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Case Study

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DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN A RARE CASE FLORID CUSHING'S SYNDROME DUE TO ECTOPIC ACTH SECRETION FROM BRONCHIAL CARCINOID AND EMPTY SELLA: A CASE REPORT

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ABSTRACT

Objective: Ectopic Cushing's syndrome (EAS) is a rare disorder. The incidence of EAS varies from .2- 5 cases per million per year. The Ectopic Adrenocarticotrophic harmone(ACTH) secretion primarily from small cell carcinoma and carcinoid of lung. Chronic hypercortisolism due to EAS causes Cushing's syndrome (CS) with significant morbidity and mortality. Early diagnosis and management of EAS is essential to ameliorate multiple symptoms and complications of CS. The purpose of this case report is to highlight challenges and difficulties in diagnosis and management of EAS. **Case Presentation:** A 72 year presented with progressive weight gain, proximal muscle weakness, shortness in breath on mild exertion and new onset of diabetes and persistent hypokalemia. Clinically she had signs and symptoms of CS. Laboratory tests and radiological imaging was in favor of EAS due to possible bronchial carcinoid. Confirmatory tests and surgery couldn't be done due multiple acute complications and poor general health. On multidisciplinary team consensus decision she was treated with octreitide. She showed excellent sustained response to somatostatin analogue octreitide physically and biochemically. **Conclusion:** This rare case of high lights challenges of diagnosis and management of EAS in elderly lady with multiple acute comorbid conditions hindering full investigations to confirm diagnosis and surgical intervention.

KEYWORDS: Cushing's syndrome, Ectopic ACTH, Bronchial carcinoid, empty sella.

CASE REPORT

A 72 year female presented to Emergency room complaining of progressive shortness of breath and fatigue and weakness and lower limb edema of 2 weeks duration. She was admitted to the hospital with a diagnosis of heart failure. She has history of Bronchial asthma with occasional exacerbations, hypertension and primary hypothyroidism. There was past history of seizure disorder and meningioma which was surgically removed. She gave history of weight gain, facial plethora, and abdominal striae developed over a period of one year. She diagnosed to have diabetes recently and was started on insulin due to severe uncontrolled blood sugars. There was no family history of endocrine diseases. At presentation physical examination revealed a morbidly obese lady with BMI 44 Kg/m^2, BP, facial plethora, dorsocervical subcutaneous fat pad, purple strie on abdomen, pitting edema of legs and proximal muscle weakness.

The results of basal endocrinological tests at base line and on follow-up treatment were summarized in Table no: 1.

Table no 1: Laboratory evaluation at baseline and Follow UP.

	Reference range	At Baseline	8 month after starting octreotide	3 years on octreotide
Cortisol AM (nmol /L)	105-535	2885	190	254
Cortisol random (nmol /L)		6156	278	368
Corticotropin(ACTH) (pg/ml)	7.2 – 63.6	770	114	59
24h urinary free cortisol (ug/24hr)	7-80	1280	-	-
Chromogranin A (ug/L)	<102	194	-	-
Gastrin (pmol/L)	Fasting: <54.4	204.0	-	-
Potassium(mmol/L)	3.5 – 5.1	2.5	3.7	4

Hco3 (mmol /L)	22-29	31	23	23
Hb1c %	4-5.6	9.1	5.8	5.3

MRI brain: Empty Sella (Fig no: 1), CT abdomen: normal, CT chest (Fig no: 2, 3) axial view demonstrating enhancing soft tissue nodule in right pericardial space, sagittal view demonstrating distal bronchial origin of the nodule. Octreotide scan (Fig no: 4, 5 and 6) Showed focal uptake noted in the medial right lower lung measuring 1x2.24 cm, most likely represent functional bronchial carcinoid.

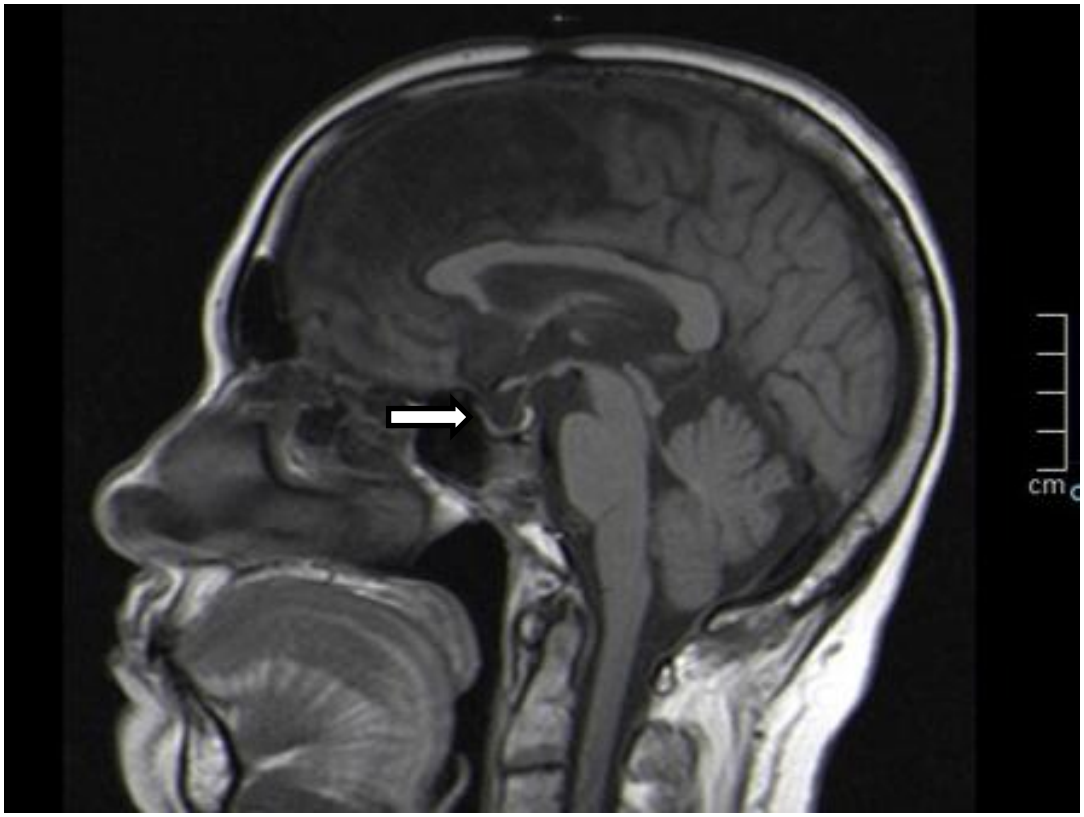


Figure 1: MRI Of The Brain Sagittal View Demonstrating Empty Sella.

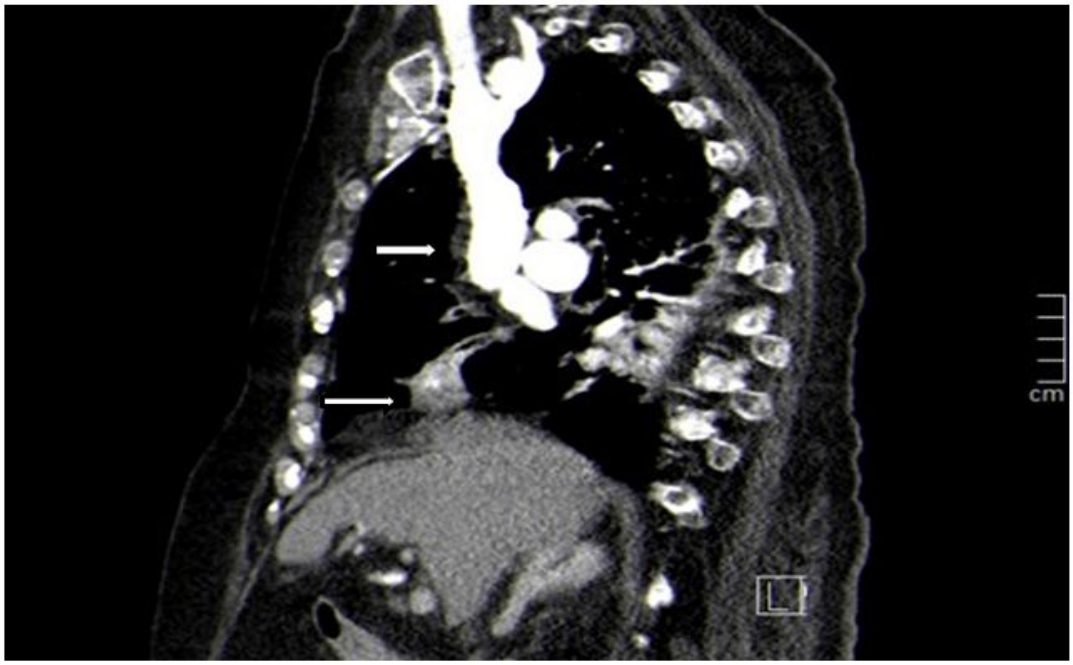


Figure 2: CT Scan Of The Chest Axial View Demonstrating Enhancing Soft Tissue Nodule In Right Pericardial Space.

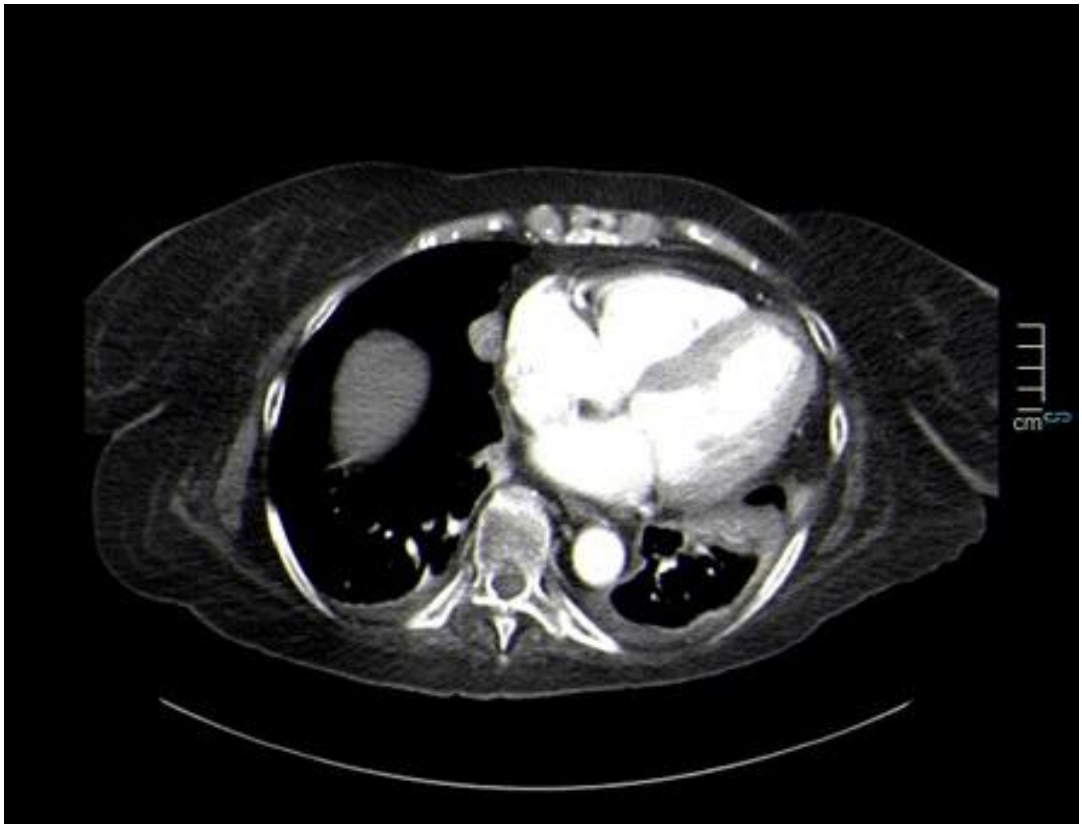
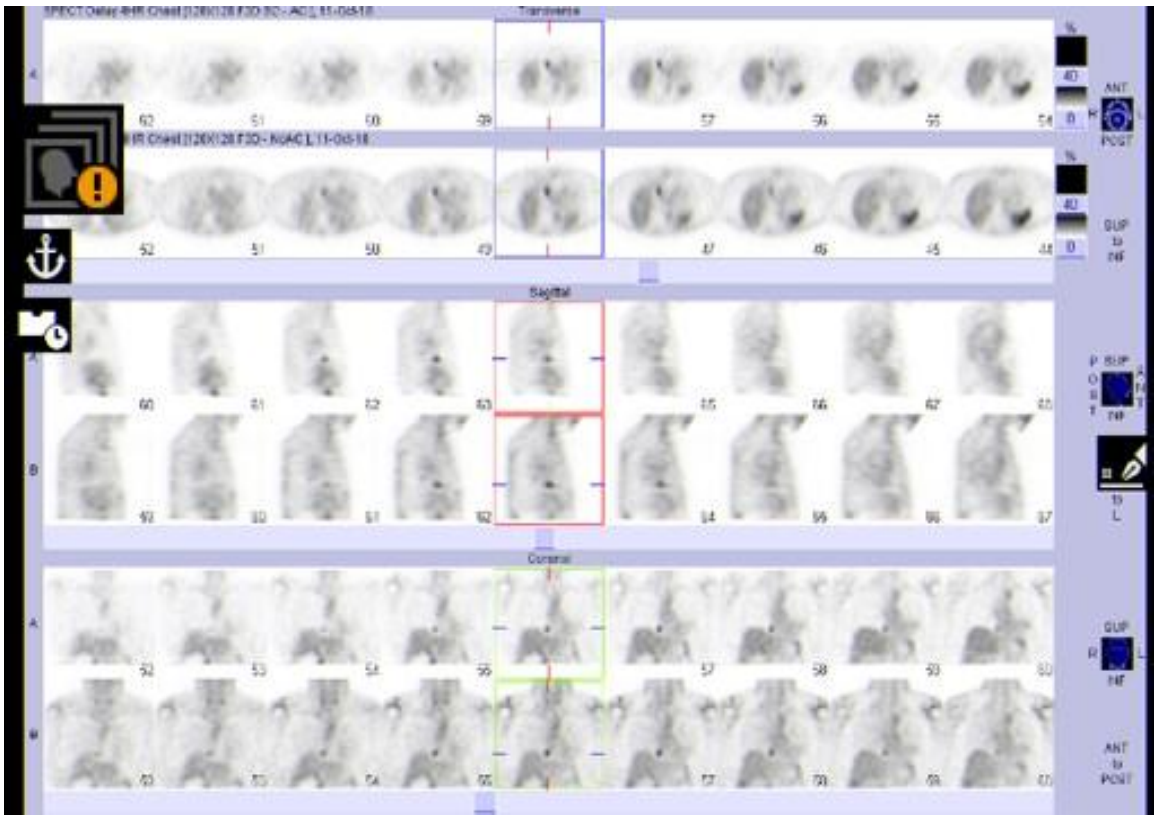


Figure 3:CT Scan Of The Chest Sagittal View Demonstrating Distal Bronchial Origin Of The Nodule.



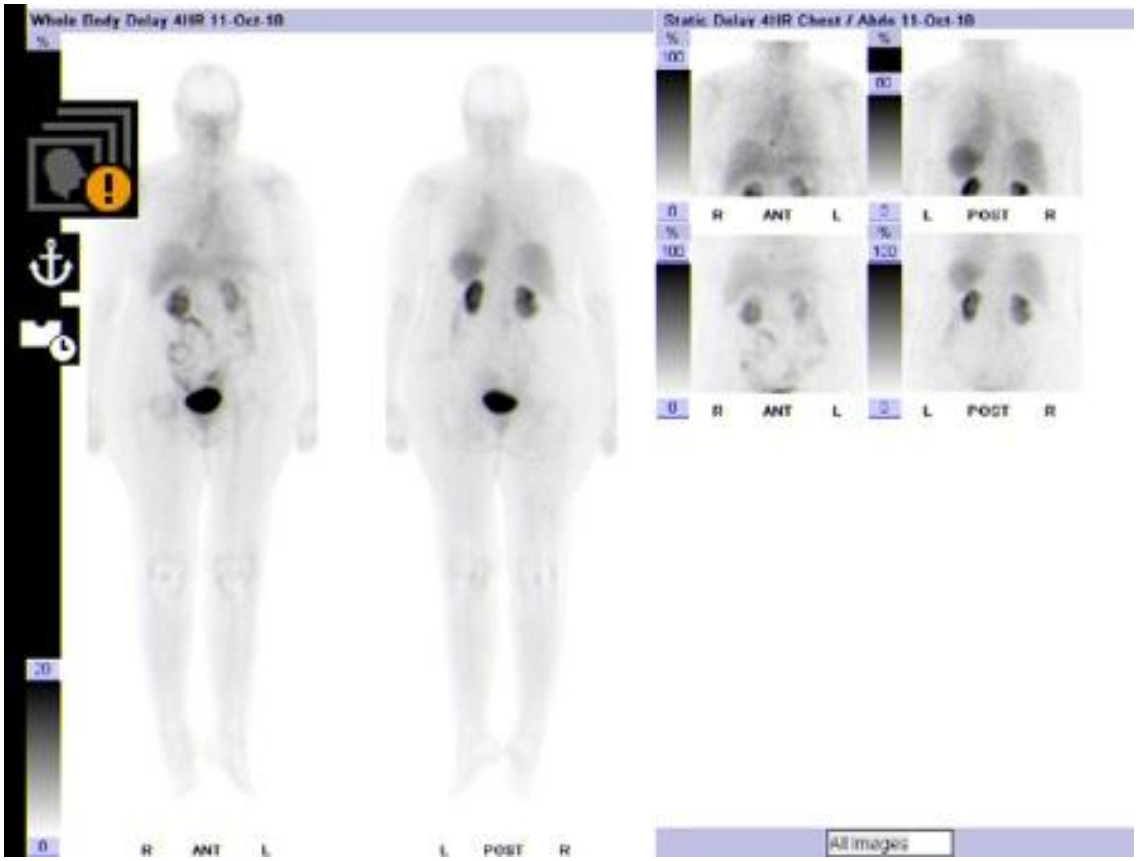


Figure 4,5: Multiple Views From Octreotide Scan Demonstrating Focal Increased Tracer Uptake Corresponding To The Soft Tissue Nodule Noted On CT Scan Of The Chest.

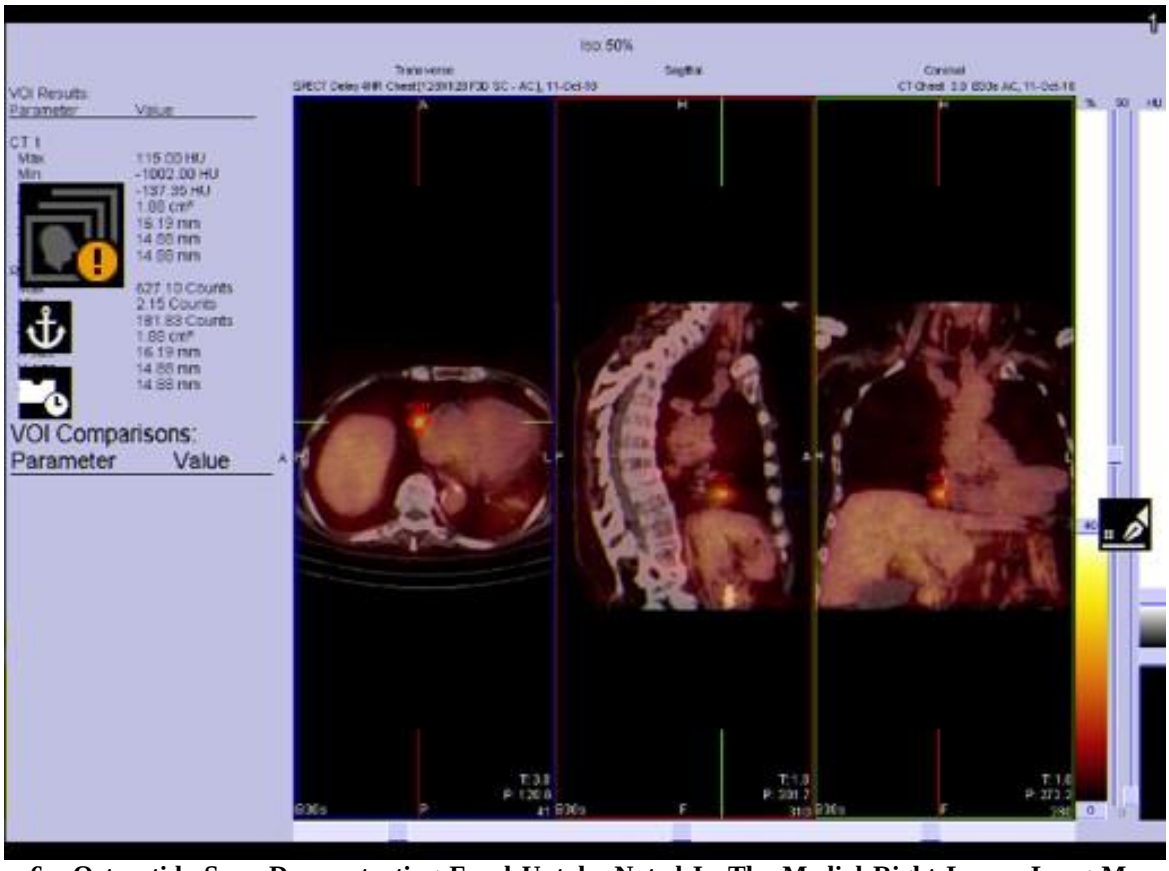


Figure 6: Octreotide Scan Demonstrating Focal Uptake Noted In The Medial Right Lower Lung Measuring 1x2.24 Cm, Most Likely Represent Functional Bronchial Carcinoid.

The typical clinical picture, severe hypokalemia, metabolic alkalosis, hyperglycemia ,high AM and random cortisol with loss of diurnal variation and markedly elevated 24 hours urinary cortisol confirmed the diagnosis of CS. Markedly Elevated ACTH ,MRI pituitary showing empty Sella and focal uptake in the lung on octreotide scan strongly suggested EAS from bronchial carcinoid resulting in CS.

Inferior petrosal sinus sampling and CRH tests to confirm EAS were not pursued due patients deteriorating poor health and series of multiple acute complications sepsis, thromboembolism and heart failure. Thoracic surgeons were consulted for surgical resection of the bronchial carcinoid. Surgery was deferred due advance age, heart failure, poor physical performance status and technically difficult surgery due to precarious location of the tumor. A multi-disciplinary team consisting of endocrinologists, thoracic surgeons and radiologists took consensus decision to treat the patient conservatively with medical therapy and octreotide was initiated. 3 months follow up in clinic after initiation of octreotide patient experienced marked improvement on her symptoms and significant weight loss. Her hypokalemia, metabolic alkalosis were corrected without other intervention. Her blood sugars control became easy with reduced doses of insulin and HBA1C dropped from 9.1 to 5.3. Her cortisol, ACTH levels significantly decreased (Table no: 1).After 3 years after initiation and continuation of octreotide treatment she was symptomatically well and free from hypercortisolism.

DISCUSSION

Cushing's syndrome (CS) is a rare and severe endocrine disorder characterized by a variety of typical signs and symptoms which result from excessive steroid hormone production from adrenal gland. The estimated prevalence for CS is 2-3 cases per million populations per year.[1] CS is divided into 1) adrenocorticotropin (ACTH) dependent CS caused by either ACTH-secreting pituitary adenoma (Cushing's disease) or nonpituitary neoplasm ectopic ACTH-secreting tumor 2) ACTH-independent CS is caused by benign or malignant adrenal tumors or exogenous use of glucocorticoid (1), Differentiating between the ACTH-dependent from ACTH-independent Cushing's syndrome is consider the first step in diagnosis usually by 2300h/0800h ACTH level and CRH stimulation test distinguishing Cushing's disease from the ectopic ACTH syndrome can be difficult (ref 5 of 3). Cushing's disease is predominantly a disorder of women with most reported series showing a 6:1 female/male ratio[2], On the other hand, the ectopic ACTH syndrome is equally distributed between the sexes. Patients with Cushing's disease signs and symptoms of hypercortisolism usually develop over several years. In contrast, patients with ectopic ACTH-secreting neoplasms usually have the onset of signs and symptoms of hypercortisolism over a period of time of less than 1 year.[2] The variety of sign and symptoms also can play role in diagnosis, for example: hypokalemia and metabolic alkalosis is unusual in Cushing's disease (10% of patients), but is present in almost 50% of patients with the ectopic ACTH syndrome.[3] Dynamic biochemical testing with high-dose (8 mg) dexamethasone suppression test (HDDST) may be helpful in distinguishing pituitary CS from ectopic ACTH syndrome, To diagnose pituitary CS, serum cortisol should suppress to <5 ug/dL or morning cortisol (drawn at 8 am) after HDDST should decrease by 50%. However, HDDST does not always distinguish pituitary from ectopic ACTH-dependent CS, with sensitivity and specificity each ranging from 60% to 100%.[4,5] Patients with EAS usually have high ACTH levels ($\geq$ 20 ng/l)[6] and demonstrate absent pituitary adrenal response to CRH.[7] CT scan chest is a valuable tool for detecting bronchial carcinoids. CT chest demonstrated enhancing soft tissue nodule in right pericardial space Bronchial carcinoids are richly vascularized tumours are notoriously difficult to detect due to their small size and proximity to pulmonary vessels. Pulmonary oedema and sepsis at the time of Imaging might of masked the bronchial carcinoid in our patient. Inferior petrosal sinus sampling is gold standard test with patients pituitary lesions show a gradient in ACTH concentration between affected sinus and periphery whereas no gradient seen in patients with EAS.[8] In our patient inferior petrosal sinus not pursued as EAS was very likely due of severity of hypercortisolism, MRI pituitary showing empty Sella, octreotide scan showing high uptake lesion in lung and the patient was too unwell to perform the invasive test. Incidental relevant finding was empty sella on pituitary MRI, which doesn't exclude pituitary CS but strongly supports the diagnosis of EAS. A similar case of EAS due to thymic carcinoid and empty sella was published in literature.[9] It was speculated that strong negative glucocorticoid feedback from EAS resulted in empty sella in these cases. EAS represents 20% of ACTH-dependent CS and about 10% of all types of CS. Neuroendocrinal tumours (NETs)associated with CS are often derived from the lung, thymus, pancreas, thyroid ,chromaffin cell tumors and rarely from the ovary or prostate (4) Recent epidemiologic studies show that the age-adjusted incidence of all gastroenteropancreatic (GEP)-NETs is 3.65, for pancreatic NETs 0.43, and for thymic NETs, this is 0.4/100 000 population per year. With a incidence of 0.2 -2.0 cases /100000 population per year bronchial NETs (bronchial carcinoids) extremely rare cause of EAS[10], Pulmonary carcinoids are traditionally subdivided into central and peripheral on the basis of their origin in respect of the bronchial tree; Respiratory symptoms are generally present only in central forms, while peripheral forms are generally discovered as an incidental.[11] The mainstay of treatment of bronchial carcinoids is surgical resection.[12] But our patient with advanced age has severe comorbid conditions, several acute complications of CS and tumor at precarious position. The multidisciplinary team decided to manage the patient with medical treatment. NETs (bronchial carcinoids) have frequently expression of SST2 receptors and respond well to stomatostatin

analogues like octreotide and Lanreotide.[13,14,15] Octreotide was initiated in our patient and she showed excellent persistent response which was persistent for the 3 years of follow on octreotide treatment.

CONCLUSION

WE describe a rare case of **EAS** from bronchial carcinoid which produced severe form of CS. Diagnosis of CS due to EAS present most challenging especially when endocrine tests and imaging modalities are inconclusive or couldn't be performed due severe morbidities and availability of resources. These cases are best managed with good out comes in a multidisciplinary team with endocrinologists ,radiologists, radiologists and thoracic surgeons taking decision for the best management plan with available data.

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