EJCRIM
European Journal of Case Reports in Internal Medicine

PULMONARY SCLEROSING PNEUMOCYTOMA MAY BE AN UNDER-RECOGNIZED PULMONARY MANIFESTATION OF THE PHOSPHATASE AND TENSIN HOMOLOG DELETED ON CHROMOSOME 10 (PTEN) HAMARTOMA TUMOUR SYNDROME

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Received: 09/09/2026
Accepted: 05/10/2026
Published: 21/10/2026

Conflicts of Interests: The Authors declare no conflict of interest.
Patient Consent: Written informed consent for the publication of her case was obtained from the patient.
Acknowledgments: The authors would like to thank the Saudi Thoracic Society (STS) for their support.
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How to cite this article: Alghamdi A, Alotaibi A, Aljohani A, Almaymuni A, Althakfi W, Hajjar WM. Pulmonary sclerosing pneumocytoma may be an under-recognized pulmonary manifestation of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) hamartoma tumour syndrome. EJCRIM 2026;13:doi:10.12890/2026_007500

ABSTRACT

Introduction: Pulmonary sclerosing pneumocytoma (PSP) is a rare, benign neoplasm driven by somatic AKT1 mutations that activate the PI3K/AKT/mTOR pathway. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) hamartoma tumour syndrome (PHTS) results from germline pathogenic variants affecting the tumour suppressor gene PTEN, which regulates the same pathway. Although PSP is not an established manifestation of PHTS a small number of reports have suggested a possible association.

Case description: A 23-year- old Saudi woman presented with an incidental 9 mm pulmonary nodule detected during imaging. Her history included bilateral benign thyroid nodules, a left breast nodule (BI-RADS 3) and a venolymphatic malformation. Family history was significant for maternal breast cancer, a sister with diffuse lipomatosis, and a brother with autism spectrum disorder. Video-assisted thoracoscopic surgery (VATS) wedge resection was performed; histopathology and immunohistochemistry confirmed PSP. Chromosomal microarray analysis revealed a pathogenic germline deletion at 10q23.31 encompassing PTEN, confirming the diagnosis of PHTS.

Conclusion: This case adds molecularly confirmed adult evidence to the limited literature describing PSP in patients with PTEN alterations. The coexistence of germline PTEN loss and a tumour characterized by PI3K/AKT/mTOR pathway activation provides a biologically plausible basis for further investigation.

KEYWORDS

Pulmonary sclerosing pneumocytoma, PTEN hamartoma tumour syndrome, lung neoplasm, AKT1 mutation, PI3K/AKT/mTOR pathway

EFIM European Federation of Internal Medicine

Publisher smc media srl

LEARNING POINTS

- Pulmonary sclerosing pneumocytoma (PSP) may represent an under-recognized pulmonary manifestation of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) hamartoma tumour syndrome (PHTS).
- The association between PSP and PHTS may be explained by shared involvement of the PI3K/AKT/mTOR signalling pathway.
- The presence of PSP in a young patient with a suggestive personal or family history may warrant consideration of an underlying PTEN-related disorder.

INTRODUCTION

Pulmonary sclerosing pneumocytoma (PSP) is a rare, typically benign pulmonary neoplasm, previously classified as sclerosing haemangioma[1,2]. It is now recognized as an epithelial tumour of putative type II pneumocyte origin, characterized by immunohistochemical expression of thyroid transcription factor-1 (TTF-1) and epithelial membrane antigen (EMA)[1,2]. PSP demonstrates a strong female predominance, most frequently presenting as an incidental, well-circumscribed peripheral lung nodule in middle-aged adults[1,3]. Imaging features frequently overlap with those of malignant lesions, necessitating histopathological confirmation[3].

Although PSP is generally considered an indolent lesion, rare reports of multifocality, lymph node involvement, and distant metastases have been described[1,3,4]. Recurrent somatic AKT1 mutations have been identified as a driver in many cases, leading to activation of the PI3K/AKT/mTOR pathway[1,5].

PTEN hamartoma tumour syndrome (PHTS) is an autosomal dominant disorder caused by germline mutations in the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) tumour suppressor gene[6]. The PTEN protein negatively regulates the PI3K/AKT/mTOR pathway, and its loss predisposes to a wide spectrum of benign and malignant growths, including breast, thyroid, and endometrium[5,7]. AKT1, the most commonly mutated gene in sporadic PSP, is a direct downstream effector in the same pathway regulated by PTEN[7,8]. Thus, germline PTEN loss and somatic AKT1 activation may represent convergent mechanisms leading to pathway dysregulation and tumorigenesis[7,8].

Although primary lung tumours are not a classically recognized component of the PHTS phenotype, a small number of prior reports have proposed a link between PSP and PTEN alterations[9,10].

Here, we present a case of PSP in a young adult female with a confirmed pathogenic germline PTEN deletion and a personal and family history consistent with PHTS.

CASE DESCRIPTION

A 23-year-old, non-smoking, Saudi woman was found to have an incidental pulmonary nodule on a follow-up computed tomography (CT) scan initiated for a known benign breast lesion. Her medical history was notable for bilateral benign thyroid nodules (Bethesda Category II on fine-needle aspiration), a left breast nodule (BI-RADS 3), and a venolymphatic malformation. She was taking no regular medications.

Her mother died of breast cancer, her sister had diffuse lipomatosis affecting the neck, axilla, breast and chest wall, and her younger brother had autism spectrum disorder.

Physical examination revealed normal vital signs and subtle congenital dysmorphic features including bilateral ptosis, hypertelorism, down-slanting palpebral fissures, epicanthal folds, and telecanthus. The patient also had hyperpigmented freckles and 1-2 café-au-lait macules. These findings prompted an ophthalmo-genetic evaluation.

Initial chest computed tomography (CT) scan revealed multiple nodules. The dominant lesion measures 9 mm, located in the apical segment of the right upper lobe *(Fig. 1A)*. A separate nodule in the right lung was also identified *(Fig. 1B)* which was selected for CT-guided coil localization and subsequent video-assisted thoracoscopic

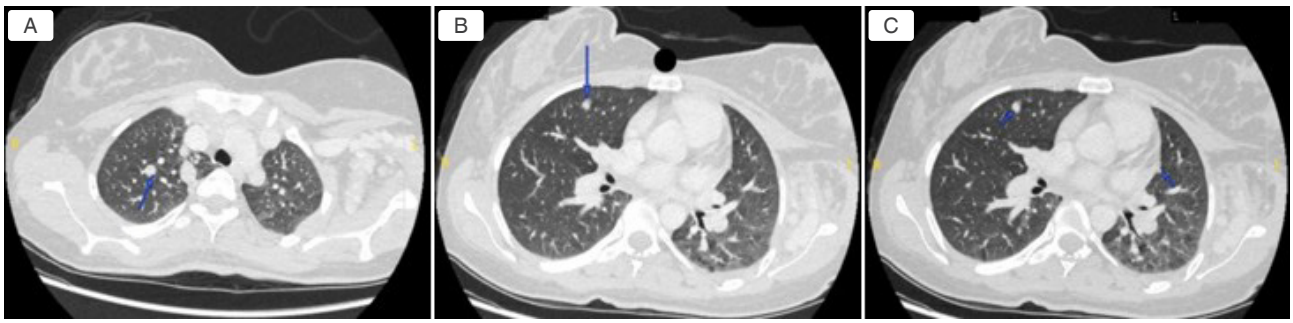


Figure 1. *Preoperative computed tomography scan, lung-window, axial views, showing multifocal pulmonary nodules. A) 9 mm nodule in the apical segment of the right upper lobe (arrow); B) Right-sided pulmonary nodule (arrow); this was the coil-localized nodule subsequently resected by video-assisted thoracoscopic surgery wedge resection. C) Nodule in the left upper lobe (arrow).*

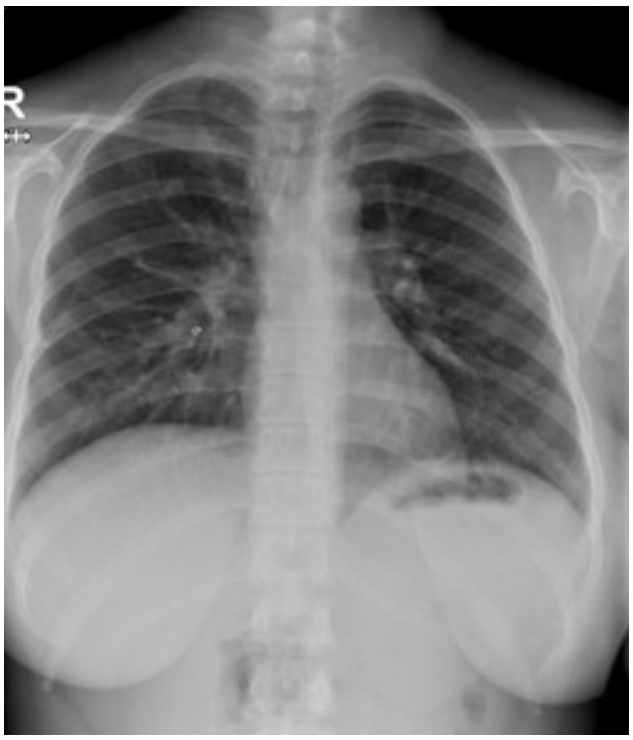


Figure 2. *Postoperative posteroanterior chest radiograph showing a well-expanded lungs bilaterally with no pneumothorax or effusion.*

surgery (VATS) wedge resection. A further nodule was noted in the left upper lobe *(Fig. 1C)* and was retained for radiological surveillance. Additional findings on the same study included a thin-walled cyst in the right lower lobe, an enlarged heterogeneous right thyroid lobe causing mild mass effect on the proximal trachea, a left axillary venolymphatic malformation measuring 12 × 6.8 × 8.7 cm, and a left breast soft tissue nodule with calcifications (BI-RADS 3).

Preoperative CT-guided localization coils were performed to clearly localize the pulmonary nodules, which was then followed by right VATS wedge resection of the coil-marked nodule. Postoperative CT scan confirmed full bilateral lung expansion with no pneumothorax or significant pleural effusion *(Fig. 2)*.

Histopathological evaluation revealed a well-defined pulmonary lesion characterized by prominent papillary architecture with focally sclerotic fibrovascular cores *(Fig. 3A and 3B)*. Showing two distinct cell populations: surface cuboidal cells lining the papillary structures and round stromal cells within the sclerotic cores. No significant cytologic atypia, necrosis, or increased mitotic activity was identified. Immunohistochemical staining showed nuclear expression of TTF-1 and membranous expression of epithelial membrane antigen in both cell populations *(Fig. 3C and 3D)*. The Ki-67 proliferation index was low. The overall histomorphological and immunohistochemical features are consistent with PSP.

Chromosomal microarray analysis (CMA) identified a heterozygous, pathogenic 1.015 Mb interstitial deletion at chromosome 10q23.31 (arr[GRCh37] 10q23.31(89686943_90701645)x1), classified as pathogenic according to American College of Medical Genetics and Genomics /Clinical Genome Resource dosage-sensitivity criteria. The deletion is contiguous, encompassing 11 RefSeq genes In addition to PTEN

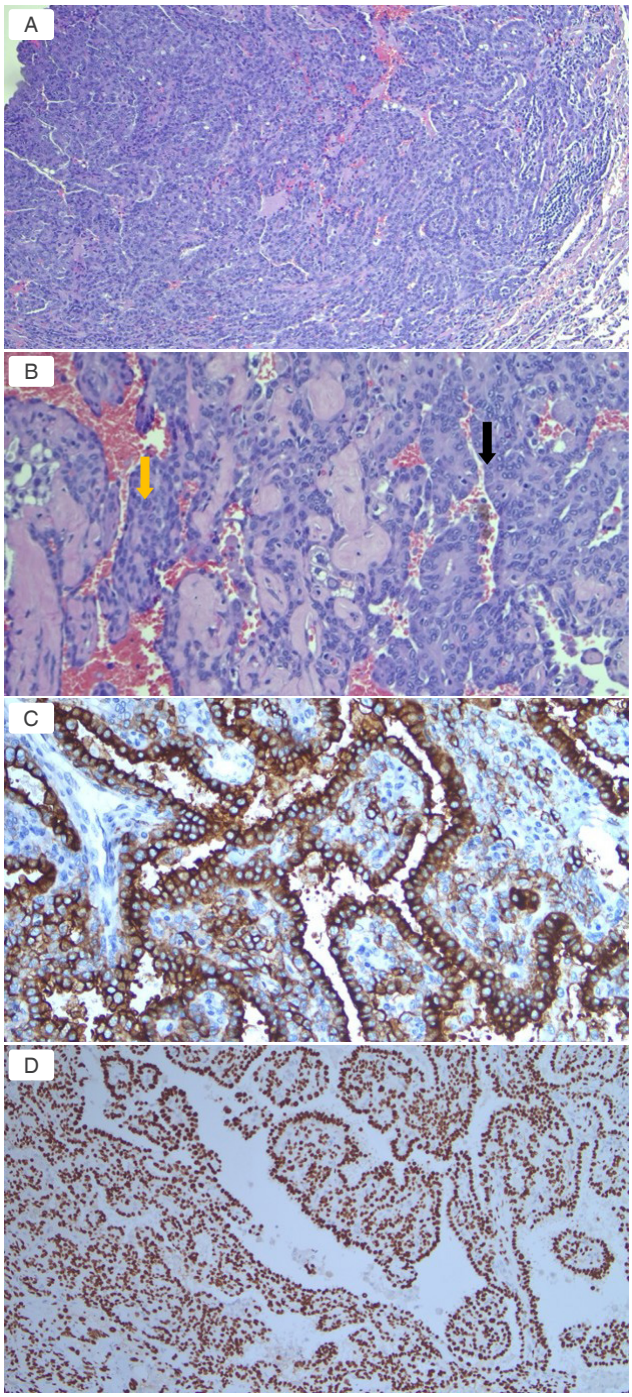


Figure 3. *Histopathology of the pulmonary lesion A) prominent papillary architecture with focally sclerotic fibrovascular cores. H&E sections (A: ×100); B) H&E section showing two cell populations, surface cuboidal cells (black arrow) and round stromal cells (yellow arrow). No significant atypia, necrosis, or increased mitotic activity is seen (B: ×200); C) Immunohistochemistry shows positive epithelial membrane antigen staining and diffuse nuclear TTF-1 expression (C: ×200); D) Immunohistochemistry shows positive epithelial membrane antigen staining and diffuse nuclear TTF-1 expression (D: ×100).*

(RNLS, LIPJ, LIPF, LIPK, LIPN, LIPM, ANKRD22, STAMBP1L, ACTA2-AS1, ACTA2), and partially involves exons 4–9 of PTEN (NM_000314). PTEN is considered the clinically relevant gene within this interval given the patient's phenotype; none of the co-deleted genes have an established haploinsufficiency-associated human disease phenotype. This finding confirmed the diagnosis of autosomal dominant PHTS.

DISCUSSION

We report a case of pulmonary sclerosing pneumocytoma occurring in a young woman with a germline PTEN deletion, confirming the diagnosis of PHTS. To our knowledge, this is the first case of PSP arising in an adult with molecularly characterized germline PTEN mutation. The case is notable for the patient's young age, absence of respiratory symptoms, incidental detection during imaging for a breast lesion, and strong family history consistent with PHTS.

PSP is a rare benign pulmonary neoplasm that predominantly affects women and is frequently detected incidentally because of its nonspecific or absent clinical manifestations. Although most tumors follow a benign course, cases of lymph node and extrapulmonary metastasis have been reported[1,2]. Consistent with this pattern, our patient was asymptomatic, and the lesion was identified during imaging for a breast lesion.

The molecular pathogenesis of PSP has recently been elucidated, with recurrent somatic AKT1 mutations identified as the most common genetic alteration, followed by β-catenin mutations. AKT1 mutations lead to activation of the PI3K/AKT/mTOR pathway and are considered a hallmark mutation of PSP[5,8].

PHTS is caused by germline mutations in the PTEN tumour suppressor gene, which negatively regulates the PI3K/AKT/mTOR pathway. Loss of PTEN function results in pathway activation and predisposes to multiple hamartomas and malignancies, including those of the breast, thyroid, and endometrium[6,7]. The phenotypic features identified in our patient—including thyroid nodules and breast lesions—are consistent with PHTS[7].

In sporadic PSP, somatic AKT1 mutations directly activate the PI3K/AKT/mTOR pathway, driving tumorigenesis[3,5,8]. In PHTS, germline PTEN loss removes a critical brake on the same pathway, creating a permissive environment for tumour development[6,7]. Together, these findings provide a biologically plausible explanation for the coexistence of PSP and PHTS. This permissive environment may facilitate the development of PSP through additional somatic mutations, such as AKT1, or through loss of the remaining PTEN allele in pulmonary cells[8]. Further molecular characterization of the tumour, including assessment for AKT1 mutations and PTEN loss of heterozygosity, would have strengthened the biological rationale for this association.

The association between PSP and PTEN alterations has been raised in a small number of prior reports. Guerra-Gutiérrez et al.[10] described an 18-year-old woman with Cowden syndrome who was found to have a pulmonary sclerosing haemangioma; however, no specific PTEN variant was reported. Nasr et al.[9] reported the first molecularly confirmed case, a 13-year-old girl with a germline PTEN mutation (c.388C>T), in whom the same mutation was identified within the tumour tissue. Dantis et al.[4] described a 23-year-old woman with synchronous PSP in both lungs, with tumour-level PTEN protein loss alongside a BRAF V600E mutation; however, this was a sporadic case without germline testing or a syndromic phenotype.

Collectively, these reports suggest an emerging association between PSP and PTEN alterations, although the molecular evidence remains variable. Our case represents, to our knowledge, the first report of PSP arising in an adult with a specific, molecularly characterized germline PTEN mutation confirming PHTS, supported by a suggestive phenotype and family history, and adds to the emerging literature supporting PSP as a possible pulmonary manifestation of PHTS. Nonetheless, the available evidence remains limited.

This report has several limitations. As a single case report, it cannot establish causation but only suggests an association. Previously reported associations between PSP and PTEN vary in molecular rigor, ranging from genetic evaluation without a specified variant, to tumour-level immunohistochemical findings without germline testing, to full germline molecular confirmation. Tumour tissue in our patient was not tested for additional somatic mutations such as AKT1or for PTEN loss of heterozygosity, which would have strengthened the molecular argument.

CONCLUSION

This case suggests that PSP may be an under-recognized manifestation of PHTS. Patients with PSP, particularly those presenting at a young age, with multifocal disease, or syndromic features, may warrant genetic evaluation for PTEN mutations. Although routine lung imaging may not be justified given the typically benign nature of PSP, clinicians should maintain a low threshold for investigating pulmonary findings. Future molecular studies of PSP in PHTS patients are needed to clarify the underlying mechanisms and determine whether routine lung surveillance is warranted.

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