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Case Report

Multifocal Pulmonary Sclerosing Pneumocytomas Mimicking Adenocarcinoma Associated With Somatic FGFR3 Mutation: A Case Report.

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Abstract

Background : Pulmonary sclerosing pneumocytoma (PSP) is a rare solitary benign tumor. The unusual multifocal presentation creates a big challenge in diagnosis and management. We report such a case, linking the spectrum morphology of multiple evolving PSP to a novel genetic change for the first time.

Case presentation : A 47-year-old asymptomatic, non-smoker female presented with incidental 14 bilateral lung nodules. The initial biopsy strengthened the clinical suspicion of metastatic lung adenocarcinoma. However, no extrapulmonary involvement was detected and the liquid biopsy was also negative. The left upper lobectomy was performed for a definitive diagnosis. This has led to a pathological finding of seven PSP tumors, with the largest 3 cm mass showing characteristic solid, papillary, hemorrhagic and sclerotic patterns, and five smaller nodules showing a spectrum morphology of PSP starting from pneumocytes hyperplasia, evolving to four histological patterns and ended with fibrosis. Somatic Fibroblast Growth Factor Receptor 3 (FGFR3) pE360K mutation is present in the tumors and background lung parenchyma. While additional AKT1 internal tandem duplication (p.R67_L78 dup), which is a known hallmark for PSP, is limited to the largest mass. No other driver gene mutations classic for lung cancer are detected among over 2000 genes examined. Patient is free of recurrence or metastasis during two-year follow up.

Conclusion : The diagnosis of PSP could be difficult in small biopsy and frozen. Synchronous presentation of PSP is attributable to the somatic mutation of FGFR3 (pE360K). Secondary AKT abnormality promotes tumor growth but does not change the benign course of PSP in this case.

Keywords : *FGFR3, multifocal pulmonary sclerosing pneumocytoma, AKT1.*

INTRODUCTION

The initially described pulmonary sclerosing hemangioma has been renamed as pulmonary sclerosing pneumocytoma (PSP), in the fourth and fifth edition of the World Health Organization (WHO) classification of lung tumors. PSP is considered a pneumocyte derived adenoma. This rare tumor shows a predilection of female never smoker and Eastern Asian population [1]. Most of the time, PSP is a solitary peripheral nodule, incidentally discovered, and follows a benign clinical course [1]. Multifocal PSP are reported in twenty-four cases [2-9], approximately accounting for 4% of PSP [2]. Of those 24 cases, malignant characters of lymph node metastasis [3], distant metastasis and mortality [4,5] are presented in three patients. PSP can be very challenging to diagnose in frozen section, biopsy and cytology [1], The multifocal presentation of SP would further add this difficulty. Even after a rendered histological diagnosis following surgery, clinical management of multifocal PSP is still a dilemma. We report such a case, describing the spectrum morphology, associated molecular change and predictable outcome.

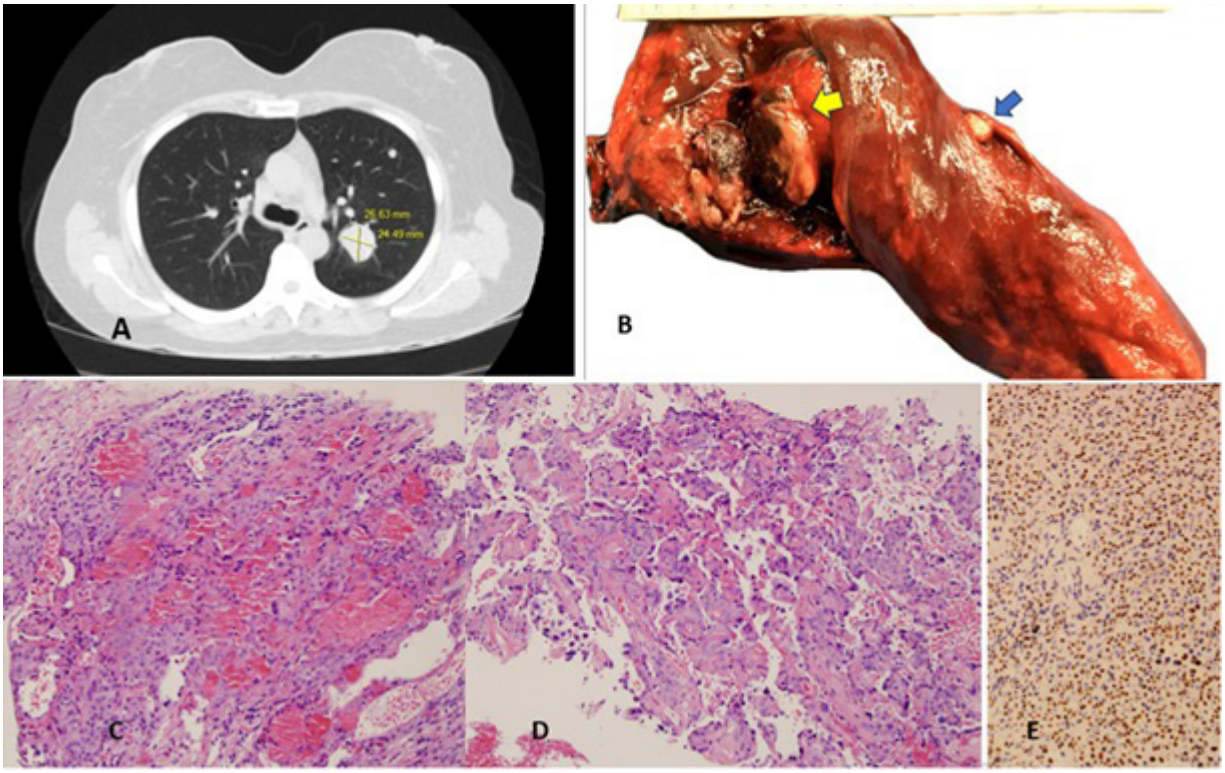
CASE PRESENTATION

A 47-year-old asymptomatic, non-drinker, non-smoker female without personal malignant history presented with incidental fourteen bilateral lung nodules involving all lobes with five on the right and nine on the left (see supplementary video). The

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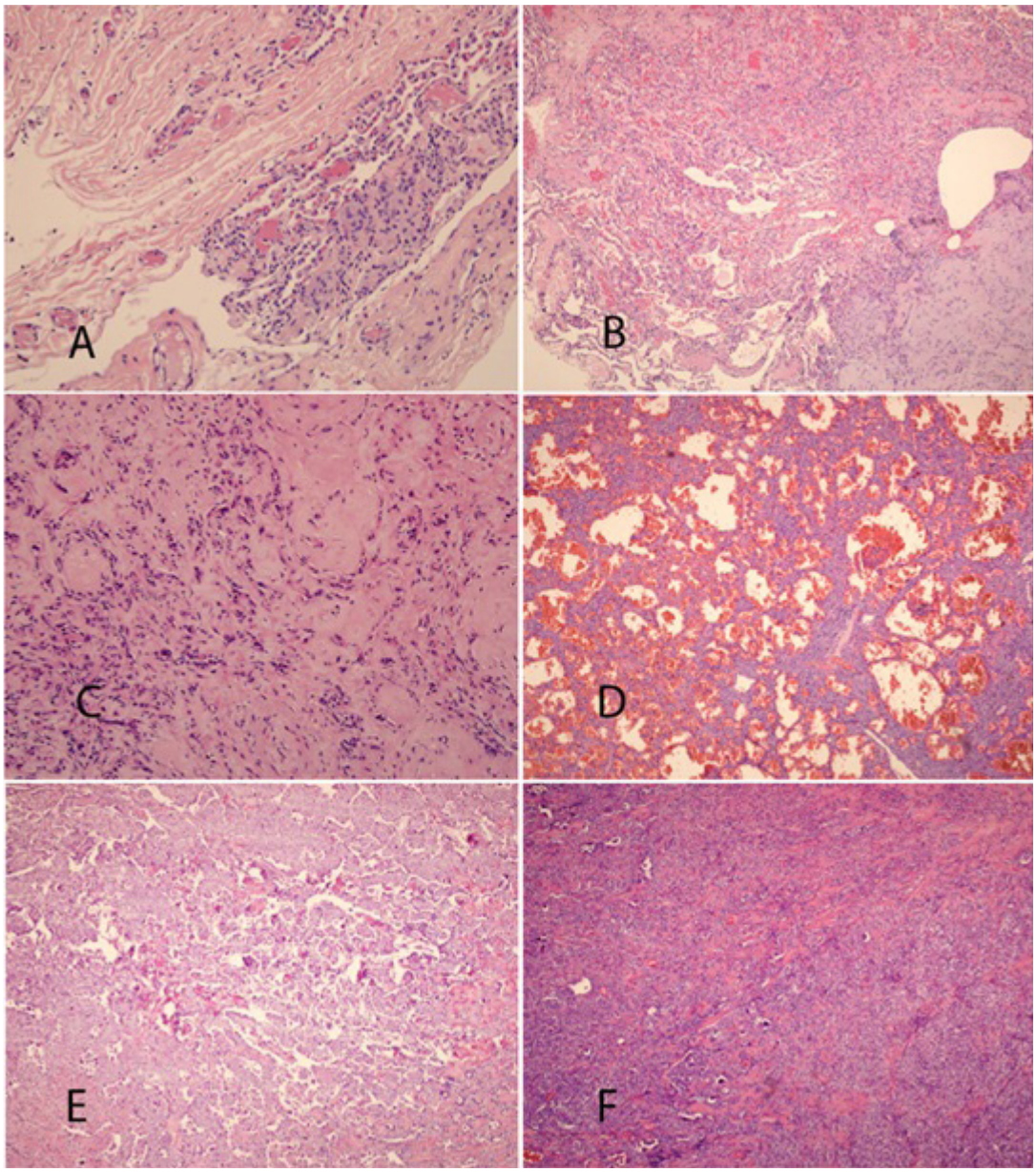
largest one was in the left upper lobe initially measuring 2.4 cm, avid in Positron Emission Tomography (PET) scan. The other nodules are sub centimeters. The largest nodule showed interval growth. It was biopsied 3 months later in an outside institute and interpreted as "moderately differentiated lung adenocarcinoma" (**Figure 1 C-E**). Five months later, the largest nodule grew to 2.6 cm according to MRI, PET and chest X-ray follow up (**Figure 1A**), but still no extrapulmonary lesions were identified despite high clinical suspicion for metastatic disease. Thoracotomy was soon performed. A nodule marked as left pulmonary lymph node was submitted for frozen. The frozen section showed atypical cells of indeterminate significance associated with desmoplasia but without lymph node or lymphoid tissue present (frozen section in **Figure 2C**). Left upper lobectomy was eventually performed. Gross examination showed one large mass in the apical posterior and anterior segment, measuring 3 x 2.7 x 2.5 cm, with a grey-tan solid, hemorrhagic, and cystic cut surface, accompanied by four smaller discrete white, tan nodules 0.4 cm to 1.0 cm in size, 1 cm to 9 cm away from the mass (**Figure 1 B**). An additional 0.2 cm nodule was also identified in a random section microscopically.

Figure 1. CT image, corresponding surgical gross finding, and pre-surgical biopsy. A) CT scan transverse axis showed a 2.6 cm mass in left upper lobe, and another nodule at periphery of the same lobe. B)Left upper lobectomy correlation showed the largest mass (yellow arrow) in the apical posterior and anterior segment and a 1 cm mass (blue arrow) located 4.5 cm inferior and lateral from the largest mass. C-E) Histology of CT guided biopsy of the largest mass showed: (C) – hemorrhagic pattern (x40), (D)-papillary pattern(x40) and (E) -TTF1 immunohistochemical stain (x40).



All nodules in the left upper lobe including the frozen nodule are characterized by two cellular components: cuboidal surface cells and round to short spindle stromal cells. The composite cells are bland with some surface cells showing mild atypia and degeneration. The smaller nodules showed a spectrum morphology from pneumocytes proliferation to sclerosis (**Figure 2 A-C, supplementary Figure 1**). The largest mass showed a combination of hemorrhagic, papillary, solid, and sclerotic pattern in resection (**Figure 2 D-F**). The hemorrhagic and papillary patterns are seen in previous biopsy (**Figure 1 C-D**). Both composite cells are strongly positive for TTF1 (**Figure 1 E**). However, the CK7, panCK and Napsin A are mostly positive in epithelial cells, and rarely positive in stromal cells. There is focal weak expression of synaptophysin in the largest tumor. CD34, STAT6, HMB45, S100 and chromogranin A are all negative. No granuloma, infectious disease or inflammation is seen. Microbiology culture is negative.

Figure 2. Spectrum morphology of pulmonary sclerosing pneumocytomas (PSP) from surgical resection specimen. A) subpleural nodule (x10), B) an evolving nodule (1 cm in size) with hemorrhagic and sclerotic pattern, C) permanent section of a nodule at the left pulmonary lymph location showing a quiescent PSP in total sclerosis (x 40), D-F) the largest growing PSP mass with hemorrhagic (D), papillary (E) and solid pattern (F) (x40)



Lymph node staging was performed during surgery. One hilar, one inferior mediastinal lymph node and four segmental lymph nodes are all negative for metastasis.

Extensive molecular studies are performed aiming to find potential treatment targets, due to the initial high suspicion of metastatic disease and the need for post-surgical follow up. Over 2000 genes have been analyzed by two commercial company platforms, FoundationOne and Caris. Their concurred key findings are as the follows:

1. Somatic Fibroblast Growth Factor Receptor 3 (FGFR3) mutation (protein alteration pE360K and DNA alteration exon 9, c.1078G>A) and AKT1 internal tandem duplication (R67_L78 dup) are repeatedly identified by both FoundationOne and Caris in the largest tumor.
2. The same FGFR3 mutation is detected in the smaller tumors and background lung parenchyma (morphology of the paraffin block seen in Figure 2 A-B), but no AKT variation is identified (Caris platform).
3. The liquid biopsy of blood (FoundationOne) was negative for clinically significant abnormality. No AKT1 or FGFR3 variations are seen. Only somatic alteration of DNMT3A (splice site 2082+1delG) was identified, which was interpreted as non-tumor derivative, possibly representing clonal hematopoiesis.

Of note, PD-L1 is borderline positive in the smaller tumors and background lung (2+, 5%, Antibody SP142), but negative (0%) in the largest tumor (Antibodies: SP142, 22C3, SP263 and 28-8). The tumor mutation burden (1%) and genomic loss of heterozygosity (2%) are both low. The microsatellite instability is also low.

The second opinion consultation in outside institute agreed the final diagnosis of multifocal PSPs. The surgical and pathological findings of multiple PSP are a relief to the patient and her family. They are happy to opt for a clinical follow up without chemotherapy. The patient has been stable for two years after surgery.

DISCUSSION

Multifocal PSP has been reportedly misinterpreted as lung adenocarcinoma [2,3]. The correct diagnosis relies on histopathological recognition of the distinct two types of cells and four patterns [1]. The positive Napsin A and CK7 in the epithelial cells may deceptively forge an initial wrong diagnosis of adenocarcinoma of lung, as in this case. WHO tumor classification has recognized both epithelial and stromal cells to be tumor components. The epithelial cells which are positive for CK7 and Napsin A could be more differentiated tumor cells.

We have, for the first time, demonstrated the morphology of the initiation, evolution and sclerotic end stage of PSP driven by FGFR3 (pE360K) mutation. The earliest change of PSP is a subpleural nodule comprising of proliferation of pneumocytoid cells (Figure 2 A). This is followed by variable hemorrhagic, papillary, solid and sclerotic pattern (Figure 2 B, supplementary Figure 1), and eventually ceasing growth wound up to stromal fibrosis (Figure 2 C). This is the first report of FGFR3 (pE360K) mutation in multifocal PSP.

FGFR3 protein spans the cell membrane, regulating cell growth, division, differentiation, angiogenesis, wound healing and embryo development. FGFR3 variations have been associated with non-tumoral (skin nevus, sebaceous keratosis, syndromic diseases) and tumoral (bladder tumor, cervical cancer and multiple myeloma etc) conditions [10].

FGFR3 point mutations other than pE360K has been rarely reported in lung squamous cell carcinoma (pR248H, 0.9%, 2/362 of lung cancer cases) in a Japanese population [11]. Those two patients also had additional p53 mutation or PIK3A and SOX2 amplification [11]. FGFR3 point mutation other than (pE360K) has also been identified at a higher frequency of 5.5% (120/363) in stage IV lung adenocarcinoma in an Indian population (pS249C, 16/363; and pG691R, 4/363) [12]. pR248C, pS249C and pG691R are proved activating mutations and are drug sensitive [12]. It is unknow whether the novel FGFR3 (pE360K) mutation presented in our case would be drug sensitive.

It appears that the FGFR3 (pE360K) mutation stand-alone is not enough for a continuous tumor growth, as those PSP nodules without AKT1 variation are sub centimeter in size and are in a spectrum of morphology ending in fibrosis, as shown in our case.

Only the largest mass (3 cm) showed continuous growth, benefiting from an additional AKT1 Internal Tandem Duplication (ITD) (p.R67_L78 dup). The same (p.R67_L78 dup) alteration has also been reported in one of the two synchronous benign PSP tumors [7], and 4 solitary benign PSP tumors [13] in two studies. The ITD is in a narrow region of the Pleckstrin homology domain of the AKT1 protein, known to play a critical role in the activation of AKT1 [13]. AKT1 hot point mutation (30-43%) and AKT1 ITD (50% -65%) are both hallmarks of PSP [7,13]. Both alterations activate PI3K/AKT/mTOR pathway similarly, and share the same mutation signatures [7].

Besides the prevailing AKT1 abnormality, other genetic changes including PTEN, PIK3R1 and β-catenin have also been reported in benign PSP [7, 9, 13].

Interestingly, tobacco smoking and apolipoprotein B mRNA-editing enzyme, catalytic polypeptides (APOBEC) mutational signatures which are well known in lung cancer, do not appear to play a role in tumorigenesis of PSP [7]. This correlates with the prevalence of PSP in non-smokers. It is speculated that both FGFR3 (pE360K) and AKT1 (p.R67_L78 dup) might follow the same mutational pathway, a pathway different from malignant lung cancer.

Majority of PSP, including multifocal cases, carry AKT1 variation, and are benign [6,7,9,13]. One study on 107 patients with PSP (surgery:non-surgery = 80:27) and 520 matched controls showed that all-cause mortality did not differ between patients with PSP and those without, irrespective of undergoing surgery [6]. However, rare metastasis and even death have been reported [3,4,5]. Peculiarly, those malignant cases do not have point mutation, short indel or ITD of AKT1. Genetic studies carried out in three cases showed the following mutations which are negative in our case:

1. Mutations of PIK3CA (c.1633G>A; p. E545K) and TP53 (c.455C>T; p.152L) in an incidental 1.8 cm left upper lobe PSP tumor in a 60-year-old man, associated with one positive interlobar lymph node, but no recurrence or metastasis in 9-month follow up. The frozen diagnosis was misinterpreted as adenocarcinoma [3].
2. Activation of the AKT1- p.E17K pathway observed in 31 genes by whole - exome sequence (AKT1, ALK, APC, ATM, BRAF, BRCA1, BRCA2, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, HRAS, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK3, PDGFRA, PIK3CA, PTEN, RET, ROS1, SMAD4, TP53, TSC1, and TSC2) in a large malignant PSP of right lung with lymph node, liver and bone metastasis in a 25-year old man, who passed away six months after

diagnosis confirmed. The previous biopsy 6 years ago was papillary adenoma [5].

3. IDH1 (isocitrate dehydrogenase 1) (c.394C>G, p.Arg132Gly) mutation identified in multiple bilateral lung metastasis of progressive PSP in a 72-year old Caucasian woman, who succumbed 1 month after re-thoracotomy. Patient also had a history of hand chondrosarcoma [4].

The clinical risk factors of solitary PSP have been addressed in a retrospective cohort study of 46 malignant PSP cases and 38 benign PSP controls [14]. Their analysis suggested that young age (<=41 years old), large tumor (>=36 mm), lymph node metastasis and East Asian descent are risk factors for malignancy [14]. Those risk factors are not present in our case.

The morphology and molecular profile of our case, together with literature review predict a benign post-surgical course in our case. The patient is stable without recurrence or metastasis beyond two years of follow up.

CONCLUSION

PSP is a pathological diagnosis which can be very difficult in small biopsy or frozen. Multifocal PSP can mimic metastatic adenocarcinoma clinically. Somatic FGFR3 (pE360K) mutation is attributed to the development of multifocal PSP which showed a spectrum growth pattern and ended with fibrosis. The added AKT1 (p.R67_L78 dup) variation provides growth advantage but does not transform the tumor to a malignant one in our case.

This is a single case study. Further research on FGFR3, AKT1 and their interaction might shed light on tumorigenesis and prognosis of multifocal PSP.

Clinical practice points

- Pulmonary sclerosing pneumocytoma (PSP) is usually a rare, incidentally identified solitary lesion located at the periphery of lung.
- We reported an unusual presentation of bilateral multifocal PSPs.
- The tumor clinically mimicked metastatic disease and was misinterpreted as lung adenocarcinoma in the initial biopsy.
- The next generation sequencing (NGS) revealed somatic FGFR3 (pE360K) mutation in multifocal PSPs associated with a spectrum of morphology ending in fibrosis. The added AKT1 (p.R67_L78 dup) variation provides growth advantage but does not malignantly transform the tumor.
- The correct diagnosis avoided unnecessary chemotherapy for this patient.

Author contributions

Manuscript drafted by LZ, corrected and approved by all authors. Supplementary video by HIL.

Conflict of interest

The authors do not declare any conflicts of interest.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval statement

Not required for a case report.

Patient consent statement

Consent for publication obtained.

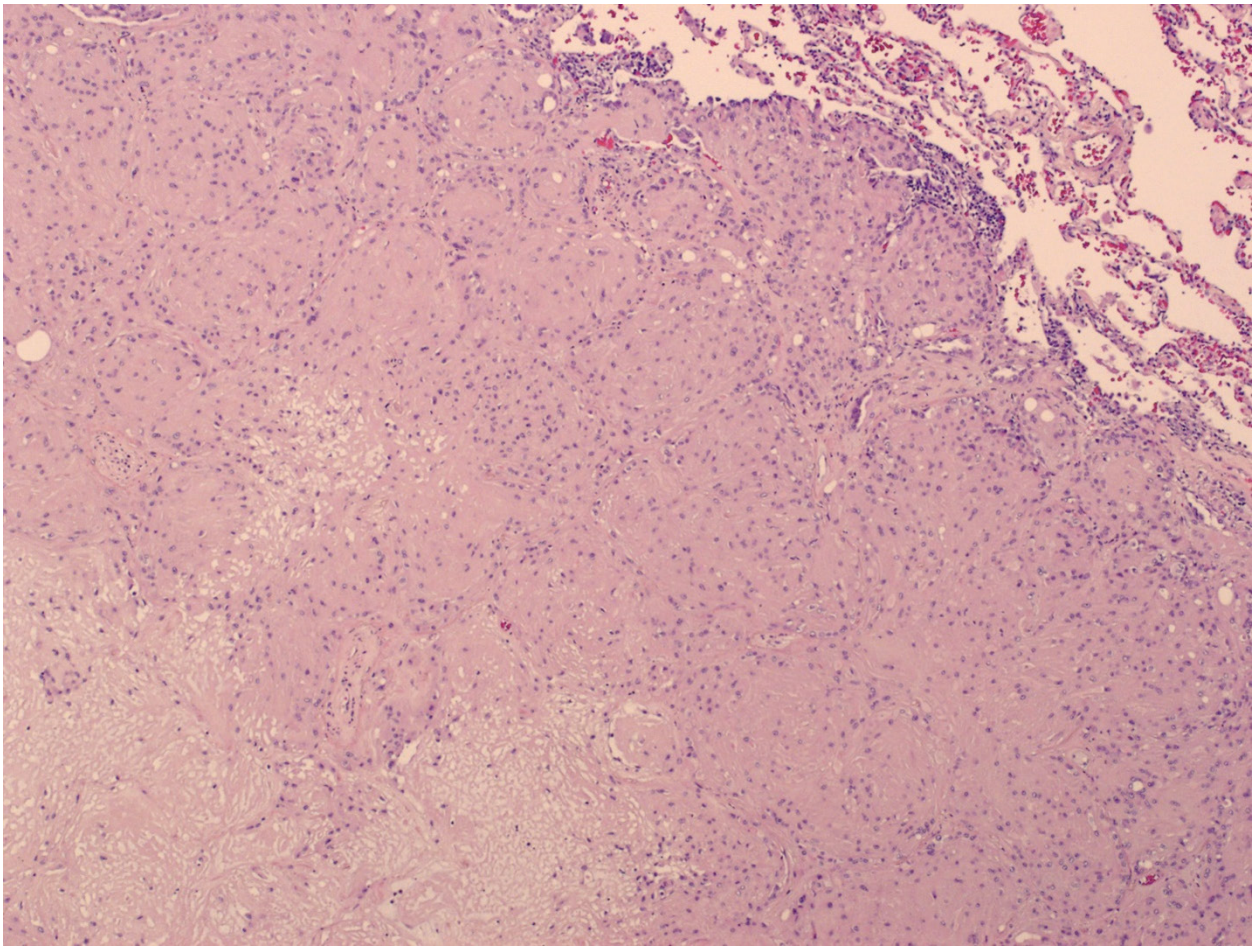
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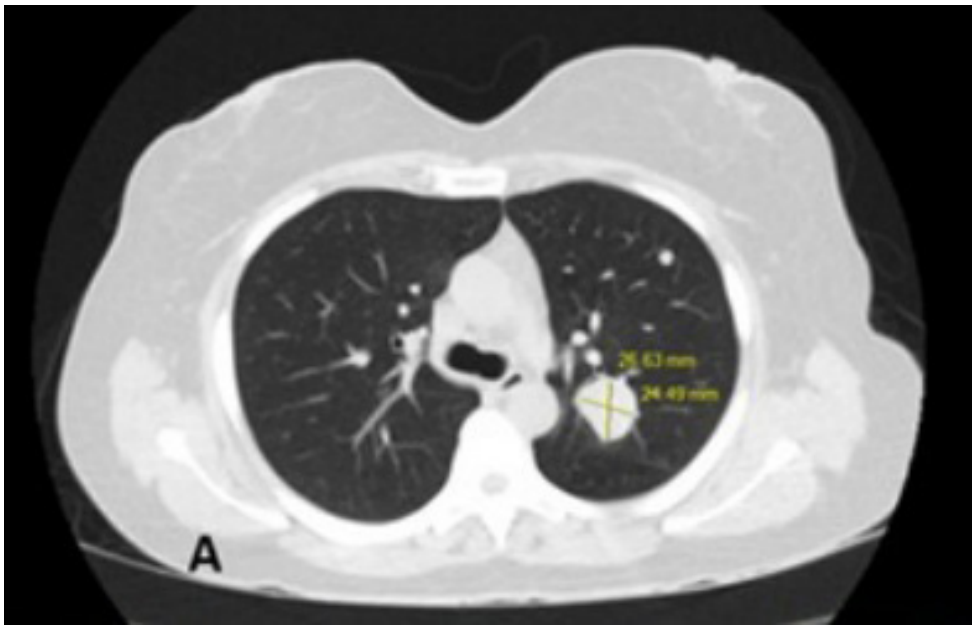
Clinical trial registration

Not required for a case report.

Supplementary Figure 1. A 0.5 cm sclerotic PSP nodule inferior to the largest 3 cm PSP mass (x4) Pictures are taken using Olympus Microscope Model BX45TF, Olympus camera Model DP71 and Olympus CellSens software at a resolution of 72dpi, and processed in adobe photoshop CS5.1 at a resolution of 300 dpi.



SUPPLIMENTRY-VIDEO



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