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Managing Severe and Complicated Cushing's syndrome: Etomidate and Bilateral Adrenalectomy Can be Life-Saving

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Abstract

Cushing's syndrome is a rare but potentially life-threatening disease. We present a case of severe Cushing's syndrome of unknown origin, who suffered and survived most of the known acute complications associated with hypercortisolaemia. We emphasize the importance of etomidate use in such emergency situations and the value and role of bilateral adrenalectomy, when rapid restoration of the euadrenal state is paramount, especially when ectopic ACTH is suspected and the source is unclear or impossible to resect. The importance of multidisciplinary endocrine care and the necessary laboratory facilities when dealing with highly complex cases is highlighted.

Keywords: Cushing's syndrome • Etomidate • Bilateral adrenalectomy

Introduction

Cushing's Syndrome (CS) is a rare but potentially life-threatening disease [1]. The significant morbidity and mortality arise mainly from severe systemic infections and cardiovascular complications, but a variety of medical emergencies can develop, the management of which can be extremely difficult in the face of hypercortisolemia [2]. Prompt restoration of eucortisolaemia is of paramount importance [3]. We present a case of severe CS of unknown origin, who survived most of the known acute complications associated with hypercortisolaemia, in an unfavorable clinical setting. Sporadic availability of basic endocrine assays and institutional unfamiliarity with specialized endocrine therapies and the concept of multidisciplinary working, made management particularly difficult. The role of etomidate and the value of bilateral adrenalectomy, when urgent restoration and maintenance of the euadrenal state is needed, are highlighted, especially when ectopic ACTH is suspected and the source is unclear or impossible to resect.

Case Presentation

A 61-year-old male with ACTH-dependent CS of unknown origin, complicated by acute respiratory distress syndrome, was transferred from a public tertiary hospital to the Intensive Care Unit (ICU) of a private hospital for spinal cord decompression and bilateral adrenalectomy. The transfer decision was based on the patient's family's choice. Three weeks earlier, he had presented to the public hospital's emergency room complaining of acute back pain, proximal myopathy and bilateral lower limb oedema of a month's duration, recent onset of diabetes mellitus, hypokalaemia and severe hypercortisolaemia with a serum cortisol of 1931 nmol/l (70 mcg/dl) and plasma ACTH of 43 pmol/l (195 pg/ml). Intravenous etomidate had been administered for four days, but was then discontinued, due to a sudden hypoxia and development of bilateral lung infiltrates, requiring intubation and assisted ventilation.

The patient admitted to the private hospital ICU, intubated and ventilated in view of hospital-acquired pneumonia (Table 1). Right pleural percutaneous drainage catheter had been placed in the public hospital due to a significant right pleural effusion shown on his CT scan. He was markedly pigmented, Cushingoid and had bilateral paraparesis of his lower limbs. His past medical history was positive for percutaneous coronary intervention and coronary artery bypass surgery 18 and 8 years ago, respectively.

Diagnostic presentation

Upon admission on day 1, the patient had severe hypokalaemia and anaemia and a random serum cortisol of 428 nmol/l (15.5 mcg/dl). CT scans revealed bilateral lung infiltrates, pleural effusions consistent with empyemas, a T8 compression fracture causing spinal cord compression, a likely epidural abscess at the T8, a 15 mm pancreatic body lesion and bilateral adrenal hyperplasia. A 3-phase CT scan (Neuroendocrine Tumor (NET) protocol) of thorax, abdomen and pelvis, on day 3 showed a 12 mm pancreatic body lesion with features suggestive of a NET, but an octreoscan performed on day 4 showed no abnormal uptake. Thyroid ultrasound (to pursue the possibility of medullary thyroid cancer) on day 7 was negative. A pituitary MRI on the same day revealed a 3 mm lesion suggestive of an adenoma. On day 14, a fine needle aspiration of the pancreatic lesion *via* endoscopic ultrasound was performed. Samples sent to an external laboratory reported cells positive for NET markers (chromogranin, synaptophysin, INSM1, somatostatin receptors SSTR2A and 5), but negative for ACTH. Dynamic endocrine tests were impossible due to the critical illness [4]. From day 2 to day 14 his cortisol levels ranged between 96.5 and 411 nmol/l (3.5-14.9 mcg/dl) but ACTH remained high (Figure 1). On day 15, his serum cortisol rose to 519 nmol/l (18.8 mcg/dl), ACTH reached 62.3 pmol/l (283 pg/ml), then on day 18, the serum cortisol dropped to 105 nmol/l (3.8 mcg/dl). On day 21, while septic, the serum cortisol was 1021 nmol/l (37 mcg/dl), while on day 22, cortisol increased further to 1206 nmol/l (43.7 mcg/dl) and ACTH to 79 pmol/l (357 pg/ml).

Treatment

Intravenous antimicrobial and supportive treatments were commenced on day 1 (Table 1). On day 2, drainage and decortication of the right lung, T8 spondylectomy, spinal cord decompression, drainage of the epidural abscess, and fusion and fixation of T7 through T9, were performed. Over the following week, his condition deteriorated requiring further drainage and decortication of his left lung. On day 14 he had a tracheostomy. On day 23, metyrapone was started. Ketoconazole was unavailable but also relatively contraindicated due to hepatic dysfunction. On day 27, the patient developed atrial fibrillation,

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Table 1. Positive cultures from blood and pulmonary secretions for the following microbes during patient's hospitalization and corresponding administered antimicrobial treatment.

Day	Pulmonary Secretions	Blood	Catheters	Therapy
1	*Pneumocystis jirovecii* *Cytomegalovirus*	*Cytomegalovirus*	-	Meropenem, linezolid, colistin, trimethoprim- sulfamethoxazole, caspofungin, ganciclovir and oseltamivir
3	*Acinetobacter baumanni complex*	-	-	Linezolid, colistin, trimethoprim- sulfamethoxazole, caspofungin, ganciclovir, ampicillin/sulbacta m and rifamycin
11	*Klebsiella pneumoniae*	-	-	Ampicillin/sulbacta m, rifamycin, colistin, trimethoprim- sulfamethoxazole, caspofungin, ganciclovir, tigecycline
16	*Klebsiella pneumoniae* *Candida*	-	-	Meropenem, rifamycin, colistin, trimethoprim- sulfamethoxazole, caspofungin, ganciclovir, tygecycline
18	-	*Klebsiella pneumoniae*	*Candida*	Ceftazidime- avibactam, isavuconazole, tigecycline, trimethoprim-ganciclovir, amikacin and fosfomycin
22	-	*Enterobacter clocae*	*Enterobacter clocae*	Ceftazidime- avibactam, isavuconazole, tigecycline, trimethoprim- sulfamethoxazole, ganciclovir, amikacin and fosfomycin
30	*Acinetobacter baumanni complex* *Candida*	-	-	Ceftazidime and avibactam, fosfomycin, trimethoprim- sulfamethoxazole and miconazole
33	*Cytomegalovirus*	-		Ceftazidime and avibactam, fosfomycin, trimethoprim- sulfamethoxazole and miconazole
37	*Acinetobacter baumanni complex Candida*	-	*Candida*	Ceftazidime and avibactam, fosfomycin, trimethoprim- sulfamethoxazole and colistin
45	*Acinetobacter baumanni complex*	-	-	Ceftazidime and avibactam, fosfomycin, trimethoprim- sulfamethoxazole and colistin
50	*Candida*	-	-	Ceftazidime and avibactam, fosfomycin, trimethoprim- sulfamethoxazole and colistin
57	-	-	-	Tigecycline, fosfomycin, trimethoprim- sulfamethoxazole, meropenem and micafungin
62	*Acinetobacter baumanni complex* *Candida*	-	-	Tigecycline, fosfomycin, trimethoprim- sulfamethoxazole, meropenem and micafungin
69	*Cytomegalovirus*	-	-	-
78	*Klebsiella pneumoniae*	-	-	Tigecycline, fosfomycin, trimethoprim- sulfamethoxazole, meropenem and micafungin
82	-	-	-	STOP antimicrobial tx

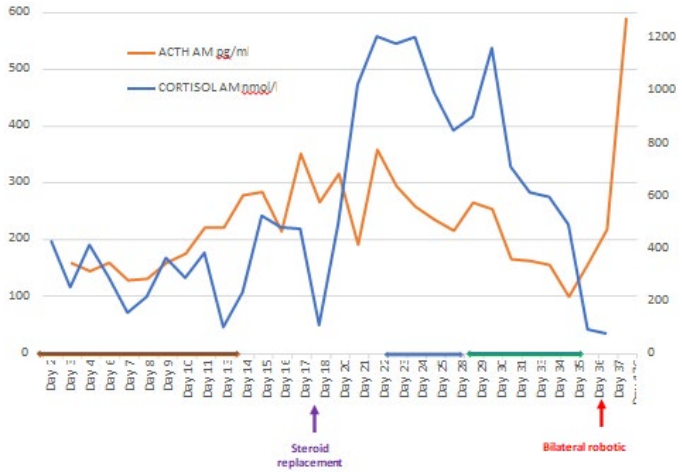

Figure 1. Cortisol and ACTH levels across time. Dates of steroid replacement, metyrapone, etomidate infusion and bilateral adrenalectomy. Brown line: 2-14 Days of steroid replacement (dexamethasone 1- 8 mg), Blue line: 23-29 Days of metyrapone treatment per os (block & replacement), Green line: 29-36 Days of etomidate iv infusion (block and replacement).

thrombocytopenia and on day 28 melena. Gastroscopy revealed duodenal bleeding. Metyrapone was replaced by IV etomidate at 1.8 mg/h. A block and replace strategy was chosen and dexamethasone was selected to avoid cross-reaction with the cortisol immunoassay. His cortisol levels dropped to 72-709 nmol/l (25.7-2.6 mcg/dl) and a small clinical improvement was noted, but the patient needed two transfusions daily, eventually requiring gastroduodenal artery embolization (day 34), which allowed bilateral robotic adrenalectomy under steroid cover to take place on day 37. Histology showed diffuse adrenal hyperplasia.

Outcome and follow-up

The day after adrenalectomy, the patient developed acute hepatitis, a liver hematoma, thrombocytopenia (platelet count = 39,000 mcl) and renal failure, requiring dialysis. On day 62, he was able to breathe unassisted and was transferred to the ward. The tracheostomy was removed on day 91. On day 92, weakly bisphosphonates and daily vitamin D were introduced. All his blood tests returned to normal. He was euadrenal, but had significant myopathy affecting his upper limbs and lower limb paraparesis with severe loss of sensory function below T8. On day 111, the patient was transferred to a rehabilitation center, for four months. Endocrine support was provided by the corresponding author. At five and eight months since admission to the private hospital he was able to move all his limbs and to walk. At this time, his ACTH was 130 pmol/l (588 pg/ml). He was seen in the outpatient clinic a month later. He was significantly pigmented, normotensive, euadrenal, mobile with a walking stick, on hydrocortisone 20 mg am, 5 mg at 4 pm, fludrocortisone 0.1 mg, pitavastatin 4 mg, alendronate 70 mg weekly and vitamin D 2000 IU daily. Imaging, 10 months after admission, revealed a 3 mm cystic pituitary lesion, improvement of the pulmonary infective changes, resolution of the liver hematoma and a persistent 12 mm pancreatic lesion. A full pancreatic NET work-up had been scheduled, but the patient was lost to follow up.

Discussion and Conclusion

The case presented illustrates the complexity of managing CS patients, a disease that often is difficult to diagnose, uncover the underlying cause, and treat [2-4].

Diagnosis of Cushing's syndrome in the critically ill

The diagnosis of CS, especially in a critically ill patient, may be difficult, due to considerable overlap in cortisol and ACTH levels between the physiological stress response and CS [5]. Clinical assessment by an experienced physician is critical, as patients with ectopic ACTH may present predominantly with pigmentation, myopathy, bruising, hypokalaemia and diabetes, without displaying some of the other classical features of CS [6].

Complexity of management of severe Cushing's syndrome

The management was challenging because of several life-threatening

complications of CS: respiratory infection, thoracic empyemas, septicaemia with opportunistic infections, spinal cord compression and paraparesis due to osteoporotic fracture, upper gastrointestinal bleeding, as well as superimposed respiratory and renal failure, arrhythmias and hepatic injury.

Emergency control of hypercortisolaemia

A further challenge in this patient's endocrine care was the medical management of his hypercortisolaemia before the bilateral adrenalectomy. Up until day 14 cortisol levels were relatively low, while ACTH remained high and therefore, medical treatment for CS was withheld up to that point (Figure 1). Interpretation of the pituitary-adrenal axis (HPA) dynamics was difficult [7]. His clinical status was compatible with severe hypercortisolaemia due to ectopic ACTH secretion [6], but his measured cortisol levels were not as high as would be expected, possibly indicating an effect of the severe illness on the HPA axis on a background of a pituitary driven Cushing's Disease (CD) [5]. The reason for this, is unclear but potential contributors include inflammatory cytokines of critical illness, sepsis, anesthetic and anti-infective agents [8]. Regardless of the etiology, cortisol was inappropriately low for the severity of his critical illness and therefore the decision was made to cover with steroids [7]. When hypercortisoleamia re-appeared, its rapid and sustained control was a key and imperative component of management, in the face of severe sepsis [3]. Three main medical treatments are available, metyrapone, etomidate and the antifungal agents ketoconazole and fluconazole [9]. In this case, both etomidate and metyrapone were used (Figure 1). Etomidate is administered parenterally and is particularly useful for rapid control of CS and in patients who are unable to take oral medication [3]. Biochemical monitoring on these drugs is hindered by steroid metabolites which can interfere with cortisol immunoassays; furthermore, in ACTH- dependent CS, plasma ACTH is unhelpful in monitoring treatment.

Prioritisation of treatments

At the time of presentation to the private hospital and subsequently, the complications due to CS were direct threats to life [2]. Surgical interventions had to be prioritized based on clinical appraisal of the balance between threat to life at each stage and fitness to survive the procedure. To tackle the sepsis and cord compression, a decision was made for aggressive surgical treatment. Having survived this surgery, effective and sustained control of hypercortisolaemia became top priority [3]. The cause of CS was unclear. Clinically, the presence of hypokalaemia, myopathy, diabetes and significant pigmentation favor ectopic ACTH syndrome [6]. The pancreatic lesion was considered the probable source. Cushing's disease however, is the commonest cause of ACTH dependent CS, a possible 3 mm pituitary lesion was seen on MRI, and therefore this diagnosis cannot be ruled out [5]. Selective pituitary adenomectomy, pancreatic lesion enucleation, or bilateral adrenalectomy, had to be considered for definitive treatment. Pituitary adenomectomy is the least invasive surgery and a physically compromised patient is expected to tolerate it better. Neurosurgical expertise is crucial for a successful outcome, but even then, eucortisolaemia may not be achieved. A hypophysectomy would have had a higher chance of success, but at the expense of hypopituitarism and if the source of the excess ACTH was ectopic, doomed to be a failure. Small pancreatic NETs can be enucleated successfully, but may not be the source of ACTH and surgery is more invasive, with serious potential complications. A bilateral adrenalectomy has the advantage of achieving a cure rapidly, whatever the ACTH source, and was therefore the surgery of choice [10].

Limitations in evaluation and management

Etomidate use for urgent control of hypercortisoleamia requires frequent cortisol monitoring [3]. When the patient is septic and hypotensive, the challenge is to strike a balance between ensuring adequate glucocorticoid supply for the level of physiological stress, while avoiding glucocorticoid excess that may exacerbate the effects of sepsis. In this case, laboratory limitations posed a significant barrier. Cortisol and ACTH assay runs were batched and measured once weekly and external private laboratories were closed on Sundays and national holidays. This mandated titration of the etomidate dose empirically, at a time when cortisol levels started to rise before several consecutive national holidays. Another source of difficulty related to the absence of multidisciplinary endocrine care and neurosurgical expertise in CS. Instead, a culture of decision making based on the revenue physicians generated for the hospital, meant that the decisions for prioritization of surgical procedures were made by some surgeons, without endocrine consultation. Paradoxically, while cortisol measurements and multidisciplinary discussions were rationed, some procedures (e.g. heamodialysis, robotic adrenalectomy) were readily accessible. Significant questions also arise about how a decision should be made regarding the suitability of transferring patients between public and private care and whether hospitals lacking certain facilities or expertise should receive complex cases. Physicians who are placed in a position of having to manage complicated cases without the necessary facilities and support from a multidisciplinary team, face ethical dilemmas, a significant strain and an unacceptable risk.

Learning Points

- The diagnosis of CS in critical illness is challenging and may need to be made on clinical grounds.
- A random serum cortisol and plasma ACTH may be helpful in confirming the diagnosis of CS and differentiate ACTH-dependent from other causes.
- Etomidate is effective for rapid control of hypercortisolaemia in the critically ill patient, especially if oral intake is inappropriate.
- Bilateral adrenalectomy is effective immediately and can be life-saving in ectopic ACTH if the primary cause cannot be removed

Declarations

None declared

PP has received homoraria from IBSA

Informed Patient Consent for Publication

Signed informed consent obtained from the patient.

Competing Interests

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Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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