Fulminant Cushing’s Syndrome due to an ACTH-Producing Thymic Carcinoid

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Thymic carcinoid is a rare cause of Cushing’s syndrome. We present a case of fulminant Cushing’s syndrome that led to a severe catabolic state with multi-organ involvement. Aggressive and specific medical treatment with organ support in the intensive care setting resulted in sufficient clinical improvement that enabled definitive surgery.

Case Description

A 32-year-old man was hospitalized because of severe fatigue and blurred vision. Evaluation revealed glaucoma, hypertension, new-onset diabetes mellitus and severe hypokalemia with metabolic alkalosis. A month later he was admitted to the urology department because of a perianal and scrotal abscess, which was surgically drained. Following surgery, he developed shortness of breath and hypoxia. Chest X-ray and a spiral computed tomography scan showed massive atelectasis of the left lower lobe with consolidation of the left upper lobe and multiple thrombi in the right and left pulmonary tree. An anterior mediastinal mass was also seen. Three days later he was admitted to our medical intensive care unit with respiratory insufficiency.

On admission the patient was in respiratory distress (40 breaths/min), with pulse 115/min, blood pressure 100/60 and temperature 38°C. He was wasted, with hyperpigmentation of the face and palms; his periphery was warm and his neck veins were distended. Oral examination showed evidence of thrush. Examination of the chest revealed decreased air entry to the left lung with diffuse course crackles; the heart sounds were regular with a 2/6 systolic murmur over the left sternal border. The abdomen was soft, without organo-megalgy or ascites and there was no evidence of peripheral edema, stria or deep vein thrombosis. Examination of the perineum showed an open wound draining pus, with cellulitis of the scrotum.

The blood count showed 16,000 leukocytes/mm³ with 96% polymorphonuclear cells, eosinopenia and lymphopenia, hemoglobin 11.6 g/dl, and platelet count 112,000/mm³. Biochemistry results were as follows: Na- 140 mEq/L, K- 2.3 mEq/L, urea 4 mmol/L, creatinine 36 mmol/L, glucose 18 mmol/L, and P- 0.4 mmol/L. Arterial blood gas analysis revealed hypoxia and hypocarbia. The patient required intubation and mechanical ventilation and was started on intravenous heparin. Sputum cultures grew a resistant strain of Acinetobacter calcoaceticus var anitratus that was sensitive only to imipenem, which was therefore administered.

The history of weakness, hypertension, new-onset diabetes mellitus, hyperpigmentation, electrolyte disorders and susceptibility for infection raised the possibility of hypercortisolism. Plasma cortisol was above maximal level, urinary free cortisol was above 2,000 nmol/24 hour (<250 nmol/24 hour), and plasma ACTH was 785 pmol/L (<11.4 pmol/L). Urinary excretion of 5-hydroxy-indole-acetic acid was normal. A high dose dexamethasone suppression test did not affect cortisol levels. Since a suspected mediastinal mass was seen on CT scan, a somatostatin labeled scan (OctreoScan, indium-111 pentetretotide) was performed, which showed uptake in the anterior mediastinum. The patient at this stage was too sick to undergo resection or open biopsy of the mass. In order to reduce cortisol production, ketoconazole at a dose of 800 mg daily was begun and gradually increased to 1,200 mg daily. Since subsequent measures of cortisol production failed to elicit an improvement, the patient was started on somatostatin at an initial dose of 150 µg/day which was gradually increased to 1,500 µg/day administered by intravenous drip. Metyrapone at a dose of 4 g/day was subsequently added. The patient's uncontrolled hyperglycemia and severe malnutrition resulted in further severe infections. He developed septic shock and after resuscitation remained septic despite broad-spectrum antibiotics and drainage of the perianal abscess and...
the empyema. The intractable hypokalemia responded only to high doses of spironolactone, enalapril and potassium supplements. Only following 3 weeks of therapy did plasma cortisol and urinary free cortisol begin to decrease. This was accompanied by clinical improvement with lower blood sugar levels and higher potassium levels.

Surgical resection of the anterior mediastinal mass was performed on the 56th day of hospitalization with no intraoperative complications. Biopsy of the mass showed thymic carcinoid with invasion of the thymic capsule by carcinoid cells. Immunohistochemistry demonstrated cytoplasmic immunoreactive ACTH, with no evidence of corticotropin releasing factor immunoreactivity. The patient recovered, was discharged to a rehabilitation unit and eventually regained normal function.

Comment

Thymic carcinoid originates from neuroendocrine cells that are present in the normal thymus [1]. About 50% of thymic carcinoid tumors invade surrounding thoracic structures, as compared to 10% of thymomas [1,2]. Extrathoracic metastases are found in about 50% of thymic carcinoids, but only rarely in thymomas. To date, although approximately 100 cases of thymic carcinoid have been reported, only a few case series are available [1,2]. The mean age of presentation of thymic carcinoid is between 42 and 48 years. Male predominance is the rule.

About one-third of patients with thymic carcinoid present with Cushing’s syndrome due to an ectopic adrenocorticotropic hormone secretion from the tumor [1]. Co-secretion of corticotropin-releasing hormone from the tumor occurs rarely. Our patient presented with severe hypokalemia that may be attributed to the excess mineralocorticoid action of cortisol. It is postulated that cortisol is not converted to cortisone because of the inhibition of the enzyme 11β-hydroxysteroid [3]. To the best of our knowledge, this is the first report of an acute presentation of hypercortisolism – which includes mainly weight loss and recurrent severe infections without other classical features of Cushing’s syndrome such as central obesity and purple striae – in association with ACTH-secreting carcinoid of the thymus. As with other foregut carcinoids, thymic carcinoid is not associated with carcinoid syndrome, and urinary 5-hydroxy-indole-acetic acid is reported to be normal.

Symptoms related to pressure of the tumor mass within the thorax, such as superior vena cava syndrome, have been described in about one-third of patients. Moreover, about one-third of patients are totally asymptomatic, and in these cases the tumor is detected on routine chest X-ray [1,2]. The tumor may also be identified on CT. Scintigraphy with labeled somatostatin analogue (octreoscan) was found to be effective in localizing the tumor in 32 of 37 patients (86%) in whom carcinoid was proven histologically [4].

In rare cases of Cushing’s syndrome, ectopic tumors produced other hormones such as bombesin-like peptides. It is speculated that these substances stimulate pituitary ACTH secretion [5].

The treatment of thymic carcinoid requires excision of the tumor [1,2]. Excision was carried out in the reported patients with a resectable tumor. In some patients the tumor was found to spread to contiguous structures – great blood vessels, pericardium, pleura and lung parenchyma [1,2]. Although some reports recommend adjuvant radiotherapy, chemotherapy or both, there is no definitive information regarding the effectiveness of such therapy. In one series, metastases developed in seven of nine patients who had undergone surgery and adjuvant therapy [1].

The medical treatment of severe hypercortisolism due to ectopic ACTH secretion presents a complex challenge. Octreotide was demonstrated to suppress ectopic ACTH secretion [6]. Newer long-acting somatostatin analogues such as lanreotide have been shown to be as effective in neuroendocrine tumors, and have the advantage of being administered once every 2 weeks [7]. Ketoconazole was also found to directly suppress ACTH secreted in vivo and in vitro from an ACTH-producing thymic carcinoid [8].

We conclude that besides the conventional biochemical and imaging modalities of diagnosis, labeled somatostatin analogue scintigraphy plays an important role in the diagnosis of ACTH-secreting occult tumors, and that specific medical treatment is necessary to control the severe hypercortisolism prior to surgery.

References

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