or frequent relapses (Freeman 2009). The treatment of CD includes immunosuppressive and immunomodulatory therapies; however, many patients

may require surgical intervention in order to control the disease and its complications (Bouguen & Peyrin-Biroulet 2011).

Gastrointestinal cancer, specifically adenocarcinoma, is a well-known complication of CD, occurring with a higher incidence in these patients than in the general population (Jess *et al.* 2006). Young patient age at diagnosis, long disease duration as well as the involvement of both ileum and colon are risk factors associated with malignancy in CD patients (Ullman & Itzkowitz 2011). Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

have been rarely reported, being usually small and incidentally detected in areas uninvolved by the inflammatory disease during surgical interventions. It is not clear if the development of these tumors is directly related to the previous involvement of the tissue by CD, or just an incidental finding (West *et al.* 2007; Freeman 2003; Greenstein *et al.* 1997; Sciola *et al.* 2009; Kortbeek *et al.* 1992). NETs with aggressive course were rarely reported (Sciola *et al.* 2009; Kortbeek *et al.* 1992).

Herein we describe the case of a young female patient with Crohn's disease: she was diagnosed with a fulminant Cushing's syndrome due to Adrenocorticotropic Hormone (ACTH) ectopically secreted by an aggressive and rapidly progressing gastrointestinal NET, arising in the area of ileum, already affected by active Crohn's disease. To our knowledge this is the first reported case of a hormonally active NET in a patient with Crohn's disease.

CASE REPORT

A 26-year-old female patient was admitted to a medical facility due to fever and abdominal pain. Ten years previously she was diagnosed with Crohn's disease involving distal ileum and perianal area. The patient did not have extra-intestinal manifestations of the disease.

During the years since the diagnosis she was treated with several anti-inflammatory and immunomodulatory drugs, including methotrexate, 6-mercaptopurine, azathioprine, glucocorticoids and infliximab due to active Crohn's disease. Although it was previously considered, the patient did not undergo any surgical intervention.

On admission she had fever. A slight abdominal tenderness without peritoneal inflammation signs was noted upon physical examination. Blood tests were normal except for slight leukocytosis and neutrophilia. An abdominal CT scan without intravenous contrast demonstrated increased thickness of the distal ileum, a 5-cm pelvic mass as well as the presence of a – 30 mm hypodense lesion in the left liver lobe (Figure 1). The patient was treated with antibiotics for suspected abdominal abscesses and discharged after three days.

Two weeks later, the patient was admitted in our hospital due to recurrent abdominal pain, diarrhea, bilateral leg edema, without fever. Her blood pressure was normal. The blood tests showed leukocytosis, hypokalemia of 3 mEq/L, elevated liver transaminases and metabolic alkalosis (Table 1). The potassium remained persistently low despite treatment with intravenous and oral supplements. A repeated CT scan of the abdomen had shown multiple hypodense liver lesions up to 2.5

Tab. 1. Patient's biochemical characteristics at diagnosis and throughout different stages of therapy.

Laboratory marker	At diagnosis Oct 2009	After laparotomy Nov 2009	After embolization of adrenal veins Dec 2009	After chemotherapy Jan 2010	After bilateral adrenalectomy Feb 2010
Cortisol, nmol/L (N 220–690 nmol/L)	2058–4885	1021–1512	2433–3752	1344–5904	218
UFC, nmol/24H (55–248 nmol/24H)	19220	5287	>8592	NA	NA
ACTH, pmol/L (1.1–10.1 pmol/L)	69.5	119–219	177–277	79–94	161–229
CgA ng/mL (N 19.4–98.1 ng/ml)	NA	865	NA	NA	155
Glucose, mg/dL (N 70–100 mg/dL)	68–97	119–219	17–277	144–212	82–124
K, mEq/L (N 3.5–5.1 mEq/L)	2.4	3–4	2.4–3.1	3.6–5	3.8–4.3
ALT, U/L (N 0–45 U/L)	20	23–29	35–38	71–119	35–87
Alk Ph, U/L (N 30–120 U/L)	53	94–114	225–544	669–783	506–852
GGT, U/L (N 0–38 U/L)	NA	365–310	1986–3686	2824–4029	1615–2086
LDH, U/L (N 230–480 U/L)	313	1168–1360	2324–4325	1659–3685	863–1269
Albumin, g/dL (N 3.5–5.2 g/dL)	2.9–3.2	1.6–1.9	2–2.4	2.5–2.9	3.2–3.5
WBC 10 ⁹ /L (N 4.8–10.8 10 ⁹ /L)	6.6–14.1	19.2	11.2	9.9	10.4

cm which did not enhance with intravenous contrast (Figure 2A). The pelvic mass had slightly grown up to 5.5 cm. Treatment with ciprofloxacin, metronidazole and elemental diet was started. After two weeks, as the findings in the liver did not change, a CT-guided biopsy of one of the liver lesions was performed, showing findings compatible with neuroendocrine carcinoma (NEC) with a Ki-67 proliferation index of 60% and positively staining for neuroendocrine markers (chromogranin A and synaptophysin) on immunohistochemistry (Figure 3).

Based on intractable hypokalemia, ectopic Cushing's Syndrome was suspected. Indeed, patient's blood cortisol level was elevated up to 2232 nmol/l (normal range, 138–690 nmol/l), while the urinary free cortisol reached levels of up to 19220 nmol/24 hr (normal range 55–248 nmol/24 hr) (Table 1). The ACTH

level was increased up to 69.5 pmol/l (normal range 1.1–10.1 pmol/l) – about seven times the upper normal limit. The urinary 5-Hydroxyindolacetic acid (5-HIAA) levels were normal.

Ketoconazole, at a dosage of up to 800 mg daily, and metyrapone, up to 3 g daily, have both failed to normalize patient's elevated cortisol levels. The patient did not respond to subcutaneous octreotide up to 500 μ g three times daily. She required high doses of potassium supplements up to 9 g/day. She underwent an exploratory laparotomy, during which the thickened terminal ileum and the pelvic mass were excised. The pathological examination demonstrated a NEC, diffusely infiltrating the terminal ileum and causing intestinal wall perforation. The pelvic mass, initially suspected to represent an area of abscess, was actually found to be the primary NEC. Multiple areas of pleomorphism

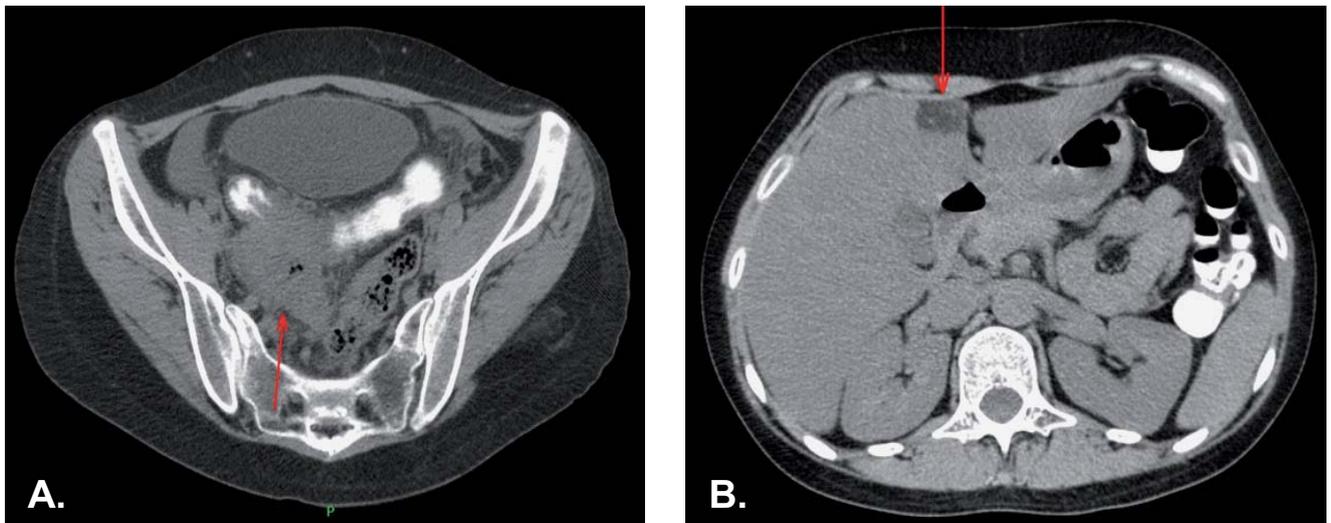


Fig. 1. Non-contrast CT images of the abdomen at diagnosis, showing a 5 cm. pelvic mass (A) and a hypointense finding in the left liver lobe (B).

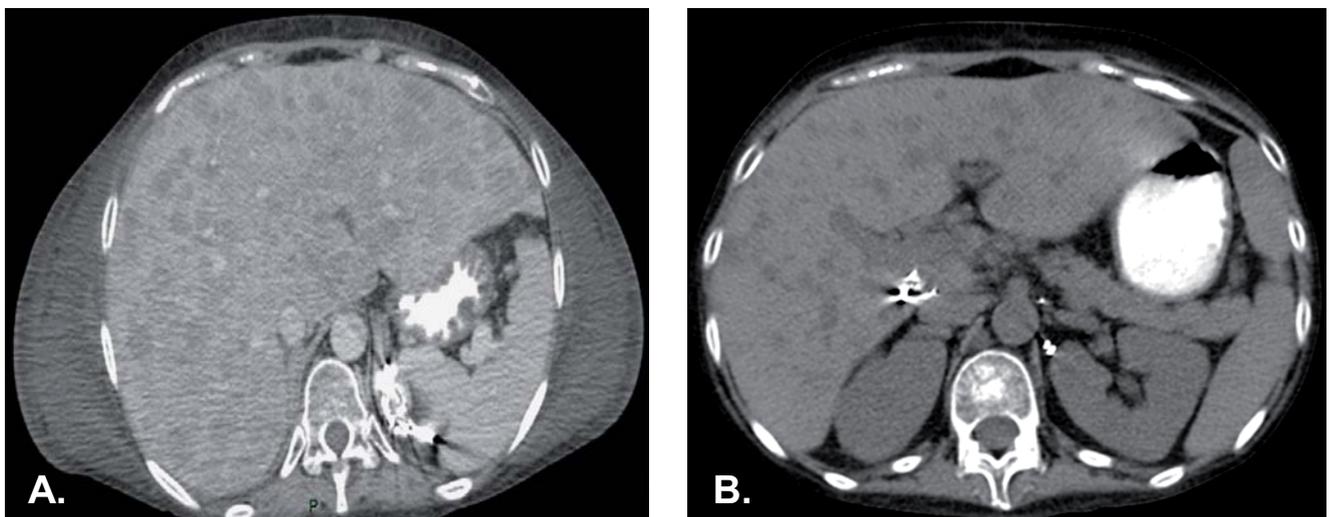


Fig. 2. Contrast enhanced CT images of the abdomen showing hepatomegaly and multiple hypointense lesions in both liver lobes (A), and mild regression of liver lesions following chemotherapy (B).

and necrosis were noted. This time, the Ki-67 proliferation index measured 95% – much higher than in the liver metastasis. Post-operatively, the blood tests have not significantly changed (Table 1), Chromogranin A (CgA) reaching a level of 865 ng/ml (normal range,

19.4–98.1 ng/ml). Following the operation, bilateral adrenal vein embolization was unsuccessfully performed to control the hypercortisolism.

The patient received three courses of chemotherapy including Cisplatin and Etoposide, with a moderate initial regression of liver lesions (Figure 2B). However, the blood and urinary cortisol levels remained extremely elevated (Table 1), in parallel with progressive manifestations of Ectopic Cushing's Syndrome (the appearance of hypertension, diabetes, hyperpigmentation and a rapid 8 kg weight loss). During her hospitalization the patient developed a severe right eye fungal endophthalmitis, which, despite treatment with vitrectomy and voriconazole, produced permanent sight loss. In order to relieve the severe hypercortisolism, the patient underwent laparoscopic bilateral adrenalectomy. On pathological examination, the adrenals were found to be extremely enlarged, with diffuse cortical hyperplasia. Following adrenalectomy, the blood levels of potassium, glucose and cortisol normalized (Table 1).

Despite several additional courses of chemotherapy the patient's condition had progressively deteriorated and she died nine months after the initial diagnosis of NEC due to liver failure.

DISCUSSION

NETs arise from neuroendocrine cells, widely dispersed throughout the body. Gastroenteropancreatic (GEP) NETs comprise a heterogeneous group of neoplasms with distinctive morphologic and biologic features (Kloppel *et al.* 2007). Most of the GEP-NETs are nonfunctioning, whereas some of them, termed functioning, may secrete bioactive substances, producing distinct clinical syndromes (Kaltsas *et al.* 2004). The new 2010 WHO classification introduced a grading system for GEP-NETs, and accordingly, these tumors are now defined as grade 1 or 2 NETs, or grade 3 poorly differentiated neuroendocrine carcinoma (NEC), known also as small-cell or large-cell carcinomas (Rindi 2010).

Although plasma levels of Chromogranin A, the most valuable serum marker of NETs, may be significantly elevated in patients with Crohn's disease compared with healthy population (Sciola *et al.* 2009), GEP-NETs have been seldom described in patients with Crohn's disease. The first case of a rectal NET in a patient with Crohn's disease was reported by Stout in 1942 (Stout 1942). Only 45 additional cases were reported until 2007 (West *et al.* 2007). It was suggested therefore that the medical literature might underestimate their actual incidence (Sciola *et al.* 2009). Most reports included cases of small NETs incidentally found during operations in areas uninvolved by the active CD (West *et al.* 2007; Freeman 2003; Greenstein *et al.* 1997; Sciola *et al.* 2009). In 1998, a series including eight patients with NETs developing in areas involved by CD was reported, most of them being small, well differentiated and clinically indolent tumors (Sigel & Goldblum 1998). Patients with

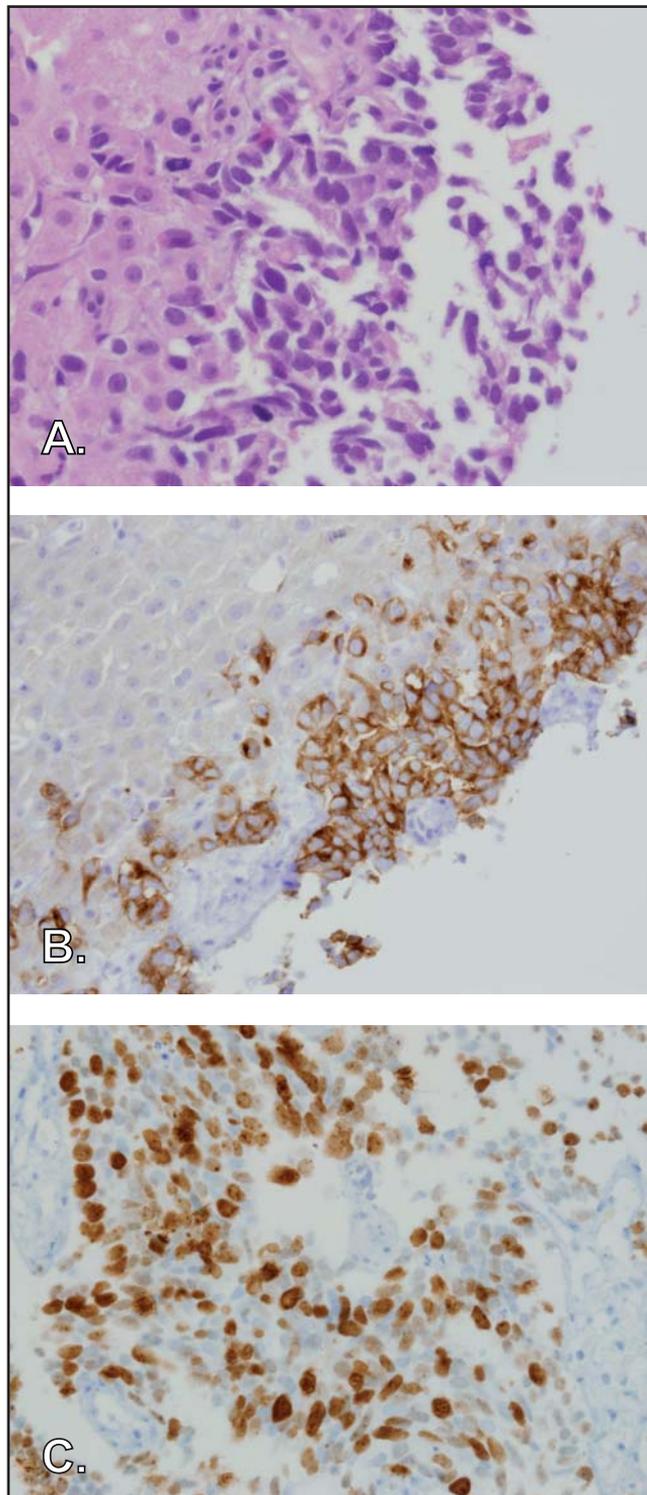


Fig. 3. Histopathological characteristics of the liver metastasis. Typical NET cell appearance (A), positive staining for synaptophysin (B) and a high Ki-67 proliferation index staining (C) were demonstrated.

locally aggressive and metastatic NETs have been rarely reported (Sciola *et al.* 2009; Kortbeek *et al.* 1992; Siegel & Goldblum 1998), the most common locations being the area of terminal ileum and the appendix (West *et al.* 2007), in concordance with the natural occurrence of these tumors in patients without CD (Maggard *et al.* 2004).

Several theories have been proposed to explain the possible connection between CD and NETs: local inflammation which can create a favorable environment for the development of NETs (Maggard *et al.* 2004), elevation in pro-inflammatory and additional cytokines (West *et al.* 2007), as well as hyperplastic and dysplastic changes that may involve neuroendocrine cells (Szabo *et al.* 1999). Systemic immunosuppressive therapy (e.g., methotrexate, 6-mercaptopurine, azathioprine, infliximab, etc.) may be a risk factor for the development of melanoma, lymphoma, nonmelanoma skin cancer and aggressive neuroendocrine tumour of the skin (Merkel cell carcinoma) (Krishna & Kim 2011), however it was not reported in GEP-NETs.

In previously reported cases of patients diagnosed with both NETs and CD, the tumors were nonfunctioning, except for a rare case of carcinoid syndrome (Le Marc'hadour *et al.* 1994). To our knowledge, the present case-report is the first one in which a NEC metastatic to the liver in a patient with CD caused ectopic ACTH secretion (EAS) and the related fulminant Cushing's syndrome. EAS, first described by Liddle almost 50 years ago, is usually caused by small cell lung cancer (Liddle *et al.* 1963); in a recent large series of patients with EAS, most of the cases were caused by NETs, pulmonary NETs being responsible for approximately one half of the diagnosed cases (Ilias *et al.* 2005).

EAS may present with a wide range of clinical features including weight gain or loss, infections, fractures, metabolic, psychiatric and cognitive abnormalities, and nonspecific systemic complaints (Ilias *et al.* 2005). As a result, patients may present to different specialists, and the recognition of the disorder may be delayed. In our patient the presenting features of EAS were persistent hypokalemia, bilateral leg edema, metabolic alkalosis and fever, followed by intractable hypertension, diabetes, weight loss and fungal infection of the right eye. The final diagnosis was tempered by the concomitant existence of Crohn's disease and the suspicion of an abscess in the area of terminal ileum

The optimal treatment of EAS is the surgical removal of ACTH secreting tumor (Ilias *et al.* 2005). In the presence of metastatic disease, this option was not feasible for our patient. Multiple therapeutic approaches, such as the administration of steroidogenesis inhibitors (e.g. ketoconazole and metyrapone), octreotide, etoposide and cisplatin chemotherapy or the attempted embolization of adrenal veins, have proven to be ineffective in the normalization of extremely elevated cortisol levels. The normalization of cortisol levels was finally achieved by bilateral adrenalectomy, which led to

normokalemia, and the relief of both the hypertension and the diabetes. Despite the risk of permanent hypoadrenalism, bilateral adrenalectomy is frequently employed in patients with EAS, in whom other means have failed (Ilias *et al.* 2005). Recently, the combination of the adrenolytic drug mitotane, and the steroidogenic inhibitors metyrapone and ketoconazole have been suggested as an alternative to bilateral adrenalectomy in patients with EAS and severe Cushing's syndrome, but this therapy may be associated with significant toxic effects (Kamenicky *et al.* 2011).

In conclusion, the case herein presented describes for the first time the rare association between a clinically fulminant ectopic Cushing Syndrome induced by a rapidly progressive NEC of the terminal ileum, in a patient with concomitant Crohn's disease. While rare, neuroendocrine tumours should be considered in the differential diagnosis of patients with Crohn's disease and abdominal masses, mostly when they appear in the area of terminal ileum and are not-responsive to the usual anti-inflammatory/anti-infectious therapies. This would also be a consideration when systemic immunosuppressive therapy is administered in young patients with active Crohn's disease, as in our patient.

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