ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Case Report

Diffuse Neuroendocrine Cell Hyperplasia in a Sarcoidosis Patient

Cuneyt Tetikkurt[1]*, Halil Yanardag[2], Sebnem Batur[3], Burcak Haluk Sayman[4] and Muammer Bilir[2]

[1]Professor, M.D, Department of Pulmonary Medicine, Cerrahpasa Medical Faculty, Istanbul Cerrahpasa University, Turkey

[2]Professor, M.D, Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul Cerrahpasa University, Turkey

[3]Assistant Professor, M.D, Department of Pathology, Cerrahpasa Medical Faculty, Istanbul University Cerrahpasa, Turkey

[4]Professor, M.D, Department of Nuclear Medicine, Cerrahpasa Medical Faculty, Istanbul Cerrahpasa University, Turkey

***Corresponding Author:** Tetikkurt C, Professor, M.D, Department of Pulmonary Medicine, Cerrahpasa Medical Faculty, Istanbul Cerrahpasa University, Turkey.

Received: November 11, 2021; **Published:** November 30, 2021

Abstract

A 48 year old female smoker presented with dry cough, anorexia, and weight loss. Physical examination was normal. Chest x-ray and HRCT showed parenchymal infiltrations in both lungs along with right paratracheal, bilateral hilar, and mediastinal lymphadenopathy. PFTs showed a restrictive defect with a decreased DLCO/VA value. ^{18}FDG PET/CT revealed enlarged hilar and mediastinal lymph nodes while ^{68}Ga-citrate and ^{68}Ga-DOTA-TATE showed physiologic tracer uptake throughout the body. Histopathologic examination of the bronchoscopic bronchial mucosa biopsy specimen identified neuroendocrine cell hyperplasia.

We report a case of DIPNECH in a sarcoidosis patient diagnosed by an incidental bronchoscopic biopsy. Our case may highlight the pathogenesis of this syndrome and may as well clarify the mechanisms or pathways associated with both disorders. Simultaneous use of three nuclear imaging modalities including ^{18}F-FDG PET/CT, ^{68}Ga-citrate PET/CT, and ^{68}Ga-DOTA-TATE PET/CT did not provide any data for the identification of DIPNECH that were performed for its diagnosis and coexistent sarcoidosis.

Keywords: *Malignancy, Neuroendocrine Cell Hyperplasia, Sarcoidosis, DIPNECH*

Introduction

Sarcoidosis is a systemic chronic inflammatory disease of unknown etiology characterized by the presence of non-caseified mainly granulomas primarily in the lung and lymph nodes while various other organs like eye, skin, liver, or spleen may also be involved. Pathogenesis is associated with antigen-driven CD_4 T-cell activation due to inhaled antigens in genetically susceptible individuals followed by the release of inflammatory cytokines such as IL-2, TNF-α, interleukin-5, and interleukin-17 leading to granuloma formation [1,2]. Askling., *et al* has reported a two fold relative risk of cancer in 474 sarcoidosis patients [3]. Other studies have also disclosed the association of sarcoidosis with malignant disorders such as Hodgkin lymphoma and leukemia [4,5]. DIPNECH [Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)] is a rare disorder characterized by the abnormal overgrowth of neuroendocrine cells in the lungs. On the other hand, coexistence of sarcoidosis and DIPNECH is an extremely rare condition that has been enunciated as sporadic case reports [6,7] in literature.

Normal lung tissue comprises scattered neuroendocrine cells within the bronchiolar epithelium. In the absence of lung injury DIPNECH is considered a preinvasive condition that necessitates follow-up (8-11). Hyperplasia of neuroendocrine cells may ocur as a response to chronic inflammation such as chronic bronchitis, emphysema, or asthma (12-14). We report a case of DIPNECH that was diagnosed coincidentally in the bronchial biopsy specimen. Clinicians should consider the presence of preneoplastic lesions that may develop insidiously in patients with an asymptomatic clinical profile without any evidence of laboratory or imaging manifestations in sarcoidosis

patients. This is the first case where three different nuclear imaging modalities have been used for DIPNECH diagnosis that may shed light on the utility of these procedures in regard to final diagnosis. Coexistence of these two disorders may elucidate the involved pathologic mechanism for both disorders.

Case Report

A 48 year old female was admitted for dry cough, anorexia, and ten kilograms weight loss within three months. She had sarcoidosis of twenty years and diabetes mellitus for five years. Vital signs revealed a blood pressure of 110/70 mm Hg, a 86 beats/minute resting pulse and a 14 breaths/minute respiratory rate. Blood count and serum biochemistry were normal. Serologic markers for collagen vascular diseases including ANA, RF, anti-dsDNA ENA, cANCA and pANCA were negative. Serum ACE was 28 U/L. ECG showed a sinus rhythm. Tumor markers CEA [Carcino-embryonic antigen (CEA)] and NSE [Neuron-spesific enolase (NSE)] were within normal limits. Chest x-ray demonstrated bilateral parenchymal infiltrations with a right paratracheal and bilateral hilar lymphadenopathy. HRCT [High resolution computed tomography (HRCT)] revealed bilateral parenchymal infiltrations, supraclavicular, anterior mediastinal, prevascular, right paratracheal, bilateral hilar, and subcarinal enlarged lymph nodes.

Pulmonary function tests showed a restrictive pattern with a FEV_1: 1640 ml (82%), FVC: 1780 ml (64%), FEV_1/FVC: 92%, TLC: 2.35 (68%), and a decrease in DLCO/VA 4.86 (62%). Arterial blood gas analysis revealed a mild decrease in pO_2 (72 mm Hg) and a normal pCO_2 (38 mm Hg) values. Six minute walking distance was 450 meters. Bronchoscopic evaluation was normal while BAL [Bronchoalveolar lavage (BAL)] revealed 56% macrophages, 42% lymphocytes, 12% neutrophils, and a 4.2 CD_4/CD_8 ratio. BAL culture and smear were negative for bacteria, tuberculosis, and fungus. Histopathologic examination of the bronchoscopic biopsy specimens showed proliferating cells in the bronchial mucosa that crossed beyond the basal lamina to form a tumorlet. Immunohistochemistry analysis revealed CD_{56} and snaptophysin positivity that identified neuroendocrine cell hyperplasia (Figure 1A-D). The final diagnosis was stage II sarcoidosis with DIPNECH. ^{18}F-FDG PET/CT revealed multipl enlarged mediastinal and hilar lymph nodes with a SUVmax between 12.80 and 21.90 along with a minimally increased ^{18}F-FDG uptake in multiple parenchymal foci of the lung indicating mild granulomatous inflammation. ^{68}Ga-citrate PET/CT and ^{68}Ga-DOTA-TATE PET/CT demonstrated physiologic ^{68}Ga-citrate avidity throughout the body (Figures 2 and 3) including the lungs and mediastinum.

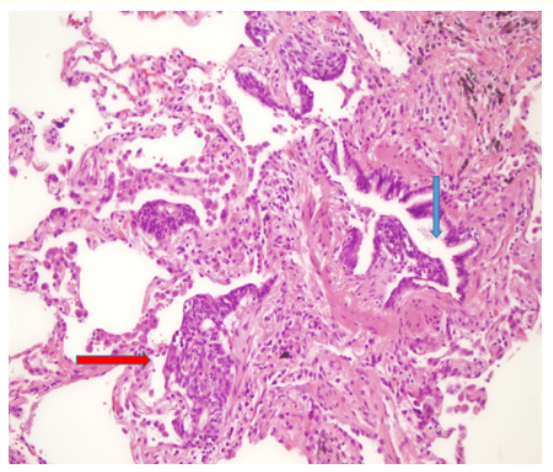

Figure 1A: *Proliferating neuroendocrine cells (blue arrow) that cross beyond the mucosal basal lamina to form a tumorlet (red arrow) in the alveoli (HEx200).*

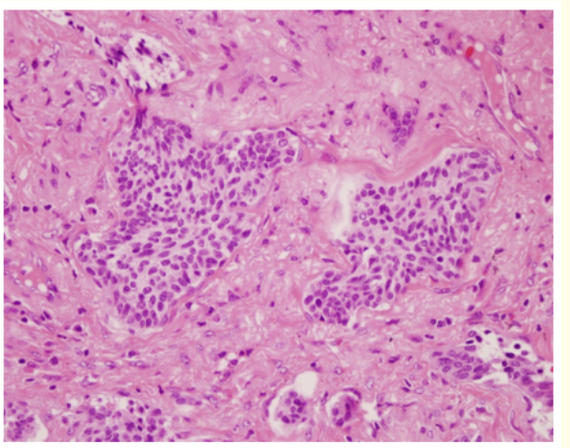

Figure 1B: *Tumorlet presenting as small nodules of neuroendocrine cells in the fibrous stroma (HEx100); (HEx200).*

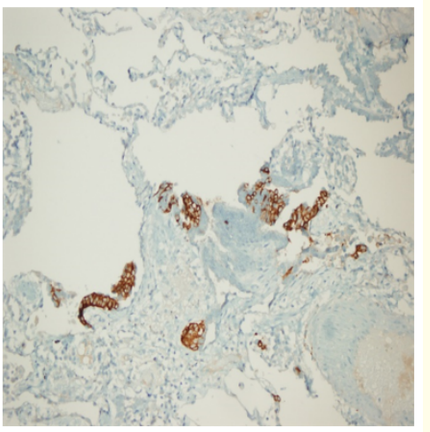

Figure 1C: *Positive staining of neuroendocrine cells with CD56 (CD56x100).*

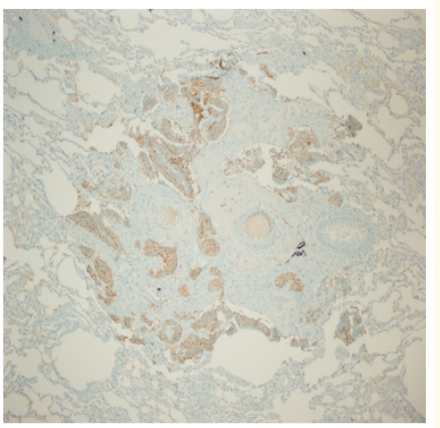

Figure 1D: *Snaptophysin immunoreactivity of neuroendocrine cell aggregates (Snaptophysinx200).*

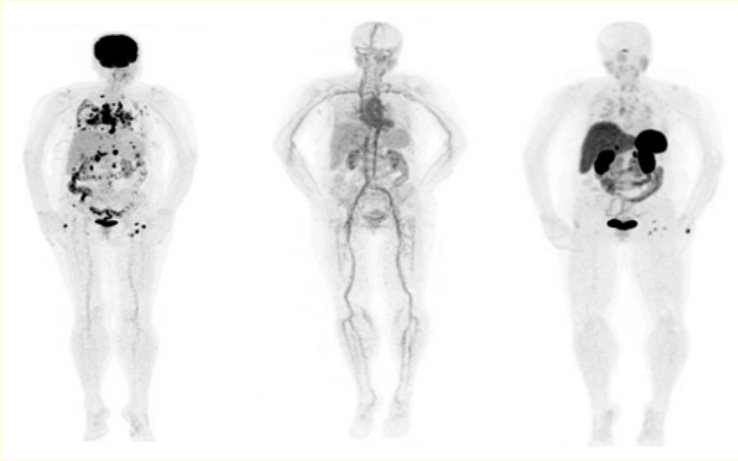

Figure 2: *Coronal MIP images of 18 F-FDG, 68Ga-citrate, and 68Ga-DOTA-TATE PET/CT showing physiologic tracer uptake throughout the body.*

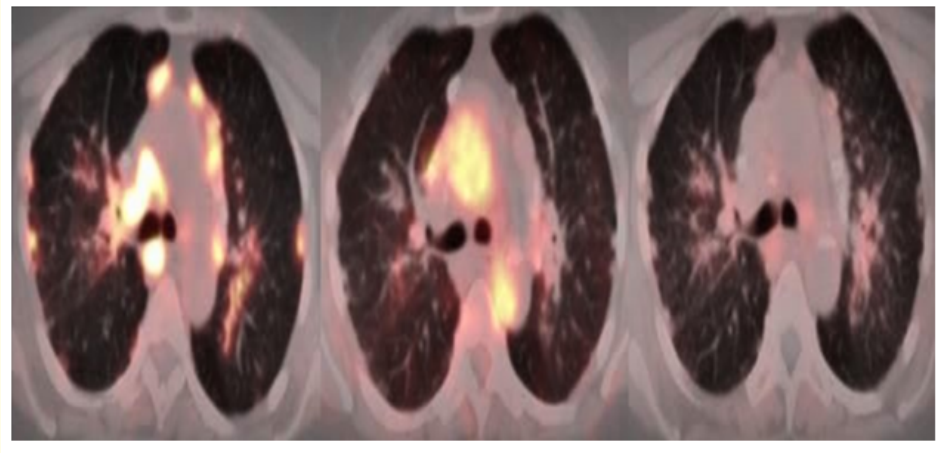

Figure 3: *Axial images of 18F-FDG, 68Ga-citrate, and 68Ga-DOTA-TATE PET/CT revealing physiologic tracer uptake in the lungs and mediastinum.*

Discussion

Sarcoidosis is a chronic granulomatous disease characterized by the presence of non-caseified granulomas in miscellaneous organs, most commonly the lungs and the mediastinal lymph nodes while extrapulmonary organs such as the skin, eye, liver, or spleen may also be comprised. Antigen-driven CD_4 T-cell activation due to inhaled antigens in genetically susceptible individuals followed by the release of inflammatory cytokines such as IL-2, TNF-α, interleukin-5, and interleukin-17 leading to granuloma formation is the hallmark of sarcoidosis pathogenesis [1,2]. Granuloma formation occurs as an abnormal response to a particular antigenic impulse. The association of

sarcoidosis with malignancy is well-known [3-6] but the pathogenesis of this involvement is unclear currently. Sarcoidosis coexistence with malignancy may have arisen by two basic pathogenetic mechanisms displaying different pathways. Immunological abnormalities in sarcoidosis may have triggered the development of neoplasms, malignant disease may have endorsed the evolution of sarcoidosis by leading to sarcoid reactions, or straightly has commenced the manifestations of sarcoidosis [3,6,7].

Neuroendocrine cells are mainly located in the gastrointestinal system, thyroid, and lungs. The pituitary gland, the parathyroid glands, and the adrenal medulla are made up of neuroendocrine cells along with other sites such as the thymus, liver, or kidneys [8]. Although these cells are structurally nerve cells, they may produce hormones, like endocrine cells in response to signals from the nervous system. Pulmonary neuroendocrine cells are scattered in the respiratory epithelium. Their main function is to sense airway oxygen, regulate pulmonary blood flow regulation, control bronchial tonus, and modulate immune response [8,9]. Neuroendocrine cell hyperplasia may develop due to chronic inflammation that usually occurs in emphysema or chronic bronchitis [12-14]. In the absence of inflammation and consequent lung injury, neuroendocrine cell hyperplasia is considered as a premalignant lesion. On the other hand, metabolites and peptides secreted by the neuroendocrine cells can lead to cancer cell proliferation through their cellular signal, autocrine, and paracrine effects. These events may culminate in tumor formation from benign to highly aggressive and malignant character [10-14]. Consequently, it is expected that neuroendocrine cells should reveal a high tracer uptake and avidity in nuclear imaging modalities due to their high metabolic activity and rapid cell proliferation with fast cell turnover.

Our case presents a useful diagnostic algorithm for clinicians concerning the association of DIPNECH and sarcoidosis. The first point was the presence of a silent clinical profile of the patient. Second, DIPNECH was identified incidentally by the histopathologic examination of the bronchial biopsy specimen performed for sarcoidosis. Third, none of the laboratory or the nuclear imaging modalities including ^{18}F-FDG PET/CT, ^{68}Ga-citrate PET/CT, and ^{68}Ga-DOTA-TATE PET/CT revealed any diagnostic data presumption for DIPNECH. Our case constituted a vital source for the diagnosis of patients with coexistent sarcoidosis and DIPNECH. Extensive intramucosal proliferation of pulmonary neuroendocrine cells is found in DIPNECH. This type of cells come out in the setting of inflammatory, fibrotic lesions, or chronic diseases of the lungs. Since neuroendocrine cell hyperplasia may lead to malignant transformation as a premalignant lesion, it has to be differentiated from localized pulmonary neuroendocrine cell hyperplasia that may occur in chronic lung diseases. These two conditions can be distinguished by the presence of an underlying chronic lung disorder and by the absence of carcinoid tumors. On the other hand, clinicians should be aware that DIPNECH may arise in patients with a chronic lung disease without revealing any clinical, laboratory, or imaging manifestations as it is the case in our patient.

Chest radiology and thorax CT displayed equivocal manifestations that were non-diagnostic for DIPNECH. On the other hand, this case also bears the property as to be the first patient for whom three different nuclear imaging modalities have been applied simultaneously for identification of DIPNECH. ^{18}FDG PET/CT revealed minimal increased uptake in the lung parenchyma and mediastinal lymph nodes which is most likely due to the granulomatous inflammation of sarcoidosis. On the other hand, ^{68}Ga-citrate PET/CT and ^{68}Ga-DOTA-TATE PET/CT demonstrated only physiologic tracer avidity in the lung and lymph nodes that was also presumably compatible with the inflammatory state of sarcoidosis. The only diagnostic clue for the existence of DIPNECH was the presence of increased ^{18}FDG avidity in the lung parenchyma but which may also have arisen due to the presence of granulomatous inflammation of sarcoidosis supposably. The final diagnosis was reached by the presence of DIPNECH by an incidental bronchoscopic biopsy specimen while none of the laboratory or imaging procedures including the three simultaneously applied nuclear screening modalities displayed any diagnostic or even suspicious evidence for DIPNECH presence.

BAL lymphocytosis and high CD_4/CD_8 were consistent with an active state of sarcoidosis in this patient. Brincker and Wilbeck have first stated the association of sarcoidosis and malignancy (15,16). Brincker showed that non-caseified granulomas of malignancy usually develop as a reaction to soluble antigenic determinants derived from malignant cells which is designated as a tumor-related sarcoid reaction. Many other studies have also established the spectrum of pulmonary neuroendocrine proliferations associated with neoplasms in

regard to their malignant potential [17-20]. Our patient had a history of sarcoidosis for twenty years. During her follow-up multiple bronchoscopic interventions including BAL and bronchial biopsies had been performed. The histopathologic examination of these specimens revealed exclusively non-caseified granulomatous inflammation consistent with sarcoidosis. Consequently, diffuse neuroendocrine cell hyperplasia in this patient may have arisen from the long lasting sarcoidosis associated immune reactions. The findings of this case explicit significant contrast to Brincker who revealed that malignancy has induced the development of sarcoidosis. The pathogenic mechanism in our case may be designated as sarcoidosis-associated diffuse neuroendocrine cell hyperplasia revealing that sarcoidosis had elicited DIPNECH is the highly probable pathologic and the exclusive mechanism for the occurence of this lesion.

Clinical, laboratory and imaging findings may reveal equivocal or subtle results in patients with DIPNECH where in half of the patients while the diagnosis is reached incidentally on chest CT or lung biopsy done for other suspected pulmonary disorders. Chest x-ray and CT findings are never specific and sensitive for DIPNECH. Simultaneous use of ^{18}F-FDG PET/CT, ^{68}Ga-citrate PET/CT, and ^{68}Ga-DOTA-TATE PET/CT may provide a useful diagnostic clue. They may differentiate whether the increased tracer avidity is a consequence of granulomatous sarcoidosis inflammation, a malignant lesion, or a disorder with a pre-malignant potential. This case reveals that the clinical, laboratory, and imaging manifestations may exhibit indistinct or equivocal diagnostic results for the identification of DIPNECH patients. The inadequacy of imaging modalities in DIPNECH is most probably relevant to the diminutive size of these lesions. The handicap of nuclear screening modalities such as the ^{18}F-FDG PET/CT, ^{68}Ga-citrate PET/CT, and ^{68}Ga-DOTA-TATE PET/CT depends upon the fact that a lesion dimension limit of at least ten milimeters is required to identify malignant or inflammatory lesions. Another fact for the inefficacy of such modalities to detect DIPNECH is their inadequacy to identify malignant lesions that may exhibit an infiltrative pattern of spread which is also the case for our patient.

The clinical profile of DIPNECH may exclusively be associated with the underlying primary lung disease or may be obscured by it. Laboratory findings may reveal completely inapprehensive or futile results. Chest X-ray and thoracic CT may be definitely inefficient because the lesions may be out of the image resolution due to their small size that render equivocal conclusions. Although ^{18}F-FDG, ^{68}Ga-citrate, and ^{68}Ga-DOTA-TATE PET/CT may be diagnostic, it should be kept in mind that these screening modalities may also reveal inconclusive diagnostic conclusions as in our patient. The diagnostic inadequacy of the nuclear imaging modalities in detecting DIPNECH in this case may be relevant with the inability to reach an adequate imaging resolution due to the diminutive size of the lesion, infiltrative spread, or dissemination features of the neuroendocrine cells, and to the presence of underlying sarcoidosis-like comorbid primary pulmonary diseases that may cause overlapping similar imaging findings. The hallmark of this case report is that the absence of clinical findings including patient symptoms, laboratory, or imaging manifestations does not exclude the presence of DIPNECH that accompanies pulmonary sarcoidosis.

Conclusions

Sarcoidosis and DIPNECH may coexist. Although such an association has been reported, it is anonymous which disorder induces or leads to the other. A crucial point in regard to the association of DIPNECH and sarcoidosis in this patient is the possibility that patient symptoms, laboratory, or imaging findings may lead to inadequate diagnostic consequences, notably for DIPNECH. The other clinical landmark is that sarcoidosis may utterly suppress the symptoms or the laboratory findings of DIPNECH rendering it with an absolutely silent clinical profile. This is the first case where three different nuclear imaging modalities have been utilized for identification but all of which have revealed an unequivocal conclusion for DIPNECH diagnosis. Clinical, laboratory, and the radiological manifestations of DIPNECH may exhibit uncertain or precarious outcomes for a definitive conclusion or may even remain inconclusive for at least establishing a suspicion or a presumption relevant with the diagnosis.

Author Contributions

Cuneyt Tetikkurt has designed and wrote the case report.

Hali Yanardag prepared the clinical findings of the patient.

Sebnem Batur has done the pathologic analysis and wrote the pathologic findings of the patient.

Burcak Haluk Sayman prepared the nuclear imaging data.

Muammer Bilir prepared the contents of the case report and wrote the references.

Conflicts of Interest

Cuneyt Tetikkurt does not have any conflicts of interest to declare relevant to this case report.

Halil Yanardag does not have any conflicts of interest to declare associated with this case report.

Burcak Haluk Sayman does not have any conflicts of interest to declare associated with this case report.

Sebnem Batur does not have any conflicts of interest to declare relevant to this case report.

Muammer Bilir does not have any conflicts of interest to declare associated with this case report.

Funding

All authors declare that there is not any kind of funding or any kind of financial support from any institution, organization, firm, or company associated with this case report.

Bibliography

1. Statement on sarcoidosis. "Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999". *American Journal of Respiratory and Critical Care Medicine* 160.2 (1999): 736-755.

2. Bonham CA., *et al*. "From granuloma to fibrosis: sarcoidosis associated pulmonary fibrosis". *Current Opinion in Pulmonary Medicine* 22.5 (2016): 484-491.

3. Askling J., *et al*. "Increased risk for cancer following sarcoidosis". *American Journal of Respiratory and Critical Care Medicine* 160.5 (1999): 1668-1672.

4. Sacks EL., *et al*. "Epithelioid granulomas associated with Hodgkin's disease: clinical correlations in 55 previously untreated patients". *Cancer* 41.2 (1978): 562-567.

5. Alliot C., *et al*. "Malignancy Case Report: Systemic Sarcoidosis Preceeding Acute Myeloid Leukemia". *Hematology* 5.2 (2000): 127-128.

6. Levy NT., *et al*. "Carcinoid tumors and sarcoidosis--does a link exist?" *Mayo Clinic Proceedings* 72.2 (1997): 112-116.

7. Karnatovskaia LV., *et al*. "Sarcoid-like reaction in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia". *American Journal of Respiratory and Critical Care Medicine* 190.10 (2014): 62-63.

8. Boers JE., *et al*. "Number and proliferation of neuroendocrine cells in normal human airway epithelium". *American Journal of Respiratory and Critical Care Medicine* 154 (1996): 758-763.

9. Xu J., *et al* "Less Is More: Rare Pulmonary Neuroendocrine Cells Function as Critical Sensors in Lung". *Developmental Cell* 55.2 (2020): 123-132.

10. Chen HJ., *et al*. "Generation of pulmonary neuroendocrine cells and SCLC-like tumors from human embryonic stem cells". *Journal of Experimental Medicine* 216.3 (2019): 674-687.

11. Caplin ME., *et al*. "Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids 26.8 (2015): 1604-1620.

12. Sanaee MS., *et al*. "Diffuse idiopathic pulmonary neuroendocrine hyperplasia, chronic eosinophilic pneumonia, and asthma". *European Respiratory Journal* 34 (2009): 1489-1492.

13. Rossi G., *et al*. "Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia syndrome". *European Respiratory Journal* 47.6 (2016): 1829-1841.

14. SJ Davies., *et al*. "Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognized spectrum of disease". *Thorax* 62.3 (2007): 248-252.

15. Brincker H and Wilbek E. "The incidence of malignant tumours in patients with respiratory sarcoidosis". *British Journal of Cancer* 29 (1974): 247-251.

16. Brincker H. "Sarcoid reactions in malignant tumours". *Cancer Treatment Reviews* 13 (1986): 147-156.

17. L Carr., *et al*. "The clinical course of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia". *Chest* 147.2 (2015): 415-422.

18. A Chauhan and R Ramirez. "Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) and the role of somatostatin analogs: a case series". *Lung* 193 (2015): 653-657.

19. CW Koo., *et al*. "Spectrum of pulmonary neuroendocrine cell proliferation: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, tumorlet, and carcinoids". *American Journal of Roentgenology* 195.3 (2010): 661-668.

20. Marchevsky AM and Walts AE. "Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)". *Seminars in Diagnostic Pathology* 32.6 (2015): 438-444.

Volume 10 Issue 12 December 2021