Abstract:
Mr. B, 25 year old of age, was referred for management of his complaints, which were suggestive of hypercortisolism. He had features of central obesity, wrinkled skin with recurrent skin infections, he also reported of generalized weakness and had uncontrolled hypertension. The dexamethasone suppression test on him was indicative of an endogenous ACTH producing source (tumor). Blood labs were revealed elevated levels of cortisol and acth. His MRI brain was normal with no pituitary abnormalities. His whole body FDG-PET scan was suggestive of a nodule in the left upper lobe with aorticopulmonary nodes. He underwent left upper lobectomy, he recovered well symptomatically, blood pressures returned to normalcy and so as his acth and cortisol levels. His immunohistochemistry was suggestive of carcinoid tumour and nodes were negative for malignancy. He remains healthy till date.

Keyword: endogeous acth, ectopic acth producing tumour.

INTRODUCTION:
Endogenous Cushing's syndrome is a clinical state resulting from prolonged, inappropriate exposure to excessive endogenous secretion of cortisol and hence excess circulating free cortisol, characterized by loss of the normal feedback mechanisms of the hypothalamo-pituitary-adrenal axis and the normal circadian rhythm of cortisol secretion. The etiology of Cushing's syndrome may be excessive ACTH secretion from the pituitary gland, ectopic ACTH secretion by nonpituitary tumor, or excessive autonomous secretion of cortisol from a hyperfunctioning adrenal adenoma or carcinoma. Other than this broad ACTH-dependent and ACTH-independent categories, the syndrome may be caused by ectopic CRH secretion, PPNAD, MAH, ectopic action of GIP or catecholamines, and other adrenal-dependent processes associated with adrenocortical hyperfunction.

CASE REPORT:
A 25 year-old man with 6-month history of hyperpigmentation, weight gain and proximal
myopathy was referred to Institute of Endocrinology for evaluation of hypercortisolism. At admission, patient had classic cushingoid habitus with plethoric face, dermal and muscle atrophy, abdominal striae rubrae and centripetal obesity.He also had uncontrolled hypertension and was on elaborate anti hypertensive medications. The standard laboratory data showed hyperglycaemia and hypokaliemia with high potassium excretion level. The circadian rhythm of cortisol secretion was blunted, with moderately elevated ACTH level, and without cortisol suppression after low-dose and high-dose dexamethason suppression test. Urinary SHIAA was elevated. Abdominal and sellar region magnetic resonance imaging was negative. CRH stimulation resulted in ACTH increase of 87% of basal, but without significant increase of cortisol level, only 7%.

DISCUSSION:
A multitude of normal nonpituitary cells from different organs and tissues have been shown to express the POMC gene from which ACTH is derived. The tumors most commonly associated the ectopic ACTH syndrome arise from neuroendocrine tissues, APUD cells. POMC gene expression in non-pituitary cells differs from that in pituitary cells both qualitatively and quantitatively. Aggressive tumors, like small cell cancer of the lung (SCCL) preferentially release intact POMC, whereas carcinoids rather overprocess the precursor, releasing ACTH and smaller peptides like CLIP. Some tumors associated with ectopic ACTH syndrome express other markers of neuroendocrine differentiation like two specific prohormone convertases (PCs). Assessment of vasopressin (V3) receptor gene expression in ACTH-producing nonpituitary tumors revealed bronchial carcinoid as a particular subset of tumors where both V3 receptor and POMC gene may be expressed in pattern indistinguishable from that in corticotrophic adenoma. In most, but not all, patients with ectopic ACTH

MRI Brain
Thoracic CT scan revealed 14 mm mass in left apical pulmonary segment. FDG-PET scan was suggestive of an avid nodule in the left upper lobe of the lung with aorticopulmonary nodes. Patient underwent a left upper lobectomy. Microscopic evaluation showed tumor tissue consisting of solid areas of uniform, oval cells with eosinophilic cytoplasm and centrally located nuclei. Stromal tissue was scanty, and mitotic figures were infrequent. Tumor cells were immunoreactive for synaptophysin, neuron-specific enolase, and ACTH. The postoperative course was uneventful and the patient was discharged on glucocorticoid supplementation. Signs of Cushing's syndrome were in regression, and patient remained normotensive and normoglycaemic without therapy.
syndrome, cortisol is unresponsive to high-dose dexamethasone suppression test, what is used as diagnostic tool. It is not clear if the primary resistance resulted from structural abnormality of the native glucocorticoid receptor (GR), a low level of expression, or some intrinsic property of the cell line. It appears that ectopic ACTH syndrome is made of two different entities. When it is because of highly differentiated tumors, with highest level of pituitary-like POMC mRNA, expressing PCs, high level of V3 receptors and GR, like bronchial carcinoids, it might be called ectopic corticotroph syndrome. In contrast, when it is caused by aggressive, poorly differentiated tumors, with much lower expression of V3 receptor, like SCCL, it might be called aberrant ACTH secretion syndrome. Carcinoid tumors have been reported in a wide range of organs but most commonly involve the lungs, bronchi, and gastrointestinal tract. They arise from neuroendocrine cells and are characterized by positive reactions to markers of neuroendocrine tissue, including neuron specific enolase, synaptophysin, and chromogranin. Carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules composed of variety of hormones and biogenic amines. One of the best characterized is serotonin, subsequently metabolized to 5-hydroxy-indolacetic acid (5-HIAA), which is excreted in the urine. In addition to serotonin, carcinoid tumors have been found to secrete ACTH, histamine, dopamine, substance P, neurotensin, prostaglandins and kallikrein. The release of serotonin and other vasoactive substances is thought to cause carcinoid syndrome, which manifestations are episodic flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease. These tumors have been classified as either well-differentiated or poorly differentiated neuroendocrine carcinomas. Pulmonary carcinoids make up approximately 2 percent of primary lung tumors.

The majority of these tumors are peripheral in location, and patients often presents with recurrent pneumonia, cough, hemoptysis, or chest pain. The carcinoid syndrome occurs in less than 5 percent of cases.

CONCLUSION:
Ectopic secretion of ACTH from pulmonary carcinoid accounts for 1 percent of all cases of Cushing's syndrome. They are distinct clinical and pathologic entity, generally peripheral in location. Although they are usually typical by standard histologic criteria, they have much greater metastatic potential than hormonally quiescent typical carcinoids. Surgical treatment therefore should be one proposed for more aggressive malignant tumors. In all cases of ACTH-dependent Cushing's syndrome with regular pituitary MRI and bilateral inferior petrosal sinus sampling, thin-section and spiral CT scanning of the chest should be routine diagnostic procedure.

REFERENCE: