An Unusual Cause of Severe Immunosuppression

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Abstract

Ectopic adrenocorticotrophic hormone secretion (EAS) is a rare cause of endogenous Cushing's syndrome and is associated with immunosuppression and opportunistic infections. We report the case of a person who presented with rapid onset of hypertension, diabetes mellitus, and severe hypokalemia in the context of significantly elevated adrenocorticotrophic hormone (ACTH) levels and marked hypercortisolism. Subsequent investigations led to a diagnosis of EAS without an identifiable source. Her clinical status continued to deteriorate despite medical management of her hypercortisolemia, thus an urgent bilateral adrenalectomy was performed. This patient's course was complicated by multiple opportunistic infections with cytomegalovirus, *Pneumocystis jirovecii* (PJP), *Mycobacterium tuberculosis* and possibly BK virus. To the best of our knowledge, this is the first description of this specific constellation of opportunistic infections in the setting of EAS. Our case highlights the need to consider multiple and rare opportunistic infections while managing EAS and supports early bilateral adrenalectomy in critically ill patients with EAS of unknown origin.

Résumé

La sécrétion ectopique de l'hormone adrénocorticotrope (SEA) est une cause rare du syndrome de Cushing endogène et est associée à un déficit immunitaire et à des infections opportunistes. Nous rapportons ici le cas d'une femme qui a présenté un début rapide d'hypertension, de diabète sucré et d'une sévère hypokaliémie dans un contexte de niveaux considérablement élevés de l'hormone adrénocorticotrope (ACTH) et un hypercortisolisme prononcé. Des investigations complémentaires ont mené à un diagnostic de SEA sans détermination de l'origine de celle-ci. Puisque la condition clinique de la patiente continuait de se détériorer malgré la prise en charge médicale de l'hypercortisolémie, une surrénalectomie bilatérale a été réalisée en urgence. Le traitement de cette patiente a été compliqué par de nombreuses infections opportunistes dues au cytomégalovirus, au *Pneumocystis jirovecii*, au *Mycobacterium tuberculosis* et peut-être également au virus BK. À notre connaissance, ce cas constitue la première description de cette constellation particulière d'infections opportunistes dans un contexte de SEA. Le cas rapporté souligne la nécessité d'envisager la présence d'infections opportunistes multiples et rares lors de la prise en charge d'une SEA et vient à l'appui de la réalisation d'une surrénalectomie bilatérale rapide chez les patients gravement malades en raison d'une SEA d'origine inconnue.

Case

A 74-year-old female woman presented to a community hospital with a one-month history of progressive fatigue, weight loss, and muscle weakness. She was diagnosed with hypertension, diabetes mellitus, and severe hypokalemia. Physical examination demonstrated severe proximal muscle weakness and cachexia. Classic cushingoid features were absent, but investigations revealed markedly elevated levels of adrenocorticotrophic hormone (ACTH) and 24-hour urinary free cortisol (Table 1). Cortisol levels did not suppress with high dose dexamethasone (8 mg). A magnetic resonance imaging (MRI) head with gadolinium did not exhibit any sellar lesions. Given a negative dexamethasone suppression test, no pituitary lesion on MRI, and the rapidity of disease progression, a diagnosis of ectopic ACTH syndrome was made. Corticotropin-releasing hormone (CRH) testing was unavailable and thus could not be performed. Given the evidence pointing towards EAS over a pituitary source of ACTH, the risk of inferior petrosal vein sampling was felt to outweigh the benefits.

Computerized tomography (CT) of the chest, abdomen, and pelvis demonstrated bilateral adrenal enlargement.

An octreotide scintigraphy with single-photon emission (SPE)-CT (with imaging at 24 and 48 hours) showed increased uptake in the left adrenal gland without evidence of lesions elsewhere, suggesting a possible adrenal source of ectopic ACTH production. The patient was started on insulin for diabetes and spironolactone, as well as potassium replacement for hypertension and hypokalemia. She was discharged home from the community hospital with a referral to an endocrinologist at our centre.

Within days following discharge, the patient presented to our tertiary care hospital with confusion, productive cough, and dyspnea. She was treated for pneumonia with levofloxacin. On the fourth day of admission, she was intubated for decreased level of consciousness. Her clinical status continued to deteriorate despite management with ketoconazole and octreotide for hypercortisolemia. She also developed a gastrointestinal (GI) bleed with a hemoglobin nadir of 56 g/L. Endoscopy revealed diffuse gastritis with duodenal ulceration and biopsy showed cytomegalovirus (CMV) duodenitis (Figure 1). Her plasma CMV PCR was 1,705,000 IU/mL (Figure 1) and HIV serology was negative. Ganciclovir was initiated, along with trimethoprim-sulfamethoxazole (TMP-SMX) for PJP prophylaxis.

Table 1. Initial Laboratory Data

Laboratory	Value (normal range) references: g
24-hr urinary-free cortisol	5871 nmol/d (30–300 nmol/d)
Random ACTH	52.4 pmol/L (<10.3 pmol/L)
High dose (8 mg) overnight dexamethasone suppression test	2279 nmol/L → 2549 nmol/L No suppression

Panel A: Numerous CMV inclusions were evident in epithelial (arrows) and endothelial cells of the inflamed edematous and hemorrhagic duodenal mucosa. **Panel B:** Crypt epithelial cell with CMV nuclear inclusion (arrow). **Panel C:** CMV immunohistochemistry highlights nuclear inclusions.

Figure 1. Duodenal Biopsy Specimen

Adrenal vein sampling was performed, given the increased uptake demonstrated on the octreotide scan. This failed to demonstrate an ACTH gradient, ruling out the left adrenal gland as the ACTH source. Catheter position during the sampling was verified with corresponding adrenal vs. peripheral cortisol levels (approximately six-fold higher in the adrenal veins). Given the patient’s rapid life-threatening deterioration and no identifiable source of ACTH production, urgent bilateral adrenalectomy was performed. Pathology revealed bilateral adrenal hyperplasia.

Post-operatively, the patient’s hypokalemia resolved, anti-hypertensives were discontinued, and insulin was weaned. The patient was started on a steroid replacement regiment of hydrocortisone 50 mg IV every 8 hours, eventually weaning to 20 mg IV every 12 hours.

Unfortunately, her respiratory status and chest radiography worsened. Bronchial alveolar lavage (BAL) demonstrated PJP despite TMP-SMX prophylaxis. Accordingly, the patient was switched to treatment doses of trimethoprim-sulfamethoxazole (TMP-SMX). Three weeks later, her bronchoalveolar lavage (BAL) cultures grew *Mycobacterium tuberculosis*. Quadruple anti-tuberculosis therapy was initiated. She also developed hemorrhagic cystitis, possibly secondary to BK virus, as urine cytology revealed atypical urothelial cells with viral cytopathic changes.

The patient was extubated after two months of mechanical ventilation. Her steroid regimen at the time of discharge was prednisone 10 mg daily and fludrocortisone 0.1 mg daily. After extensive rehabilitation for critical illness polyneuropathy and myopathy resulting from the extended ICU stay, she returned home.

Post-discharge, she was followed for ongoing outpatient surveillance and work up for a possible ACTH source. Calcitonin was 7 ng/L (normal < 7 ng/L) and no discrete thyroid nodule was seen on ultrasound. Repeat imaging was done approximately nine months after her initial scans. A CT

thorax showed new pulmonary nodules and necrotic right cervical and supraclavicular lymph nodes. The Octreoscan showed uptake in the right supraclavicular lymph nodes. Biopsy of the supraclavicular lymph nodes was nondiagnostic. Subsequent biopsy of a pulmonary nodule showed necrotizing granulomatous inflammation, but was negative for neoplasia, mycobacteria, and fungal organisms. Bronchoscopy was negative for malignant cells, Mycobacteria, PJP, HSV, CMV, respiratory virus PCR, or pathogenic bacteria. Her steroid regimen has been titrated to prednisone 5 mg daily by mouth and fludrocortisone 0.2 mg daily by mouth.

Discussion

EAS is a relatively uncommon condition accounting for approximately 10% of endogenous Cushing’s syndrome cases.¹ Compared with other causes of Cushing’s syndrome, EAS is associated with a higher magnitude of hypercortisolemia and, therefore, potentially life-threatening complications.^{2,3}

Additionally, in our case, the patient’s lack of classic cushingoid features at initial presentation, despite extremely high cortisol levels, suggests a rapid onset of disease. As such, prompt recognition and investigation of EAS is vital and should be considered in patients presenting with muscle weakness, new onset hypertension, diabetes, or hypokalemia. A diagnosis of EAS warrants investigation into the source of ACTH. Yet, despite an exhaustive search, the source may not be found in up to 12% of cases.¹

Individuals with EAS are at risk for more severe immunosuppression than other causes of Cushing’s syndrome, likely related to the higher degree of hypercortisolemia.^{2,3} Among patients presenting with manifestations of such severe immunosuppression as opportunistic infections, in the absence of known malignancy, immunosuppressive medications, inflammatory disorders, or HIV, endogenous hypercortisolemia is important to consider in the differential diagnosis.²⁻³ Timely identification and control of hypercortisolemia are

Table 2. Infectious Complications Encountered

Complications	Investigations	Treatment
Upper GI bleed	OGD: diffuse gastritis and duodenal ulceration Pathology: CMV duodenitis CMV PCR: 1,705,000 IU/ml	Blood transfusions PRN Gancyclovir → Valgancyclovir
Respiratory failure	BAL: PJP pneumonia HIV testing negative	TMP-SMX treatment doses initiated
Difficulty weaning off ventilator	BAL (3 weeks incubation): <i>Mycobacterium tuberculosis</i>	Quadruple therapy initiated (rifampicin, isoniazid, pyrazinamide and ethambutol)
Hemorrhagic cystitis	Urine cytology: atypical urothelial cells with viral cytopathic changes: ? BK virus	No treatment

central to the successful prevention and management of EAS complications.⁴ As our case demonstrates, when the source of ACTH cannot be localized, bilateral adrenalectomy may be necessary and life-saving in critically ill patients.⁴

In several small case series, the most common opportunistic pathogens identified in patients with endogenous Cushing's were *Aspergillus fumigatus*, *Pneumocystis jirovecii*, *Cryptococcus neoformans*, and *Nocardia* sp.^{5,6} CMV infection is rarely a complication of endogenous Cushing's syndrome, with only three previously published cases.⁷⁻⁹ In most instances, patients developed a single or perhaps two simultaneous opportunistic infections.^{5,6}

Two previously published cases describe multiple opportunistic infections in conjunction with EAS. Sieber and colleagues described a man who developed CMV pneumonia, *Pneumocystis jirovecii* pneumonia and disseminated aspergillosis due to an ectopic ACTH-producing oat cell lung carcinoma.⁷ An additional case of EAS was complicated by simultaneous infections with *Pneumocystis jirovecii*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus fumigatus*, and *herpes simplex*.⁶

Our case uniquely demonstrates simultaneous infections with CMV, *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, and possibly BK virus. This specific constellation of opportunistic infections in the setting of EAS has not, to the best of our knowledge, been previously reported. Additionally, it is the first report of EAS resulting in CMV gastritis and duodenal ulceration manifesting as an upper gastrointestinal bleed. It is also the first report of possible BK virus hemorrhagic cystitis as a complication of EAS in the literature. It therefore highlights the extent of immunosuppression that may result from EAS and the need to maintain a high index of suspicion for multiple, uncommon, opportunistic co-infections in such cases. Furthermore, our case supports early bilateral adrenalectomy as a potentially life-saving treatment in severely ill patients with EAS of unknown origin.

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