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CASE REPORT

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Pulmonary sclerosing pneumocytoma: A potential pitfall mimicking lung adenocarcinoma

Himani Rai[1], Ipsita Dhal[1,*], Zachariah Chowdhury[1], Swapnil Patel[2], Durgatosh Pandey[2]

[1] Department of Onco-pathology, Homi Bhabha Cancer Hospital and Mahamana Pandit Madan Mohan Malaviya Cancer Centre, Varanasi, India;
[2] Department of Surgical Oncology, Homi Bhabha Cancer Hospital and Mahamana Pandit Madan Mohan Malaviya Cancer Centre, Varanasi, India.

Abstract: Pulmonary sclerosing pneumocytoma (PSP), a rare benign lung tumor of primordial epithelial origin, commonly effects middle-aged Asian females. Diagnosis of this entity is challenging because of the non-specific radiological characteristics that resemble malignancies and its histological heterogeneity. Main differential diagnoses considered are adenocarcinoma lung and carcinoid tumor. In this case report, we discuss our experience of diagnosing a case of pulmonary sclerosing pneumocytoma, which showed increased SUV uptake in PET-CT indicating towards a malignancy and was also misdiagnosed as adenocarcinoma in CT-guided FNAC. The histology showed variable morphological features and there was a differential staining pattern of TTF1 and napsin A in the cells. We have highlighted the differential diagnosis and the challenges faced for diagnosing this benign, rare entity.

***Keywords*:** pulmonary sclerosing pneumocytoma, adenocarcinoma, fine needle aspiration cytology

Introduction

Pulmonary sclerosing pneumocytoma (PSP) is a rare benign neoplasm, which most frequently affects middle-aged women. This entity was named "sclerosing pneumocytoma" and was moved from the "miscellaneous tumors" category to "Adenomas" in the 2015 WHO Classification of lung tumors. It is typically a benign tumor, however, lymph node recurrence, pleural and bony metastases and malignant transformation can occur very rarely. The presence of two cell types, cuboidal surface cells and stromal round cells, both of which are regarded as neoplastic, are the primary characteristic morphological features of PSP (*1*).

An isolated, well-circumscribed lump or tumor is the typical radiological appearance of a pulmonary sclerosing pneumocytoma. Most cases are detected as an incidental finding during routine medical examinations without any noticeable clinical symptoms. Chest tightness, coughing, and chest pain may be present in certain individuals, which may be because of lung tissue compression by an enlarged lesion (*2*). When the nature of the lesion cannot be determined on computed tomography (CT), the 18F-fluorodeoxyglucose positron emission tomography (FDG PET)/CT is an appropriate option. However, a larger lesion size may have more active cell proliferation, which could result in a higher uptake of the fluorodeoxyglucose 18F-FDG and be mistaken for a malignant tumor (*3*).

Here we discuss a case of a woman who underwent a right lung lower lobectomy after receiving a diagnosis of lung adenocarcinoma which subsequently turned out to be PSP in detailed histological and immunohistochemical evaluation after receiving informed consent from the patient.

Case Report

A 30-year-old-female came to our emergency department with complaint of hemoptysis for 25 days. She was admitted to our hospital on September 2, 2021. She had no history of smoke exposure (either active or passive). PET-CECT was done in an outside centre, which showed a mass in the right lung lower lobe with increased SUV uptake and no other abnormal findings elsewhere.

CT guided FNAC from lung mass revealed small clusters of medium to large sized cells showing moderate pleomorphism, nuclear hyperchromasia, inconspicuous nucleoli and moderate amount of cytoplasm (Figure 1A). Cytology was reported as positive for malignancy, suggestive of non-small cell carcinoma with possibility of adenocarcinoma and histopathological examination was advised for confirmation. The outside biopsy was also reported as adenocarcinoma.

Right lower lobectomy was done and we received the surgical specimen. On gross examination, a well-defined solid lesion was identified, measuring 3.8 × 2 × 3 cm. Cut section showed variegated and hemorrhagic areas (Figure 1B). On microscopy, lower magnification demonstrated cells arranged in a papillary pattern and

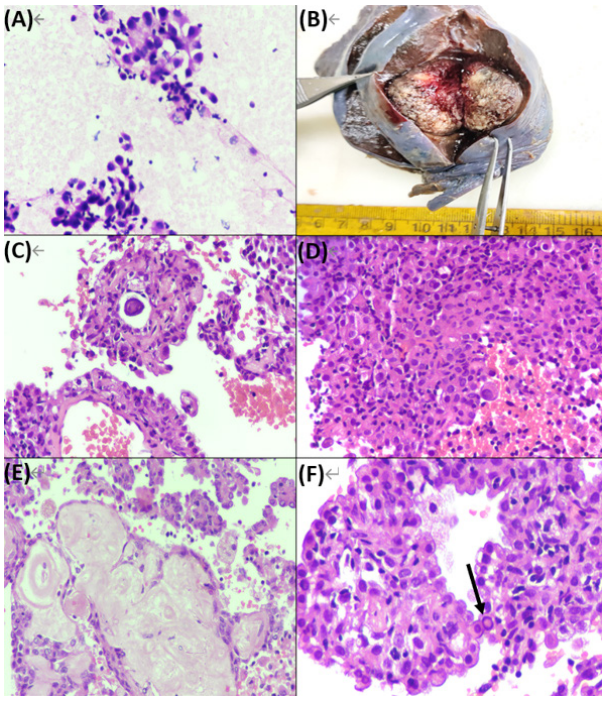

Figure 1. (A) Cyto smears showed small clusters of cells having nuclear hyperchromasia, inconspicuous nucleoli and moderate amount of cytoplasm. **(B)** Gross image: Cut section is variegated and shows hemorrhagic areas. **(C)** Histopathology shows cells arranged in papillary pattern with dual cell population: papillae are lined by cuboidal surface cells and papillary cores show round stromal cells (H&E, 40×). **(D)** Cells are arranged in solid sheets along with areas of hemorrhage. Cells are polygonal with abundant eosinophilic cytoplasm, oval nuclei, even chromatin, indistinct nucleoli, hyperchromasia, pleomorphism (H&E, 40×). **(E)** Sclerotic stroma along with foamy histiocytes (H&E, 40×). *(F)* Papillae are lined by cuboidal cells and papillary cores show round cells. Few cells show intranuclear inclusions (arrow).

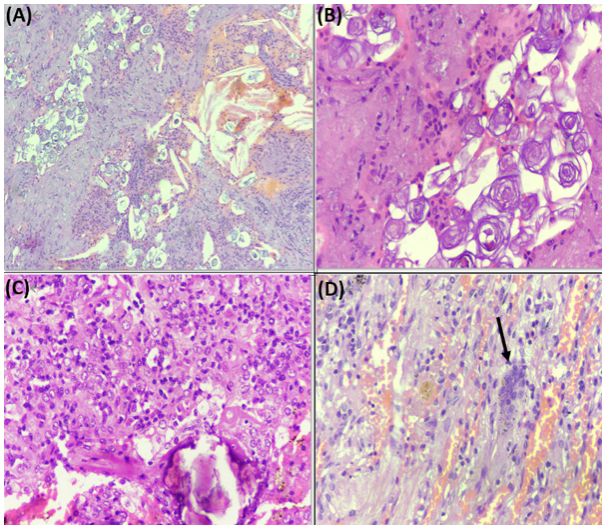

Figure 2. (A) Microsection shows cholesterol clefts along with numerous rounded lamellated structures (H&E, 20×). **(B)** Lamellated surfactant-like substance (H&E, 40×). **(C)** Areas of calcification with surrounding stromal cells exhibiting mild nuclear pleomorphism (H&E, 40×). **(D)** Multinucleated giant cells are seen (arrow).

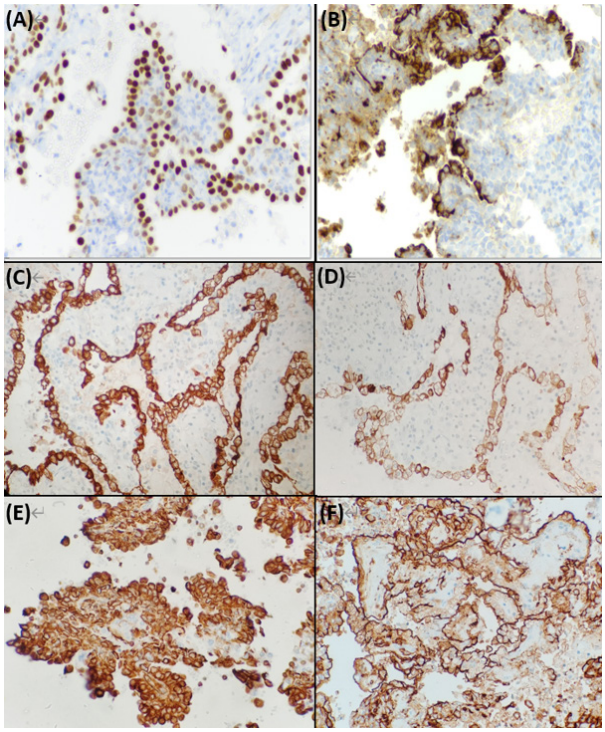

Figure 3. (A) TTF1 highlights the surface epithelial cells along with few stromal cells. **(B)** Surface epithelial cells show positivity to napsin A while stromal cells are negative. **(C)** AE1/AE3 highlights the surface epithelial cells. **(D)** CK7 shows positivity in surface epithelial cells while stromal cells are negative. **(E)** Both stromal cells and surface cells are positive for vimentin. **(F)** EMA highlights the surface epithelial cells and not the stromal cells. (40× magnification)

solid sheets with large areas of hemorrhage. Higher power revealed proliferation of dual cell population, comprised of surface cuboidal cells resembling type II pneumocytes lining the papillary structures, and rounded stromal cells within the papillary cores, having moderate to abundant eosinophilic to vacuolated cytoplasm, oval nuclei with mild pleomorphism, fine even chromatin, and indistinct nucleoli (Figure 1C). The stroma was sclerotic with presence of sheets of foamy histiocytes. Areas of blood lakes, hemosiderin-laden macrophages, and cholesterol clefts were noted. Numerous lamellated surfactant like structures were seen interspersed within the tumor cells. Occasional multinucleated giant cells were also identified (Figure 2).

On immunohistochemistry (IHC), a distinct pattern of staining was identified, as TTF1 was positive in both the stromal cells as well as the pneumocytes, while napsin A highlighted the pneumocytes only. Stromal cells were negative for napsinA. The surface lining cells also were positive for Pan CK, CK7, vimentin and EMA (Figure 3). Diagnosis of PSP was done and the patient was advised to follow up. The last follow up of the patient was on January 3, 2023, and she was completely symptom free except for mild headache.

Discussion

This case report demonstrates the best diagnostic procedure for a patient with a questionable radiographic and pathological finding. Because PSP is often misdiagnosed as well-differentiated lung adenocarcinoma, it is critical to recognize this entity and its significant pathological variations.

PSP should be taken into account for a young woman who has a single round to oval-shaped nodule, smooth boundaries, and strong, homogenous enhancement on contrast-enhanced CT, with or without overlaying vascular sign, halo sign, or air crescent sign. However, only 30% of enhanced CT diagnoses for PSP are accurate (*2*).

In general, 18F-FDG PET/CT scan results are interpreted as positive for malignancy when FDG uptake of a pulmonary nodule on qualitative assessment is greater than background mediastinal blood pool activity or when SUVmax values exceed 2.5 (*4*). In the present case, 18F-FDG PET/CT showed a false positive result, indicating malignancy. 44.7% of tumors are juxtapleural or juxtafissural, and the lesions are typically smaller than 30 mm in diameter and frequently situated in the periphery. It can occasionally be misinterpreted as a bronchial cyst, lung cancer, pulmonary carcinoid, pulmonary hamartoma, tuberculoma, or inflammatory nodule. Although PSP displays varied FDG accumulations, 18F-FDG PET is frequently helpful in identifying benign from malignant tumors. As compared to the asymptomatic group, PSP patients, which are symptomatic displayed a greater maximal standardised uptake value (*5*). The cause of this intense SUV uptake can be due to active proliferation of round cells with poor differentiation and various tumor cells (*6,7*). When the lesion is tiny and located peripherally, bronchoscopic diagnosis can be challenging (*5*).

When possible, pre-operative diagnosis is useful for determining the best course of treatment. PSP is well known for having two distinct cell populations, surface lining cells and round stromal cells, which are commonly arranged in four different architectural patterns: papillary, sclerotic, solid, and hemorrhagic. At least two of the four architectural patterns, most typically the papillary and solid patterns occur in all patients, and three of the patterns are present in 95% of patients (*8*). The present case has all the four described histological patterns.

Gal *et al.* were the first to note that the identification of the dual cell population, which is made up of a lot of stromal cells and few surface cells, is necessary for the cytologic diagnosis of this condition (*9*). Due to the rarity of the disease and possible pathologists' lack of acquaintance with its cytologic features, fine-needle aspiration (FNA) cytology is problematic since it is not always able to distinguish between the two tumor cell types. Few case reports exist that describe preoperative cytologic and histological PSP findings, and in these studies, intraoperative frozen sections (FS), EBUS-TBNA, or computed tomography (CT)-guided FNA frequently resulted in incorrect diagnosis (*7*). In the present case report, also cytology report was suggestive of non-small cell carcinoma, as the cytological features were overlapping with that of lung adenocarcinoma. In any case, the cytologic heterogeneity of this tumor makes the diagnosis difficult because the smears can range from hypocellular, bloody, sclerotic to hypercellular, loaded with stromal fragments, and/or showing epithelial cell proliferation, depending on the needle biopsy sampling area (*8*).

Cytological features of PSP demonstrated cells arranged in cohesive papillae, clusters or flat sheets, an abundant dual population of polygonal type II pneumocytes and spindle cells. These cells have spherical, bland nuclei with inconspicuous nucleoli and an abundance of pale, eosinophilic cytoplasm. Patent intranuclear inclusions are a valuable indicator that has to be looked into and should be appreciated (*10*). Hyalinized stromal tissue microfragments are also seen. The absence of necrosis and mitoses, which highlight the benign nature of the tumor, is a crucial observation. If all of these important cytological quirks are seen on smears, a skilled cytopathologist can quickly determine the diagnosis (*10*).

However, we must remember that there are various pitfalls in the cytopathological diagnosis of PSP, because papillary pattern of arrangement of the tumor cells in PSP can mimic lepidic type well-differentiated lung adenocarcinoma, papillary thyroid gland carcinoma and mesothelioma. In these scenarios, nuclear morphology can be helpful. Round cells and typical papillary areas in cytology smears may mimic a carcinoid tumor. The key differentiating features are a monotonous population of only one cell type, that helps distinguish it from PSP. Also areas of neoplastic clear cells in cytology may be confused with renal cell carcinoma with metastases which we can be ruled out by nuclear morphology, pleomorphism and frequent mitotic figures and also with the help of proper clinical history, and radiological correlation (*10*).

Microscopy in PSP shows morphological heterogeneity. The surface cells line the papillae and the round cells are found inside papillary cores and can also be arranged in solid sheets. The surface cells are cuboidal in shape and few of them may have nuclear pseudoinclusions. Multinucleated cells, and foamy histiocytes are common. Stromal cells have irregular cell boundaries, oval nuclei, even chromatin, indistinct nucleoli, and are polygonal. They may also exhibit cytoplasmic vacuolization, hyperchromasia, and pleomorphism. Stroma is predominantly sclerotic, frequently exhibit areas of haemorrhage, blood lakes, histiocytic aggregates, chronic inflammation, lamellar structures (extracellular surfactant), and cholesterolosis.

The present case has all these morphologic findings. Rare granulomatous reaction can also be seen and mitosis is infrequent. Angiolymphatic invasion and necrosis are absent (*1*).

The common differential diagnosis are well-differentiated adenocarcinoma of lung, particularly the lepidic variety, carcinoid tumor, alveolar adenomas, and lung papillary adenomas. Cellular and nuclear morphology plays a significant role in these situations. Lung adenocarcinomas, often show necrosis, irregular nuclear shapes, amd higher N/C ratio. IHC analysis shows diffuse positivity of tumor cells with TTF-1 and napsin A, without a differential staining pattern like PSP. Carcinoid tumors lack the hyalinized stroma and consist of a uniform population of cells with salt and pepper nuclear chromatin. Immunohistochemical analysis shows positive staining of the tumor cells for neuroendocrine markers (INSM 1, synaptophysin and chromogranin) in all cases, and is positive for TTF-1 (*1*). Alveolar adenomas shows lack of the typical morphological patterns of PSP (solid, papillary, sclerotic and hemorrhagic). Also the stromal cells are negative for TTF1 in alveolar adenomas. Sclerosing pneumocytoma lacks cystic spaces and shows TTF1 positive stromal cells (*1*). Lung papillary adenomas are well-circumscribed papillary neoplasms composed of cuboidal to columnar cells that line the fibrovascular centres and are cytologically bland. Only the surface epithelial cells are positive for TTF1, CK7, pancytokeratin, surfactant protein, and EMA while the stromal cells are negative. In contrast, sclerosing pneumocytoma is composed of two cell types, with papillary structures containing a TTF1-positive cellular rather than a fibrovascular core and more-varied growth patterns (*1*).

There have been a number of reports on the malignant potential of PSP, lymph node metastases and/or local recurrence. Although these malignant potentials do not appear to have an impact on the prognosis of PSP, there are other variables that may be relevant. The common presentation in females is supposed to be due to the presence of progesterone (*11*).

Treatment options for this benign tumor are still debatable. The main course of treatment is surgery. For peripheral small-sized tumors, sublobectomy, most commonly segmentectomy and wedge resection are favoured. However, it has not been fully addressed as to what resection extent is ideal (*11*).

Few studies have reported gene mutations in PSP. AKT1, was the genetic signature of PSP. It causes cell growth and morphological changes, however, it does not cause progression to cancer. The second most frequent gene mutation in PSP is beta-catenin, which may also contribute to the development of benign tumors rather than malignant ones. In addition to AKT1 and beta-catenin, mutations in the tumor-related genes PTEN, BRAF V600E, BLM, and KMT2D were also found in the sclerosing pneumocytoma, though at a comparatively lower frequency (*11*).

Conclusion

Diagnosis of pulmonary sclerosing pneumocytoma is difficult in frozen sections, small biopsies and cytology where they can be mistaken for adenocarcinoma or carcinoid tumors. These tumors have a benign clinical course and metastases are extremely rare. Surgical resection is part of the treatment for PSP, and the prognosis is favourable. There have been no reports of recurrence after surgery or death due to PSP. A critical factor in optimising the treatment strategy is the differential diagnosis of PSP from adenocarcinoma and carcinoid by characteristic round and surface cells and specific IHC staining.

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References

1. WHO Classification of Tumor Editorial Board. Thoracic Tumors. Lyon (France): International Agency of Research on Cancer; 2021.
2. Song L, Yan P, Mo G. Sclerosing pneumocytoma: A carcinoma mimicker. Integr Cancer Sci Ther. 2021; 8:1-3.
3. Cheung YC, Ng SH, Chang JW, Tan CF, Huang SF, Yu CT. Histopathological and CT features of pulmonary sclerosing haemangiomas. Clin Radiol. 2003; 58:630-635.
4. Lim JH, Lee N, Choi DW, Oh HJ, Park HY, Kim KH, Kim TO, Park CK, Shin HJ, Choi YD, Yun JS, Song SY, Oh IJ. Pulmonary sclerosing pneumocytoma mimicking lung cancer: Case report and review of the literature. Thorac Cancer. 2016; 7:508-511.
5. Muto Y, Kuse N, Inomata M, Awano N, Tone M, Minami J, Takada K, Fujimoto K, Wada A, Nakao K, Furuhata Y, Hori C, Bae Y, Kumasaka T, Izumo T. A case of pulmonary sclerosing pneumocytoma diagnosed preoperatively using transbronchial cryobiopsy. Respir Med Case Rep. 2021; 34:101494.
6. Lee E, Park CM, Kang KW, Goo JM, Kim MA, Paeng JC, Lee HJ, Park HS, Chung DH. 18F-FDG PET/CT features of pulmonary sclerosing hemangioma. Acta Radiol. 2013; 54:24-29.
7. Jiang L, Huang Y, Tang Q, Zhao Q, Li Y, Wu X, Wang H. 18F-FDG PET/CT characteristics of pulmonary sclerosing hemangioma vs. pulmonary hamartoma. Oncol Lett. 2018; 16:660-665.
8. Trabucco SMR, Brascia D, Cazzato G, De Iaco G, Colagrande A, Signore F, Ingravallo G, Resta L, Marulli G. Pulmonary sclerosing pneumocytoma: A pre and intraoperative diagnostic challenge. Report of two cases and review of the literature. Medicina (Kaunas). 2021; 57:524.
9. Gal AA, Nassar VH, Miller JI. Cytopathologic diagnosis of pulmonary sclerosing hemangioma. Diagn Cytopathol. 2002; 26:163-166.

10. Onorati M, Nicola M, Bianchi CL, Bini F, Bellaviti N, Di Nuovo F. Pitfalls and key features of a case of sclerosing pneumocytoma: A cytological challenge? Acta Cytol. 2016; 60:85-88.
11. Zheng Q, Zhou J, Li G, Man S, Lin Z, Wang T, Chen B, Lin F. Pulmonary sclerosing pneumocytoma: Clinical features and prognosis. World J Surg Oncol. 2022; 20:140.

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Address correspondence to:
Ipsita Dhal, Department of Onco-pathology, Homi Bhabha Cancer Hospital and Mahamana Pandit Madan Mohan Malaviya Cancer Centre, Varanasi, Uttar Pradesh 221005, India.
E-mail: dripsitadhal@gmail.com