Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia in a Patient with Multiple Pulmonary Nodules: Case Report and Literature Review

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Abstract

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary disease, where carcinoid tumorlets invade the pulmonary parenchyma and bronchioles. These nests of cells release a variety of mediators including bombesin and gastrin releasing peptide that cause heterogeneous bronchoconstriction, creating a mosaic appearance on chest imaging studies, especially on expiratory scans. Clinically patients usually have long standing symptoms of shortness of breath (SOB) and cough that are difficult to distinguish from asthma. In this article we describe a case of DIPNECH in a patient with several years' history of SOB and cough, and review 179 cases of DIPNECH reported in the literature since 1992.

Case Presentation

A 72-year-old, non-smoking lady was admitted to the hospital in preparation for bilateral mastectomy. She recently received a diagnosis of bilateral breast invasive ductal carcinoma grade 2, estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 (HER-2) positive in the left tumor but negative in the right tumor.

Her past medical history was significant for hypertension, long standing cough and dyspnea on exertion labeled as asthma poorly responsive to nebulizers. Socially, she was a house wife with no history of occupational exposure.

The patient was found to be tachypneic (respiratory rate 22 breaths/minute) and hypoxemic (oxygen saturation 86% on room air). Heart rate and blood pressure were within normal limits. She had bilateral decreased breath sounds and diffuse expiratory wheezes.

Chest CT scan revealed diffuse mosaic pattern and multiple pulmonary nodules in both lungs suggestive of metastases (Figure 1).

Figure 1. Representative images from chest CT scan showing a diffuse mosaic pattern and multiple pulmonary nodules in both lung fields suggestive of metastases.

These lesions did not take up fludeoxyglucose (FDG) on positron emission tomography (PET) scan. Her pulmonary function tests (PFT) were unremarkable except for reduction in expiratory reserve volume (ERV) at 22%, and increased residual volume to total lung capacity ratio (RV/TLC) at 136% probably related to air trapping. Diffusion lung capacity was within normal limits.

Video assisted thoracoscopic biopsy of one of the nodules in left lower lobe was done. Pathology showed both a carcinoid tumor and tumorlets invading lung bronchioles (Figure 2A & B) and these tumorlets were positive for chromogranin (Figure 2C & D) and pancytokeratin (Figure 2E & F).

Figure 2. A & B: histology (H&E stain) showing carcinoid tumorlets invading lung bronchioles; C & D: positive staining for chromogranin; E & F: positive staining for pancytokeratin.

A diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) was made, and the patient was treated with intravenous steroids and nebulizers. Her oxygen saturation improved to 94% on room air. She was later discharged on oral steroids. Her CT scan also showed no significant improvement in changes described above.

Review of the Literature

Methods

We searched PubMed for all cases of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia reported in the English literature since 1992 when the entity was first described. A total of 179 patients were identified in 55 articles, in the form of case reports and case series. In this article we contribute an additional patient (1-55).

Patient Characteristics

A total of 180 patients (including our patient) were identified. There were 161 females (89.5%) and only 19 males (10.5%). Mean age at diagnosis was 57.75 years (males tended to present at a younger age of 52 years, compared to 58.4 years in females). Most patients were never smokers 52.8%, smokers/exsmokers 27.2%, and in 20% smoking status was not mentioned.

The majority of patients presented with cough (91 patients, 50.5%), followed by exertional dyspnea (81 patients, 45%), and hemoptysis (6 patients, 3.3%). Incidental imaging findings led to diagnosis in 22 patients (12.2%). Mean duration of symptoms before diagnosis was 8.25 years (Table 1).

Table 1. Patients` characteristics and presenting symptoms.

		Number (180 pts)	%
Demographics			
Males		19	10.50 %
Females		161	89.50 %
Mean Age		57.75 Y	
Mean Age (Males)		52 Y	
Mean Age (Females)		58.4 Y	
Smoking History	Smoker	14	7.80%
	Exsmoker	35	19.40 %
	Never Smoker	95	52.80 %
	Not Mentioned	36	20%
			50.50 %
Presenting Complaint*	Cough	91	50.50 %
	Shortness of Breath	81	45%
	Hemoptysis	6	3.30%
	Incidental	22	12.20 %
	Not Mentioned	27	15%
Mean Duration Before Diagnosis		8.25 Y	
* A patient may present with more than one symptom			

Diagnosis, Therapy and Outcome

Most patients underwent imaging with chest CT scan, the most common findings were nodules in 148 patients (82.2%), ground glass opacities/mosaic pattern in 66 patients (36.6%), and bronchial wall thickening in 37 patients (20.5%). Most patients had an abnormal spirometry: obstructive pattern (48.9%), restrictive (5%), or mixed obstructive restrictive pattern (6.7%) (Table 2).

Table 2. Spirometry and imaging.

		NUMBER (180 pts)	%
Spirometry	Obstructive Pattern	88	48.90%
	Restrictive Pattern	9	5%
	Mixed Pattern	12	6.70%
	Normal	28	15.50%
	Not Mentioned	43	23.90%
Imaging Findings*	NODULES	148	82.20%
	GGO & Mosaic Pattern	66	36.60%
	Bronchial Wall Thickening	37	20.50%
	Bronchiectasis	13	7.20%
	Lymphadenopathy	4	2.20%
	Atelectasis	21	11.60%
	Normal	1	0.50%
	Honeycombing & Fibrosis	1	0.50%
	Not Mentioned	13	7.20%

* A patient may have more than one finding on chest CT scan

Because of their symptoms, and spirometry findings 45 patients (25%) were labeled with another disease including asthma in 29 patients (16.1%), COPD in 12 patients (6.6%) and bronchiolitis in 4 patients (2.2%).

The diagnosis was made using surgical lung biopsy in 148 patients (82.2%), bronchoscopic biopsy in 10 patients (8 transbronchial biopsy, 2 endobronchial biopsy) (5.6%), CT-guided biopsy in 7 patients (3.9%), postmortem diagnosis in 3 patients (1.7%), post lung transplantation in 2 patients (1.1%) and clinically in 2 patients (1.1%). The diagnostic method was not mentioned in 8 patients (4.4%).

Patients received a variety of therapies including inhaled bronchodilators, inhaled or systemic steroids, and somatostatin analogues among others. Response to treatment was mentioned for 89 patients, (59 patients reported that their symptoms remained stable, 11 patients improved with treatment, while 18 patients reported symptom progression and 2 patients died. (Table 3).

Table 3. List of DIPNECH articles ordered by publication year. This table shows number of patients in each article, diagnostic method, therapy given and outcome.

Author (Ref. No.)	Year	No. of patients	Diagnostic method	Therapy, (outcome)
Aguayo (1)	1992	6	Surgical Lung biopsy	Pt 1: Chemotherapy (Disease progression), Pt 2 :Chemotherapy (stable), Pts 3-6: Inhaled bronchodilators (stable)
Miller (2)	1995	19	Surgical Lung biopsy	Not mentioned
Armas (3)	1995	1	Surgical Lung biopsy	Not mentioned
Brown (4)	1997	1	Surgical Lung biopsy	Not mentioned
Alshehr (5)	1997	1	Surgical Lung biopsy	Not mentioned
Lee (6)	2002	5	Surgical Lung biopsy	Not mentioned
Ruffini (7)	2004	3	Surgical Lung biopsy	Not mentioned
Fessler (8)	2004	1	Surgical Lung biopsy	Systemic steroids (Disease progression)
Carmichael (9)	2005	1	Surgical Lung biopsy	Not mentioned
Swigris (10)	2005	4	Surgical Lung biopsy	Pt 1: Surgical resection (Improved), Pts 2-4 not mentioned
Terminella (11)	2005	1	Surgical Lung biopsy	Steroids (progression)
Adams (12)	2006	1	Surgical Lung biopsy	Not mentioned
Johney (13)	2006	1	Surgical Lung biopsy	Surgical resection (stable)
Reyes (14)	2007	2	Surgical Lung biopsy	ORAL/ INHALED STEROIDS+BRONCHODILATORS (1 improved, 1 stable)
Singhania (15)	2007	1	TBBX	Not mentioned
Ge (16)	2007	1	Surgical Lung biopsy	Not mentioned
Davies (17)	2007	19	Surgical Lung biopsy	2 steroids, 7 observation, 10 not mentioned (11 stable, 1 progression, 7 not mentioned)
Alqadah (18)	2007	1	TBBX	Not mentioned
Warth (19)	2008	1	Surgical Lung biopsy	Surgical resection (stable)
Coletta (20)	2009	3	1TBBX, 2 surgical biopsy	Pt 1 : steroids (Progression), Pt 2: inhaled steroids and bronchodilators (Progression), Pt3: Oral & Inhaled Steroids (stable)
Sanaee (21)	2009	1	Surgical Lung biopsy	Steroids (improved)
Lim (22)	2010	2	Surgical Lung biopsy	Not mentioned
Irshad (23)	2010	1	Surgical Lung biopsy	Surgical resection (improved)
Stenzinger (24)	2010	1	Post mortem	Not applicable
Tippett (25)	2010	1	Surgical Lung biopsy	Therapy not mentioned (Stable)
Nassar (26)	2011	1	Surgical Lung biopsy	Steroids (improved)
Cameron (27)	2011	1	TBBX	Lanreotide (stable)
Falkenstein-Ge (28)	2011	1	Surgical Lung biopsy	ORAL & INHALED STEROIDS (stable)
Gorshtein (29)	2012	11	9 surgical biopsy, 2 CT-guided biopsy	5 Octreotide, 1 Lanreotide, 5 not mentioned (4 improved, 2 stable, 5 not mentioned)
Patel (30)	2012	1	CT-guided biopsy	Observation (stable)
Montoro (31)	2012	1	Surgical Lung biopsy	Observation (stable)
Walker (32)	2012	1	Surgical Lung biopsy	Steroids (improved)
Mireskandari (33)	2013	4	Surgical Lung biopsy	Not mentioned
Dvořáčková (34)	2013	1	Surgical Lung biopsy	Not mentioned
Oba (35)	2013	1	EBBX	Surgical resection (stable)
Karnatovskaia (36)	2014	1	Surgical Lung biopsy	Steroids (progression)
Al-Ayoubi (37)	2014	1	Surgical Lung biopsy	Died of concomitant lung adenocarcinoma
Killen (38)	2014	1	Surgical Lung biopsy	Inhaled steroids and bronchodilators (stable)
Zhou (39)	2014	2	Post lung transplant	DOUBLE LUNG TRANSPLANT (stable)
Erdini (40)	2015	1	Surgical Lung biopsy	Not mentioned
Abrantes (41)	2015	3	1 CT-guided biopsy 2 surgical biopsy	Therpay not mentioned (2 patients remained stable)

Pietrangeli (42)	2015	1	Surgical Lung biopsy	Not mentioned
Chauhan (43)	2015	5	Surgical lung biopsy	4 Octreotide (stable), Observation (not mentioned)
Hassan (44)	2015	1	Post mortem	Not applicable
Godwin (45)	2015	1	Surgical lung biopsy	Not mentioned
Carr LL (46)	2015	30	18 Surgical lung biopsy	20 Inhaled steroids, 14 oral steroids, 11 Octreotide LAR
			4 TBBX, 2 EBBX	9 resection of a carcinoid
			3 CT-guided biopsy	(16 stable, 8 rapid progression, 2 longterm progression
			2 Clinical, 1 post mortem	1 died of progressive BO, 3 Unknown)
Baniak (47)	2016	6	Not mentioned	Not mentioned
Kuruva (48)	2016	1	Surgical Lung biopsy	Not mentioned
Cevriye (49)	2016	2	Surgical Lung biopsy	Pt 1: surgical resection (progression), Pt 2: not mentioned
Ishizaki (50)	2016	1	Surgical Lung biopsy	Not mentioned
Kshitij (51)	2016	1	Surgical Lung biopsy	Steroids and Octreotide (improved)
Escudero (52)	2016	3	Surgical Lung biopsy	Therapy not mentioned (patients remained stable)
Trisolini (53)	2016	13	Surgical Lung biopsy	Not mentioned
Whitney (54)	2016	1	Surgical Lung biopsy	Inhaled steroids and bronchodilators (stable)
Hsu (55)	2017	2	Not mentioned	Not mentioned
Our case	2017	1	Surgical Lung biopsy	Inhaled steroids and bronchodilators (stable)

Total number of patients 180

Of note, 15 out of 23 patients who received a somatostatin analogue reported stable, or improvement in their symptoms (65.2%), which did not necessarily translate into improvement in air flows on spirometry (27, 29, 46, 51).

Discussion

Pulmonary neuroendocrine cell hyperplasia was described early in the previous century (56), however the significance and role of the pathologic changes were not precisely determined. It was thought that they were secondary to other lung diseases such as interstitial lung disease, bronchiectasis, cystic fibrosis, smoking exposure, or in people who live at high altitude. In addition to the previously mentioned associations, hyperplasia of pulmonary neuroendocrine cells was also thought to be a pre-neoplastic process, since the lesions can potentially progress to carcinoid tumors even without causing symptoms or airflow limitation. In 2004 the changes were recognized by WHO as one end of the spectrum of pulmonary neuroendocrine tumors.

The relationship between carcinoid tumorlets and other pulmonary diseases and its role in precipitating respiratory symptoms remains puzzling. The term DIPNECH was coined in 1992 by Aguayo (1) who described a new entity where idiopathic hyperplasia or dysplasia of pulmonary neuroendocrine cells occurred in the absence of other lung disorders. The changes were associated with physiologic and radiologic airflow limitation similar to obliterative bronchiolitis. This was the first description of pulmonary neuroendocrine hyperplasia as a primary process.

Because of similar symptoms, an obstructive pattern on pulmonary function tests, and chest imaging suggestive of air trapping, many patients receive a diagnosis of asthma for several years before the correct diagnosis is made. This similarity to other obstructive lung diseases can be explained by the pathologic changes of airway obstruction seen on biopsy. Pulmonary neuroendocrine cells, or Kulchitsky cells, are

normally present in small numbers in airways, where they release a myriad of bioactive amines and peptides like serotonin, chromogranin A, gastrin-releasing peptide (GRP), and calcitonin.

Airway obstruction is believed to occur both due to physical obstruction of bronchioles by tumorlets and smooth muscle constriction caused by active mediators released. Bombesin and related peptides like gastrin releasing peptide, neuromedin B and neuromedin C are thought to cause bronchoconstriction indirectly through the release of several other bronchoconstrictors that act on smooth muscle cells (57). However, *in vitro* studies in guinea pig lungs suggest that bombesin may act directly by binding to specific receptors on smooth muscle cells (58).

Pulmonary neuroendocrine pathology occurs in a spectrum of three forms: hyperplasia, tumorlets and carcinoid tumors. DIPNECH is characterized by proliferation of neuroendocrine cells initially limited to the basement membrane of airways, when disease extends beyond the lumen of airway it is called carcinoid tumorlets. Tumorlets larger than 0.5 cm become carcinoid tumors and appear as nodules on chest CT scans. Diagnosis requires lung biopsy, with a surgical biopsy procedure more likely to provide diagnostic tissue than bronchoscopic transbronchial biopsies.

According to Aguayo's definition of DIPNECH, patients have pulmonary symptoms with radiographic and physiologic abnormalities suggestive of obstructive lung disease, but in our review 12.2% of patients had no symptoms at all, and 15.5% had normal spirometry. We believe hyperplasia, tumorlets and carcinoid tumors represent different aspects of the same disease, the occurrence of symptoms, radiologic and physiologic airflow limitation depends on the time frame at which diagnosis was made, should those patients be followed up, they could develop symptoms and airflow limitation in the future. Thus, we propose to expand the definition to include patients with no symptoms or spirometry abnormalities. However, it remains uncertain whether asymptomatic patients who are diagnosed at an earlier stage need specific treatment or not.

It is also clinically difficult to establish a causal relationship, or determine the direction of the relationship between pulmonary neuroendocrine cell hyperplasia and other concomitant lung disorders, or harmful exposures (1,59, 60). In our review 27.2% of patients were active or previous smokers, only one patient lived at high altitude (more than 2000m) (14), 29 patients had a history of previous or current malignancy including 8 lung cancers (not shown in table), 13 patients had evidence of bronchiectasis, and one patient had honeycombing on imaging. These findings are similar to data obtained from individual case reports and series (2, 6, 14, 17, 19, 22, 29, 33, 37, 46, 47 and 53).

When the diagnosis is made, therapeutic options may include observation for mild symptoms, inhaled or systemic steroids, in addition to bronchodilators, especially if patients who show reversible airway obstruction on PFT. Other potential therapies are somatostatin analogues, however more studies are needed to determine their precise role. (27, 29, 43, 46)

Conclusion

DIPNECH is a rare clinical entity that requires a high clinical suspicion. Because of clinical, spirometry, and imaging similarity to other obstructive lung diseases, and the requirement for lung biopsy to make the diagnosis, DIPNECH is probably an under-diagnosed entity, with still limited treatment options. The diagnosis should probably be considered in any patient with difficult to treat obstructive lung disease, unexplained bronchiolitis, particularly if there are multiple small lung nodules present on chest CT scan. We propose to expand the definition of DIPNECH to include patients with even no symptoms or spirometric evidence of airflow limitation, as development of these abnormalities depends on the time frame at which diagnosis is made. It is also difficult to establish a causal relationship with other concomitant lung conditions, the presence of which should not rule out a diagnosis of DIPNECH.

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