Case Report
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A Challenging Case Of A Severe Ectopic Cushing Syndrome Due To Recurrent Thymic Carcinoid Tumour

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Abstract

Introduction:

Cushing syndrome due to thymic carcinoids is rarely seen. Severe Cushing syndrome is an endocrine emergency requiring prompt treatment initiation. Here, we report a case of severe Cushing syndrome due to a thymic neuroendocrine tumour.

Case Description:

A 60-year-old female presented with symptomatic severe hypokalaemia. She didn't have the typical cushingoid appearance, but dark pigmentation was evident over the knuckles and nails. She had severe hypokalaemia (2.2 mmol/L). Further assessment confirmed the diagnosis of ACTH-dependent Cushing syndrome. Ten years back, she underwent surgery for thymic atypical carcinoid tumour followed by chemoradiation. History revealed probable Cushing syndrome during that period, but medical record was not available. Considering this, CECT Chest, Abdomen and Pelvis was arranged, and it showed recurrence of invasive thymic neoplasm. Histology was atypical thymic carcinoid with synaptophysin positivity. Diagnosis of severe ectopic Cushing syndrome was made with cortisol burden of up to 1500 nmol/L with refractory hypokalaemia worsening glycaemic control and high blood pressure. The multidisciplinary team decision was to do urgent bilateral adrenalectomy. She underwent bilateral adrenalectomy after preoperative reduction of cortisol with etomidate infusion. Unfortunately, her post-operative course was complicated with severe COVID pneumonia with secondary bacterial sepsis, and she succumbed to death after 3 weeks of surgery.

Conclusion:

Ectopic Cushing syndrome is well-known to cause severe hypercortisolism with catastrophic complications. Emergency bilateral adrenalectomy is a safe option in this situation, especially when the primary tumour is not identified or can't be resected completely within a short time. Increased risk of infection persists even after cortisol reduction with surgery and appropriate infection control measures and surveillance are of paramount importance.

Keywords: Ectopic Cushing syndrome, Hypokalaemia, Bilateral adrenalectomy

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Introduction

Ectopic Cushing syndrome is a rare but severe condition because of very high cortisol burden and severity of the underlying malignancy. It accounts for 5-10% of all the types of Cushing syndrome [1]. It is an Endocrine emergency requiring rapid diagnosis and prompt management. Though the most common tumours causing ectopic Cushing syndrome are lung malignancies, ectopic Cushing syndrome has been reported with tumours at various sites [2]. Cushing syndrome due to thymic carcinoids are rarely seen. The ideal treatment is complete excision of the culprit tumour, but a multidisciplinary experienced team should make therapeutic decision in non-resectable tumors. In addition to specific management, preventive and treatment measures for the complications associated with severe hypercortisolaemia is of paramount importance. Ectopic Cushing syndrome is always challenging due to several problems related to diagnosis, identifying the tumour source and management. Here, we report a case of severe Cushing syndrome due to a thymic neuroendocrine tumour.

Case Presentation

A 60-year-old female diagnosed with hypertension and type 2 diabetes presented with symptomatic severe hypokalaemia. She had muscle cramps and lower limb weakness worsening over 5 days. She didn't have typical cushingoid appearance, but new onset dark pigmentation was evident over the knuckles and nails. She had severe hypokalaemia (2.2 mmol/L), and it was refractory, requiring very high doses of oral and parenteral potassium chloride and spironolactone. Further assessment confirmed the diagnosis of ACTH-dependent Cushing syndrome [cortisol after overnight dexamethasone suppression test (ODST) 881 nmol/L, ACTH 147 pg/ml]. 10 years back, she had undergone surgery for a thymic atypical carcinoid tumour followed by chemoradiation. History revealed probable Cushing syndrome during that period, but medical records were not available. Considering this, CECT Chest, Abdomen and Pelvis was arranged, and it showed recurrence of invasive thymic neoplasm (See Fig. 1). Ultrasound guided biopsy was performed, and histology was suggestive of atypical thymic carcinoid with ACTH and synaptophysin positivity (See Fig. 1). Diagnosis of severe ectopic Cushing syndrome was made with cortisol burden of up to 1500 nmol/L with refractory hypokalaemia worsening glycaemic control and high blood pressure.

Her glycaemic control and blood pressure worsened, requiring escalation of medications. Infection control measures and thromboembolism prophylaxis were considered. Oral fluconazole was started to reduce cortisol levels but there was no response. Co-trimoxazole was given as Pneumocystis carinii pneumonia prophylaxis. Multidisciplinary team decision was to do urgent bilateral adrenalectomy, considering the severity of Cushing syndrome, and due to impossibility of complete resection of the tumour and the unavailability of medical therapies in the government sector. She underwent bilateral adrenalectomy after preoperative reduction of cortisol with etomidate infusion. Unfortunately, her post-operative course was complicated with severe COVID pneumonia with secondary bacterial sepsis, and she succumbed to death after 3 weeks of surgery.

Discussion

Ectopic Cushing syndrome is challenging to treating medical team due to multiple reasons. The clinical presentation is diverse and non-specific compared to other causes of Cushing syndrome due to characteristics of underlying malignancy and rapid onset severe hypercortisolism. Most patients do not have typical features of Cushing syndrome, such as cushingoid facies, weight gain and wide purple striae. In contrast, they have predominant catabolic signs such as weight loss, severe hypokalaemia and other metabolic complications [3]. Therefore, diagnosis gets delayed in most of the cases. In such circumstances, hypokalaemia may be the clue evoking the diagnosis. In this case also, refractory hypokalaemia was the first clue to considering possible Cushing syndrome. The possibility of Cushing syndrome should be thought of while evaluating patients with unexplained hypokalaemia [4]. The main reason for severe hypokalaemia is ectopic Cushing syndrome is due to relatively higher cortisol burden leading to saturation of the enzyme 11-beta hydroxy steroid dehydrogenase which inactivates cortisol and its mineralocorticoid activity.

In patients with severe Cushing syndrome, the assessment for complications and the etiological evaluation should be done parallelly (See table 1). There should be a checklist to assess for complications and start on prompt management (See table 2).

The diagnostic approach has two main tasks: diagnosing Cushing syndrome biochemically and locating the responsible tumour. In some cases of ACTH-dependent Cushing syndrome, differentiating between pituitary Cushing disease and ectopic Cushing disease is difficult. In our case, in the presence of an overt ectopic tumour, pituitary MRI is not required to exclude Cushing disease [4].

The specific management is surgical excision of the tumour. In many cases, tumours are not completely resectable due to metastasis or severe local extension. In addition, it is difficult to identify the occult underlying malignancies in some other cases. In these circumstances, medical management can be considered to reduce cortisol levels. Most patients with ectopic Cushing syndrome have severe cortisol burden and do not respond to medical therapy.

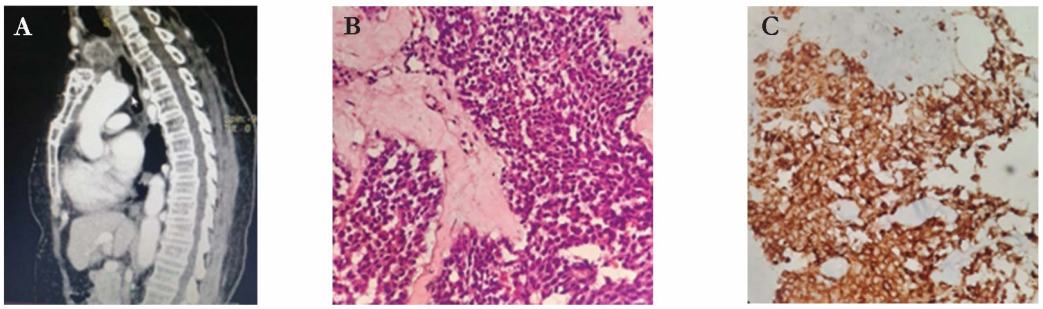

Figure 1: Computed tomography showing thymic tumour with extension to left paratracheal, pre-tracheal level to supraclavicular region **A**; Atypical carcinoid tumour [H & E (10 × 40)] **B**; Strong synaptophysin positivity **C**.

On the other hand, the first line drugs such as ketoconazole and metyrapone are not currently available in Sri Lankan settings. Fluconazole is used as an off-label treatment. Bilateral adrenalectomy is a well reported option of management in these patients with good outcomes [5]. Intravenous etomidate infusion can be used to reduce the cortisol level pre-operatively to reduce peri-operative complications.

The risk of infections and thromboembolism persists for a few weeks even after surgery. Thus, vigilant preventive measures are essential during the post-operative period as well after surgical resection of the tumour or bilateral adrenalectomy [6].

Conclusion

Ectopic Cushing syndrome is well-known to cause severe hypercortisolism with catastrophic complications. The possibility of Cushing syndrome should be kept in mind in patients with unexplained persistent hypokalaemia. Emergency bilateral adrenalectomy is a safe option in this situation, especially when the primary tumour is not identified or can't be resected entirely within a short time. Increased risk of infection persists even after cortisol reduction with surgery and appropriate infection control measures and surveillance are of paramount importance.

Table 1: Diagnostic criteria for severe/catastrophic Cushing syndrome[4]

Clinical criteria
A patient with Cushing syndrome and recent onset of one or more of the following: - Sepsis, opportunistic infection - Intractable hypokalaemia - Uncontrolled hypertension - Heart failure - Gastrointestinal haemorrhage - Glucocorticoid – induced acute psychosis - Progressive debilitating myopathy - Thromboembolism - Uncontrolled hyperglycaemia and ketoacidosis
Biochemical criteria
A patient with Cushing syndrome and at least one of the following conditions - Serum cortisol >1100nmol/L and/or - Severe hypokalaemia (<3mmol/L)

Table 2: Checklist to manage patients with severe Cushing Syndrome [4]

Thromboembolism	Preventive/curative anticoagulation
Hypertension	Antihypertensives
Hyperglycaemia	Oral drugs/insulin
Infection	Appropriate antibiotics
Pneumocystosis	Preventive co-trimoxazole
Hypokalaemia	IV potassium/MR antagonist
Nutrition status	Adequate nutritional support
Steroid Psychosis	Sedatives and lower cortisol levels urgently

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