Neuroendocrine Tumors (NETs) of the Mediastinum and Thymus

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Introduction

Neuroendocrine tumors (NETs) of the mediastinum and thymus are rare, and as such they have received far less attention from investigators, compared to their gastrointestinal (GI) and lung counterparts. Where research over the last several years has proven reproducible molecular alterations in GI and lung cancers, there have only been a handful of studies investigating the findings in mediastinal and thymic NETs. Diagnosis of mediastinal and thymic NETs, description of the predictive molecular markers in NET tumors with background on the role in tumorigenesis, and evidence for their value as productive markers will be discussed in this chapter.

Terminology

The term carcinoid was first presented in 1907 by Oberndorfer [1]. Later, Gosset and Masson established the existence of argentaffin granules in the tumor cells. In due time, the occurrence of these tumors in other anatomic areas was recognized [2]. Rosai and Higa were the first to acknowledge the existence of carcinoid tumors in the thymus and to separate them from more common tumors arising in this

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location, such as thymoma [3]. Since there is obvious variability in the histologic and biologic range of these lesions, Rosai et al. proposed a nomenclature [4] in 1976 for mediastinal NETs that included carcinoid grade I, for the well-differentiated tumors (conventional carcinoids); carcinoid grade II, for the moderately differentiated lesions (atypical carcinoid); and carcinoid grade III, for poorly differentiated lesions (small cell carcinoma/oat cell carcinoma). Thymic neuroendocrine tumors (neuroendocrine carcinoma) can be separated adequately based on their histopathologic features into well-differentiated, moderately differentiated, and poorly differentiated neoplasms.

According to the World Health Organization (WHO), they are classified into four histological types: typical carcinoid (TC), atypical carcinoid (AC), small cell neuroendocrine cell carcinoma (SCNEC), and large cell neuroendocrine cell carcinoma (LCNEC) [5].

Epidemiology

Primary neuroendocrine tumors of the mediastinum and thymus are uncommon neoplasms [6] with an annual incidence of 0.01/100,000 in the USA [7] with ~400 cases reported in the literature to date [8]. The prevalence of thymic NET is ~3 % of the total number of NETs at all sites [9] and estimated to account for approximately 2–4 % of all anterior mediastinal neoplasms [6, 10]. Both bronchial and thymic NETs may be part of the multiple endocrine neoplasia type 1 syndrome (MEN-1, 5–15 %) [6, 7, 9, 11, 12]. The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years [9]. They are more common in males (M:F ratio, 3:1) [6, 9].

Location

The neuroendocrine tumors are generally located in parenchymal organs [13, 14] and are the most frequently reported tumors which include neuroendocrine tumors of the lung, thymus, and parathyroid [3, 9]. Rare cases of neuroendocrine tumors located in the mesentery, retroperitoneum, inferior vena cava, presacral region, and posterior mediastinum have been reported [3, 15–18]. One NET case has been described arising from a foregut cyst [19].

Diagnostic Radiology

Chest X-ray may suggest a diagnosis of both bronchial and thymic NETs, but CT scan is the recommended investigation, and magnetic resonance imaging (MRI) is recommended to detect tumor metastases. ^{18}F-FDG PET generally demonstrates

significantly increased glucose metabolism in the poorly differentiated tumors, but it is limited in NETs [20]. However, 68Ga-DOTATOC is a somatostatin analog for highly sensitive and specific PET imaging of NETs, with a high affinity for the human SSTR2 (somatostatin receptor subtype-2) [21].

Symptoms

Most NETs of the mediastinum and the thymus are asymptomatic and are usually discovered incidentally. Clinical symptoms generally occur at an advanced stage. The patient may complain of chest discomfort, dyspnea, and cough or may present with superior vena cava syndrome. NETs may be accompanied by hormonal hypersecretion, and the patient may present with Cushing's syndrome due to ACTH secretion or may have acromegaly due to growth hormone-releasing hormone (GHRH) hypersecretion [6, 22–25]. Not infrequently, distant metastases are present at the time of diagnosis.

Tumorigenesis

The source of the primary NETs of the mediastinum is not clear; however, there are two main hypotheses. The first hypothesis proposes that the NET tumor cells arise from ectopic tissues (migratory abnormalities), and the other hypothesis suggests that they form teratomatous components [15, 16]. The source of the primary NETs of the thymus has been proposed that they are derived from Kulchitsky cells. It has been mentioned in old reports that in the high-grade NETs, you might see areas showing well-differentiated neuroendocrine tumor of the thymus in direct transition with areas of poorly differentiated neuroendocrine carcinoma indistinguishable from those of small cell carcinoma of the lung [26] which has been used to support that these tumors represent part of a continuous spectrum of differentiation that ranges from well-differentiated through poorly differentiated neuroendocrine neoplasms.

Morphology

Gross Features

Usually the neuroendocrine tumors (NETs) of the mediastinum and the thymus are well circumscribed, large (ranging from 2 to 20 cm), soft, tan brown, and with a lobulated homogeneous rubbery cut surface. Focal areas of hemorrhage, necrosis, or both might be seen.

Microscopic Features

The NETs are composed of small to medium-sized cells that are usually arranged in solid and trabecular pattern with scant cytoplasm, granular nuclear chromatin, and indistinct nucleoli (Fig. 1). You may observe pseudo-rosette formation as well. The tumors may or may not have tumor necrosis, and the mitotic rate may be less than 2, 2–10 or more than 10/10 HPF). Small cell carcinoma shows small round blue cells, with scant cytoplasm, high N:C ratio, apoptosis, necrosis, and brisk mitosis. By electron microscopy, the tumor cells demonstrate numerous desmosomes and neurosecretory granules [15].

Immunohistochemical Stains

The tumor cells express both epithelial and neuroendocrine markers. Most NETs are positive for CAM 5.2 low-molecular-weight cytokeratins (100 %), broad-spectrum keratin (AE1/3) (88 %), chromogranin (75 %), synaptophysin

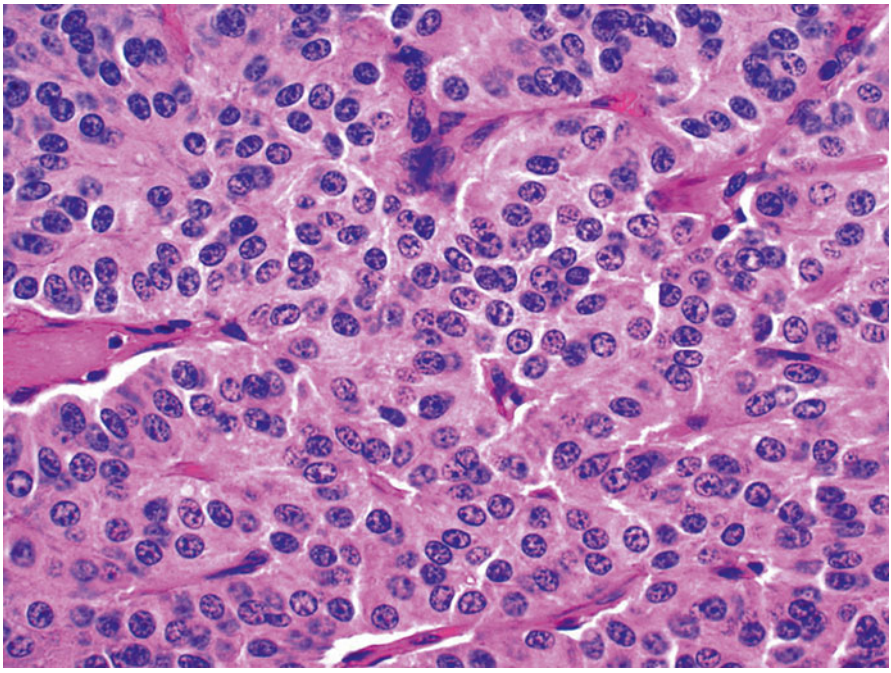

Fig. 1 Typical carcinoid (well-differentiated neuroendocrine tumor) shows nesting pattern. The nests are composed of medium-sized cells with eosinophilic cytoplasm, round to oval nuclei with granular chromatin, and no minimal mitotic activity (<2/10 HPF). There is no necrosis present in the additional section.

(72 %), and Leu-7 (68 %) [27] but negative for thyroid transcription factor-1 (TTF-1) [28].

Classification

The tumors were classified into four types: typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell neuroendocrine carcinoma (SCNEC). The WHO criteria based on the histopathologic differentiation are shown below:

1. TC: A well-differentiated tumor with mitotic figures, fewer than 2 mitoses per 10 high-power fields (HPFs) and no necrosis (Fig. 1)
2. AC: A well-differentiated tumor with mitotic figures, 2–10 mitoses per 10 HPFs and/or presence of necrosis
3. SCNEC: A poorly differentiated tumor with small cell cytology, mitotic figures with more than 10 mitoses per 10 HPFs and extensive areas of necrosis
4. LCNEC: A poorly differentiated tumor with non-small cell NEC, mitotic figures with more than 10 mitoses per 10 HPFs and extensive areas of necrosis [5]

LCNEC is extremely rare, with only few cases that have been reported so far [28, 29]. It is a relatively new category of NECs that was first described by Travis et al. [29, 30]. The majority of the reported causes of mediastinal LCNEC originated from the thymus [29, 31–33]. However, there is a case report of mediastinal LCNEC in a young patient with increase in the serum AFP which includes embryonal carcinoma in the differential diagnosis. LCNEC is strongly positive for CK7 and neuroendocrine markers (CD56, synaptophysin, and chromogranin) and negative for CD5, CD30, HCG, and PLAP, also for hepatocyte antigen [29].

Differential Diagnosis

The differential diagnosis for NECs includes other primary mediastinal tumors, which include thymoma particularly the spindle type, paraganglioma, lymphoma, parathyroid adenoma or parathyroid carcinoma, and medullary carcinoma of the thyroid arising in the mediastinum. The differential diagnosis also includes a group of small round cell tumors as PNET/Ewing sarcoma, neuroblastoma, lymphoma, and rhabdomyosarcoma [3, 15]. Spindle cell thymomas may display zones with neuroendocrine appearance and epithelial pseudo-rosettes [34, 35], like NETs, and both lesions share strong CAM 5.2 reactivity, but thymomas are negative for the neuroendocrine markers. Mediastinal paraganglioma is a real pitfall when mediastinal biopsy is performed for NETs, because they often have large hyperchromatic atypical nuclei and demonstrate prominent organoid or neuroendocrine growth pattern. They are reactive for neuroendocrine markers, but they usually are not mitotically active and most often do

not have necrosis or vascular invasion [36]. Ectopic mediastinal parathyroid tumors (adenomas and carcinomas) have intracellular glycogen that is positive with periodic acid–Schiff [37]. Immunohistochemical stains for parathyroid hormones also may be useful. Medullary thyroid carcinoma arising in ectopic mediastinal location is positive for calcitonin and carcinoembryonic antigen (CEA).

Molecular Pathology

The genetic abnormalities in thymic NETs have not been as well characterized as the other foregut NETs, but carcinoids have a distinct gene expression pattern from the normal thymus, and they are characterized by deregulations of a series of biofunctions, which may be involved in the development of NETs. Literature shows that the development of NETs may involve different genes, each of which may be associated with several different abnormalities that include point mutations, gene deletions, DNA methylation, chromosomal losses, and chromosomal gains. The foregut, midgut, and hindgut NETs have different molecular pathways. Foregut NETs have frequent deletions and mutations of the MEN-1 gene, midgut NETs have losses of chromosome 18, 11q, and 16q, and hindgut NETs express transforming growth factor alpha and the epidermal growth factor receptor. On the other hand, the most common abnormality in lung NETs is loss of chromosome 3p. Moreover, p53 mutations and 5q21 loss have more aggressive behavior and are associated with poor survival [38].

There are chromosomal imbalances that have been found by some investigators in thymic tumors, which include gains of chromosome Xp, 7p, 7q, 11q, 12q, and 20q and losses at 6q, 6p, 4q, 3p, 10q, 11q, and 13q [39, 40]. Loss of heterozygosity (LOH) at chromosome 1p has been reported in two thymic neuroendocrine tumors [39, 41]. Loss of chromosomes 3, 9p21, and Y and gain of chromosome 19p were discovered in one case [38, 39]. Although 25 % of the reported thymic NETs are from MEN-1 patients [39, 41], LOH of the MEN-1 locus on chromosome 11q13 has not been reported in thymic NETs, except in one patient [39].

Of the abnormal expression of genes that involve in cell differentiation, Wnt-signaling pathway was shown as being tightly associated with thymic carcinoids. Bi Y.F. et al. examined the b-catenin target genes MYC (c-Myc) and CCND1 (cyclin D1) expression in AC tissues to search for more evidence of Wnt pathway activation and found consistently elevated level of cyclin D1 in AC tumors, but c-Myc expression changed only moderately.

Management, Response Evaluation, and Follow-Up

The NETs of the mediastinum and thymus are characterized by more atypical histologic features and more aggressive behavior than conventional carcinoid

tumor of the lung [42, 43]. It is not uncommon to find lymph node metastases even with the low-grade NETs. A standard therapeutic approach for mediastinal NETs has not yet been defined. However, surgery remains the typical way for the management for thymic tumors [7, 8]. Localized NETs should, whenever possible, be subjected to radical surgical resection. Unfortunately, the percentage of recurrence remains remarkably elevated, higher than in bronchial NETs counterparts [44]. Surgical resection followed by cytotoxic drug therapy has become standard for metastatic bronchial and thymic NETs. Somatostatin analogs may be an option for low-grade NETs, and alpha interferon might be an option for functional tumors. Tyrosine kinase inhibitors (e.g., sunitinib) and TOR inhibitor everolimus have been stated to show better prognosis in a small series, and cisplatin-based regimens have also been of value in thymic NETs [44]. Also temozolomide-based treatment is reported to provide some advantage [45, 46]. The role of neoadjuvant/adjuvant treatment for mediastinal LCNEC has not been sufficiently evaluated because of the limited number of reported cases. SCLC is sensitive to chemotherapy, and since the biological characteristics of LCNEC are similar to those of SCLC [3], both are treated with chemotherapy regimens.

After primary surgery, patients with NETs should be followed at least yearly, up to 15 years, to detect surgically manageable recurrences. CT scan should typically be performed once a year in AC and every 2 or 3 years in TC. Patients with metastatic or recurrent disease should be followed during treatment with cytotoxic or biological agents more often, at 3–6-month intervals with imaging, preferably by CT and biological markers to assess possible benefits of the treatment administered [44, 47].

Prognosis

NETs arising in the thymus may show a more aggressive behavior than their pulmonary equivalents [5]. The most important prognostic factors with validated significance are tumor size, histological grade, paraneoplastic symptoms, thymic Masaoka staging, and surgical resection [7, 8, 48, 49]. Ki67 proliferation index is the key player in the stratification of patients with good and bad prognosis in other neuroendocrine tumors [50], but it has yet to be validated for use in thymic carcinoids [42]. Regional lymph nodes are often affected and distant metastases are common [11].

Thymic neuroendocrine tumors must be regarded as malignant neoplasms that are prone to metastasize to mediastinal lymph nodes and to distant sites, even after total excision [3, 6, 51–54], and follow-up is therefore recommended. LCNEC is associated with a 5-year survival rate of 15–57 % and the 5-year survival rate for SCLC is ∼5 % [22, 44, 55–57]. Very poor prognosis is due to high propensity for early distant hematogenous metastases [58].

Abbreviations

AC	Atypical carcinoid
LCNEC	Large cell neuroendocrine cell carcinoma
NET	Neuroendocrine tumor
SCNEC	Small cell neuroendocrine cell carcinoma
TC	Typical carcinoid

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