THYMIC CARCINOID CAUSING PARANEOPLASTIC CUSHING’S SYNDROME - A RARE CASE REPORT

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Abstract: Cushing’s syndrome reflects a constellation of clinical features from chronic exposure to excess glucocorticoids of any etiology. This disorder can be ACTH dependent (pituitary corticotrope adenoma, ectopic secretion of ACTH) or ACTH independent (adrenocortical adenoma, adrenocortical carcinoma, nodular adrenal hyperplasia) as well as iatrogenic. The term Cushing’s disease reflects to Cushing syndrome caused by pituitary adenoma. We present here a case of ectopic ACTH producing thymic carcinoid in a 17 year old male patient who was diagnosed and treated in our hospital. He presented to us with acute onset Cushing’s syndrome, on evaluation he was found to have an anterior mediastinal mass which was excised. On histopathological examination and immunohistochemistry showed a thymic carcinoid. Patients symptoms and features of Cushings syndrome reduced after excision of the tumour.

Keyword: ACTH, THYMIC CARCINOID, CUSHING’S SYNDROME

19 year old male patient came to us with the complaints of acute weight gain and blackish discoloration of face and hands for the past 1 month. He had gained around 6 kgs in the past one month. History of facial puffiness and leg swelling with increased acne formation in the face and the chest(Fig.1). He had difficulty in getting up from squatting position and diffuse muscle cramps. There were no other history suggestive of hypothyroidism, cardiac or renal failure. He did not give any history of steroid intake. His past, personal and family history were nil significant

On clinical examination
Patient was conscious, oriented and afebrile with features of Cushing’s syndrome like central obesity, moon like facies, extensive acne in the face and chest(Fig.1), purple striae was noted in the abdomen(Fig.2), forearm and legs. Blackish discolouration of face and hands especially knuckles. He had bilateral pitting pedal oedema. Thyroid examination was normal. His blood pressure was elevated with 150/100. Cardiovascular, respiratory and abdominal examinations were normal. He had proximal muscle weakness of power 4/5 in all four limbs, other neurological examinations were normal. We made a provisional diagnosis of acute onset Cushing’s syndrome and investigated the patient

Blood investigations showed a normal blood sugar, renal function test, liver function test and urine routine. He had hypokalemia (2.9 meq/l) on admission. Electrocardiogram showed features of hypokalemia. Echocardiogram showed good LV function and the ejection fraction was 60%. Complete hemogram showed neutrophilic leucocytosis with eosinopenia. Thyroid profile was normal. 24hrs Urinary free cortisol test showed marked elevation – 300 g/day (normal 30 – 40 g/day), which confirmed the diagnosis of Cushing’s syndrome. Serum cortisol and serum ACTH level were measured which showed both of them were elevated with values 71.80 g/dl (normal 4.30 – 22.40 g/dl) and 934.0 pg/ml (normal 10 – 46 pg/ml) respectively.
From that we came to a conclusion of ACTH dependent Cushing’s syndrome. Dexamethasone suppression test was done to differentiate a ACTH secreting pituitary adenoma from Ectopic ACTH secreting tumour, which showed no suppression of serum cortisol. This implies that an ectopic source of ACTH secretion was present. Dehydroepiandrosterone levels and 24 hrs vinillylmandelic acid levels were done, which were also normal. Chest x ray showed an upper mediastinal widening(Fig.3). CT scan of the abdomen showed bilateral adrenal hyperplasia(Fig.4). MRI brain showed no pituitary masses. CT chest showed an anterior mediastinal mass measuring 3 * 3 cms suggestive of thymic mass(Fig.5). After blood investigations we came to a conclusion of Ectopic ACTH secreting mediastinal mass ?thymic mass producing Cushing’s syndrome. We planned thymectomy as the next step. During the whole stay of the patient before surgery the patient had hypokalemia which was corrected with oral potassium supplementations. Thymectomy was done. Right lobe of thymus was diffusely enlarged with 3 x 5 cm mass, left lobe appeared normal, capsule was intact, lymph node of varying size 1 - 2 cm present, other structures were normal. Specimen was sent for histopathological and immunohistochemical studies. Histopathological report was consistent with well to moderately differentiated neuroendocrine carcinoma with ACTH expression. Immunohistochemistry showed that the tumor positive for Cytokeratin, Synaptophysin, Chromogranin and ACTH.

Post-operative status
Post-operative period was uneventful except for recurrent hypokalemia, which was treated. CT chest was done which showed B/l lung field were normal. Mediastinum showed post-operative changes and no e/o mediastinal adenopathy. Patient was discharged on 12th post-operative day. On follow up after 1 month, Blood investigation showed marked reduction in serum cortisol and ACTH 8.22 g/dl (Normal - 3 – 16.66) and 114.00 pg/ml (Normal 7.20 – 63.30). Weight reduction of 8 kg was observed, blood pressure became normal even after discontinuation of anti hypertensive drugs. Serum potassium level normalized, Acne and blackish discoloration face were reduced (Fig.6).

DISCUSSION:
Cushing’s syndrome
Cushing’s syndrome often presents a diagnostic challenge, particularly in the early stages when the signs and symptoms are nonspecific. Obesity, hypertension, and glucose intolerance are just a few of the early clues that unfortunately are also very prevalent in our society. The classic description of proximal muscle weakness, wide purple abdominal striae, and increased supraclavicular fat occurs in only a minority of patients(1). Although considered a classic finding of Cushing’s syndrome, central obesity with limb wasting is a feature of long-standing cortisol excess and, therefore, is a late finding. In 1 study of 70 patients clinically suspected to have Cushing’s syndrome, discriminatory indices were assigned to symptoms based on their prevalence in patients proven to have Cushing’s syndrome versus those who did not. Three clinical features; ecchymoses, myopathy, and hypertension, were found to have the highest discriminatory value for Cushing’s disease in those studied(2). Adding to the clinical dilemma are the serious consequences of unrecognized hypercortisolism. A National Institutes of Health study found that hypercortisolism conferred a heightened risk of both infection and pulmonary embolism(3). The hypertension, hypercoagulability, and metabolic syndrome that result from hypercortisolism increase cardiovascular risk, the main cause of increased mortality in this patient population(1,4,5). Pathologic fractures are also common, occurring in 30–50% of Cushing’s patients(5). A high index of suspicion is necessary for patients with clinical features suggestive of cortisol excess.
A 24-hour urine-free cortisol level that is more than 4 times the upper limit of normal is diagnostic for Cushing’s syndrome. Our patient had 6 times elevation in 24hrs urinary free cortisol. Levels between 1 and 4 times the normal require further testing for definitive diagnosis. An elevated midnight salivary cortisol result can aid in this confirmation; however, the diagnostic criteria of this test need further validation(1). Definitive diagnosis can be achieved by a 2-day dexamethasone stimulation (0.5 mg every 6 hours for 2 days) combined with corticotropin-releasing hormone (CRH) (1 mg given 2 hours after the last dexamethasone dose). A plasma cortisol level of 1.4 g/dL or higher is positive for Cushing’s syndrome with almost 100% sensitivity and specificity(8). Alternatively, the diagnosis of Cushing’s syndrome is achieved when a 1-mg overnight dexamethasone suppression test results in an 8 a.m. serum cortisol level higher than 14.3 g/dL. This test has limited utility, however, because total suppression of cortisol does not rule out Cushing’s syndrome (1). Plasma ACTH levels distinguish ACTH-dependent from ACTH-independent causes of Cushing’s syndrome. A plasma ACTH level lower than 5 pg/mL with a serum cortisol level higher than 15 g/dL indicates an ACTH-independent source. ACTH-independent sources are primary to the adrenal glands and include adenocortical adenomas and carcinomas and, less often, bilateral micronodular dysplasia. A plasma ACTH level higher than 10 pg/mL despite a serum cortisol level higher than 15 g/dL indicates an ACTH-dependent cause. ACTH-dependent sources include pituitary hypersecretion of ACTH (Cushing’s disease), ectopic ACTH-secreting tumors, and ectopic CRH-secreting tumors(1,7). Intermediate ACTH levels are indeterminate and require further evaluation, which can be accomplished using a CRH stimulation test. This test is also useful in differentiating pituitary from ectopic ACTH secretion in known ACTH-dependent Cushing’s syndrome (1,8). After baseline ACTH and cortisol levels are measured, 1 g/kg (alternatively, 100 g) of CRH is administered. Levels of ACTH are measured at 15 and 30 minutes and cortisol at 30 and 45 minutes after administration. A 35% rise in ACTH and a 20% rise in cortisol together have a 90% sensitivity and specificity for a pituitary source of excess ACTH(8).

Another method to distinguish a pituitary source from an ectopic source is an overnight 8-mg dexamethasone suppression test. High-dose dexamethasone overcomes feedback inhibition in pituitary tumors but does not in ectopic tumors. A greater than 68% suppression of serum cortisol offers 71% specificity and 100% sensitivity in identifying a pituitary source for ACTH-dependent Cushing’s syndrome(8). Our patient did not show cortisol suppression with overnight 8mg dexamethasone confirming that it is a ectopic ACTH secreting tumor causing Cushing syndrome Ectopic ACTH-secreting tumors include carcinomas of the lung, thymus, and pancreas, as well as carcinoid tumors. Secretion of ACTH results in bilateral adenocortical hyperplasia, adrenal hyperfunction, and resultant Cushing’s syndrome(9,10). Rapid development of features of hypercortisolism associated with skin hyperpigmentation and severe myopathy suggests ectopic source of ACTH. Hypertension, hypokalemic alkalosis, glucose intolerance and oedema are also more pronounced in these patients. Serum potassium less than 3.3mmol/L are evident in 70% of patients with ectopic ACTH secretion, but are seen in less than 10% of patients with pituitary dependant Cushing’s syndrome(38). Table 1.0 illustrates difference between ACTH secreting pituitary tumor and ectopic ACTH secreting tumor. Our case illustrates an unusual case of Cushing’s syndrome secondary to ectopic ACTH produced by thymic carcinoid.

Table 1

Carcinoid

Carcinoid is an extremely rare neuroendocrine tumor(11). Although classically associated with carcinoid syndrome (paroxysmal diarrhoea, flushing, and hypertension), carcinoid tumors are often asymptomatic and discovered incidentally during unrelated surgery or imaging(9,11). The location and likely presentation of a carcinoid tumor depends on the division of the embryonic gut from which the tumor cells originate. Carcinoid tumors originating from foregut cells arise in the lungs, bronchi, and stomach and, when symptomatic, are likely to cause recurrent pneumonia, cough, anaemia, or abdominal pain. Hindgut derivatives arise in the distal colon and rectum and are likely to cause pain, bleeding, and constipation. It is the midgut tumors, which are found in the small intestine, appendix, and proximal large bowel, that are most commonly associated with carcinoid syndrome(9,11).

Derived from neuroendocrine cells, carcinoid tumors have the ability to secrete various peptides and bioactive amines. The most commonly secreted substance is the bioactive amine serotonin (5-hydroxytriptamine), the amine responsible for the classic manifestations of carcinoid syndrome (paroxysmal diarrhoea, flushing, and hypertension) (11). Bioactive amines such as serotonin and histamine are cleared by the liver, explaining why carcinoid syndrome is unlikely unless liver metastases have occurred(9,11). When it does occur, carcinoid syndrome is seen with midgutderived carcinoid tumors that have metastasized to the liver (although rarely it may be seen with any serotonin-secreting carcinoid that drains directly into the systemic circulation)(9). As uncommon as the presentation of classic carcinoid syndrome may be, a far less common presentation is that of Cushing’s syndrome because of ectopic ACTH production. Although serotonin is the most common substance secreted by carcinoid tumors, a number of peptides are possible, including ACTH(11). Excess ACTH results in hypercortisolism, which in turn causes both Cushing’s syndrome and hypokalemia. The degree of hypokalemia is directly related to the amount of urine-free cortisol(8). Cushing’s syndrome results from a nonpituitary tumor, such as carcinoid, in somewhere between 10% and 20% of cases(1,3,8). When Cushing’s syndrome is caused by ACTH-secreting carcinoid tumors they are most often bronchial or thymic in origin, although cases of gastrointestinal carcinoids have been reported. Primary carcinoid lesions are either occult or unlocalized in up to 20% of cases(3,12,13). Rare cases of primary liver carcinoid tumors have been reported; however, fewer than 80 cases exist in the literature, only 1 of which has been reported as an ectopic source of ACTH production(14).
Definitive treatment of carcinoid involves surgical resection of the primary lesion. In the case of ACTH-producing carcinoid tumors, this will induce both remission of symptoms and return of normal adrenal function(1). The somatostatin analog octreotide is currently the mainstay of treatment for carcinoid symptoms. Octreotide reduces the symptoms of diarrhea and flushing and is thought to have a concentration-dependent effect on tumor suppression(15). For resectable lesions, if preoperative evaluation determines that at least 90% of the gross tumor is treatable, hepatic resection offers an alternative that may increase 5-year survival and decrease the requirement for somatostatin analog treatment. Hepatic resection is by no means curative and high recurrence rates are reported(16,17).

When ACTH secretion results in Cushing’s syndrome, immediate control of hypercortisolism is required to reduce morbidity and mortality. This was illustrated by a large retrospective case study that found patients with occult ACTH-secreting tumors had a good prognosis, despite failure to localize their tumor, if adequate control of hypercortisolism was achieved(3). Adrenocorticotropic medications such as ketoconazole may have a role in suppressing cortisol levels; however, they are often less successful in these patients because of the amount of adrenal stimulation observed(13). Bilateral adrenalectomy continues to be an effective measure to eliminate severe hypercortisolism in these patients(12,18,19). Immediate bilateral adrenalectomy was indicated for our patient because of life-threatening hypertension, intractable diarrhea, and severe debilitation. Bilateral adrenalectomy combined with octreotide resulted in a dramatic reduction of symptoms and improvement in overall quality of life. Serum S-HIAA levels have returned to within normal limits and chromogranin A levels have decreased dramatically.

**Thymic carcinoid**

Carcinoid tumors of the thymus were first described as a specific entity in 1972 by Rosai and Higa(20). They are thought to arise from the foregut and, unlike the more common midgut carcinoids, generally are not associated with carcinoid syndrome(21). Thymic carcinoid tumors occur rarely during childhood and adolescence. When present, they are often associated with the overproduction of ACTH, which leads to Cushing’s syndrome.

Since 1972 when thymic carcinoid tumors were first described, approximately 150 cases have been reported in the literature(20,21). In the thymus, neuroendocrine carcinomas account for approximately 2% to 4% of all anterior mediastinal tumors.(22-23). Neuroendocrine carcinomas of the thymus associated with Cushing’s syndrome can occur at any age between 4 and 64 years, but their peak prevalence is between the second and the fourth decades of a patient’s life (24), as frequently in men as in women (25-26). Diagnosis must be confirmed by increased cortisol levels in the serum or in the 24-hour urine collection, which must remain elevated despite a low-dose dexamethasone suppression test. The presence of elevated ACTH levels excludes the possibility of an autonomous secretion of cortisol by an adrenal tumor. Ectopic ACTH-secreting tumors can be exceedingly small and may not be visible on CT; therefore, a chest CT with 5-mm-thick slices is recommended(27-28). Our patient had elevated 24-hour cortisol and ACTH levels.

Relatively few cases of thymic carcinoid tumors in children and adolescents have been reported in the literature. Wick et al(24) reviewed 74 cases of thymic carcinoid tumors and identified three patient groups: those with Cushing’s syndrome (38.0%); those with neuroendocrine carcinoid syndrome (44.5%); and those with MEN syndromes (17.5%). It has been reported that the prognosis is worse for patients with thymic carcinoid who have Cushing’s syndrome(24). MEN-1–related thymic carcinoid is rare; only 45 cases of this tumor have been reported(29).

Approximately 25% of patients with thymic carcinoid have MEN-1 syndrome(30). Thus, patients with thymic carcinoids are thought to be good candidates to undergo MEN-1 gene screening. The screening results are good indicators for deciding whether to search for other malignancies associated with MEN-1 syndrome. Surgery is the therapy of choice for neuroendocrine carcinoma of the thymus. Aggressive local resection of these tumors usually includes the entire thymus and the peri-thymic fat. Therefore, a median sternotomy is indicated in most cases, and a limited approach should be avoided(26). The role of radiotherapy, chemotherapy, or both in the treatment of thymic carcinoid tumors has not been adequately established. Single agents or combination drug therapies with fluorouracil, streptozocin, etoposide, or cisplatin have been proposed by several investigators; however, these interventions do not significantly affect survival or recurrence rate(31-32) or prognosis. In our case we proceeded with thymectomy and did not follow it up with chemotherapy. Most patients present with local recurrence or metastasis within 5 years after surgery and die within 10 years(31-33-34). Prognosis is directly linked to the degree of tumor differentiation(35).

The 5-year survival rate is approximately 50% for patients with well-differentiated thymic carcinoid tumors, 25% for those with moderately differentiated tumors, and 0% for those with poorly differentiated tumors. (36) Postoperative follow-up with serum and urinary free cortisol testing, as well as with regular chest CT or MRI scans, is also recommended because of the risk of recurrence(24). In our patient the postoperative CT showed no residual tumour and the serum cortisol and ACTH levels were in decline.

Patient was advised to come for regular follow up. Assessment of serum chromogranin A levels seems to be useful for monitoring the disease. Any suspicion of relapse must be confirmed with a CT scan and an OctreoScan (Covidiens, Dublin, Ireland)(37).

**CONCLUSION:**

Paraneoplastic Cushing’s is a rare entity. Thymic carcinoid producing it makes it even rarer. Aim of presentation is to highlight the early recognition of the signs and symptoms of ectopic ACTH for prompt and adequate intervention. Treatment for carcinoid tumors with ectopic ACTH secretion involves surgery as mainstay. Surgery resulted in a dramatic reduction of symptoms (Fig.6) and improvement in overall quality of life for our patient.

**References**


