REVIEW PAPER

Rare benign lung tumours presenting with high clinical suspicion for malignancy: a case series and review of the literature

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Abstract

Introduction. Incidentally discovered lung nodules can be worrisome for both the patient and their physicians. Although 95% of solitary lung nodules are benign, it is important to distinguish which nodules have high clinical suspicion for malignancy. Existing clinical guidelines do not apply to patients with signs and symptoms related to the lesion and with an increased baseline risk of lung cancer or metastasis. This paper highlights the vital role of pathohistological analysis and immunohistochemistry in the definitive diagnosis of such incidentally discovered lung nodules.

Material and methods. The three cases presented were selected based on their similar clinical presentations. A review of the literature was performed using the online database PubMed, for articles published in the period between January of 1973 to February of 2023 using the following medical subject headlines: "primary alveolar adenoma", "alveolar adenoma", "primary pulmonary meningioma", "pulmonary meningioma", and "pulmonary benign metastasizing leiomyoma".

Results (Case Series). The case series consists of three incidentally discovered lung nodule(s). Although they presented with high clinical suspicion for malignancy, detailed workup confirmed the diagnosis of three rare benign lung tumours: primary alveolar adenoma, primary pulmonary meningioma, and benign metastasizing leiomyoma.

Conclusions. Clinical suspicion for malignancy in the presented cases arose from previous and current medical history of malignancy, family history of malignancy, and/or specific radiographic findings. This paper highlights the need for a multidisciplinary approach in the management of incidentally discovered pulmonary nodules. Excisional biopsy and pathohistological analysis remain the gold standard in confirming the presence of a pathologic process and determining the nature of the disease. Common features of the diagnostic algorithm utilized among the three cases include multi-slice computerized tomography, excisional biopsy *via* atypical wedge resection (if the nodule is peripherally located), and lastly, pathomorphological analysis using haematoxylin and eosin staining and immunohistochemistry. *(Folia Histochemica et Cytobiologica 2023, Vol. 61, No. 2, 130–142)*

Keywords: pulmonary nodule; alveolar adenoma; pulmonary meningioma; benign metastasizing leiomyoma; immunohistochemistry; wedge resection

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Introduction

Incidentally discovered lung nodules can be a diagnostic challenge and are worrisome for both the patient and their physicians. Given that 95% of solitary lung nodules are benign [1], it is important to distinguish which nodules have high clinical suspicion for malignancy. The Fleischner Society, British Thoracic Society, and American College of Chest Physicians have published guidelines for the management of incidentally discovered pulmonary nodules [2–4]. However, these guidelines do not apply to patients with signs and symptoms related to the lesion and with an increased baseline risk of lung cancer or metastasis [1, 2]. In other words, patients who are undergoing screening for lung cancer with low-dose computerized tomography scan, immunocompromised, and those with current or previous history of malignancy have a higher clinical suspicion for malignancy if a pulmonary nodule is detected [1]. Rounded opacities three centimetres in diameter or greater are called lung masses and are considered to be lung cancer until pathohistological evaluation proves otherwise [1]. In addition, imaging findings of multiple pulmonary nodules greater than 5 mm and nodule cavitation are two features that are associated with the highest risk of pulmonary metastatic disease [5]. Lung metastasis can also present as a solitary pulmonary nodule [5]. It is important to consider malignancy (both primary and secondary) as a potential differential diagnosis of an incidentally discovered pulmonary nodule, especially when they present with the previously mentioned characteristics.

The aim of this paper was to present a case series of three rare benign lung tumours that were associated with high clinical suspicion for malignancy at the time they were discovered, as well as to perform a review of the literature for the three extremely rare benign tumours.

Material and methods

First, the three cases presented here were selected based on their similar clinical presentations. Each case presented with incidental pulmonary lesions with high clinical suspicion for malignancy, but detailed workup confirmed the diagnosis of a rare benign lung tumour. This study was retrospective and all procedures took place solely for standard diagnostic purposes; no additional or altered procedures were performed for the purpose of scientific research. The Ethical Committee of the Clinical Centre of Montenegro approves of these types of studies by default.

Sections preparation and staining. Lung mass excision was performed *via* atypical wedge resection in all three cases. The collected specimens were fixed with 10% neutral buffered formalin, embedded in paraffin, and then cut into 4 μm-thick sections. The sections were stained with haematoxylin and eosin (H&E) for pathohistological analysis.

Immunohistochemical staining was also performed on paraffin sections with the antibodies shown in Table 1. The sections were stained using the Ventana BenchMark XT (Roche Diagnostics, Basel, Switzerland) and DAKO Link 48 autostainers (DAKO, Glostrup, Denmark). The Ventana BenchMark XT autostainer was used for the Ventana antibodies, and autostaining was performed using the UltraView 3,3-diaminobenzidine (DAB) Detection Kit (Roche Diagnostics, Basel, Switzerland) and Bluing Reagent (Ethos Biosciences, Newtown Square, PA, USA) for visualisation. The DAKO Link 48 autostainer was used for DAKO antibodies and visualisation was performed using the EnVision FLEX (Agilent Technologies, Inc., Santa Clara, CA, USA) in accordance with the manufacturer's instructions. The sections were then analysed using a light microscope.

Table 1. Antibodies used for immunohistochemistry in this case series

Antibody	Manufacturer	Clone	Dilution
Pan-cytokeratin	DAKO	AE1/AE3	1:500
Cytokeratin 8	DAKO	35βH11	1:1
Thyroid transcription factor-1	DAKO	8G7G3/1	1:100
Napsin A	Ventana	IP64	1:100
Carcinoembryonic antigen	DAKO	Polyclonal	1:300
Vimentin	DAKO	V9	1:400
Ki67	DAKO	MIB-1	1:50
Epithelial membrane antigen	DAKO	E29	1:200
Progesterone receptors	DAKO	PgR636	1:50
Estrogen receptors	DAKO	1D5	1:50
h-Caldesmon	DAKO	MSVA-538R	1:150
α-smooth muscle actin	DAKO	1A4	1:400

Literature review. The literature review was performed using the online database PubMed, for articles published in the period between January of 1973 to February of 2023. In addition, several historically significant articles were included in the review. For this search, the medical subject headlines used were "primary alveolar adenoma", "alveolar adenoma", "primary pulmonary meningioma", "pulmonary meningioma", and "pulmonary benign metastasizing leiomyoma". Our review was limited to articles published in the English language.

Results

Case series

Patient No. 1

A 69-year-old Caucasian female with a previous medical history of renal cell carcinoma underwent routine follow-up multi-slice computerized tomography (MSCT) scan. The patient's previous medical history includes the clear cell renal cell carcinoma (World Health Organization/International Society of Urological Pathologists histological grade I, TNM 1a), which was treated surgically by partial nephrectomy without adjuvant chemotherapy or radiation; polycystic ovarian syndrome, and liver haemangioma. Family history includes two maternal uncles with a history of lung cancer. The patient is a non-smoker.

Chest MSCT scan showed a solitary right lower lobe nodule which was well-demarcated and approximately 12 mm in diameter. All other findings in the skeletal, lung parenchyma, mediastinal structures were normal. As a result of her previous medical history, there was high clinical suspicion that this was a metastatic tumour, so wedge resection of the nodule *via* anterolateral thoracotomy was performed. Gross examination of the subpleural lung specimen revealed a white, well-demarcated, partly cystic nodule, 12 × 10 mm in size, with a soft consistency. The overlying pleura was smooth, shiny, and thin.

Microscopic examination with H&E staining demonstrated a well-demarcated nodule made up of multiple cystic spaces resembling alveolar spaces (Fig. 1). The cystic spaces were either empty or filled with a granular, eosinophilic substance. The cystic spaces were lined with one row of cuboidal and flattened epithelial cells. The underlying stroma was composed of both spindle-shaped cells and connective tissue of variable thickness, with foci of a myxoid matrix.

The immunohistochemical analysis of the Patient 1 specimen demonstrated that the cells lining the cystic spaces stained positive for pan-cytokeratin (Fig. 2A), cytokeratin 8, thyroid transcription factor-1 (TTF-1; Fig. 2B), Napsin A (Fig. 2C), and carcinoembryonic antigen (CEA, not shown), indicating type 2 pneumocyte origin. A positive Ki-67 proliferation index was
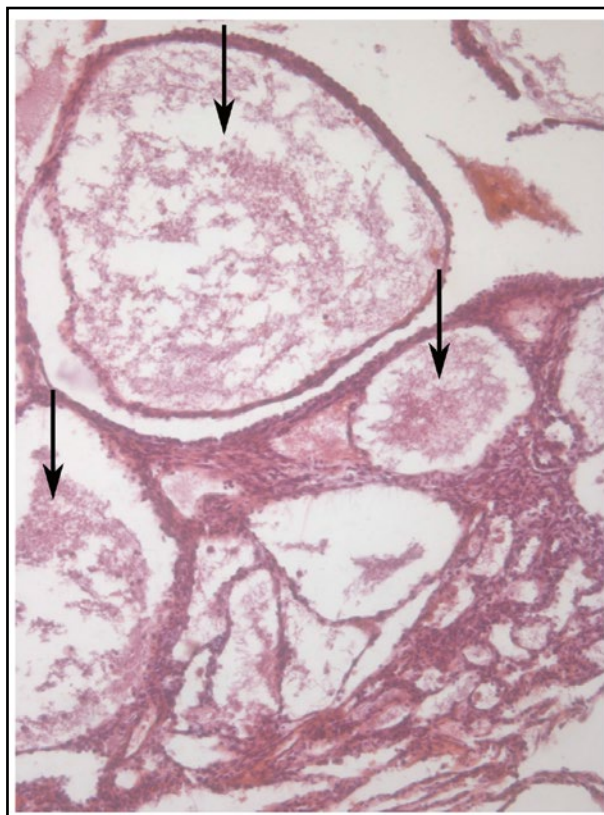
Figure 1. Pathohistological findings in the lung specimen of Patient 1 stained with H&E. Multiple cystic, alveoli-like structures can be visualized. Some cystic spaces contain a granular, eosinophilic substance (shown with arrows). Original magnification: 100×.

present in less than 1% of cells. The stromal cells were negative for these markers but positive for vimentin (Fig. 2D). As a result of the pathohistological appearance and immunohistochemical findings, a diagnosis of primary alveolar adenoma was made. Two follow-up MSCT scans were performed, one year and two years post-resection, both of which had normal findings.

Patient No. 2

A 60-year-old Caucasian female with current medical history of diffuse large B cell lymphoma (diagnosed 1 year earlier) underwent follow-up chest MSCT. Chest MSCT revealed a homogenous, hyperdense lesion in the upper left lobe of the lung approximately 5 cm in diameter. Due to the patient's medical history and imaging findings, there was high clinical suspicion for metastasis of the patient's primary malignancy. An excisional biopsy *via* wedge resection was performed.

Gross examination of the lung specimen revealed a homogeneous, white to grey nodule 50 × 37 mm in size, without pleural retraction overlying the nodule.

Microscopic examination of the Patient 2 specimen with H&E staining demonstrated that the tumour was
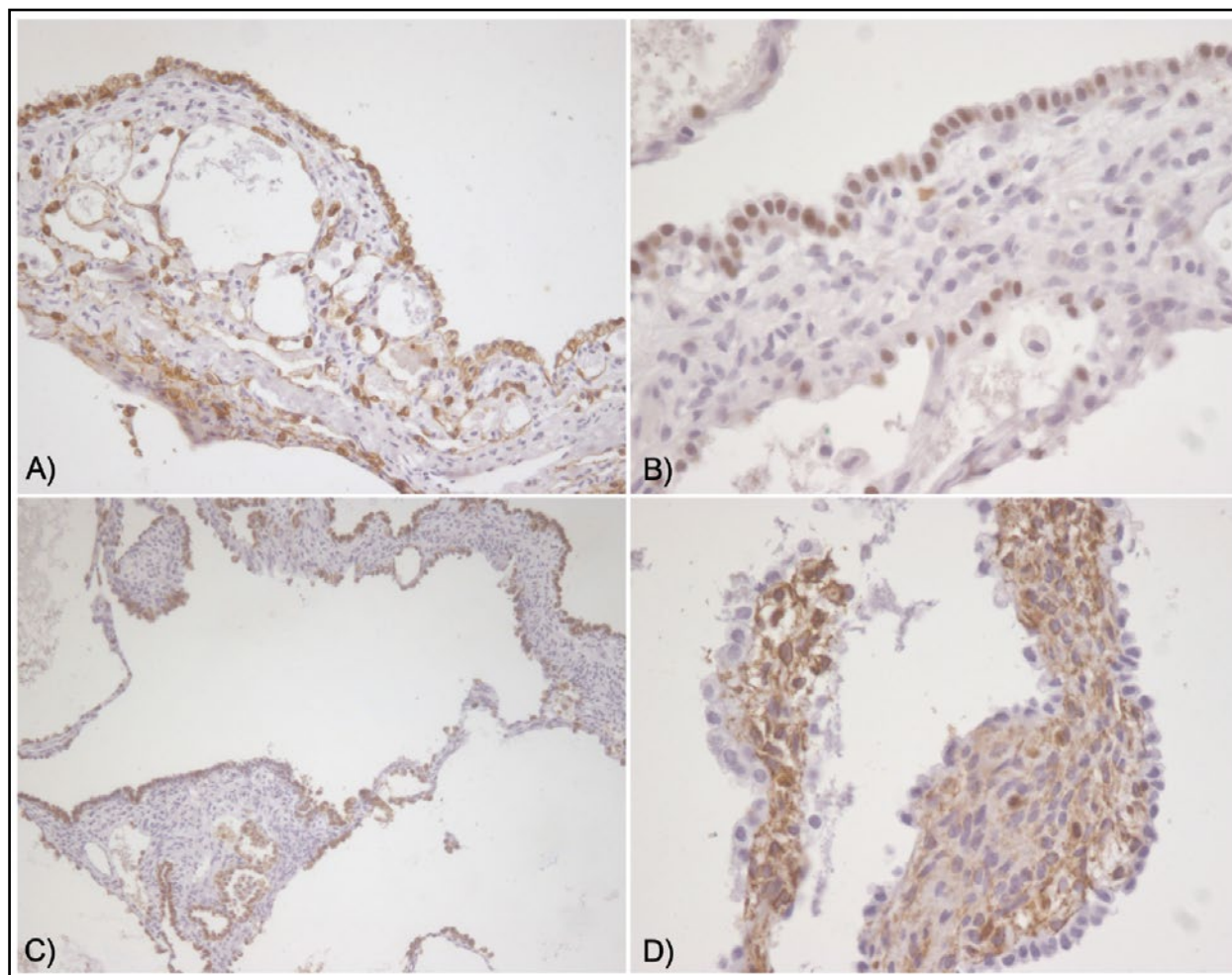
Figure 2. Immunohistochemical analysis of the lung specimen of Patient 1. **A.** The cells lining the cystic spaces were positive for pan-cytokeratin. Original magnification: 100×; **B.** Immunospecific staining for thyroid transcription factor 1. Original magnification: 200×; **C.** Immunospecific staining for Napsin A. Original magnification: 100×; **D.** The stromal cells positive for vimentin. Original magnification: 200×.

comprised of nests of meningothelial-like cells arranged in a whorl-like pattern (Fig. 3A). The cells were small, uniform, polygonal, and had poorly defined cell borders. They also had elongated nuclei and a low mitotic index. The interstitium contained a small number or spindle-shaped cells and a substantial amount of collagen fibres. A small number of psammoma bodies were interspersed between the tumour cells. The pleura was not infiltrated with tumour tissue.

Immunohistochemical analysis of the tumour cells revealed that they were positive for epithelial membrane antigen (EMA; Fig. 3B), vimentin (Fig. 3C), progesterone receptors (PR; Fig. 3D), and had a positive Ki-67 proliferation index in approximately 2% of cells. Based on these findings, the diagnosis of primary pulmonary meningioma was made.

Patient No. 3
A 46-year-old nulliparous Caucasian female presented with a fever and cough. The patient had a previous me-

dical history of uterine leiomyoma which was treated with vaginal myomectomy two years prior, as well as history of one spontaneous abortion. The patient is in perimenopause. Family history includes breast cancer in her sister and prostate cancer in her father.

Chest X-ray revealed multiple bilateral round lesions. A chest MSCT was performed revealing multiple bilateral nodules. The largest nodule in the left lung was 13 mm in diameter and was located in the upper lobe, while the largest nodule in the right lung was 7 mm in diameter and was located in the mediobasal segment of the lower lobe. The nodules had radiologic features suggestive of pulmonary metastasis. Excisional biopsy *via* wedge resection of a nodule in the right lung was performed.

Gross findings of the subpleural specimen of lung tissue demonstrated a well-demarcated, white nodule, 11 mm in diameter, with a moderately firm consistency.
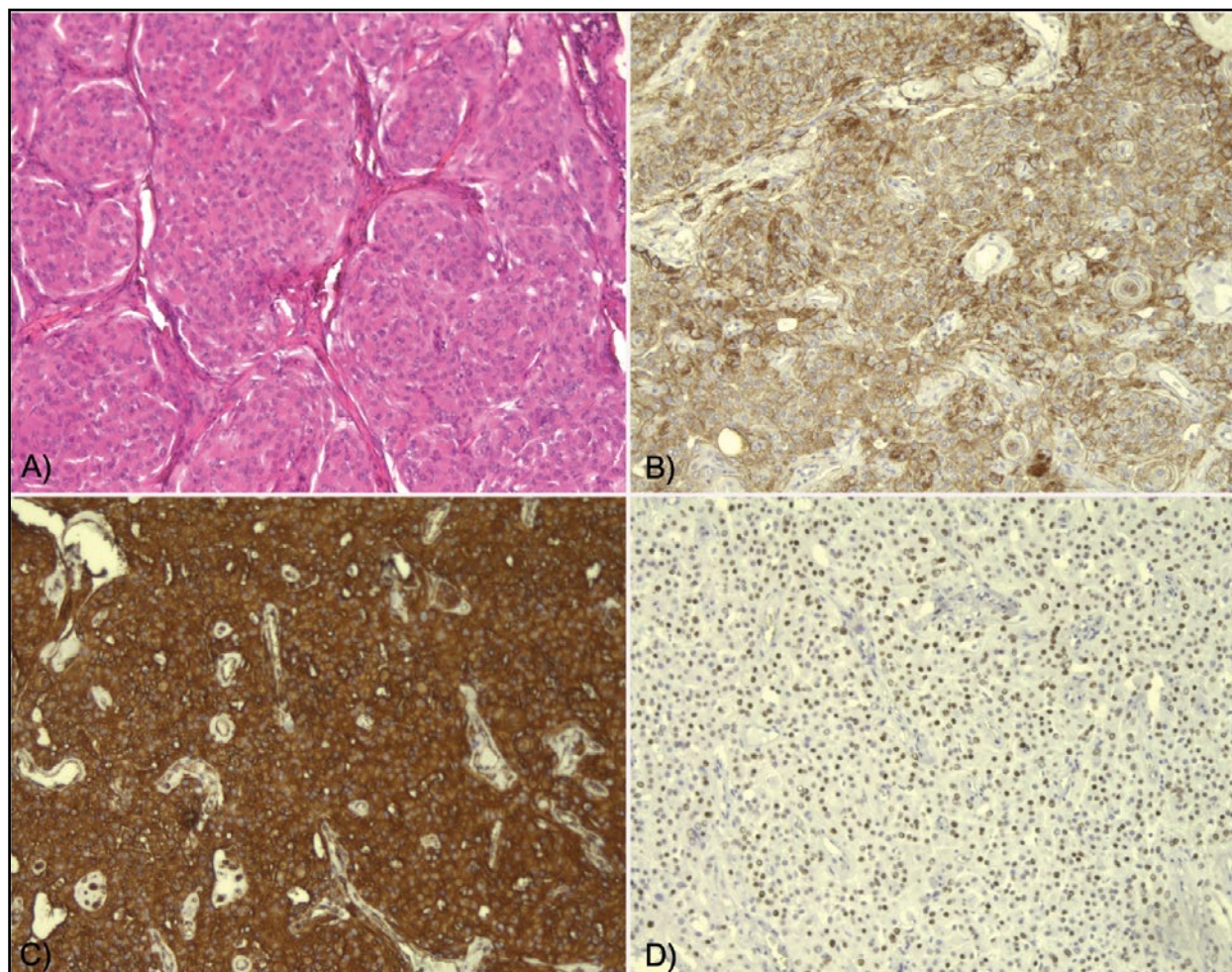
Figure 3. Pathohistology of the lung specimen of Patient 2. **A.** Microscopic section stained with H&E shows uniform, polygonal meningothelial-like cells arranged in a whorl-like pattern. **B.** Immunospecific staining for epithelial membrane antigen. **C.** Immunospecific staining for vimentin. **D.** Immunospecific staining for progesterone receptors. Original magnifications: 100×.

Microscopic findings of the Patient 3 specimen with H&E staining show bundles of uniform, spindle-shaped cells, without nuclear pleomorphism and visible mitosis (Fig. 4). The interstitium was made up of copious collagen fibres. In the periphery of the nodule, there was an empty pocket of air lined with normal respiratory epithelium. The surrounding pulmonary parenchyma had slightly thickened alveolar septi with a chronic inflammatory infiltrate. The pleura was slightly thickened and permeated with connective tissue. Immunohistochemical analysis showed that the tumour cells stained positive for h-caldesmon, α-smooth muscle actin (SMA), estrogen receptors (ER), PR, and a positive Ki-67 proliferation index in approximately 1% of cells (data not shown). These findings are consistent with the diagnosis of benign metastasizing leiomyoma.

The patient was treated with intramuscular injections of the gonadotropin-releasing hormone analogue
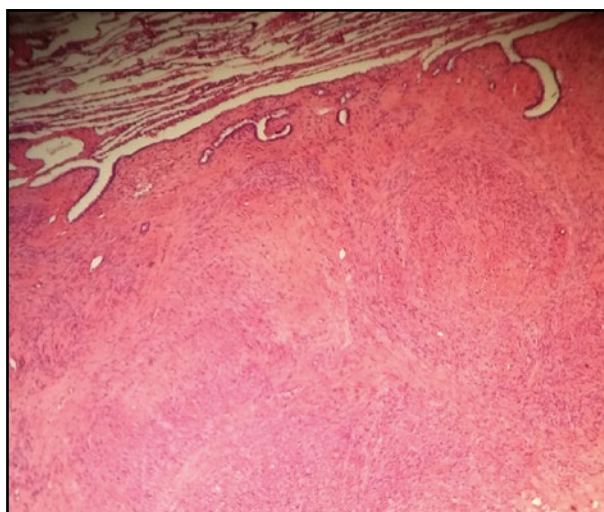
Figure 4. Microscopic section of the lung specimen of Patient 3 stained with H&E. The findings are typical of leiomyoma: uniform, spindle-shaped cells arranged and whorl- and chain-like patterns. Original magnification: 100×.

triptorelin (*Diphereline*) for two years to suppress estrogen and progesterone serum concentrations to subphysiological levels in order to induce medical castration. Two years after initial diagnosis, the patient entered menopause which elicited the decision to perform a bilateral laparoscopic salpingo-oophorectomy. Two follow-up chest MSCT scans (about 2 months pre- and 7 months post-salpingo-oophorectomy) revealed that the nodular lesions in the lungs remained stable, with no change in size compared to the chest MSCT performed 2 years prior.

Discussion

Despite the fact that 95% of incidentally discovered lung nodules are benign [1], it is important to consider malignancy as a potential differential diagnosis. This is especially important when the pulmonary nodule presents with features similar to those present in this case series. We have performed a review of the literature for the three rare benign tumours discovered in this case series, as they represent an important differential diagnosis for malignancy.

Primary alveolar adenoma

Alveolar adenoma is an extremely rare benign tumour of the lung comprised of proliferative type 2 pneumocytes and septal mesenchyme [6]. This tumour was first described by Yousem and Hochholzer in 1986 [7]. There are 58 cases reported up to date; however, the exact number of cases is unknown due to possible underreporting and difficulty differentiating from other rare lung tumours [8]. Alveolar adenoma is more common in females (with a female-to-male ratio of 2:1) and in people of Caucasian descent, which correlates with findings in our case [8]. Our case presented in a 69-year-old female patient, which is above the average reported age range of 40 to 60 [8]. The patient in the present case was asymptomatic and the nodule was incidentally discovered during follow-up imaging, which correlates with the presentation of a majority of reported cases [7, 9]. A small proportion of patients reported symptoms such as chronic non-productive cough, loss of appetite, weakness, and rash [9]. On radiographic imaging our patient presented with a subpleural coin lesion, similarly to other reported cases [10]. Our patient had a previous medical history of renal cell carcinoma. To the best of our knowledge, there has been only one other case that occurred in a patient with previous medical history of malignancy (prostate adenocarcinoma) [11]. There has also been a case reported with coexisting alveolar adenoma and cerebral arteriovenous malformations [12].

Gross examination of our lung specimen revealed a well circumscribed, subpleural nodule, 10 × 12 mm in size, which is in alignment with typical gross findings in alveolar adenoma [9]. The tumour tends to be light in colour and can vary in consistency (soft, gelatinous, spongy, firm, rubbery, or elastic) [9]. In our case, the tumour was white, cystic, and had a soft consistency. The cut surface is usually smooth, lobulated, and multicystic [9]. Microscopic findings of alveolar adenoma include a well-demarcated, multicystic lesion [7, 9]. The cysts can vary in size, with the smaller cysts resembling alveolar spaces [9], which correlates with findings in our case report. The cystic spaces are lined with a single layer of cuboidal or hobnail shaped, eosinophilic epithelial cells with a foamy cytoplasm [9]. They have round to oval uniform nuclei, without nuclear pleomorphism, and low mitotic activity [7]. Occasional flattened, squamous cells resembling type 1 pneumocytes can be seen [9]. Similarly, the cystic spaces in the present case report were lined with a single layer of cuboidal cells and occasional flattened epithelial cells. The interstitial component of the tumour in the present case resembled normal alveolar septi and was made up of connective tissue of variable thickness and spindle-shaped cells, which is in alignment with the literature [13]. The septi can occasionally be extremely thick, giving the cystic spaces a slit-like appearance [7, 9]. The cystic spaces usually contain a granular, eosinophilic, acellular material [7, 9, 13], as was found in some of the cystic spaces in the current case report. In the reported case, the tumour was positive for pan-cytokeratin and cytokeratin 8 indicating epithelial derivation, TTF-1 and Napsin A indicating pulmonary origin, as well as CEA. The interstitial spindle-shaped cells were negative for all of these markers, but positive for vimentin. These findings correlate with immunohistochemical findings typical for alveolar adenoma [13]. The eosinophilic granular material in the cystic spaces is periodic acid Schiff (PAS) positive [9]. The proliferation index Ki-67 in alveolar adenoma less than 1%, supporting it's benign nature. The p53 immunohistochemical expression is absent in a majority of reported cases [6, 13–17]. In the presented case it was not determined. Based on the pathohistological appearance and immunohistochemical profiles of the cells, the epithelial component of alveolar adenoma is most likely derived from type 2 pneumocytes, while the interstitial component is most likely derived from fibroblasts or fibroblast-like cells [7, 9, 18, 19].

The differential diagnosis for this tumour includes sclerosing pneumocytoma, papillary adenoma, lymphangioma, and pulmonary adenocarcinoma in situ (Table 2) [9, 20–24].

Table 2. Differential diagnosis for alveolar adenoma, pulmonary meningioma, and benign metastasizing leiomyoma based on pathohistological findings

Tumour	Differential diagnosis	Reasons to rule it out	References
Primary alveolar adenoma	Sclerosing pneumocytoma	Presence of papillary structures TTF-1- Absence of the PAS-positive, eosinophilic granular material	[9, 20]
	Papillary adenoma	Presence of papillary structures Heterogeneous cell population (type 2 pneumocytes, Clara cells, ciliated cells)	[9]
	Lymphangioma	Absence of the PAS-positive, eosinophilic granular material CD34+, Factor VIII+ D2-40+	[21, 22]
	Pulmonary adenocarcinoma *in situ*	Poorly demarcated borders Cytologic and nuclear pleomorphism Lepidic growth pattern	[23, 24]
Pulmonary meningioma	Minute pulmonary meningothelial nodules	NSE+ Bombesin+ Chromogranin+	[37]
	Schwannoma	S100+ EMA– SMA– Desmin–	[45]
	Solitary fibrous tumour	CD34+ STAT6+ EMA–/+ focally SMA– Desmin–	[47–49]
	Epithelial thymoma	Dual cell population (epithelial cells and thymocytes) Pan-cytokeratin+ EMA–	[37, 45]
	Paraganglioma	NSE+ Chromogranin+ Synaptophysin+ CD57+ GFAP+	[44]
Pulmonary benign metastasizing leiomyoma	Solitary fibrous tumour	CD34+ STAT6+ EMA–/+ focally SMA– Desmin–	[47–49]
	Metastatic low-grade leiomyosarcoma	Cellular atypia High mitotic activity Nuclear pleomorphism MiRNA expression	[54, 82]
	Lymphangio-leiomyomatosis	HMB-45+ MelanA+ MITF+	[83, 84]
	Schwannoma	S100+ EMA– SMA– Desmin–	[45]

The treatment for primary alveolar adenoma is by surgical resection. The prognosis of alveolar adenoma is favourable. The wedge resection in the present case was considered curative, as two follow-up MSCT scans had normal findings with no metastases or recurrences found. This is in agreement with the literature, which states that a vast majority of cases up to date have had an indolent clinical course, with no metastases or recurrences. There has only been one reported case of malignant transformation of alveolar adenoma [16].

Pulmonary meningioma

Meningiomas are benign neoplasms that originate from arachnoid cap cells. They are the most common intracranial tumour (39% of all primary central nervous system tumours) [25,26]. Primary ectopic meningiomas are rare tumours that usually arise in the head and neck region. They account for only 1–2% of all meningiomas [23, 27]. Primary pulmonary meningioma is even more rare [28]. It was first described by Kemnitz *et al.* in 1982 [29]. To this date, only about 68 cases have been reported [30]. Among the reported cases, the vast majority were benign meningiomas, with only five being malignant [30–34]. The patient in our case was a 60-year-old female. These tumours are slightly more common in females (female-to-male ratio is 14:11) and can occur in all age groups [35, 36]. To the best of our knowledge, our case is the first reported case of primary pulmonary meningioma with concurrent lymphoma. However, it is not the first case of primary pulmonary meningioma in a patient with history of malignancy- there have been nine previously reported cases with concomitant malignancy (two had history of lung adenocarcinoma, two colorectal adenocarcinoma, one buccal cancer, one papillary thyroid carcinoma, one kidney cancer) [28]. In these cases, primary pulmonary meningioma simulated lung metastasis, similar to the present case report. Most cases of primary pulmonary meningioma are asymptomatic and are discovered incidentally as solitary nodules on routine chest radiography, as was the case in our patient. In some cases, patients had persistent cough, chest pain, chest tightness, or haemoptysis [27, 28, 31, 37]. Typical radiological findings were present in our case report and consist of a solitary, peripherally located, well-demarcated nodule without calcification. Since they lack specific radiologic characteristics, they can often mimic lung metastasis, especially in patients with history of malignancy [26,37]. Positron emission tomography (PET) cannot be used to distinguish primary pulmonary meningioma and metastasis because both pathologies have an increased 18-fluorodeoxyglucose (18-FDG) uptake [27, 38–40]. PET was not performed in the presented case. Lastly, since intracranial and spinal meningiomas can metastasize to the lungs in some rare cases, central nervous system imaging is needed to confirm the pulmonary origin of primary pulmonary meningioma [37]. In the present case, an endocranial MSCT was performed due to her primary illness and confirmed normal findings.

Primary pulmonary meningiomas have similar pathohistological features to meningiomas of the central nervous system [26, 37]. Gross examination typically reveals a solitary, well-circumscribed and rounded nodule, with yellow to grey cut surface [41,

42]. Our case had typical macroscopic findings for this tumour. There is no pleural and bronchial involvement [36]. Microscopic evaluation reveals spindle-shaped cells with round to oval, uniform nuclei [26, 41]. In the present case, they were arranged in a whorl-like pattern. They can also be arranged in sheets of onion peel-like structures or lobules [26, 36]. Psammoma bodies were scattered among the tumour cells, which is in agreement with other cases in the literature [26, 41]. Immunohistochemical analysis revealed vimentin and EMA positivity, which is indicative of primary pulmonary meningioma [26, 41]. The tumour was also focally positive for PR, which has also been reported in several other cases as well [43]. They can also occasionally have focal expression of S100, which was negative in the present case report [43]. The tumour is usually negative for the following markers: pan-cytokeratin, CD34, STAT6, SMA, TTF-1, NSE, chromogranin, and synaptophysin [41, 43].

The differential diagnoses includes minute pulmonary meningothelial nodules, pulmonary schwannoma, epithelial thymoma, solitary fibrous tumour, paraganglioma, and metastatic carcinoma (Table 2) [27, 37, 44–49].

The treatment for pulmonary meningioma is surgical resection. The type of surgical resection depends on the location of the tumour-wedge resection is indicated for peripheral tumours, while lobectomy is indicated for central tumours [36]. In the present case, wedge resection was performed for excisional biopsy and pathohistological diagnosis and is also most likely curative, as the prognosis after radical excision is favourable [37]. There have been no cases of recurrence of metastases during follow-up in benign cases of primary pulmonary meningioma [43].

Pulmonary benign metastasizing leiomyoma

Uterine leiomyomas are an extremely common benign neoplasm of the myometrium that occur in women of reproductive age [50]. Most uterine leiomyomas are benign, with only 0.13–6% being malignant [51]. Despite being benign, in some cases they display bizarre growth patterns such as intravascular leiomyomatosis, disseminated peritoneal leiomyomatosis, and benign metastasizing leiomyoma [52]. Benign metastasizing leiomyoma is defined as a rare condition with histologically benign leiomyomas with metastatic potential [53, 54]. Although the pathogenesis is still unclear, the most commonly accepted theory is that it is the result of hematogenous dissemination of benign uterine leiomyomas. This disease was first described by Steiner in 1939 [55]. In our case report, it presented in a 46-year-old woman with previous history of vaginal myomectomy. This is in alignment with the literature,

as it most commonly affects premenopausal women with previous history of uterine leiomyoma, usually years following surgical manipulation (myomectomy or hysterectomy) [53, 56]. It can sometimes occur in menopausal or postmenopausal women who had previously undergone surgical treatment for uterine leiomyomas, with the metastases being discovered many years later [57, 58]. It is hormone-dependent, with estrogen-promoting tumour growth and progesterone causing tumour regression [59]. The most common location of benign metastasizing leiomyoma is the lung, which occurred in the presented case report. Other potential localizations are the heart, pelvic and abdominal cavity, omentum, lymph nodes, muscles, brain and spinal cord, bone, abdominal wall skin, and scars [53, 60, 61]. The disease is characterized by slow progression and is usually incidentally discovered during routine chest X-rays. The symptoms of benign metastasizing leiomyoma depend on the location of the metastasis, however, most cases are asymptomatic. The patient in our case presented with fever and cough, most likely of infectious aetiology, which led to the incidental discovery of multiple bilateral pulmonary nodules. Other potential symptoms when the lungs are affected include dyspnoea, chest pain, hemopytsis, haemothorax, and/or pneumothorax [62]. Haemoptysis and respiratory failure can occur in the presence or large or numerous tumours [53].

Imaging findings (chest X-ray and MSCT) in our case reported revealed multiple, bilateral, well circumscribed round lesions, up to 13 mm in size. This is in alignment with the literature, as it usually presents with multiple, bilateral (70% of cases), well-circumscribed round lesions of varying sizes [63]. It can occasionally present with a miliary pattern, cavitary nodules, interstitial lung disease, or multiloculated fluid-containing cystic lesions [64–67]. They do not involve bronchi and pleura [68]. The most commonly used imaging method in pulmonary metastasizing leiomyoma is chest MSCT. Intravenous contrast does not enhance the nodules [66]. Studies have shown that benign metastasizing leiomyoma has low 18-FDG uptake on PET, making this method useful in differentiating it from malignancy which shows high uptake [69, 70]. PET was not performed in the present case.

Metastatic leiomyomas have a similar pathohistological morphology to their uterine counterparts [71, 72]. Gross examination included a well demarcated, white nodule, 11 mm in diameter, with a moderately firm consistency, which correlates with findings in other cases [73]. Cut surface often reveals a whorl-like pattern [73]. Microscopic findings show bundles of uniform, spindle-shaped cells, without nuclear pleomorphism and visible mitosis. These cells can often be arranged in a palisade, bundle, or whorl pattern. The smooth muscle cells have abundant eosinophilic cytoplasm and uniform nuclei that are cigar or boxcar shaped [73, 74]. The interstitium was made up of a large amount of collagen fibres. The tumour can rarely have small areas of coagulative necrosis, cysts, or entrapped epithelium [71, 72, 74] — in the current case, a cystic lesion described as an empty pocket of air lined with normal respiratory epithelium was noted. Immunohistochemical analysis in the presented case revealed positive markers for cells of mesenchymal derivation with smooth muscle cell differentiation, including SMA and h-caldesmon, which correlates with the literature [62]. It is usually positive for desmin and calponin as well, which were not performed in this case. The tumour was also positive for ER and PR, explaining the hormone-dependent nature of these tumours [75]. A low tumour proliferative Ki-67 index (under 1%) was noted in the current case, as was in other reported cases [76]. It is negative for TTF-1, S100, EMA, pan-cytokeratin, chromogranin, synaptophysin, and melanocytic markers [77]. Molecular studies have shown that 19q and 22q terminal deletion are characteristic for benign metastasizing leiomyoma [78]. Other cytogenic mutations associated with this disease include 1p terminal deletion, 6p21 and 12q15 rearrangements involving the *HMGA2* and *BMP8B* gene [79–81]. Cytogenic analyses were not performed in the present case.

The differential diagnosis includes metastatic low-grade leiomyosarcoma, pulmonary lymphangioleiomyomatosis, solitary pulmonary fibroma, and schwannoma (Table 2) [45, 47–49, 54, 74, 82–84].

There are no specific guidelines for treating benign metastasizing leiomyoma [85]. An individual treatment strategy should be developed based on the size and localization of the tumours, symptoms, and hormonal status of the patient (pre-, peri-, or post-menopausal) [77]. Possible treatment strategies include close monitoring, surgical castration (bilateral salpingo-oophorectomy), medical castration with gonadotropin-releasing hormones analogues (triptorelin, goserelin), oral progestins (uliprístal acetate, megestrol acetate), selective ER antagonists (tamoxifen), or aromatase inhibitors (anastrozole, letrozole) [77, 86]. Our patient was treated with intramuscular injections *Diphereline* for two years to induce medical castration. Following this treatment, surgical castration was performed due to the patient entering perimenopause. Two follow-up chest MSCT scans (about 2 months pre- and 7 months post-salpingo-oophorectomy) revealed that the nodular lesions in the lungs remained stable, with no change in size compared to the chest MSCT performed 2 years prior. In patients with single

or few pulmonary nodules, curative surgical resection plays an important role in achieving a good outcome [77]. In some cases, especially in young women with asymptomatic multiple nodules, close monitoring is recommended in order to avoid symptoms of estrogen deficiency [77]. Due to the hormone dependent nature of the disease, pulmonary benign metastasizing leiomyoma may naturally decrease in size following menopause or delivery [87, 88].

Common features in the case series: high clinical suspicion for malignancy

This paper presents three cases of accidentally discovered pulmonary nodules with high level of suspicion for malignancy. The Fleischner Society and the British Thoracic Society have published guidelines for the management of incidentally discovered pulmonary nodules [2, 3]. However, neither of these guidelines apply to patients with signs and symptoms related to the lesion and with an increased baseline risk of lung cancer or metastasis [1, 2], so they could not be applied in the presented cases. The American College of Chest Physicians also has published guidelines for the management of solitary pulmonary nodules based on size (greater or less than 8 mm) and presence of risk factors for malignancy (patient age, smoking status, history of cancer, nodules size, morphology, and location) [4]. For solitary nodules 8 to 30 mm in diameter with a high probability of cancer (as in the first case), video-assisted thoracoscopic surgery with resection and pathohistological examination is recommended [4]. These guidelines cannot be applied in the second case due to size of the nodule, nor the third case, as there were multiple nodules present. In the second case, the incidentally discovered lesion was over 30 mm in size. Rounded opacities three centimetres in diameter or greater are called lung masses, and are considered to be lung cancer until pathohistological evaluation proves otherwise [1]. As a result, excisional biopsy *via* wedge resection and pathohistological examination was imperative. As for the final case, imaging findings of multiple pulmonary nodules greater than 5 mm are associated with the highest risk of pulmonary metastatic disease [5], which resulted in high clinical suspicion for malignancy. This also prompted the need for surgical resection and pathohistological examination. Common features of the diagnostic algorithm in all three cases:

- imaging: MSCT was performed in all three cases. 18-FDG PET was not performed, but it can used to differentiate malignant and benign nodules in some, but not all, cases;
- excisional biopsy: atypical wedge resection was performed in all three cases because each had nodule(s) that were peripherally located;
- pathohistological diagnostic algorithm: despite having clinical features of malignancy, microscopic evaluation revealed tumours with benign features such as organized and expansive growth, well differentiated cells, uniform nuclei, low nuclear to cytoplasmic ratio, minimal mitotic activity, and a low Ki-67 index. Further immunohistochemical staining prompted the diagnosis of three rare benign tumours of the lung: primary alveolar adenoma, pulmonary meningioma, and benign metastasizing leiomyoma, respectively. Differential diagnosis for all three cases can be found in Table 2.

Conclusions

In this case series, we described three patients with incidentally discovered pulmonary nodule(s) with high clinical suspicion for malignancy. Clinical suspicion for malignancy arose from previous personal medical history of malignancy, family history of malignancy, and/or radiographic findings. However, in all three cases pathohistological evaluation revealed extremely rare benign tumours. This highlights the need for a multidisciplinary approach in the management of incidentally discovered pulmonary nodules. Microscopic analysis remains the gold standard in confirming the presence of a pathologic process and determining the nature of the disease, if present.

Conflict of interest

The authors claim that they have no competing interest.

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