Thymic Neuroendocrine Carcinoma Producing Ectopic Adrenocorticotropic Hormone and Cushing’s Syndrome

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Neuroendocrine carcinoma of the thymus, previously termed thymic carcinoid, is a rare clinical entity. Rarer still are such cases presenting with endocrinopathies. We report a case of thymic neuroendocrine carcinoma presenting with ectopic adrenocorticotropic hormone production and resultant Cushing’s syndrome.


Neuroendocrine carcinoma of the thymus (formerly known as thymic carcinoid) is a rare entity, with even fewer cases determined to cause Cushing’s syndrome. Thymic carcinoids make up only 2% to 7% of anterior mediastinal masses, which more commonly include thymoma, lymphoma, parathyroid adenoma or carcinoma, or ectopic thyroid goiter [1–3]. Only 46 cases of thymic neuroendocrine carcinoma presenting with paraneoplastic adrenocorticotropic hormone (ACTH) production and Cushing’s syndrome have been reported in the medical literature since 1972 [2, 4–6].

A 52-year-old man patient presented with Cushing’s syndrome caused by a neuroendocrine carcinoma of the thymus and ectopic ACTH secretion. His original signs and symptoms consisted of pedal edema, hypertension, hyperglycemia, decreased libido, dizziness, facial flushing, and a 50-pound weight gain. Fat deposition was classic for Cushing’s syndrome, with round face, blanching telangiectasias over the cheeks, redundant submandibular skin, and bilateral conjunctival swelling (Fig 1).

At presentation, his urinary free cortisol was 1336 μg/24 h (normal, 0–50 μg/24 h) and ACTH was 239.9 pg/mL (normal, 7.2–63.3 pg/mL). Chromogranin A and metanephrines were within normal limits. Serum cortisol remained markedly elevated at 60.2 μg/dL after a high-dose dexamethasone suppression test. Corticotropin releasing hormone was mildly elevated at 96 pg/mL (normal, <42 pg/mL). Computed tomography demonstrated bilateral adrenal hyperplasia and a 2.5 cm oval anterior mediastinal mass of heterogeneous density (Fig 2). Magnetic resonance imaging of the brain showed a 5-mm pituitary tumor, which had remained stable over the previous 2 years. It has been shown previously that ACTH-producing tumors may also secrete corticotropin releasing hormone, which that can lead to pituitary hyperplasia [7].

The thoracic surgery department was consulted, and thymectomy was recommended. The patient underwent radical excision of the anterior mediastinal contents...
through a median sternotomy. All fatty tissue between the phrenic nerves was taken from the level of the dia-
phragm to the neck, including the cervical poles of the
thymus. A firm, well-circumscribed nodule within the
thymus was adherent to the pericardium; therefore, a
portion of the pericardium was resected en bloc.

Pathologic examination of the specimen demonstrated
a 3.5 × 0.8 × 0.8 cm encapsulated tumor of thymic origin
with ACTH production demonstrated by immunohisto-
chemistry. The tumor lacked significant mitotic activity
and was chromogranin, synaptophysin, and pancytokeratin
positive, consisting of a ball of cells surrounded by S100-
positive cells. The tumor was initially classified as a par-
aganglioma. The case was referred to the Armed
Forces Institute of Pathology, where it was categorized as
a typical thymic carcinoid (Fig 3). Two and a half years
after resection, the patient has no evidence of recurrence,
and his Cushingoid features have regressed (Fig 4).

Comment

Histology
Given their aggressive behavior, carcinoid tumors of the
thyrmus have been renamed thymic neuroendocrine
tumors. They are classified into three stages: stage 1, well-
differentiated neuroendocrine carcinoma, previously
termed typical carcinoid tumor; stage 2, moderately differ-
entiated neuroendocrine carcinoma, previously termed
atypical carcinoid tumor; or stage 3, poorly differentiated or
small cell carcinoma [1, 4]. This case was a stage 1 neuro-
endocrine carcinoma.

Epidemiology
In the largest series of thymic neuroendocrine tumors (160
patients) by Gaur and colleagues [3], the male-to-female
ratio was 3:1, and the mean age at presentation was
57 years. These tumors show more aggressive behavior
than their counterparts in other locations [1]. The overall
survival rates are poor, with 10-year survival previously
reported as 10% to 35% and median survival as 64
months [1–3]. However, a more recent study reports 10-
year survival near 60%, and emphasizes the importance
of complete (R0) resection, which was achieved in 34 of
35 patients [6]. The gold standard treatment for these
tumors is radical en bloc resection to include thymec-
tomy with adjacent mediastinal fat, pericardium, pleura,
or great vessels if needed. Recurrent disease can also be
surgically excised [3, 6]. Adjuvant chemotherapy and
radiation were previously thought to improve the prog-
nosis, but a more recent study demonstrated no differ-
ce in survival with adjuvant radiation [3, 7]. As many
as 20% to 30% of patients will have metastasis at pre-
sentation, most frequently to the lymph nodes, lung,
chest wall, pleura, bone, esophagus, spleen, and liver
[1, 3, 7].

Approximately 25% of patients with thymic neuroen-
docrine carcinoma have multiple endocrine neoplasia
type 1 syndrome, and genetic testing is warranted,
especially in patients with hypercalcemia [8, 9]. Roughly
one third of patients with thymic neuroendocrine carci-
noma present with associated endocrinopathies, and 28%
of thymic neuroendocrine tumors secrete ectopic ACTH
[6]. These tumors tend to behave more aggressively than
their counterparts without endocrinopathies [10].
Cushing’s Syndrome

The most common cause (70%) of Cushing’s syndrome is a pituitary tumor secreting ACTH (Cushing’s disease). Approximately 20% of cases are caused by excessive ACTH secretion from the adrenal glands, and the remaining 10% to 15% are from ectopic ACTH secretion (EAS) [8]. Sources of EAS include bronchial, appendiceal, pancreatic, and thymic carcinoids; gastrinoma; small-cell lung cancer; pheochromocytoma; medullary thyroid cancer; and olfactory esthesioneuroblastoma [5, 8]. Skin pigmentation, hypertension, edema, and severe hypokalemia are more predominant in EAS than in Cushing’s disease [2]. Ectopic ACTH results from precursor pro-opiomelanocortin (POMC), which is overexpressed in thymic carcinoid tissue. POMC overexpression is likely the result of expression of Tpit and NeuroD1, known cell-specific activators of pituitary POMC transcription [2]. When a source of EAS is being searched for, computed tomography of the chest is recommended. Persistent anterior mediastinal soft tissue in the vicinity of the thymus in patients over 40 is usually pathologic.

Thymic neuroendocrine carcinomas may be a source of ectopic ACTH causing Cushing’s syndrome. A high level of suspicion regarding this possibility should be maintained in the evaluation of a patient with Cushing’s syndrome and EAS. Complete oncologic resection is recommended and can lead to resolution of symptoms and long-term cure.

References