Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) to Carcinoid: Exploring the Link

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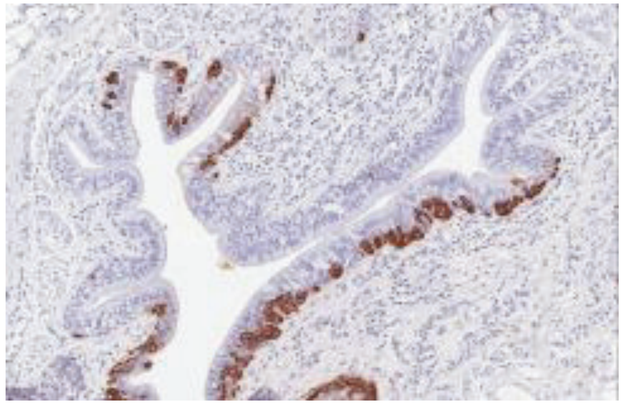
Background

Neuroendocrine cells (NECs) play important roles in normal lung development, autonomic regulation of lung function, and response to hypoxia or injury. They are located between the respiratory epithelium and the basement membrane of bronchi and bronchioles (below), often as single cells or small clusters.



NEC proliferation is a common pathologic occurrence, well established as a *reactive* response to chronic lung injury. Much less commonly, NEC proliferation is observed in the absence of apparent inciting factors. This *neoplastic* phenomenon is termed "diffuse idiopathic pulmonary neuroendocrine cell hyperplasia" (DIPNECH).

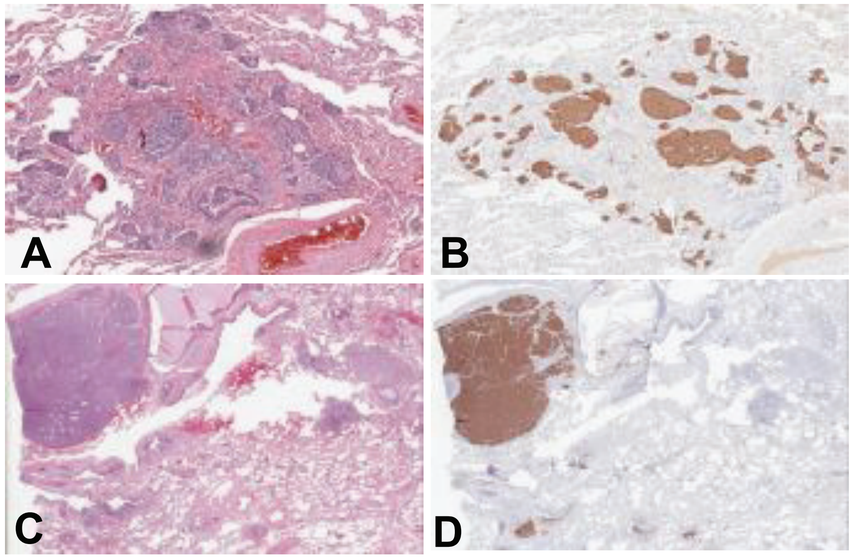
DIPNECH is recognized as a precursor lesion for carcinoid tumors. While the progression of DIPNECH to carcinoid is an accepted transformation, little is known about the genetic events that drive the pulmonary neuroendocrine cells to proliferate, penetrate the basement membrane, and sustain growth from the tumorlet stage (NEC mass <5mm) to the carcinoid stage (≥5mm). The best described genetic involvement implicates the *MEN1* tumor suppressor gene on chromosome 11 as an important early event in the transformation process, but similar disease models suggest that this will prove to be just one event in the spectrum.

Objective

This project aims to explore current knowledge on the transformation of DIPNECH to carcinoid tumors, using a review of literature to describe the implicated genetic events and two case studies to highlight clinicopathologic findings.

Case Reports

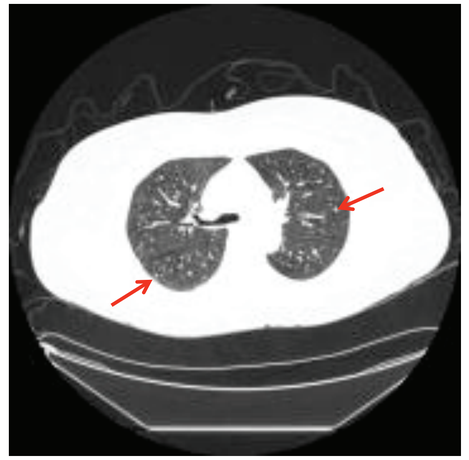
	Patient 1	Patient 2	"Typical Patient"
Demographics	56 year old female, nonsmoker	60 year old female, nonsmoker, +PPD	58yo white female, nonsmoker
Method of detection	Pulmonary nodule identified on chest CT; CT was performed for evaluation of patient's atrial fibrillation	X ray earlier in the year demonstrated multiple pulmonary nodules; CT scan performed to follow up	CT; findings often incidental
Past Medical History	HTN, paroxysmal atrial fibrillation, hyperthyroid	Active TB infection	-
Respiratory symptoms	Asymptomatic	Asymptomatic	Asymptomatic, or symptoms of cough, dyspnea, and wheezing
PFTs	-	-	Mixed obstructive/restrictive profile
Radiographic findings	"Noncalcified, lobulated indeterminate nodules in the medial segment of the right middle lobe, superior segment of the left lower lobe and a probable 6mm nodule in the lingula"	"Bilateral small pulmonary nodules. Some of the nodules have a centrilobular nodular appearance, and tend to follow a branching distribution"	Bilateral ground glass opacities, air-trapping, mosaic attentuation, and bilateral noncalcified nodules.
Pathologic dx	DIPNECH with an atypical carcinoid tumor and separate, contralateral typical carcinoid tumor	DIPNECH of the left upper and lower lobes, with a single typical carcinoid tumor	DIPNECH, with or without carcinoid tumor presence
Treatment	Lobectomy for carcinoid tumors; close followup for DIPNECH by serial CT	Close followup for DIPNECH by serial CT	Without carcinoid, tx typically not required; surgery and somatostatin analogs used in symptomatic patients
Clinical Outcome	Discharged in stable condition 3 days post-op	Diagnosis made, no treatment recommended	Generally excellent long-term prognosis, with or without tx



A. Tumorlet formation constricting airway in Pt. #2; **B.** Synaptophysin highlights tumorlet.

C. Carcinoid tumor with surrounding tumorlets & neuroendocrine cell hyperplasia in Pt #1; **D.** Synaptophysin highlights the carcinoid tumor & surrounding DIPNECH.

Imaging



High-resolution CT (Pt. #2) shows 2 centrilobular nodules in a single sagittal section. This patient had numerous nodules throughout the lungs bilaterally.

Discussion

Colorectal cancer (CRC) has a well defined sequence of mutations that describe the transformation of adenoma to carcinoma. In contrast, the progression of DIPNECH is carcinoid is poorly understood.

An early gene of interest in carcinoid tumors is the *MEN1* tumor suppressor gene of Chr11. Finkelstein *et al* used microdissection to remove tissue samples of carcinoid tumors and neighboring tumorlets from wedge biopsies and sequenced the *int2* gene, which neighbors *MEN1*. Allelic imbalances were present only in carcinoid tumors and absent in tumorlets, proving that tumorlets were not metastatic spread of carcinoid. The authors reported *MEN1* changes to be a key early event in transformation of tumorlets to carcinoid, in light of the frequency they observed and the absence of other gene involvement (including *WT1*, *VHL*, and *TP53)* (12).

Future goals

1. Utilize the microdissection-and-genotyping approach to identify significant genetic events that drives DIPNECH transformation in patients that present with both DIPNECH and carcinoid tumors.
2. Monitor current DIPNECH research and develop a database of implicated mutations, with the goal of creating a definitive mutation sequence model from DIPNECH to carcinoid.