CLINICAL VIGNETTE

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

Evangelia Kirimis, MD

A 46-year-old female with neuroendocrine tumor developed abdominal pain several years ago. Computed tomography (CT) of the abdomen did not find an underlying cause for her symptoms, but identified a 5 millimeter (mm) left lower lobe lung lesion of unclear significance. CT of the chest noted the known left lower lobe lesion as well as an 11mm right upper lobe and 11mm right middle lobe nodules. Serial Chest CTs found no major changes until three years later. At that time CT Chest identified multiple lung nodules, including growth of the left lower lobe nodule and right middle lobe nodules to 8mm and 13mm. The right lower lobe nodule was stable and there were new bilateral 2-6mm nodules. A fluorodeoxyglucose positron emission tomography (FDG-PET) noted the known bilateral pulmonary nodules with the largest lesions showing low-grade activity. Given the features noted on imaging, CT-guided biopsy on the right middle lobe lesion was consistent with a low-grade neuroendocrine carcinoid tumor. The cells were positive for CAM 5.2, CK7, TTF1, Napsin-A, synaptophysin, chromogranin and NSE while Ki-67 was less than 5%. Colonoscopy found only benign polyps. DOTATATE-PET noted two significant lesions, one in the right middle lobe measuring 14mm and a right upper lobe lesion measuring 10mm. Other small lesions were noted below the diagnostic threshold of the PET imaging. Labs including complete blood count, complete metabolic panel, and chromogranin were all unremarkable. Based on the findings, it appeared that she had primary bronchial carcinoid and that the lesions were not metastatic in nature.

The patient consulted with a cardiothoracic surgeon and proceeded with a left lower lobe resection along with lymph node dissection. Pathology noted a 5mm typical carcinoid tumor and incidental carcinoid tumorlets measuring 1mm and 4mm with a background of neuroendocrine cell hyperplasia. All lymph nodes examined were benign but given the full findings, a diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) was supported. The following month she proceeded with right middle lobectomy and right upper lobe wedge resections. Pathology again indicated DIPNECH with two typical carcinoid tumors measuring 13mm and 7mm, multiple carcinoid tumorlets and prominent neuroendocrine cell hyperplasia and peribronchiolar metaplasia. Given her bilateral disease she was staged as T1bN0M1a.

At this point, she was monitored expectantly, and her imaging remained stable for about two years. She then underwent cryoablation for a growing left upper lobe lesion followed a year later by a cryoablation of a growing right upper lobe nodule and then three months later with cryoablations for right upper and left upper lobe lesions. Her chromogranin values which were also normal on multiple checks, began to rise with the growth of the most recent lesions but later declined indicating response with local treatment.

DIPNECH is an uncommon diagnosis but is a premalignant disease that leads to increased neuroendocrine cell development as noted above.[1-3] Given its rarity and the consequent scarring due to fibrosis, pulmonary function tests may often be misinterpreted as obstructive pulmonary disease like asthma and chronic bronchitis.[1] A prior case report noted a similar presentation with a peri-centimeter nodule was monitored with no change for several years, before beginning to grow.[1] Labs were unremarkable, and wedge resection was performed with pathology confirming neuroendocrine cells and a pathologic diagnosis of DIPNECH.[1] At the time of publishing, this outside patient had been followed for a year with no further interventions.[1] DIPNECH is a relatively newly recognized diagnosis, with limited management information.[1] It is felt neuroendocrine cells in the lung are important for fetal lung development and their concentration drops with maturity, eventually becoming focal in adults.[3] Most patients present with a dry cough but many are asymptomatic.[1-3] The disease usually is bilateral and diffuse and predominantly found in middle aged and older females.[2,3] Presenting with a solitary nodule as in the prior case report is not usual, although the follow up had only been for a year.[1] Chest CT imaging can show small pulmonary nodules that grow insidiously over time as in our patient and the outside case report.[2,3] Bronchial wall thickening, bronchiectasis, and mosaic attenuation may be noted on imaging.[2,3] DIPNECH generally progresses to tumorlets and eventually carcinoid.[1,2] Specifically, DIPNECH is limited to the respiratory epithelium and has not progressed through the basement membrane.[1,3] When the collection of cells is less than 5mm, it is referred to as a tumorlet and after the tumor grows beyond 5mm it is considered a carcinoid tumor.[1,3] Confirming the diagnosis requires pathology that notes more than five neuroendocrine cells within the tissue and immunohistochemistry staining that confirms endocrine markers such as synatophysin, chromogranin A, and CD56.[1]

DIPNECH prognosis is generally considered good despite the diffuse disease given its slow-growing nature.[1-3] While there are reports of significant respiratory disease, this is rare, so expectant and conservative management is usually employed.[1-3]

Treatment guidelines are limited due to disease rarity. Somatostatin analogs, azithromycin and steroids may help patients with symptomatic cough.[1,2] Lung resection and other local therapies have been employed.[3] Lung transplant has also been performed.[1-3] Mammalian target of rapamycin (mTOR) inhibitors may be effective as seen in gastrointestinal carcinoids, but data are limited for pulmonary disease.[3] Also atypical carcinoid tumors can form and lead to metastatic disease, although usually not a common feature.[2]

Our patient was never symptomatic. The findings were incidental and she has been monitored and treated expectantly given her diffuse disease and potential for future issues without some control of growth given her relatively young age at diagnosis. She continues to do well and if further local therapy was not feasible, would likely explore somatostatin analogs as the next step for potential disease control if she develops future symptoms.

REFERENCES

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