

Ectopic ACTH syndrome: a clinical challenge

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Abstract

A patient was managed in our endocrinology unit with ectopic Cushing's syndrome from an adrenocorticotrophic hormone-producing neuroendocrine carcinoma of the anal canal. There was limited response to standard therapy, which made it difficult to correct the electrolyte and metabolic derangements associated with the disease. This is a summary of the challenges encountered during treatment.

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Case history

In June 2009, a 29-year-old woman with a six-month history of human immunodeficiency virus (HIV) infection on highly active antiretroviral therapy (HAART) was referred to our endocrinology unit. She was on efavirenz 600 mg per os nocte and lamzid one tablet per os twice daily. Her presenting complaints were a one-month history of malaise and fatigue, dyspnoea with poor effort tolerance, recent weight gain and darkening of her skin.

Physical examination revealed a normotensive Cushingoid young woman with central obesity and moon facies. She had purple striae over her flanks and thighs. She had facial acne, bruising on her forearms and hyperpigmentation of her extensor surfaces on her upper and lower limbs. Thyroid examination was normal. A significant right inguinal lymph node was palpable, which was fixed and nontender. On rectal examination a worrying ulcer was noted on her anus.

Blood test results showed severe hypokalaemic metabolic alkalosis with serum potassium 2.3 mmol/l (normal 3.3-5.3 mmol/l) and serum bicarbonate 39 mmol/l (normal 18-29 mmol/l). C-reactive protein (CRP) was 4.1 mg/l, white blood cell count $4.4 \times 10^9/l$ (neutrophils 80.8%) and absolute CD4 count $81 \times 10^6/l$. The patient had normochromic macrocytic anaemia and a mean cell volume (MCV) of 110.3 fl (normal 79.1-98.9 fl) with normal serum folate and vitamin B12 levels. The macrocytosis was attributed to the antiretroviral therapy. Random serum cortisol was in excess of 2 069 nmol/l (normal values for adults 07h00-09h00: 120-620 nmol/l; 15h00-17h00: 85-460 nmol/l) with

adrenocorticotrophic hormone (ACTH) significantly increased at 742.0 ng/l (normal < 46 ng/l). Thyroid function tests, serum aldosterone, alpha foetoprotein, luteinising hormone, follicle-stimulating hormone and oestradiol levels were all within normal limits. Early morning fasting plasma glucose levels were repeatedly > 7.0 mmol/l, and a new diagnosis of diabetes was made. Liver function tests, urea and creatinine were also within normal limits. The chest radiograph showed right midzone consolidation but without features suggestive of pulmonary tuberculosis. Initial sputa sent for tuberculosis microscopy (auramine stain) revealed no acid-fast bacilli.

A working diagnosis of ectopic ACTH syndrome (EAS) was suggested and a 24-hour urine collection for urine-free cortisol level was done. The 24-hour urinary cortisol value was 2 691 nmol/24 hours (normal 80-590 nmol/24 hours). Standard overnight low-dose (1 mg) and high-dose (8 mg) dexamethasone suppression tests were subsequently done. The former test had a result of cortisol level > 2 069 nmol/l, and the latter failed to suppress cortisol by 68%, thus supporting the diagnosis of EAS. In the interim the patient received daily intravenous potassium replacement. Her liver function tests were normal, hence ketoconazole was used as an inhibitor for glucocorticoid biosynthesis. The dose of ketoconazole was gradually increased to a dosage of 400 mg per os twice daily. Despite this therapy cortisol levels remained in excess of 2 069 nmol/l.

On the ninth day of hospitalisation a computerised tomography (CT) scan of the chest and abdomen revealed a locally invasive rectal tumour with probable metastasis to the lung (Figure 1). The patient was then prepared

for sigmoidoscopy and tissue biopsy; however, during bowel preparation she bled significantly per rectum, and complained of excruciating pain, hence the procedure was abandoned. The colorectal unit was involved and on day 16 the patient was examined under anaesthesia and a diagnostic biopsy was taken. An obstructive rectal tumour was identified which necessitated the performance of a diverting loop colostomy.

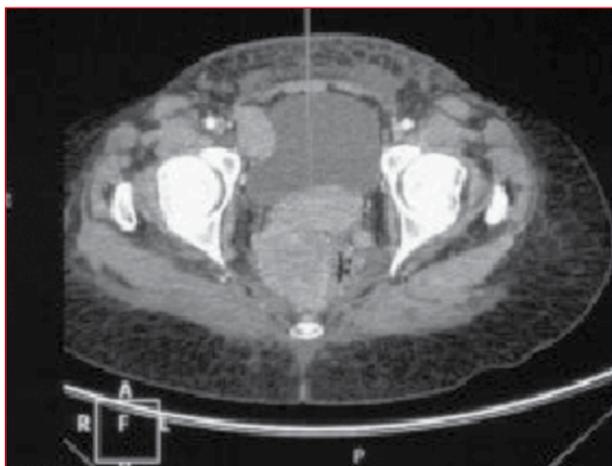


Figure 1: Computerised tomography image of an irregular bulky rectal mass measuring 12.1 × 5.3 cm. There is no plane of separation with the cervix and the distal third of the vagina. There is infiltration of pararectal fat. The bladder is spared.

In addition, CT scans also confirmed the presence of symmetrically enlarged adrenal glands with no focal lesions. This was considered to be consistent with a diagnosis of adrenal hyperplasia secondary to chronic exposure to excess ACTH (Figure 2). Furthermore, chest CT revealed a lung lesion consistent with a neoplastic mass (Figure 3).

Cortisol levels persisted and she remained emotionally labile and hypokalaemic (despite aggressive replacement)

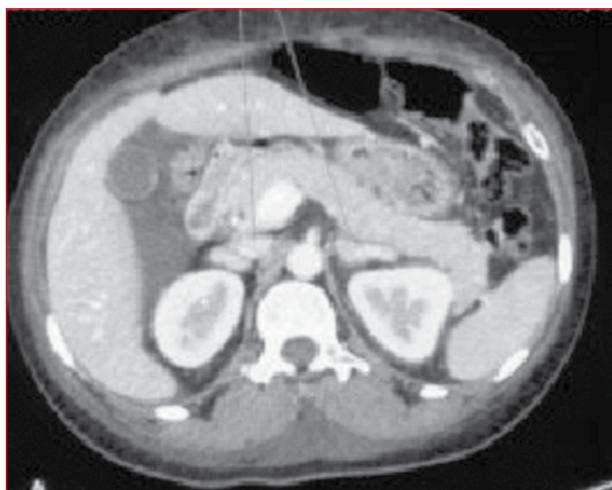


Figure 2: Computerised tomography image of symmetrically enlarged adrenal glands with no focal lesions

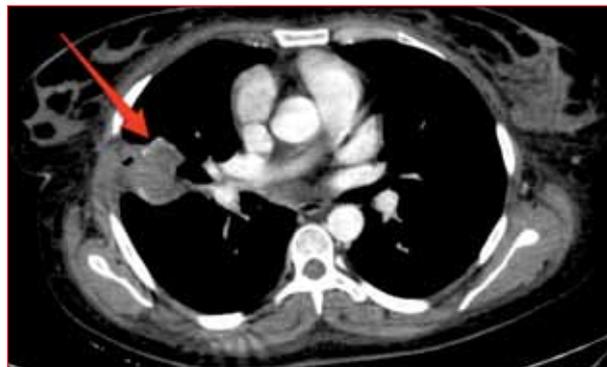


Figure 3: Mediastinal window of the chest revealing an intraparenchymal lesion measuring 4.8 × 5.1 cm (red arrow)

and required relatively high doses of insulin to control her glucose levels. She used 20 IU of Actraphane® twice daily and on average required 24 IU of Actrapid® as top-up over 24 hours as per sliding scale reading.

Histopathological examination of the biopsy from the anus showed ulceration of the squamous epithelium, beneath which there was extensive infiltration of the perianal soft tissue by discohesive nests of small cells with hyperchromatic nuclei having finely stippled chromatin with a salt-and-pepper-like appearance (Figure 4). Small, eosinophilic nucleoli were present. The cells also had a moderate amount of pale staining cytoplasm, and while occasional nuclear moulding was evident, this was not a prominent feature. Occasional mitoses were identified together with focal necrosis.

Immunohistochemistry showed paranuclear, dot-like, positive staining for the pankeratins MNF 116 and AE1/3, together with positive cytoplasmic staining for synaptophysin, chromogranin A and ACTH in the malignant cells (Figure 5). Strong nuclear staining for thyroid transcription factor 1 (TTF-1) was also obtained, and the proliferative index was assessed to be 60-70% using the Ki-67 antibody.

The overall appearance was interpreted to be compatible with that of a poorly differentiated neuroendocrine carcinoma.

Intriguingly, closer examination of the granulation tissue associated with the area of ulceration also showed that many of the endothelial cells contained intranuclear and intracytoplasmic eosinophilic inclusions in keeping with coexistent cytomegalovirus infection, this being confirmed with positive staining on immunohistochemistry.

Despite aggressive supportive and specific therapy, the disease course was complicated by nosocomial sepsis and septic shock, as evidenced by a raised CRP value of 156 mg/l, temperature spikes and hypotension. On day 24 a

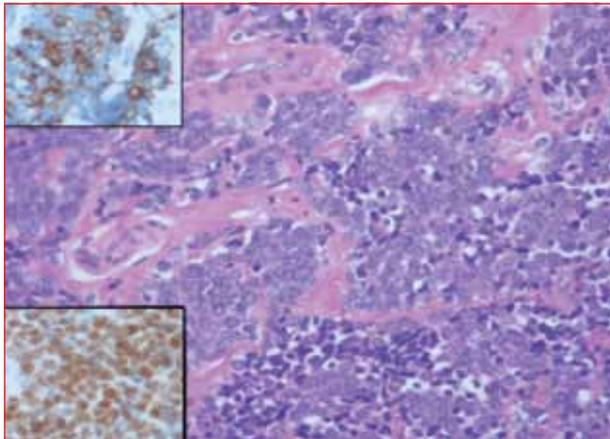


Figure 4: Histology of the anal biopsy reveals extensive infiltration by nests of discohesive small cells with moderate amounts of eosinophilic cytoplasm and small, inconspicuous nucleoli. The insets demonstrate positive immunohistochemical staining for ACTH in the cytoplasm (top) and strong intranuclear immunohistochemical staining for TTF-1 (bottom).

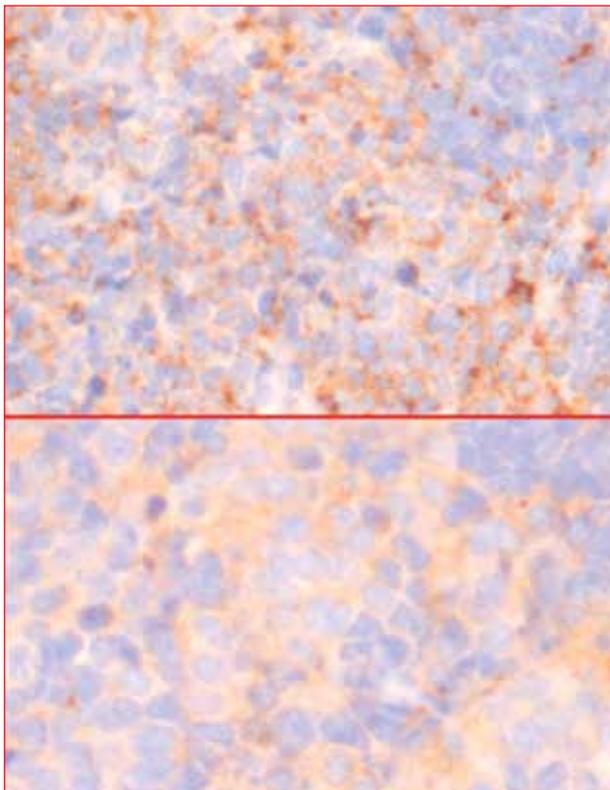


Figure 5: Light microscopic images demonstrating positive neuroendocrine markers. Top: chromogranin A, bottom: synaptophysin.

repeated sputal microscopy for tuberculosis was reported positive for acid-fast bacilli (more than 10/immersion field). Antituberculous therapy was initiated. The patient eventually succumbed on day 28. Her family did not consent to a post mortem examination, hence it was not possible to confirm the nature of the pulmonary lesion histologically.

Discussion

EAS is a rare disease.¹ Approximately 50% of cases are associated with intrathoracic tumours, usually small-cell neuroendocrine carcinomas.² Other well-described tumours of ectopic ACTH production include thymic carcinoid (15%), islet cell tumours (10%), bronchial carcinoid (10%), other carcinoids (5%) and pheochromocytomas (2%).^{2,3}

Diagnosing EAS is often difficult; none of the dynamic biochemical tests achieves 100% accuracy.^{2,4,5} The percentage of tumours not identified despite extensive evaluation is between 12% and 19%.² Imaging is essential for determining the source of ACTH in ectopic ACTH production. CT of the chest, abdomen and pelvis with intravenous injection of contrast medium is the most sensitive imaging modality for the identification of the ectopic ACTH source.⁵

Because of extremely high cortisol levels, patients may experience depression or personality changes, as in our case.^{3,5} Metabolic derangements tend to be more pronounced in EAS.^{2,3} Opportunistic infections caused by *Pneumocystis jirovecii* and mycoses are often the cause of death.³ Medical therapy is often the most practical strategy for managing hypercortisolism caused by EAS; unfortunately, many patients will eventually progress despite medical blockade.^{2,3,6,7}

We are only aware of three other cases in the literature of a similar presentation of ectopic Cushing's syndrome at this unusual site.⁷⁻⁹

In our patient the histopathological features were interpreted to be compatible with a poorly differentiated neuroendocrine carcinoma (according to the World Health Organization 2010 classification of neuroendocrine tumours) and the possibility of a metastatic origin was considered given the positive staining for TTF-1. Although nuclear TTF-1 is generally considered a specific marker for lung and thyroid neoplasm, it has been reported to be positive in other types of tumour, including colorectal carcinoma,¹⁰ and therefore close clinicopathological correlation is required for interpretation of positivity in cases such as the present one.

While most anorectal cancers are squamous cell carcinomas, they may occasionally exhibit small-cell undifferentiated histological features, as in our patient.⁹ These tumours are highly aggressive with distant metastasis common at presentation.⁹ Whenever a diagnosis of small-cell neuroendocrine carcinoma is made, it is important to exclude metastasis secondary to carcinoid tumour and bronchogenic oat cell carcinoma, which may also resemble "small-cell" anaplastic tumours. Given the lack of histology from the lung lesion, the question of metastatic tumour or

two unrelated (synchronous) tumours cannot be resolved. Nevertheless, the overall clinical features in this case would favour a primary neuroendocrine tumour of the anal canal which had spread to the lung. This is supported by the clinical presentation of anal canal obstruction with inguinal adenopathy, the latter consistent with local lymphatic spread.

There is a marked increase in the incidence of both anal intraepithelial neoplasia (AIN) and invasive anal squamous cell carcinoma in individuals who are HIV infected. It is unclear whether HIV infection itself has a direct effect on the development of anal cancer or whether this is mediated through human papillomavirus (HPV) infection.¹¹ Patients with a longer duration of HIV infection have a substantially higher rate of anal cancer, but in contrast to other AIDS-associated cancers, the use of HAART has not led to a decline in the incidence of anal cancer.¹² Without controlling for receptive anal intercourse and prior HPV infection, it is difficult to discern the true effect of HIV on the incidence of anal cancer. It is possible that HIV infection interacts with HPV to predispose to anal cancer.^{11,13} Chronic immunosuppression in HIV infection is also associated with a greater risk of progression from low-grade AIN to high-grade AIN or invasive cancer.¹⁴

Conclusion

This case clearly demonstrates all the challenges confronting the clinician when treating EAS; from investigating, diagnosing and treating the disease. A multidisciplinary management strategy involving endocrinologists, oncologists, surgeons, pathologists and psychologists needs to be employed when treating patients with this disease. Despite the aggressive treatment given (which the disease demands) often patients eventually succumb to opportunistic infections, as in our case.

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