

Fulminant ectopic Cushing's syndrome caused by metastatic small intestine neuroendocrine tumour – a case report and review of the literature

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Abstract

Cushing's syndrome (CS) secondary to adrenocorticotrophic hormone (ACTH) producing tumours is a severe condition with a challenging diagnosis. Ectopic ACTH-secretion often involves neuroendocrine tumours (NET) in the respiratory tract. ACTH-secreting small intestine neuro-endocrine tumours (siNET) are extremely rare entities barely reported in literature.

This review is illustrated by the case of a 75-year old woman with fulminant ectopic CS caused by a ACTH-secreting metastatic siNET. Severe hypokalemia, fluid retention and refractory hypertension were the presenting symptoms. Basal and dynamic laboratory studies were diagnostic for ACTH-dependent CS. Extensive imaging studies of the pituitary and thorax-abdomen areas were normal, while [⁶⁸Ga]Ga-DOTATATE PET-CT revealed increased small intestine uptake in the left iliac fossa. The hypercortisolism was well controlled with somatostatin analogues, after which a debulking resection of the tumour was performed. Pathological investigation confirmed a well-differentiated NET with sporadic ACTH immunostaining and post-operative treatment with somatostatin analogues was continued with favourable disease control. (Acta gastroenterol. belg., 2024, 87, 48-51).

Keywords: Neuroendocrine tumour, Cushing's syndrome, Paraneoplastic, ACTH, Somatostatin receptor.

Introduction

Cushing syndrome (CS) secondary to adrenocorticotrophic hormone (ACTH) production from solid tumours is a rare and often severe condition. Diagnosis and therapy are challenging as this condition mimics the pituitary-dependent form of CS (1-2). Ectopic ACTH secretion is most commonly associated with intrathoracic neuro-endocrine tumours (NET). Gastrointestinal NETs as a source of ectopic ACTH syndrome are extremely rare (1-3).

This review article includes the case of a 75-year-old woman with fulminant ACTH secretion, caused by a metastatic NET of the small intestine. It highlights the diagnostic challenges of the disease and the complexity of its multidisciplinary management.

Case report

A 75-year-old woman was referred to the emergency department with hypokalaemia (1.9 mmol/L), fluid retention and refractory hypertension. She reported a recent history of a post-traumatic osteoporotic lumbar

fracture and decrease of general condition and lucidity. Physical examination showed a moon facies, buffalo hump, friable skin and generalised muscle atrophy. Aside from metabolic alkalosis, secondary to hypokalaemia, blood analysis revealed elevated serum cortisol levels with loss of diurnal variation, no cortisol suppression following 1 mg dexamethasone overnight and elevated urinary free cortisol (UFC: 1125 µg/24h). ACTH levels were not suppressed. Diagnosis of an ACTH-dependent CS was made and complications of hypercortisolism were quickly addressed.

A pituitary MRI showed no evidence of (micro) adenoma, making an ectopic cause of the extreme hypercortisolism likely. This was confirmed with bilateral inferior petrosal sinus sampling (BIPSS), which lacked both a central-peripheral ACTH gradient and ACTH stimulation following corticotropin-releasing hormone (CRH) injection. Chest and abdomen CT did not reveal signs of an underlying malignancy.

Different treatment options were considered and, since adrenolytic therapy with ketoconazole has significant interactions and side effects, it was not recommended in this case. Treatment with somatostatin analogues (SSA) followed by bilateral adrenalectomy was proposed as a definitive solution.

However, since the hypercortisolism responded favourably to octreotide, adrenalectomy was postponed and a [⁶⁸Ga]Ga-DOTATATE PET-CT was scheduled. The images showed an intense expression of somatostatin receptors (SSTRs) in the small intestine in the left iliac fossa, suspicious for primary NET localisation (Figure 1). Furthermore, high SSTR expression in mesenteric deposits and multiple adenopathies were found.

After multidisciplinary discussion in our tertiary centre, a laparoscopic segmental resection of the small intestine and associated lymph nodes was performed to obtain a histological diagnosis and perform debulking of hormone producing tumour cells for better symptom

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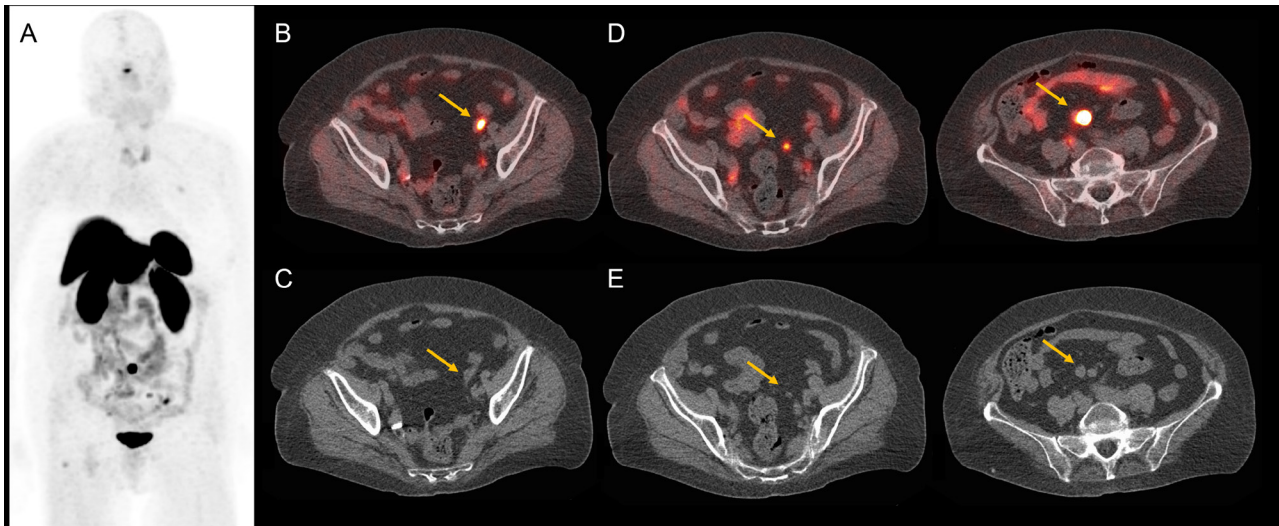


Figure 1. — [^{68}Ga]Ga-DOTATATE PET/CT images. Maximum intensity projection (MIP) image (A) shows multiple sites of focal, strong increased uptake in the abdomen. Transverse sections of the fused PET/CT images (B and D) and the native CT (C and E) show strong focal uptake in the left fossa iliaca, on a small bowel loop (arrow), corresponding to the primary neuroendocrine tumor (B and C) and strong focal uptake in mesenteric lymph nodes (D and E), corresponding to lymph nodes metastases.

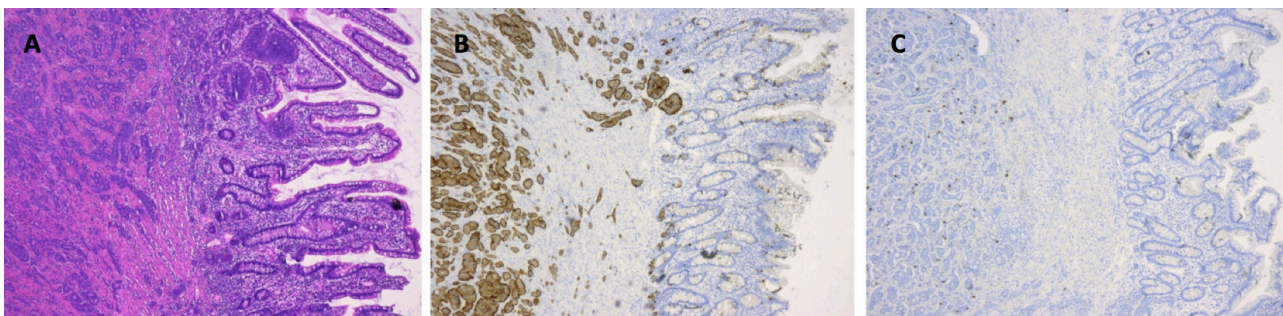


Figure 2. — Histological features of the resected small intestine mass. Hematoxylin and eosin staining showing monotonic cell population and tissue organization (A). Positive immunohistochemical stain for neuroendocrine marker synaptophysin (B) and adrenocorticotropic hormone (C).

control. Pathological examination confirmed a well differentiated NET, positive for both chromogranin A and synaptophysin. A Ki-67 labelling index of 1.5% was consistent with grade 1 disease. ACTH immunostaining was positive in a small subpopulation of the tumour cells, confirming ectopic hormone production (Figure 2). Patient recovery from surgery was uneventful.

Postoperatively, a marked decrease but no normalization of cortisol secretion was obtained, suggesting residual disease for which medical therapy with SSA was resumed.

Follow-up consultation after one month showed a satisfactory clinical and biochemical disease control with significant improvement of the cushingoid appearance, absence of arterial hypertension and normalisation of UFC (18 $\mu\text{g}/24\text{h}$). Six months later the patient was in a good general condition without significant problems. Whole body MRI confirmed stable disease. Therapy was continued unchanged and the patient remains in follow-up.

Discussion

NETs originate from the diffuse neuroendocrine cell system and may occur throughout the body. They have the ability to secrete several substances, which lead to clinical manifestations when in excess. Small intestinal NETs (siNET) are well-differentiated and often characterized by an indolent growth (4,5).

When NETs secrete ACTH, leading to excessive endogenous cortisol production, they provoke ectopic CS, a rare cause of ACTH-dependent CS. This syndrome is estimated to account for up to 18% of ACTH-dependent CS, which in turn, accounts for around 80% of all cases of endogenous CS (1,2,6). Despite their indolent character, severity cannot be underestimated as clinical repercussions are far from benign (1,5,6). The typical clinical Cushingoid presentation includes generalized fatigue and muscle weakness, hyperpigmentation with hirsutism, and the development of central obesity with the characteristic moon facies. This clinical phenotype can be highly variable and atypical (1,6). Complications are

common and potentially life-threatening. There is a high risk of systemic infections, bone fractures, cardiovascular complications and electrolyte disturbances. The presence of severe CS significantly worsens prognosis, even in the absence of tumour progression. A rapid systematic analysis and treatment of the complications is therefore mandatory. Hypokalaemia can be an important clue towards the diagnosis, since it is seen in approximately 70% of patients with ectopic adrenocorticotrophic secretion (EAS) (1,6).

Most NETs responsible for paraneoplastic CS are located in the chest, thymus and pancreas. Other organs with neuroendocrine differentiation such as the small intestine are very rarely diagnosed (1,2,6-8).

If paraneoplastic ACTH secretion is suspected, a comprehensive diagnostic workup is required (1,6). Confirmation of hypercortisolism is obtained by repeat measurement of serum cortisol and ACTH levels, along with a 24h UFC measurement. Severely elevated levels with a loss in circadian rhythm are expected in EAS (1,2). Additionally, dynamic non-invasive endocrine tests such as dexamethasone and CRH suppression tests can be helpful to prove ACTH-dependent CS and differentiate between pituitary and ectopic sources of ACTH (1,2,6). However, the most accurate investigation in differentiating the cause of hypercortisolism is BIPSS with CRH stimulation, with sensitivity and specificity of approximately 95%. Despite being an invasive procedure, it is considered gold standard, especially when first line imaging including pituitary MRI have failed to localise the culprit tumour. When a lack of both a central-peripheral ACTH gradient and a stimulation of ACTH by CRH is seen, a careful search for an ectopic secreting tumour is required (1,2,6).

Further imaging involves high resolution cross-sectional imaging of the cervical-thoracic-abdominal and pelvic regions. When imaging of these areas are negative, special attention should be paid to locations such as the bronchi, small intestine and other rare sites involved in ectopic ACTH secretion (1,3). Conventional imaging often fails to localize the tumour due to their small size. Recent advances in technology made it possible to identify occult NET by introducing functional imaging modalities in clinical practice. The introduction of SSTR PET with e.g. [⁶⁸Ga]Ga-DOTATATE-based imaging which targets the SSTR abundantly expressed in NET, has been proven to be useful in identifying occult well-differentiated primary and metastatic ectopic ACTH-secreting lesions (2,3,6,9).

To establish a definite diagnosis, histological confirmation is mandatory. Histomorphological growth pattern and cytology hint towards a pathological diagnosis, whereas neuroendocrine phenotype is proven by immunohistochemical detection of the markers such as synaptophysin and chromogranin A. To further confirm the diagnosis, additional specific staining for peptide hormones can be applied. Grading of the tumours, based

on the Ki-67 index and mitotic count classifies them grade 1, 2 or 3 lesions (1,4,9).

Treatment of small intestine NET is challenging due to the rarity and heterogeneity of the disease. It requires expertise on treatment of both CS and NET. The aim of treatment is threefold (1,2,4).

Since hypercortisolism can be life-threatening, control of hormonal secretion is the first goal of treatment. Surgical excision of the ACTH-secreting NET is the ideal curative management of CS (1,3,4,6). If surgery is not feasible or postponed, pharmacological treatment to restore eucortisolaemia is often required. A variety of drugs acting at different levels involved in the steroidogenesis are available. An expert endocrinology opinion is required to select the most appropriate agent (1,2). Bilateral adrenalectomy (BLA) is nowadays only advised in very specific cases of unresectable NET, where pharmacological therapy is ineffective or unavailable, given its significant mortality risk (1,3,6). In the case of a very rapid onset of hypercortisolism with severe catabolic symptoms, hormonal control should always be prioritized over diagnostic investigations (1,2).

The second goal is to obtain oncological control. Medical therapy with SSA is standard first-line treatment in functioning SSTR-positive NETs, aiming to provide disease stabilisation. These drugs often provide quick symptomatic relief and show a good long-term tolerability (1,4,6).

In progressive disease, either dose escalation of SSA or an add-on treatment can be considered. Prognostic factors and SSTR imaging will guide further choice of antiproliferative treatment (2,3). Peptide receptor radionuclide therapy (PRRT) can be used as second-line therapy and has shown improvement of symptomatic control, progression-free survival and quality of life (QoL) (4,10). Molecular targeted agents such as everolimus provide another treatment option in progressive disease by inhibiting the mTOR (mammalian target of rapamycin) pathway. It is approved in non-functioning gastro-intestinal NETs, however the use in patients with functioning NETs remains controversial and needs to be defined in further studies (2,4).

The indolent nature of NETs results in a prolonged disease course, entailing the development of loco-regional complications, such as intestinal obstruction and ischemia (4). The final goal of treatment is to reduce the risk of these burdensome complications, by performing resection of the (metastatic) tumour (4,5). It is still controversial whether this strategy translates into additional survival benefit, but if it improves patient QoL, it is sufficiently justified (4,5).

Conclusion

Ectopic CS caused by siNETs is extremely rare and very few cases are reported worldwide. A low threshold of suspicion of this entity is needed amongst physicians,

especially in the setting of hypercortisolism with unclear cause. Early detection of the culprit tumour is crucial as its removal can avoid BLA. Extensive investigations including functional imaging (e.g. SSTR PET) may be needed to reveal occult tumours. The importance of a multidisciplinary and personalized approach cannot be overemphasized.

Informed consent statement

All authors declare no conflicts-of-interest related to this article. Written informed consent was obtained from the patient.

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