A Rare Manifestation of a Rare Disease: Ectopic Cushing’s Syndrome Secondary to Olfactory Neuroblastoma

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Abstract

Introduction: Olfactory Neuroblastoma (ONB) is a rare malignant Neuroendocrine tumour. It is rarely reported to cause Ectopic Cushing’s Syndrome (ECS). Here, we report a case of ECS secondary to ONB.

Case Description: A 40-year-old lady presented with right sided focal seizures complicated with status epilepticus. She was diagnosed with Diabetes Mellitus with severe hyperglycaemia three weeks prior to this admission and started on insulin therapy. Investigations revealed severe hypokalaemia. MRI brain showed no focal lesions but there was mucosal thickening in the paranasal sinuses. Other electrolytes and screening for infections were normal. She didn't have obvious clinical features of Cushing syndrome except generalized monomorphic acne, but further assessment confirmed the diagnosis of severe ACTH dependent Cushing syndrome. MRI pituitary was normal. CECT Chest, Abdomen and Pelvis showed only enlarged adrenal glands. PET/CT revealed FDG avid nasal polyp. Histology of nasal polyp revealed olfactory neuroblastoma. Staging imaging with MRI brain with sinuses and orbits confirmed stage C tumour with extension into ethmoid sinuses and part of the brain. She underwent endoscopic resection of the tumour and radiotherapy.

Conclusion: In a case of ECS, we should look beyond the thoracoabdominal region including Sino nasal cavity.

Keywords: Ectopic Cushing’s Syndrome(ECS), Olfactory Neuroblastoma, Hypokalaemia

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Introduction

The Ectopic Cushing’s Syndrome (ECS) accounts for 10-20% of ACTH dependent Cushing syndrome and 5-10% of all the types of Cushing syndrome [1]. In the past, most patients with ECS presented with small cell lung cancer but with advanced current imaging techniques, the spectrum of malignancies causing ECS has been very much widened to include neuroendocrine tumours (NETs), predominantly pulmonary, thymic and pancreatic carcinoids and more rarely medullary thyroid carcinoma, pheochromocytoma and others. ECS results in significantly more morbidity and mortality compared to other causes of Cushing syndrome because of severe hypercortisolism and underlying malignancy. Thus, much effort is needed to identify the source and manage the cortisol burden promptly and aggressively. ECS is always challenging in diagnosis, identifying the tumour origin and management.

Olfactory neuroblastoma (ONB) is a rare malignant sinonasal tumour of neuroectodermal origin with neuroendocrine differentiation. It arises from the nasal epithelium. The common clinical features are local symptoms such as nasal obstruction, pain, discharge, and epistaxis. Rarely, patients with ONB can develop paraneoplastic manifestations such as ECS, SIADH as well as neurological paraneoplastic syndromes [2]. Here we report a case of ECS secondary to olfactory neuroblastoma.
Case Presentation

This previously healthy 40-year-old lady developed generalized body swelling, lethargy, and osmotic symptoms over 1 week duration and got admitted to a tertiary hospital. She was diagnosed with Diabetes Mellitus with severe hyperglycemia and was initiated on premixed insulin. She was noted to have elevated blood pressure as well. Her potassium was 3.4 mmol/L during that admission.

Three weeks later, she presented to our facility with focal seizures with secondary generalization complicated into status epilepticus. During the presentation, she had marked hypokalemic alkalosis (K+ was 1.8 mmol/L) with normal calcium and magnesium levels. There was evidence of focal epileptic activity in EEG. MRI brain didn’t reveal any focal lesions, but it showed mucosal thickening in the bilateral ethmoidal and right maxillary sinuses. Infective screening including the CSF analysis was negative.

Diagnostic assessment

Considering the new onset severe hyperglycemia and hypokalemia, the possibility of Cushing syndrome was considered. On clinical assessment she didn’t have obvious cushingoid features or hyperpigmentation, but she had generalized eruption of monomorphic acne. The diagnosis of ACTH dependent Cushing syndrome was made (ODST 820 nmol/L, LDDST 638 nmol/L, ACTH 38 pg/ml). Cortisol burden was >2000 nmol/L.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Patient Value</th>
<th>Normal value</th>
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<tbody>
<tr>
<td>ODST (nmol/L)</td>
<td>820</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>LDDST (nmol/L)</td>
<td>638</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>38</td>
<td>4.7 – 48.8</td>
</tr>
<tr>
<td>Random 9am cortisol (nmol/L)</td>
<td>&gt;2000</td>
<td>118.6-618</td>
</tr>
<tr>
<td>Pituitary MRI</td>
<td>Normal</td>
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</tbody>
</table>

MRI pituitary was normal. CECT Chest/Abdomen/Pelvis didn’t not show any focal lesions except prominent adrenals bilaterally. As the features were more suggestive of an ectopic Cushing syndrome bilateral IPSS and FDE PET/CT were parallely arranged. There was an FDG avid right nasal polyp (SUV 3.4) arising from the nasal septum measuring 1.6cm × 1.1cm.

Though high doses of parenteral and oral KCL were required initially for the management of severe refractory hypokalemia, within 10 days of admission potassium level became normal without any replacement. She was treated with multiple antiepileptic medications. She was not started on any medical therapy for Cushing syndrome. While she was awaiting IPSS, cortisol burden was reassessed because of the complete normalization of her potassium level and reduction of the severity of hyperglycemia. It revealed much reduced cortisol levels within 2 weeks of admission. So, B/L IPSS was abandoned but she underwent nasal tumor excision and biopsy. Histology revealed Olfactory neuroblastoma, Hyams Grade 11. Immunohistochemistry showed strong cytoplasmic granular positivity for Synaptophysin, ACTH and Chromogranin A (See figure 1).

Table 1: Investigations to diagnose Cushing Syndrome.

![Figure 1: Nasal septum appears to be infiltrated by tumour](image1)

After the histological diagnosis, she underwent MRI of the brain with paranasal sinuses for staging (See Figure 2). It showed a well-defined mass centered in the right olfactory bulb level measuring 2.4cm (AP)×3.0cm (Tr)×2.0cm (CC), breaching the cribriform plate with extension into right ethmoid sinus. Nasal septum was involved. There was bulging of the lesion into the anterior cranial fossa causing mild compression on right gyrus rectus. There was no extension into orbit.

Treatment, Outcome and follow-up

She underwent endoscopic resection of the tumour followed by radiotherapy. Because of the normalization of the cortisol burden even before any

![Figure 2: MRI showing well defined mass in the right olfactory bulb with breach in the cribriform plate](image2)
intervention, the possibility of cyclical nature of the tumour should be considered and continuous surveillance for Cushing syndrome has been planned. She has neurological manifestations requiring antiepileptic drugs. As these drugs can interfere with the screening tests for Cushing syndrome, that should be kept in mind while interpreting the results. She needs continuous multidisciplinary team’s follow up for further treatment and surveillance of complications. During the last visit after radiotherapy, she had normal potassium and blood sugar without any treatment. ODST was suppressed. It was planned for repeat imaging and biochemical assessment in 3 months.

Discussion

ECS is always a challenging diagnosis due to multiple reasons. The clinical presentation is much variable due to the characteristics of underlying malignancy and rapid onset severe of hypercortisolism in many cases when compared to other causes of Cushing syndrome. Significant proportion of patients present with an accelerated course with severe cortisol burden leading to profound hypokalaemia, severe hypertension, severe hyperglycaemia and weight loss with less apparent rounding of face and weight gain. When patients get admitted to non-endocrine units due to tumour related issues or complications due to Cushing syndrome, the diagnosis of ECS gets significantly delayed. In such circumstances, the hypokalaemia is the clue evoking the diagnosis. This patient did not have the characteristic features of Cushing syndrome. Eventually, severe hypokalaemia was the clue towards the diagnosis. When there is unexplained hypokalaemia, possibility of Cushing syndrome also should be considered.

Hypokalaemia is a well-recognized complication in Cushing syndrome. It is not specific but more frequent in ECS. Despite the aetiology of Cushing syndrome, when there is severe hypercortisolism, hypokalaemia can occur. When the cortisol level is very high, 11-beta hydroxysteroid dehydrogenase enzyme which inactivates cortisol is saturated resulting in increased mineralocorticoid effect of excess cortisol leading to increased urinary loss of potassium. So, treatment of hypokalaemia is controlling the cortisol excess combined with mineralocorticoid antagonists and potassium supplementation. Severe hypokalaemia can lead to fatal cardiac arrhythmias. In this case, the presentation was with focal seizures with status epilepticus with concurrent severe hypokalaemia. Unlike other electrolyte abnormalities, hypokalaemia doesn’t usually cause CNS symptoms and seizures has never been reported.

The reason underlying right focal seizures in this patient was thought to be due to either a paraneoplastic manifestation or due to local effect of the tumour compressing the right gyrus rectus part of the brain.

In severe Cushing syndrome, symptomatic evaluation with assessment for complications and etiological evaluation should be done simultaneously as it is an Endocrine emergency. It is fundamental to maintain a checklist to assess for complications to institute prompt management. This patient had severe Cushing syndrome with very high cortisol level and profound hypokalaemia. Complications were assessed and managed accordingly.

Diagnostic approach has two main objectives. First is to diagnose CS and second is to identify and locate the responsible tumour. In ECS, the first objective of diagnosing Cushing syndrome does not pose difficulties because of relatively severe hypercortisolism. Differentiating between Cushing disease and ECS is challenging specially when the ectopic tumours are small and slowly growing. Pituitary MRI is associated with quite number of false positive and false negative results. Non-invasive dynamic tests such as high dose dexamethasone suppression test (HDST), corticotropin-releasing hormone(CRH) stimulation test and vasopressin stimulation test have no consistent discriminatory power in discriminating between the two. When these tests are used together, the diagnostic accuracy increases but up to 25% of patients with EAS may have discordant dynamic test results.

Though BIPSS is the gold standard investigation to distinguish between CD and ECS, it has some limitations specially when the aetiology is more towards the ECS with severe Cushing syndrome because it is an invasive procedure and may not be compatible with the urgency to start treatment and the general condition of the patient. So, initial imaging should be arranged earlier without waiting for confirmatory distinction between CD and ECS. Initial imaging is whole body, thin slice CT scan. If there is an overt tumour found in the CT scan, in a patient with ACTH dependent Cushing syndrome with high probability for ECS, the diagnosis of ECS can be made without performing pituitary MRI, dynamic hormonal tests such as HDST and CRH stimulation test and BIPSS. In conclusion, when suspecting ECS, investigations should be individualised to make quicker diagnosis and start definitive management.

Identifying the source of ECS is another challenging aspect in the management of ECS because of several reasons such as limitations of the availability of advanced imaging modalities, tumours being generally small and since it can occur anywhere in the body. More than half of the tumours can be identified with first line imaging with computed tomography (CT) or magnetic resonance imaging (MRI). So, before going ahead to do second line nuclear imaging, a second read of the scan is important. Among nuclear imaging there is no one ‘best test’. Ga- DOTANA scan offers best sensitivity followed by FDG then octreotide scan and finally I-MIBG. In addition to nuclear imaging, MRI pelvis is offered to identify rare rectal carcinoids and prostate lesions. ON is a rarely reported cause of ECS.

Other important aspect to be discussed is about the spontaneous resolution of Cushing syndrome despite the presence of tumour and without any medical management of hypercortisolism. A small number of patients with Cushing syndrome exhibit periodic and intermittent increase in cortisol levels resulting in recurrent episodes of clinical symptoms.
Such patients are known to have cyclical Cushing syndrome (CCS). Possible mechanisms for cyclicity in ECS are bleeding into the tumour, necrosis, or disrupted hormone synthesis in the neoplastic corticotroph cells. Patients should have exhibited at least three peaks and two valleys in cortisol level to diagnose CCS. But it should be suspected in patients having two conflict results of cortisol levels, opposite results on dexamethasone suppression tests or conflicting clinical manifestations and biochemical results such as hypokalaemia in this patient.

Olfactory neuroblastoma (ONB) is a rare malignant neuroectodermal tumour, comprising about 2% of all sinonasal tract tumours. Patients commonly present with unilateral nasal obstruction, epistaxis, sinusitis, and headache. Rarely, ONB may be associated with endocrinological paraneoplastic syndromes. There are reported cases of ECS, syndrome of inappropriate ADH secretion (SIADH) and hyperprolactinemia. There are more than ten cases of ECS secondary to ONB reported. Some patients had both the local nasal symptoms and the clinical features of Cushing syndrome but few of them had only the features of Cushing syndrome as the index case. Many of them had hypokalaemia. The majority of the patients had good outcome with surgical excision of the tumour followed by radiotherapy. There are reported cases of relapses too.

Conclusion

Ectopic ACTH Secretion can occur from anywhere in the body so rare sites of origin also should be considered specially when the first line imaging with CT scan is negative. Nose and sinuses should not be missed. The possibility of Cushing syndrome should be considered when we evaluate patients with unexplained hypokalaemia. When patients have conflicting results of clinical or biochemical findings or cortisol levels, CCS is a possibility. Thus, those patients need proper surveillance in the future.

Consent: Oral consent was given by the patient for this case report.

Conflicts of interests: The authors have no conflicts of interests to declare.

References


Abbreviations:

ONB: Olfactory neuroblastoma
ECG: Electro Cardiography
ACS: Acute Coronary Syndrome
MRI: Magnetic Resonance Imaging
DM: Diabetes Mellitus
LOC: Loss of consciousness
CD: Cushing Disease
CS: Cushing's Syndrome
ECS: Ectopic Cushing's Syndrome
ODST: Overnight dexamethasone suppression Test
LDDST: Low dose dexamethasone suppression test
HDST: High dose dexamethasone suppression test
ACTH: Adrenocorticotropic hormone
BIPSS: Bilateral Inferior petrosal sinus sampling
AP: Anteroposterior
Tr: Transverse
CC: Craniocaudal
CCS: Cyclical Cushing syndrome