Familial Endocrine Syndromes

Peter M. Sadow, MD, PhD[a,b], Nicole M. Hartford, CT(ASCP)[a], Vania Nosé, MD, PhD[a,b,*]

KEYWORDS

• Endocrine tumors • Familial endocrine syndrome • Inherited neoplasm syndrome
• Inherited tumor syndrome • Multiple endocrine neoplasia • Familial diseases

ABSTRACT

Endocrine tumors may present as sporadic events or as part of familial endocrine syndromes. Familial endocrine syndromes (or inherited tumor/neoplasm syndromes) are characterized by multiple tumors in multiple organs. Some morphologic findings in endocrine tumor histopathology may prompt the possibility of familial endocrine syndromes, and these recognized histologic features may lead to further molecular genetic evaluation of the patient and family members. Subsequent evaluation for these syndromes in asymptomatic patients and family members may then be performed by genetic screening.

OVERVIEW

Endocrine tumors may present as sporadic events or as part of familial endocrine syndromes.[1] The first description of a multiple endocrine neoplasia (MEN) syndrome was in early 1900s. Aided largely by the discovery of causative genes and advanced molecular diagnostics, familial endocrine syndromes, largely emerging over the past century, are becoming more clearly elucidated.[2] Familial endocrine syndromes (or inherited tumor/neoplasm syndromes) are characterized by multiple tumors in multiple organs. In addition to the classic syndromes, such as MEN syndromes (**Box 1**), newer described entities have been identified, such as hyperparathyroidism–jaw tumor (HPT-JT) syndrome and pheochromocytoma-paraganglioma syndromes, among others. Some morphologic findings in endocrine tumor histopathology may prompt the possibility of familial endocrine syndromes, and these recognized histologic features may lead to further molecular genetic evaluation of the patient and family members. Subsequent evaluation for these syndromes in asymptomatic patients and family members may then be performed by genetic screening.

PITUITARY

Pituitary adenomas are benign neoplasms with excessive proliferation of any subtype of pituitary cells. Clinically, these tumors can give rise to profound disease due to hormonal aberration or to visual disturbance due to mass effect. Pituitary adenomas are predominantly monoclonal and various studies show that the tumor development is related to defects in oncogenes and tumor suppressor genes. These tumors can be present as an isolated event or as part of a familial endocrine syndrome.[3]

PITUITARY ADENOMA AS PART OF FAMILIAL ENDOCRINE SYNDROMES

Currently, approximately 5% of all pituitary adenoma cases have a family history of pituitary adenomas (**Table 1**), mainly because of MEN type 1 (MEN1) and Carney complex (CNC).[4–6] Familial isolated pituitary adenoma (FIPA) was described in 1999.[7]

Multiple Endocrine Neoplasia Type 1

The first pituitary adenoma in MEN1 was originally described in 1903 by Erdheim[2] at the autopsy of a patient concurrently exhibiting a pituitary adenoma and 3 enlarged parathyroid glands. Over the past century, knowledge of MEN1 in both its molecular genetic underpinnings and its clinical implications was important for the clinical management of MEN patients.

[a] Pathology Service, Massachusetts General Hospital, Boston, MA, USA; [b] Department of Pathology, Harvard Medical School, Boston, MA, USA
* Corresponding author. Pathology Service, Massachusetts General Hospital, Boston, MA, USA.
E-mail address: vnose@partners.org

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Box 1
Classic multiple endocrine neoplasia syndromes

MEN1 gene; 11q13:

PHPT (>90%): occurs at younger age than sporadic counterpart

Pituitary tumors (10%–60%): mean age of diagnosis is 38

1. PRLs: 60%
2. GH-secreting adenomas: 10%
3. Others

Enteropancreatic tumors (60%–70%)

1. Familial Zollinger-Ellison syndrome, with gastrin-producing tumors, multiple duodenal tumors
2. Insulinomas
3. Glucagonomas, VIPomas
4. Nonfunctioning

Gastric enterochromaffin-like proliferations: multiple lesions

Thymic or bronchial endocrine tumors (5%–10%)

Adrenal cortical tumors (20%–40%)

1. Aldosterone-producing tumors
2. Cortisol-producing tumors

Soft tissue tumors

Central nervous system tumors

MEN2A (*RET* gene; 10q11.2): 70%–80% of cases of MEN2 precursor lesions

Neoplastic CCH and adrenal medullary hyperplasia

MTC (90%–l00%)

Pheochromocytoma (10%–60%)

Parathyroid hyperplasia or adenoma (10%–30%)

MEN2B (*RET* gene; 10q11.2): ~5% of cases of MEN2 precursor lesions

Neoplastic CCH and adrenal medullary hyperplasia

MTC (100%): aggressive form associated with CCH

Pheochromocytoma (40%–60%)

Mucosal neuromas of lips, tongue, eyelids (>70%)

Ganglioneuromatosis of the intestine (>60%)

Marfanoid habitus (100%)

Medullated corneal nerve fibers (>60%)

CNC (*PRKAR1A* gene; 17q22-24):

PPNAD (>25%) with Cushing syndrome

Mucocutaneous pigmented lesion (100%)

Myxomas (40%–90%)

Multiple thyroid follicular adenomas (75%)

Pituitary GH-producing adenoma (10%)

Large cell calcifying Sertoli cell tumor

Psammomatous melanotic schwannoma

Osteochondromyxoma