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Case Report

Multiple Primary Pulmonary Meningiomas: Case Report and Literature Review

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Abstract

Background: Primary pulmonary meningioma (PPM) is a very rare tumour, while multiple PPMs are even more exceptional and herein, we report the sixth case, focusing on the clinicopathological and radiological features of the tumour.

Case Presentation: Herein, we report a case of an asymptomatic 51-year-old female, who presented three solid nodules in both lungs who underwent video-assisted thoracoscopic middle lobectomy and wedge resection of the right upper lobe. The third lesion was followed-up and resected three years later due to its slow but significant growth, alongside two new lesions. All lesions revealed morphological and immunohistochemical profile of meningioma. Metastatic meningioma was ruled out by brain and spine magnetic resonance imaging scans. **Conclusions:** PPM is mostly benign and slow-growing tumour with an excellent prognosis, it does not present specific radiological characteristics and it is difficult to differentiate it from other lung tumours, surgical resection with subsequent histopathological examination being essential. A causal connection between sex hormones and meningioma has long been debated and we hypothesize a causal connection between the PPM and her hormonal therapy with progesterone analogue.

Keywords: Pulmonary Meningioma; Pulmonary Nodules; Lung Neoplasm; Contraception

Abbreviations: PPM: Primary Pulmonary Meningioma: Mppm- Multiple Primary Pulmonary Meningioma; CNS: Central Nervous System; CT: Computed Tomography; PET FDG: Positron Emission Tomography with Fluorodeoxyglucose; SUV Max: Maximum Standardized Uptake Value; VATS: Video-Assisted Thoracoscopic Surgery; IHC: Immunohistochemistry; CK: Cytokeratin; EMA: Epithelial Membrane Antigen; CD34: Cluster of Differentiation 34; PR: Progesterone Receptors; ER: Estrogenic Receptors; STAT6: Signal Transducer and Activator of Transcription 6; CD68: Cluster of Differentiation 68; SMA: Smooth Muscle Actin; NSE: Neuron Specific Enolase; SSTR2: Somatostatin Receptor 2a; MRI: Magnetic Resonance Imaging; MPMN: Minute Pulmonary Meningothelial-Like Nodules; CPA: Progestin Cyproterone Acetate; ACM: Chlormadinone Acetate; IUD: Intrauterine Device; TRAF7: Tumour Necrosis Factor Receptor Associated Factor 7; NF2: Neurofibromatosis Type 2; PIK3CA: Phosphatidylinositol-4,5- Biphosphate 3-Kinase Catalytic Subunit Alpha

Introduction

Meningioma is the most common primary intracranial tumour worldwide, accounting for about 15-20% of all primary central nervous system (CNS) tumours, with a female predominance. Most of them arise in intracranial, intraspinal, and orbital locations [1]. Ectopic meningioma account for approximately 2% of all meningioma and have been reported in various anatomic sites including the head and neck region, skin, bone, peripheral nerves and lungs. Among them, primary pulmonary meningioma (PPM) is even less frequent, and since its first description by Kemnitz et al [2] in 1982, less than 70 cases have been reported [3,4]. Most tumours show a benign behaviour, with indolent growth and good prognosis. However, the etiology is still poorly documented; several mechanisms have been proposed, suggesting that extra cranial meningioma originate from heterotypic embryonic remnants of arachnoid cells, namely minute pulmonary meningothelial nodules or from pluripotent sub-pleural mesenchymal cells [3,5]. The role of sexual hormones has long been evoked and data has been conflicting across studies [6-9]. However, recently, a dose-dependent relationship between the incidence and growth of meningioma and hormonal treatment with the progestin cyproterone acetate has been established [10]. Multiple PPM (mPPM) are even more seldom and herein, we report, to the best of our knowledge, the sixth case, focusing on the clinicopathological features of the tumour.

Materials and Methods

Case Presentation

We report the case of an asymptomatic 51-year-old female presenting three solid pulmonary nodules, in the right upper lobe, middle lobe and left lower lobe, described as incidental findings on computed-tomography (CT) during a pre-bariatric surgery check-up (Figure 1). No obvious enlarged hilar or mediastinal lymph nodes were observed. The patient revealed no drinking or smoking history. The physical examination was unremarkable except for obesity. The lesions ranged between 6 and 24 mm in size and presented as solid nodules with lobulated contours. The largest lesion situated in the middle lobe had mild fluorodeoxyglucose (FDG) uptake (maximum standardized uptake value (SUV max) = 2,9) on F-18 FDG positron emission tomography (PET)/CT, highly suggestive for primary lung neoplasm. For pathological assessment, VATS middle lobe resection and wedge resection of the right upper lobe nodule were successfully performed. Gross examination revealed relatively well-delineated firm whitish nodules, while microscopic analyses revealed characteristic features of meningioma such as spindle and epithelioid cells, mainly monomorphic with abundant eosinophilic cytoplasm and round nuclei with pseudo inclusions forming syncytia-like lobules, separated by fine collagen septa. Whorls and psammoma bodies were also seen. No signs of anaplasia were observed. The meningothelial cells expressed diffusely Vimentin, Somatostatin receptor 2a (SSTR2a), focally Progesterone receptors and were negative for epithelial markers (cytokeratin (CK) AE1/AE3, CK7, CK20, Epithelial Membrane Antigen (EMA)), neuroendocrine markers (Synaptophysin, Chromogranin, cluster of differentiation CD56) and Estrogenic receptors. The proliferation labelling index Ki-67 was low (<5%). Histopathological features are graphically represented in Figure 2 and Figure 3. No mutations were identified on targeted Next Generation Sequencing. Metastatic meningioma was ruled out by brain and spine magnetic resonance imaging (MRI) scans. The third lesion located in the left lower lobe was followed-up and resected three years later because of its slow but significant growth (14mm to 16mm), alongside two new infracentimetric lesions. Those three lesions showed a morphological and immunohistochemical profiles similar to previously resected lesions.

Review of published cases

A systematic literature review was performed until 15th November 2022 in the PubMed database. The search terms included “multiple pulmonary meningioma” and only English studies (at least English abstract) were considered. We considered eligible for our review, research including radiologic and histological assessment confirming the diagnosis. Pulmonary metastases of brain meningioma, pulmonary meningothelial-like nodules, and minute pulmonary meningothelial-like nodules, primary extra cranial and extra pulmonary meningioma were excluded from this review. PubMed research revealed 177 articles from 1968 to 2022, of which seven were considered eligible after filtering our initial selection [11-17]. Three out of seven articles were authored by the same researchers and concerned the same patient (surgery, ten- and twenty-years follow-up). Six distinct patients with reported radiological study, histological assessment confirmation and negative brain scan were included for analysis.

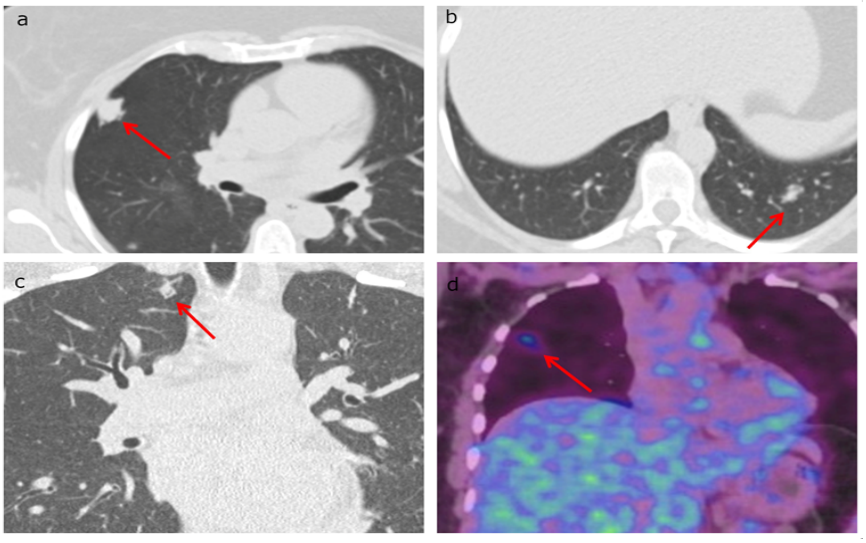

Figure 1: a-c Chest computed tomography: multiple variable-sized nodules in both lungs. a 6 mm nodule in right upper lobe- coronal plane- Apical Segment 1. b 24 mm nodule in middle lobe- lateral segment 4. c 14 mm nodule in left lower lobe- cross plane- Posterior-basal segment 10. d positron emission tomography- computed tomography hyper metabolic nodule in the middle lobe- coronal plane.

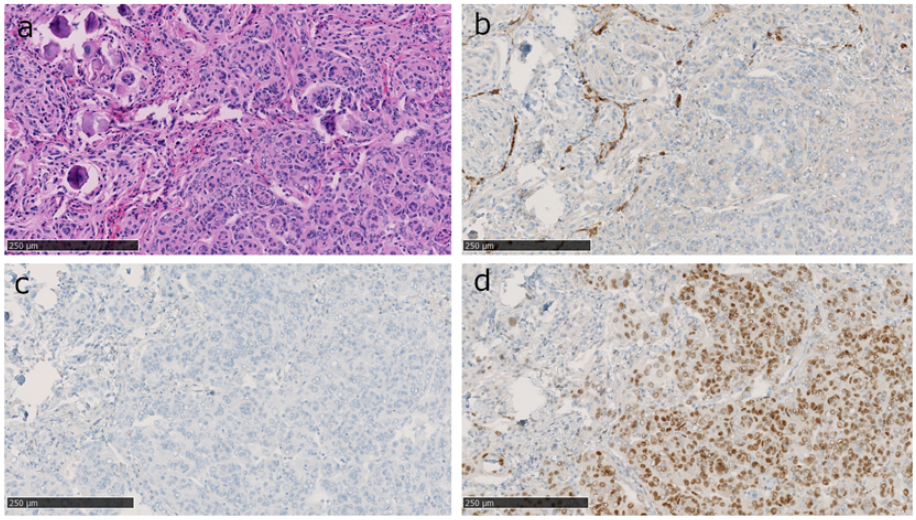

Figure 2: Pulmonary meningioma (histologic and immunohistochemistry assessment). a spindle and epithelioid monomorphic cells' proliferation with abundant eosinophilic cytoplasm and round nuclei with pseudoinclusions organized in whorls with syncytia-like lobules; presence of psammoma bodies (hematoxylin and eosin). b epithelial membrane antigen negativity. c estrogen receptor negativity. d progesterone receptor positivity (x200 magnification).

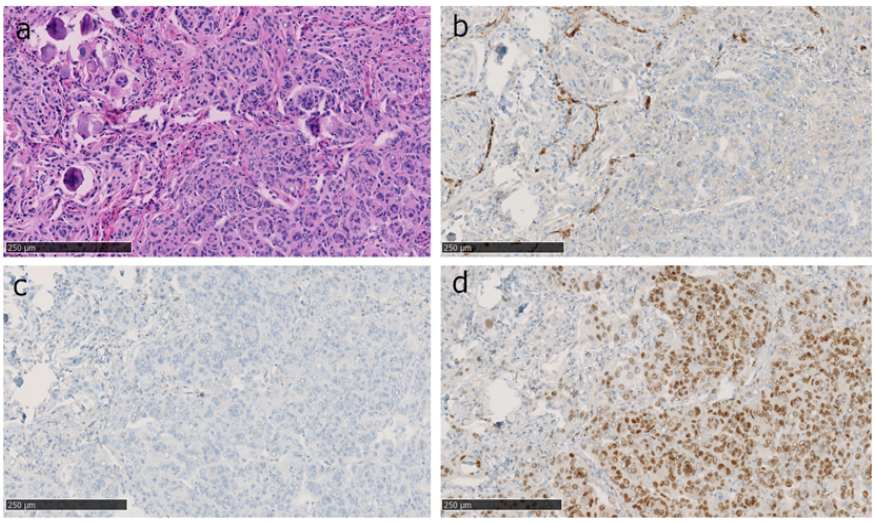

Figure 3: Pulmonary meningioma (histologic and immunohistochemistry assessment). a spindle cells in a whorl formation. b Somatostatin receptor 2a positivity (x100 magnification).

Results

Patient characteristics

The study cohort included 8 cases from six patients [11-17], five females and one male. The median age at diagnosis was 59 years old (51–64-year-old). All patients were asymptomatic. Medical history data was not contributive in two patients [12,17], revealed hypertension in two cases [11,16] and one patient [13] had previous surgeries and chemotherapy for immature ovarian teratoma 33 years prior-, mature retroperitoneal teratoma 16 years prior- and peritoneal teratoma six months prior to mPPM diagnosis. None of the patients had a previous history of CNS meningioma at the time of diagnosis. Data is summarized in Table 1.

Diagnostic procedures and therapeutic management

mPPM were diagnosed on CT-scans with pathological confirmation in all cases. The exact number of lesions was reported for five patients, ranging from three to 17 (median number: three). The size of tumours was reported in five out of six cases and ranged from 4 to 34 mm. The lesions were bilateral in all patients. mPPMs were generally well-circumscribed on radiological studies but Huang et al [11] reported ground-glass opacities while Wang et al [17] reported rounded, slight-enhanced mass and besides thin smooth walled cysts or cystic nodules with a solid component. FDG PET/CT was performed in two cases and revealed mild FDG uptake. Metastatic meningioma was ruled out in all cases by MRI scan. Five patients underwent VATS wedge resection or lobectomy and one patient underwent thoracotomy resection. Benign meningioma were diagnosed in all cases. Immunohistochemistry results were available for six cases (from five patients). Data is summarized in Table 1. Follow-up data was available for three patients. No recurrence was observed in one patient after two years [12] while one patient [16] presented a slow growth of an unresected nodule at ten-years follow-up [14], which continues to grow with the emergence of two new lesions at twenty-years follow-up [17]. We followed-up the case we have reported herein over four years and the unresected lesion showed slow, but significant growth (14mm to 16mm), alongside two new infracentimetric lesions that were subsequently resected three years after the first surgery. The patient was disease-free one-year post last surgery.

Number of cases		8*	Examined case (n)
Age at diagnosis	Median (range)	59 (51-64)	6
Sex	Male: Female	1: 5	6
Size	Range	4-34 mm	5
Number of lesions	Median (Range)	3 (3-17)	5
Location	Unilateral/bilateral	0/6	6
CT	Solid nodules/ground glass opacity/ cysts +- solid component	6/1/1	6
PET FDG	FDG uptake/no uptake	2/0	2
Treatment	VATS wedge/ VATS lobectomy/ thoracoscopic resection	5/1/1	6
Recurrence	Yes/No	2/1	3
Follow-up duration		2-20 years	
IHC		Positive rate (n)	Examined cases (n)**
	EMA	83% (5)	6
	Vimentin	100% (4)	4
	S100	0% (0)	3
	CD34	33% (1)	3
	PR	100% (4) ***	4
	ER	0% (0)	1
	STAT6	0% (2)	2
	CD68	33% (1) ****	3
	Ki67	<5%	3
	Cytokeratin	0% (0)	3
	SMA	0% (0)	1
	NSE	0% (0)	1
	SSTR2	100% (1)	1
	Neuroendocrine markers	0% (0)	0

Abbreviations: CT, computed tomography; PET FDG, positron emission tomography with fluorodeoxyglucose; VATS, video-assisted thoracoscopic surgery; IHC, immunohistochemistry; EMA, Epithelial Membrane Antigen; CD34, cluster of differentiation 34; PR, progesterone receptors; ER, estrogenic receptors; STAT6, Signal transducer and activator of transcription 6; CD68, cluster of differentiation 68; SMA, smooth muscle actin; NSE, neuron specific enolase; SSTR2, Somatostatin receptor 2a

* 3publications referred to the same patient; including once in the analysis

** 2 publications referring to the same patient were included because of two different resections and histopathologic reports

*** 2 cases showed focal expression

**** focal expression

Table 1: Clinical, radiological and pathologic features of the reported cases in literature.

Discussion

Meningioma is the most common intracranial tumour in adults and it is estimated to occur in up to 1% of the population [18]. It is usually a slow-growing tumour, but a minority of cases display an aggressive behaviour, with recurrences and extra cranial metastases. In a study conducted by Dalle Ore et al [19], the incidence of metastasis was 0.6. Lung is the most common metastatic site with occurrence up to several years after the excision of the primary tumour. Ectopic meningioma account for 2% of meningioma and PPM is rare, whilst mPPM is exceptional, with only six patients (including our report) being reported to the best of our knowledge so far [11-17]. PPM tends to occur in middle-aged females. In our cohort, the median age at diagnosis was 59 years and we had a predominance in female patients (ratio1:5), which corresponds to the literature data. Most PPMs are indolent, detected incidentally, and benign in nature and with an excellent prognosis. However, rare aggressive behaviour is associated with atypical or anaplastic features [12,17,18]. Among 25 histologically confirmed PPM patients with radiological data of the CNS and histological assessment, 23 (92%) cases had benign and 2 cases (8%) had a malignant PPM (with bone, lymph node and liver metastases). Very few cases have been reported to be symptomatic with haemoptysis, sputum, cough or chest pain [20,21]. The typical CT features of PPM are a solitary, well-defined round or lobulated nodule without calcification with variable enhancement ranging from 0.4cm to 6.5cm in size. They are mainly intraparenchymal nodules but end bronchial localization is possible [22]. In our cohort, mPPMs were generally well circumscribed on radiological studies, but we reported ground-glass opacities and cystic nodules as well. However, it is difficult to differentiate from several benign and malignant lung tumours, making pathological examination essential. It is key to rule out metastatic meningioma, thus a radiological study of the CNS, preferably by MRI, is required. The etiology of PPM remains unclear. Different theories have been proposed considering the intrathoracic differentiation of meningocytes or arachnoid cells, the ectopic proliferation of arachnoid cells in the embryonic rest theory or direct/indirect extension of primary intracranial meningioma. One hypothesis is that PPM is a giant form of minute pulmonary meningothelial-like nodules (MPMN). The MPMNs are small (100µm to 0.3cm) reactive interstitial cellular lesions that often develop in the background of chronic lung disease and have immunohistochemical and ultra-structural characteristics similar to meningothelial cells [23], but a consensus has not yet been reached. Several authors however consider this hypothesis unlikely because of the great discrepancy between the incidence of meningothelial nodules and meningioma.

Sexual hormones seem to be implicated in the pathogenesis of meningioma as firstly hypothesized by Cushing and Eisenhardt [6] in the late 1920s when describing a case of rapid progression of symptoms of meningioma during pregnancy. Since then, many similar observations have been made. Hormonal influence has been suggested by several factors as the cause of higher incidence among women, the growth in size during the luteal phase of the menstrual cycle and during pregnancy, their regression after delivery, and the increased risk of meningioma in patients with breast cancer, and the presence of hormonal receptors in some meningioma [7-10,24]. The majority of meningioma express progesterone receptors (PRs) with more than 90%. An elevated expression of PRs has been associated with a more favourable prognosis and a lower risk of recurrence. On the other hand, the expression of Estrogenic receptors (ERs) described in up to 30% of meningioma may confer an unfavourable prognosis. However, other studies report a low ER expression and the absence of a correlation with recurrences [10]. In our cohort, PR was expressed in all cases when tested (n=4) while ER was negative in one tested case. A dose-dependent relationship between the incidence and growth of meningioma and hormonal treatment with the progestin cyproterone acetate (CPA) has recently been established, with reports of regression or stabilization of meningioma on treatment withdrawal. A similar but lower risk of meningioma has been reported with the use of chlormadinone acetate (ACM) and nomegestrol acetate as progestin treatments [10,25]. Regarding other progesterone analogues, data remains scarce, notably concerning the Levonorgestrel. Piper et al [26] reported a case in 1993 of a clinical progression of a sphenoid wing meningioma after the placement of a subcutaneous contraceptive implant containing Levonorgestrel. More recently, Apra et al [27] found that 78.2% of women (n=61) with spheno-orbital meningioma take progestin's or combined estrogen-progesterone therapies, all containing an old-generation progesterone. Among them, one was treated with a levonorgestrel intrauterine device (IUD) and five with an oral combination containing Levonorgestrel. A survey on the risk of meningioma with all progestin's was conducted in France in October 2018 [28], including all cases reported to the CRPV (Centre regional de Pharmaco-vigilance) or to the pharmaceutical firm since 1985 (n=221). The majority (85%) was treated with ACM and nomegestrol acetate, 10% were treated by Levonorgestrel, of whom 5% had an IUD. Our patient was treated using a Levonorgestrel IUD. However, no root-cause relationship has yet been described and more studies are needed. Progestogen related meningioma are mainly multiple and localized in the skull base. Some authors showed a higher incidence of PIK3CA (phosphatidylinositol-4,5- biphosphate 3-kinase catalytic subunit alpha) (mutations also found in endometrial carcinoma, breast cancer, and cervical carcinoma) and TRAF7 (tumour necrosis factor receptor associated factor 7) mutations, and a lower incidence of NF2 (neurofibromatosis type 2) mutations in this category compared with non-progestogen related meningioma, suggesting

a hormone induced mutational shift [10,29]. No mutations were found in the reported case on targeted sequencing.

Histopathological examination is mandatory for diagnosis. The present case displayed characteristic features of meningothelial meningioma. In a spindle-to-epithelioid cells tumour, differential diagnosis should be made including the following elements: minute pulmonary meningothelial nodule, nerve sheath tumour, mesothelioma, solitary fibrous tumour, spindle-carcinoid tumour and non-small cell carcinoma [21]. Furthermore, a tumour with intra-nuclear inclusions and psammoma bodies should be differentiated from a thyroid papillary carcinoma metastasis. Immunohistochemistry is a helpful tool for correct diagnosis. EMA was long considered a conventional meningioma marker [30], along with Vimentin and PR receptors [21]. Ohashi-Nakatani et al [21] reported a similar IHC profile with significant positivity for Vimentin, EMA and PR as in our literature review. Lately, accumulating evidence has emerged to support the diagnostic value of SSTR2a as it is a highly sensitive and specific marker for meningioma [31]. SSTR2a was diffusely positive in the reported case, but it was not tested in other mPPM. Minute pulmonary meningothelial nodules present similar microscopic and immunohistochemical features, but they usually measure between 1 to 3 mm. The treatment for PPMs is VATS wedge resection for peripheral lesions, whereas lobectomy is suitable for central lesion. Surgery can provide a precise pathological examination and patients can achieve an excellent prognosis after surgical resection. However, a case report described a rare autopsy example in which the tumours had recurred in the lung field, regional lymph nodes and liver, one even after a 40-year history [32]. In our study, follow-up data was available for three patients. One patient presented a slow growth of an unresected nodule at ten-years follow-up [14], which continued to grow (with a doubling time of 1393 days), with the emergence of two new lesions at twenty-years follow-up [15]. We followed-up the case we have reported herein for four years. The unresected lesion showed slow but significant growth (14mm to 16mm), alongside two new infracentimetric lesions that were subsequently resected after three years since the first surgery. The patient was disease-free one-year post last surgery. For our case, we should consider a follow-up after several years. To the best of our knowledge, only five cases of multiple PPMs have been reported in literature and this is the first described case in a female patient treated by a progesterone-only IUD. PPM, defined by the typical histological and immunohistochemical features of meningioma in the lungs and the absence of CNS lesions, is an extremely rare neoplasm, mainly solitary and usually associated with an indolent growth. This leads us to recommend that in unspecific radiologic findings, PPM should be considered in the differential diagnosis of lung neoplasm.

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Conflicts of Interest: The authors declare that there is no conflict of interest. No funding was received.

Consent for publication: Patient gave the informed consent for publication.

Availability of data and materials: The data that support the findings of this study are available from the corresponding author on reasonable request.

Authors' contribution: All authors contributed to the diagnosis and/or treatment of the patient. The patient was firstly referred to Wellemans Isabelle and Compère Christophe who subsequently followed the patient. Foucart Annick performed surgery. Pathology analysis was conducted by Myriam Remmelink. Literature review was performed by Stefan Rusu. The first draft was written by Stefan Rusu and Wellemans Isabelle and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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