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Case Report

Pulmonary sclerosing pneumocytoma presenting as slow-growing multiple nodules over a long period

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ABSTRACT

Pulmonary sclerosing pneumocytoma is an uncommon slow-growing benign tumor that usually occurs in middle-aged women and generally presents as a solitary well-defined nodule. An 18-year-old woman was incidentally detected to have multiple lung nodules on chest radiography that slowly increased in size over a period of 7 years. Computed tomography images showed multiple well-defined nodules surrounded by numerous smaller nodules with a maximum diameter of 3 cm in the left lung. A percutaneous core needle biopsy was performed, but malignancy could not be excluded because of the high proportion of papillary structures. A video-assisted partial wedge resection was performed and the pathologic diagnosis was pulmonary sclerosing pneumocytoma. Pulmonary sclerosing pneumocytoma presenting as multiple lung nodules is a rare but very important condition to include in the differential diagnosis of multiple lung nodules. There is a possibility of misdiagnosis of another type of tumor or malignancy on preoperative biopsy. We should be aware not only of the clinical, radiologic, and pathologic features of pulmonary sclerosing pneumocytoma but also of the potential pitfalls in its diagnosis and management.

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Introduction

Pulmonary sclerosing pneumocytoma (PSP) is an uncommon slow-growing benign tumor that was previously known as sclerosing hemangioma and first described by Liebow and Hubbell in 1956 [1]. PSP usually occurs in middle-aged women

and is often asymptomatic. PSP generally presents as a solitary well-defined mass, and presentation with multiple nodules is rare. The histopathologic characteristics of PSP are well known; however, PSP is often misdiagnosed as another type of tumor or malignancy on preoperative biopsy and even on assessment of an intraoperative frozen section [2–4]. Here we

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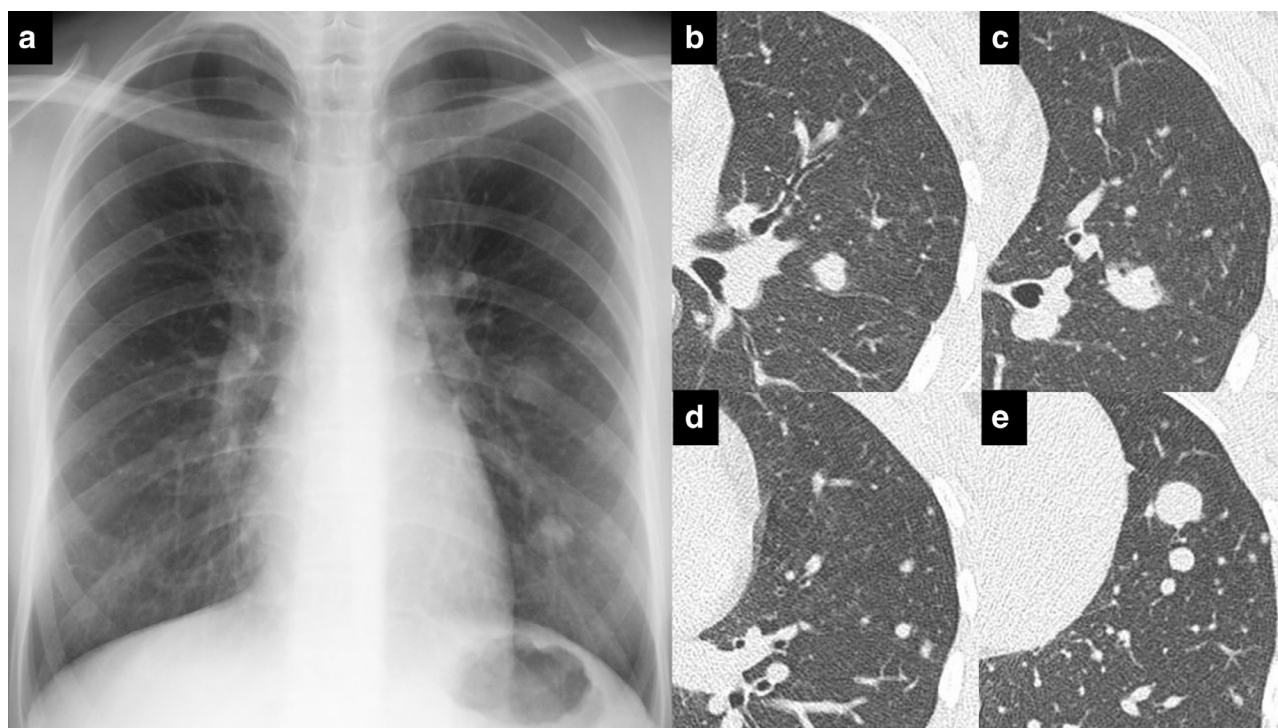


Fig. 1 – Chest radiograph and computed tomography (CT) scans of the chest performed when the patient was 18 years of age. (a) Chest radiograph shows multiple nodules in the left middle lung field. (b-e) CT scans show multiple well-defined nodules surrounded by numerous small nodules in the lingular segment.

present a case of multiple PSP in a young woman that was difficult to diagnose on percutaneous biopsy.

Case report

A 25-year-old woman with a lung lesion of long standing was presented to our outpatient clinic for further evaluation of abnormal chest shadows. The lung lesion had been detected incidentally on a chest radiograph, taken when the patient was 18 years of age (Fig 1a). Computed tomography (CT) at that time showed multiple well-defined nodules with a maximum diameter of 2 cm that were mostly in the lingular segment (Fig 1b-e). The patient had not wanted to undergo further investigations, so the abnormal chest shadow was simply followed up at another hospital once a year. However, the patient returned to the outpatient clinic when it became clear that the shadows had slowly increased in size over time (Fig 2a). The patient had no symptoms or previous medical history, and there were no abnormal findings on either physical or laboratory examination.

CT showed multiple well-defined nodules surrounded by numerous smaller nodules with a maximum diameter of 3 cm in the left upper lobe and still mostly in the lingular segment (Fig 2 b-e). The nodules had grown slowly to a maximum diameter of 2-3 cm during the previous 7 years. Minor calcification was identified in a large nodule. Contrast-enhanced CT revealed heterogeneous patchy enhancement within the

nodules on early phase images and persistent enhancement on delayed phase images (Fig 3). The patient was referred for ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) to identify the primary site, to determine if the lesions were benign or malignant, and if malignant, to detect any metastases. FDG-PET showed a maximum standardized uptake value of 2.9 in the lung nodules. No enlarged mediastinal lymph nodes or distant metastases were evident on FDG-PET (Fig 4).

The radiologic differential diagnosis included PSP, carcinoid tumor, epithelioid hemangioendothelioma, and lung carcinoma. Although the lesions were suspected to be benign because of their extremely slow growth rate, a percutaneous CT-guided core needle biopsy was performed for a precise diagnosis given their steady increase in size over time. Malignancy could not be excluded because of the high proportion of papillary structures in the biopsy specimens; therefore, surgical resection of the left upper lobe was planned. However, the patient's wish was that the diagnosis be confirmed by less invasive surgery given that the tumor was suspected clinically to be benign in view of its slow growth rate. Therefore, video-assisted wedge resection of the lingular segment was performed for a definitive diagnosis. The gross specimen showed multiple well-circumscribed solid yellowish nodules inside the lung parenchyma (Fig 5a). The nodules were variable in size, ranging in diameter from 2 mm to 20 mm. Microscopically, the resected tumors showed mainly a solid component and to a lesser extent a papillary growth pattern with sclerotic features (Fig 5b-d). No atypia or mitosis was observed.

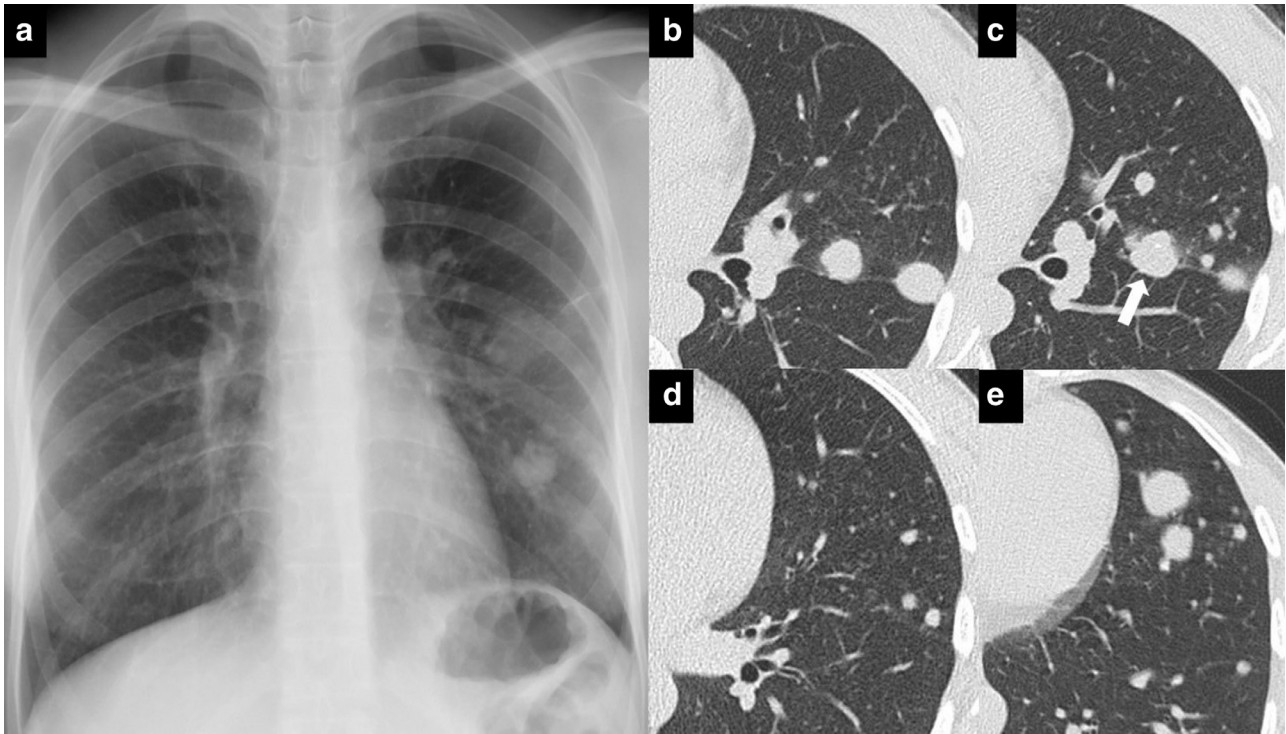


Fig. 2 – Chest radiograph and computed tomography (CT) scans of the chest performed when the patient was 25 years of age. (a) Chest radiograph shows multiple nodules in the left middle lung field, which gradually increased in size and number over 7 years. (b-e) CT scans show multiple well-circumscribed nodules surrounded by numerous small nodules in the lingular segment. The lung nodules increased in size and new nodules appeared during the previous 7 years. (c) Minor calcification is seen in a large nodule [white arrow].

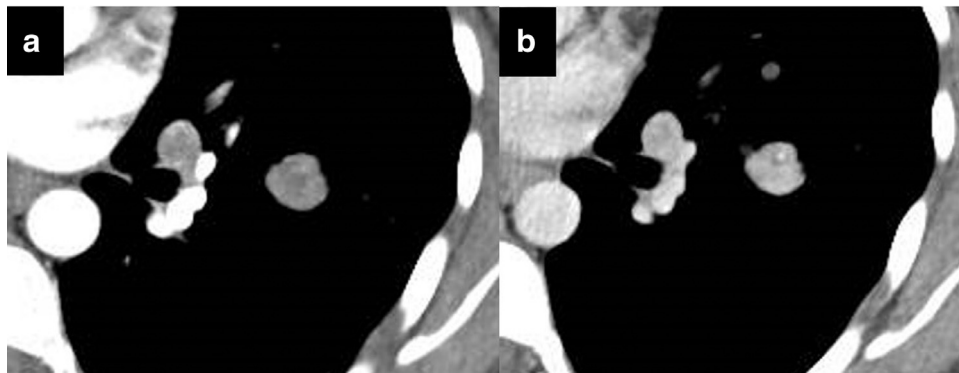


Fig. 3 – Contrast-enhanced computed tomography (CT) scans obtained at a similar time as the CT scans shown in [Figure 2](#). CT scans show heterogeneous spotty enhancement within the nodules on an early phase image (a) and persistent enhancement of the entire nodule on a delayed phase image (b).

The tumor consisted of two types of cells, ie, stromal round cells with bland nuclei and cuboidal cells with an alveolar type 2 cell-like morphology that covered papillary structures or tubules ([Fig 4c](#)). Both cell types were positive for thyroid transcription factor-1 (TTF-1) and epithelial membrane antigen (EMA). The cuboidal cells were positive for pancytokeratin (AE1/3; [Fig 6](#)). These findings are the typical morphologic features of PSP. The patient had no postoperative complications and the residual lung nodules have not changed during the 2 years since her surgery.

Discussion

Most PSP lesions are solitary and unilateral. CT images usually reveal a mass with uniform soft tissue attenuation and smooth margins, and calcification arising within a PSP is often seen. The lesions are generally less than 5 cm in diameter and may be found in any of the lung lobes; they tend to appear in a subpleural location, sometimes crossing over fissures but rarely adherent to adjacent structures [5]. Approximately, 4%-

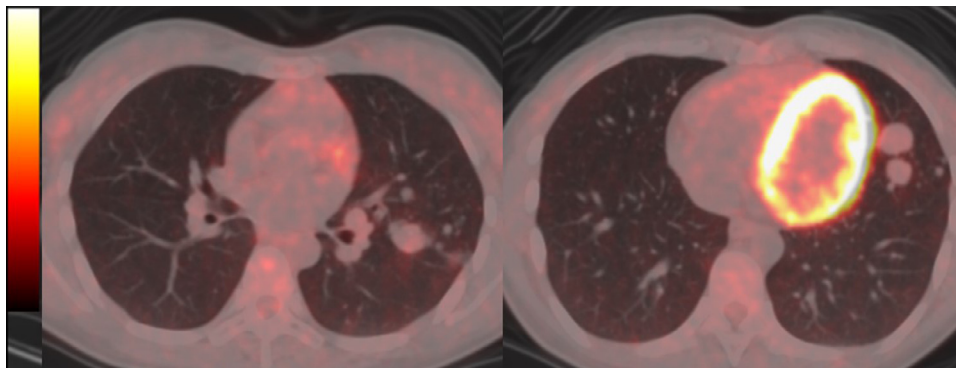


Fig. 4 – Axial fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) images show a maximum standardized uptake value of 2.9 in the lung nodules.

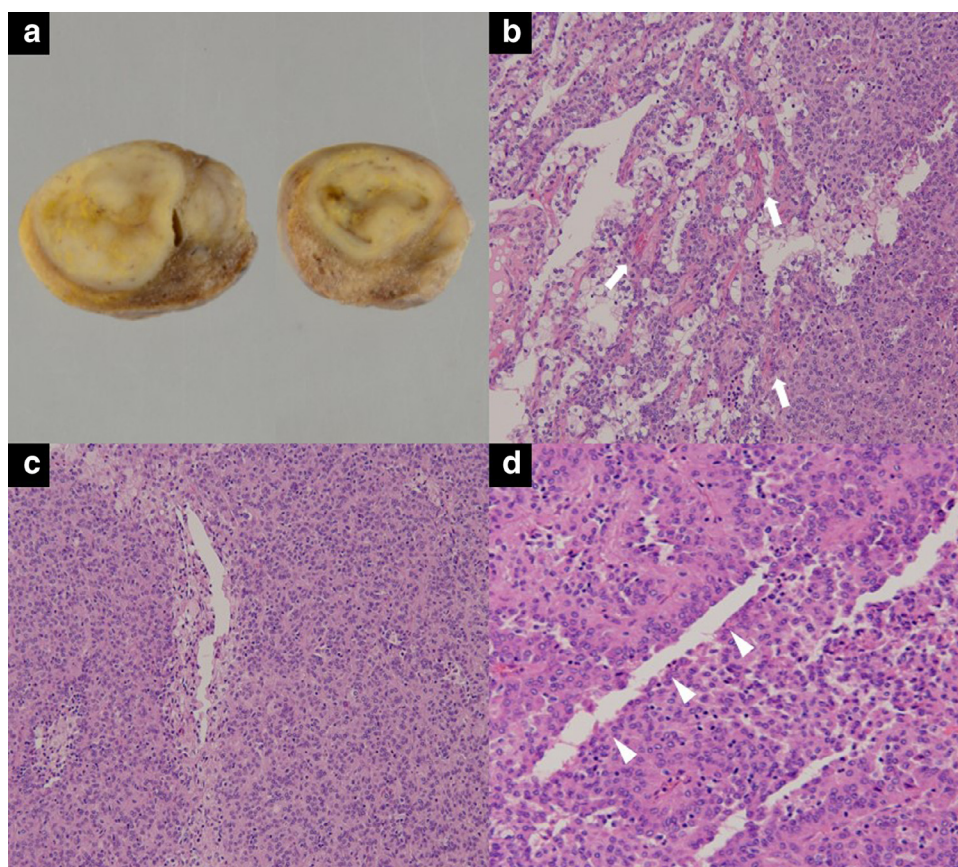


Fig. 5 – Gross specimen and microscopic findings of a lung nodule. (a) Gross specimen obtained with wedge resection shows well-circumscribed solid yellowish nodule. (b-d) Microscopic findings. Hematoxylin and eosin staining. Low power magnification (40x) demonstrates a mixture of papillary (b), solid (c), and sclerotic nodules [white arrows in (b)]. (d) Cuboidal cells (white arrowhead) with the morphology of type II pneumocytes are seen lining the papillary and tubular structures. Sheets of round cells are observed at high-power magnification (100x). (Color version of figure is available online.)

5% of PSPs have been reported to present as multiple lesions on histopathologic studies [6,7]. The configuration of multiple lesions in previous reports suggest that these tumors can be present in a single lobe or in multiple lobes and may exist in the form of a dominant tumor surrounded by multiple satellite/multicentric lesions [6,7].

Whether or not multiple PSP nodules represent pulmonary metastases or simultaneous multiple tumors is unclear. Metastasis to the lymph nodes has been reported [6,8,9], so it is clear that PSP has metastatic potential. Devouassoux-Shisheboran et al [6] reported an incidence of hilar lymph node metastasis of 1% for all PSPs, and Yano et al [9]

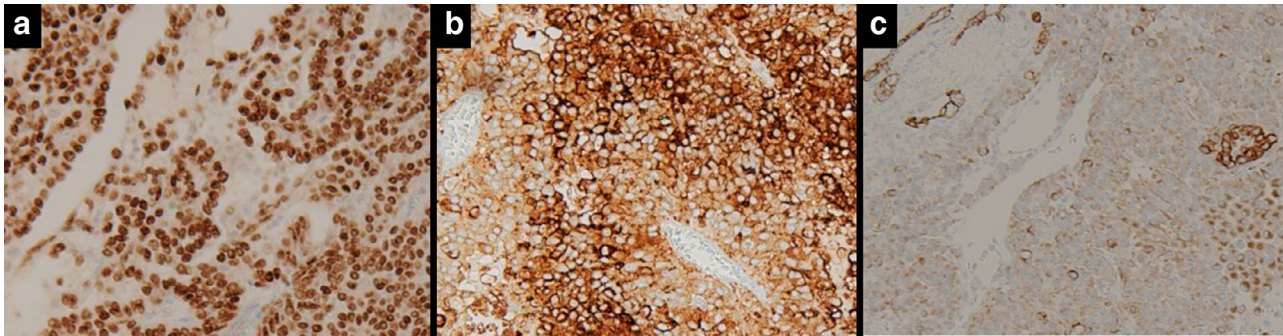


Fig. 6 – Immunohistochemistry of pulmonary sclerosing pneumocytoma. Both the surface cuboidal cells and the round cells are positive for thyroid transcription factor-1 (a) and epithelial membrane antigen (b). Cytokeratin (AE1/AE3) staining of the surface of the cuboidal cells is positive but staining of the round cells is negative.

reported that larger tumors had greater potential for lymph node metastasis. Some authors have considered multiple lesions to be intrapulmonary metastatic lesions [6,7]. Intrapulmonary metastasis may occur via a hematogenous, lymphatic, or other mechanism. In contrast, the possibility of lymphoid metastasis is presumed to be low because the frequency of lymph node metastasis is lower than for multiple nodules. There is a possibility of hematogenous metastasis, but there have been no reports of PSP metastasizing to other organs [6,7] and the mechanism involved is unclear. The new concept of a spread through air spaces (STAS) pattern, which was introduced for pulmonary adenocarcinoma in the 2015 World Health Organization classification for lung cancer, has recently been proposed [10,11]. Although no study has validated STAS in benign tumors, it is possible that STAS may be involved in benign tumors, which often occur in the same lung.

Histopathologically, PSP contains a mixture of solid, papillary, sclerotic, and hemorrhagic patterns [4,7]. Most PSPs have at least 3 of these components, and a minority has only 2. The frequency of the hemorrhagic pattern is less than that of the other 3 patterns [4,6,12]. This tumor consists mainly of proliferations of 2 types of cells, ie, solid-growing bland round cells with abundant pale cytoplasm (round cells) and lining (cuboidal) cells covering the papillary structures [6,7,13].

Immunohistologically, the epithelial origin of the tumor is supported by TTF-1 and EMA positivity in both cuboidal cells and round cells in the majority of cases [6,13]. Cuboidal cells are also positive for cytokeratin and surfactant protein A, whereas round cells are negative for these markers [13]. PSP is considered to originate from primitive respiratory epithelium [6,13–15]. Strong and diffuse positive immunostaining with neuroendocrine markers such as chromogranin and synaptophysin favors a diagnosis of carcinoid tumor; however, neuroendocrine cell markers are also sometimes positive in PSP [6]. In our patient, the resected tumors showed mainly a solid component and to a lesser extent a papillary growth pattern with sclerotic features, and were positive for TTF-1, EMA, and AE1/3.

The differential diagnosis of multiple slow-growing solid nodules in young women ranges from benign tumors to malignancy, ie, epithelioid hemangioendothelioma, carcinoid tumor, benign metastasizing leiomyoma, and granulomatous

diseases [16]. Chung et al [14] reported that the patterns seen on dynamic contrast-enhanced CT images in patients with PSP depend on the relative tissue expression of hemangioma-tous or papillary components (early strong enhancement) and solid or sclerotic components (slow persistent enhancement with limited washout). They also mentioned that morphologic analysis or patterns seen on dynamic contrast-enhanced CT images could not distinguish between lung cancer and PSP. In our patient, the tumors showed persistent enhancement pattern because they consisted of predominantly solid and sclerotic components. The radiologic findings for the tumors included in the differential diagnosis show similar sharply marginated single or multiple nodules, so histopathologic analysis is required to make a correct diagnosis of PSP. The pathologic features required for a definitive diagnosis of PSP are well known; however, a correct clinical diagnosis by biopsy is often difficult and PSP is frequently misdiagnosed as bronchioloalveolar adenocarcinoma, metastatic papillary thyroid carcinoma, carcinoid tumor, or mesothelioma if the papillary structure is predominant in the biopsy specimens [2–4,17]. Iyoda et al [4] reported that only 7 of 26 patients with PSP were diagnosed preoperatively by percutaneous needle or trans-bronchial biopsy. Low et al [2] reported that PSP is often misdiagnosed, even by assessment of an intraoperative frozen section, with an error rate of 25% and a deferred rate of 31%; these rates are higher than those for lymphoma and carcinoid tumor. They also warned that misdiagnosis may result in unnecessarily extensive surgical procedures and potentially an increase in the associated morbidity.

PSP is generally considered to be a benign lesion, and radical surgical excision with wedge resection is curative without the need for additional treatment [15]. Left upper lobectomy was necessary in our patient, although she would have preferred a watch-and-wait approach because the tumor was slow-growing and no distant metastasis was evident. According to the literature, all the cases of PSP presenting as multiple nodules have been slow-growing [18–20]. Nevertheless, careful long-term observation is needed.

In conclusion, PSP presenting as multiple lung nodules is a rare but very important condition to include in the differential diagnosis of multiple lung nodules, especially in young women. PSP is often misdiagnosed as another type of tumor or malignancy on preoperative biopsy and even on assessment

of an intraoperative frozen section. We should be aware not only of the clinical, radiologic, and pathologic features of PSP but also of the potential pitfalls in its diagnosis and management.

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