Pleuropulmonary Meningothelial Proliferations

Evidence for a Common Histogenesis

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Abstract: Primary pleuropulmonary meningothelial proliferations include minute pulmonary meningothelial-like nodules (MPMN) and pleural or pulmonary meningiomas (PPM). These lesions share histologic, ultrastructural, and immunohistochemical features with meningiomas of the central nervous system (CNS). Meningiomas of the CNS exhibit a number of genetic abnormalities, most commonly loss of the *neurofibromatosis (NF) 2* gene on chromosome 22. The molecular changes of pleuropulmonary meningothelial proliferations, however, have only rarely been investigated. This study explores the status of the *NF2* gene in pleuropulmonary meningothelial proliferations compared with CNS meningioma using interphase fluorescence in situ hybridization. Whole tissue sections of 9 pleuropulmonary meningothelial lesions (6 MPMNs and 3 PPMs) and 9 CNS meningiomas were analyzed by fluorescence in situ hybridization using a commercially available locus-specific probe for the *NF2* region. Deletion of the *NF2* gene was identified in 2 MPMNs, 1 PPM, and 4 CNS meningiomas. Chromosomal gains of 22q were noted in 2 cases of MPMN and 1 PPM. Our results indicate that pleuropulmonary meningothelial lesions share common genetic pathways with CNS meningiomas. In addition, they provide support for the hypothesis that MPMN and PPM are related lesions that may arise from the same precursor cell. As for CNS meningiomas, these mutational changes may provide additional targets for future personalized therapies.

Key Words: lung, meningothelial-like nodule, meningioma, central nervous system, fluorescence in situ hybridization (FISH)

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Minute pulmonary meningothelial-like nodules (MPMN) are small usually asymptomatic nodular proliferations in the lung parenchyma often identified incidentally in patients with underlying chronic lung disease.[1] These lesions were initially interpreted to be of chemoreceptor cell origin (minute pulmonary chemodectoma),[2] but several subsequent investigators were able to demonstrate meningothelial origin on the basis of morphologic, ultrastructural, and immunohistochemical characteristics.[3–5]

Extracranial meningiomas are rare but well-known tumors that primarily occur in the skin or head and neck area.[6,7] Primary pulmonary meningiomas (PPM) have been documented since 1982 when Kemnitz et al[8] reported the first case in a 59-year-old patient using morphologic characteristics and ultrastructural techniques. Since the initial description, it has been demonstrated that PPM share similar morphologic patterns, immunohistochemical features, and biological behavior with their counterparts in the central nervous system (CNS).[9,10] PPMs are often asymptomatic solitary coin lesions discovered during routine radiologic screening, and complete surgical resection usually results in complete cure, although rare malignant cases do exist.[9–12] The strong histologic similarity between MPMNs and PPMs, both representing meningothelial proliferations that are separated mainly on the basis of growth characteristics—MPMN are small interstitial lesions that preserve the lung architecture, whereas PPMs are nodular lesions that replace the pulmonary parenchyma—has raised the question of whether PPMs arise from MPMNs or whether they derive directly from pluripotent subpleural mesenchymal cells.[5,9,13]

In contrast, PPMs also closely resemble intracranial meningiomas in terms of demographics, spectrum of growth patterns, immunoprofile, and clinical course.[9] Contrary to pulmonary meningothelial lesions, the molecular pathways of CNS meningiomas have been extensively studied, and a number of genetic aberrations have been identified, most commonly loss of the *neurofibromatosis (NF) type 2* gene, which can be detected in NF2 syndrome-related tumors as well as in up to 60% of sporadic meningiomas.[14–17]

The purpose of the current study was to investigate the status of *NF2* in a range of primary pleuropulmonary meningothelial lesions to (a) explore whether MPMN and PPM share similar genetic aberrations that could provide new evidence with regard to their relationship, and (b) whether PPMs show the same genetic abnormalities as CNS meningiomas, which may have implications for future targeted therapies. To this purpose we assessed the *NF2* status of 9 primary pleuropulmonary meningothelial

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lesions and 9 CNS meningiomas using interphase fluorescence in situ hybridization (FISH).

MATERIALS AND METHODS

Tissue Specimens

Eighteen meningothelial lesions, including 6 MPMNs, 3 PPMs, and 9 CNS meningiomas from the Surgical Pathology files of MD Anderson Cancer Center, Houston and the Medical College of Wisconsin, Milwaukee form the basis of this study. Whole histologic sections from formalin-fixed paraffin-embedded tumor tissue stained with hematoxylin and eosin as well as corresponding unstained slides for FISH were available in all cases. Clinical information was obtained from the medical records of the patients or from referral information.

Fluorescence In Situ Hybridization

FISH was performed using a commercially available dual-color DNA probe targeting *NF2* (22q12.2) colored with Texas Red and CEN22q (22q11.22) colored with FITC (Abnova, Walnut, CA), which served as an internal control. Sections of 5 μm thickness were deparaffinized, dehydrated, and air-dried. This was followed by protease treatment at 37°C for 15 minutes. The slides were then washed in 2× standard saline citrate, dehydrated at room temperature, and then allowed to air dry. After marking the hybridization area, the FISH probe was applied to all sections, followed by denaturing of probe and target at 75°C for 5 minutes. Overnight hybridization at 37°C took place in a humidified chamber. Posthybridization washes in 2× SCC (5 min, room temperature), 2× SCC/0.3% NP40 (1 to 2 min, 75°C), and 2× SCC (1 min, room temperature) were performed and the slides allowed to air dry. DAPI (1500 ng/mL; Abnova) was used as a nuclear counterstain, and the sections were examined using a fluorescent microscope with the appropriate filters (Olympus, Melville, NY). One hundred nonoverlapping interphase nuclei were scored for the number of fluorescent signals. Hybridizations were considered noninformative if the FISH signals were either lacking or too weak to interpret. Interpretation of deletion required > 50% of nuclei containing only 1 *NF2* signal as previously reported.[18] Polysomies (gains) were arbitrarily defined as > 5% of nuclei containing 3 or more signals.

RESULTS

Clinical Features

The patients included 12 women and 5 men aged 24 to 72 years (mean: 51 y). Patient and tumor characteristics and FISH status are summarized in Table 1. All MPMNs were incidental findings during examination of lung resection specimens for unrelated tumors. Two patients with PPM were asymptomatic, and the tumors were identified during routine chest X-ray investigations; the third patient presented with chest pain. Patients with CNS meningiomas primarily presented with headache or neurological symptoms. Two of these patients had underlying NF2 syndrome. None of patients with MPMN or PPM had clinical or radiologic evidence of intracranial or spinal meningiomas or a history of NF2 syndrome.

Pathologic Features

The cases of MPMN included 6 lesions harvested from 5 patients. They consisted of small whorled nests of epithelioid cells devoid of any cytologic atypia or mitotic activity (Fig. 1). Their size ranged from 0.1 to 0.25 cm.

The 3 PPMs were classified according to the World Health Organization (WHO) criteria for CNS meningiomas.[19] Two tumors were WHO grade I lesions with

TABLE 1. Clinical and FISH Characteristics of 18 Pleuropulmonary and CNS Meningothelial Lesions

	Age	Sex	Location	Tumor Size (cm)	Histologic Type	*NF2* FISH Result	NF2 Syndrome Status
MPMN							
1	72	F	RLL	0.15	NA	Deletion	Negative
2	71	F	LUL	0.2	NA	Negative	Negative
3*	52	F	RUL	0.2	NA	Deletion	Negative
4*	52	F	RUL	0.15	NA	Polysomy	Negative
5	62	F	LUL	0.1	NA	Negative	Negative
6	60	F	LUL	0.25	NA	Polysomy	Negative
PPM							
7	56	M	RLL	2	Transitional	No signal	Negative
8	55	F	RUL	4	Fibrous	Deletion	Negative
9	33	M	Left pleura	3	Atypical	Polysomy	Negative
CNS meningioma							
10	50	M	Left occipital	14	Fibrous	Deletion	Negative
11	51	F	Left frontal	2.5	Transitional	Negative	Negative
12	56	F	Right frontal	10	Fibrous	Negative	Negative
13	63	M	Left frontal	NK	Fibrous	Deletion	Negative
14	49	F	Posterior fossa	NK	Fibrous	Deletion	Negative
15	51	F	Anterior fossa	1.5	Transitional	Negative	Negative
16	24	F	Spine	0.8	Psammomatous	No signal	Positive
17	47	F	Right cerebellopontine angle	5	Transitional	Deletion	Negative
18	26	M	Left mid fossa	4.5	Transitional	Negative	Positive

*Same patient.
F indicates female; LUL, left upper lobe of lung; M, male; NA, not applicable; NK, not known; RLL, right lower lobe of lung; RUL, right upper lobe of lung.

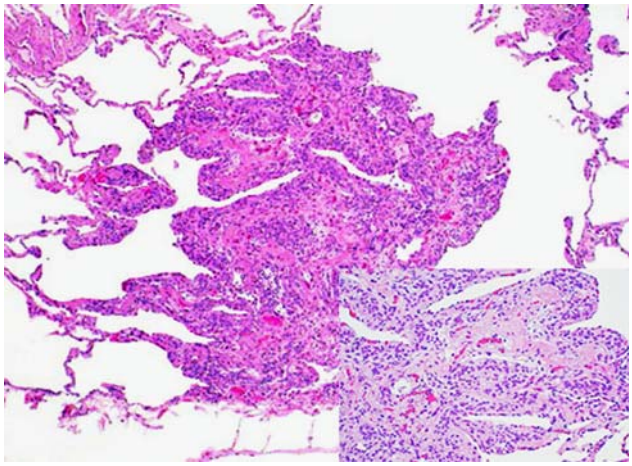

FIGURE 1. Pulmonary meningothelial-like nodule characterized by a small proliferation of meningothelial cells. Higher-power magnification shows bland epithelioid cells arranged in nests or whorls (inset).

transitional and fibrous patterns, respectively (Fig. 2). The third meningioma was pleural-based with wide pleural dissemination and classified as an atypical meningioma (WHO grade II) after careful exclusion of other neoplasms using a combination of clinical, morphologic, and immunohistochemical characteristics. The tumors ranged in size from 2 to 4 cm.

Among the CNS meningiomas, 8 were intracranial and 1 was an intraspinal tumor. All neoplasms were WHO grade I tumors and consisted of fibrous, transitional, and psammomatous variants (Fig. 3). The tumor size ranged from 0.8 to 14 cm.

FISH Results

FISH analysis was interpretable in 16 cases. Two cases (1 PPM, 1 CNS meningioma) were considered noninformative due to inadequate signal intensities. Deletion of *NF2* was identified in 51% to 90% of interphase nuclei in a total of 7 cases. These included 2 MPMNs, 1 PPM, and 4 CNS meningiomas. Polysomy of 22q was noted in 9% to 27% of interphase nuclei in 3 cases (2 MPMNs, 1 PPM) (Figs. 4A–C). Six cases were negative for *NF2* deletion or polysomy.

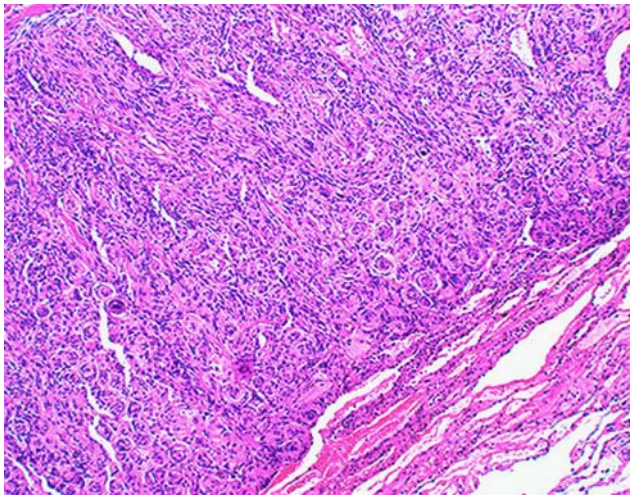

FIGURE 2. PPM arising within the lung parenchyma.

DISCUSSION

The existence of MPMN has been known for >50 years. These nodules consist of epithelioid cell nests arranged in whorls that are often incidental microscopic findings in lung specimens resected for unrelated reasons. The majority of cases affect patients in the seventh decade; rare cases have also been described in children. There appears to be a strong predilection for female patients.[1,2,20,21] Although in the majority of cases the lesions are solitary, multiple lesions affecting the same lobe or multiple lobes have also been described. A rare manifestation of MPMN characterized by diffuse bilateral pulmonary lesions associated with clinical symptoms and the radiologic impression of interstitial lung disease or disseminated malignancy has been termed "diffuse pulmonary meningotheliomatosis."[22] Regardless of presentation, the lesions have the microscopic and ultrastructural appearance of meningothelial differentiation,[3–5] although the earliest reports had initially suggested chemoreceptor origin (chemodectoma).[2] Meningothelial origin was further consolidated by the finding that immunohistochemically, MPMN had the same phenotype as meningioma.[5,23,24]

Contrary to MPMNs, PPMs are exceedingly rare with <50 reported cases in the English literature. The first case of bone fide primary meningioma of the lung was reported by Kemnitz et al[8] in 1982. The tumor was an incidental finding on radiographic imaging performed for abdominal complaints and consisted of a 4 cm lesion in the right lower lobe of the lung. Morphologic and ultrastructural examination confirmed the tumor to be a meningioma characterized by whorls of epithelioid cells, psammoma bodies, interdigitating cell membranes with desmosomes, and intracytoplasmic microfilaments. Neurological investigations failed to identify any primary dural lesion excluding a metastatic process to the lung. Since this first report, various others have confirmed the existence of ectopic meningiomas arising in the lungs and have identified several characteristics: (a) slight female predilection; (b) median age in the sixth decade; (c) asymptomatic presentation or nonspecific symptoms; (d) solitary "coin lesion" appearance on radiologic imaging; (e) size range from 0.4 to 6.0 cm; (f) histologic spectrum resembling CNS meningiomas, most commonly transitional and fibrous subtypes; and (g) often benign clinical course with only rare malignant cases.[9,10]

The strong resemblance of MPMN and PPM to CNS meningiomas based on morphologic, ultrastructural, and immumohistochemical features has raised speculation about the histogenesis of these lesions in the pleuropulmonary system as well as their relationship with each other. Controversy still persists about the true origin and nature of MPMN and PPM alike. For MPMNs, several hypotheses concerning their pathogenesis have

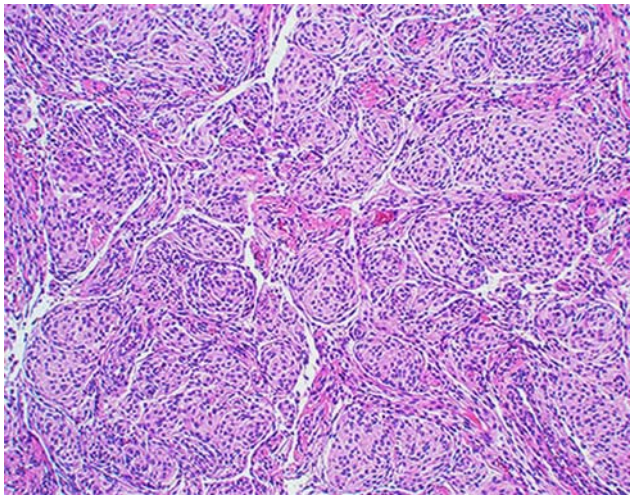

FIGURE 3. Intracranial meningioma, transitional type.

been put forward: derivation from (1) pluripotential subpleural mesenchymal cells or (2) heterotopic embryonic rests of arachnoid cells dispersed during embryonic development. Although the exact origin of MPMNs remains speculative, several attempts have been made to elucidate their nature and to assess their role as a possible neoplastic precursor of PPMs. Some investigations suggested that MPMNs were related to thromboembolic lung disease or other chronic lung disease,[1,4,25,26] and their infrequent occurrence in the pediatric population was thought to argue against origin from congenital rests.[1] Using clonal studies, Niho et al[23] examined 13 MPMNs of 2 patients and found monoclonal expansion in some, whereas others were found to be polyclonal. The authors interpreted this as support for a reactive nature of MPMN rather than a neoplastic process. More recently, Ionescu et al[20] performed mutational analysis comparing MPMNs with intracranial meningiomas and found that isolated MPMNs lacked any mutational damage, further supporting a reactive origin, whereas the majority of meningiomas showed major molecular events with high frequency of loss of heterozygosity seen at 22q. Loss of heterozygosity, however, was also identified in a subset of diffuse pulmonary meningotheliomatosis cases, suggesting a transitional state between a reactive and neoplastic proliferation. The difference in genetic alterations between MPMN and intracranial meningiomas was hence interpreted as support for the theory that the lesions arise from different cells, have different histogeneses, and progress through different molecular pathways. Further support of this view had previously been expressed by several investigators who highlighted the fact that the incidence of MPMN and PPM showed great discrepancy (0.5% vs. 0.05% at autopsy),[5,27] that cases of PPM often lacked the presence of MPMN in the same sample, that MPMNs were often multiple, whereas PPMs were mostly solitary, and that lesions intermediate in size between the small MPMN and larger PPM had not been identified and which should exist if MPMN were to progress to PPM.[5,9,27,28]

In contrast, the striking morphologic, immunohistochemical, and ultrastructural similarity of the 2 lesions cannot be denied, and it seems likely to assume that the cell of origin is identical. Furthermore, this raises speculation whether MPMN can progress to become PPM analogous to the tumorlet-carcinoid sequence of development in neuroendocrine lesions.[29] Furthermore, similar clinical characteristics—both lesions preferentially occur in women in the sixth to seventh decade—are even more in favor of a direct relationship between MPMN and PPM. More recently, this is further supported by increasing evidence in the literature that MPMN and PPM occasionally do coexist in the same specimen[30–32] and that transitional forms, in terms of size, do occur.[10]

Contrary to PPM, meningiomas of the CNS have been extensively investigated for molecular abnormalities. These tumors can exhibit a number of genetic aberrations and mutations including chromosomal abnormalities affecting chromosomes 1p, 14q, 9p, 10, 17, and 22q.[33,34] Among these, loss of the *NF2* gene on chromosome 22q has not only been associated with meningiomas arising in patients with neurofibromatosis syndrome but also in up 60% of sporadic meningiomas,[14–16] rendering this the most common genetic abnormality, particularly in WHO grade I tumors.

The cases included in this study closely correlated with prior reported cases of MPMN, PPM, and CNS

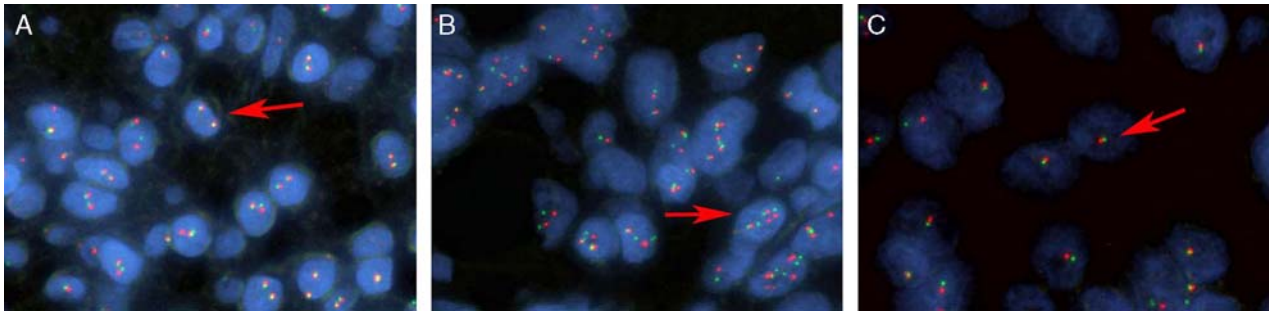

FIGURE 4. Representative FISH results. A, Normal dosages of 22q (2 red *NF2* and 2 green CEN22q signals in >50% of nuclei) (arrow). B, In some cases, the majority of tumor cells showed normal signal patterns, but a subset of cells were polysomic (cells with >2 red *NF2* and 2 green CEN22q signals) (arrow). C, Loss of 1 red and 1 green signal in >50% of tumor cells was interpreted as deletion of 22q (arrow).

meningiomas. Their close resemblance to each other based on clinical and histologic characteristics once again raises the possibility of a similar mechanism of tumor development and shared histogenetic origin. The results of our molecular analysis further endorse such a common pathogenic pathway. We were able to demonstrate loss of *NF2* in 50% of our CNS meningiomas, a rate very similar to the prior reported incidence.[14–16] In addition, 1 of the 3 PPM cases revealed *NF2* deletion, indicating that the tumorigenesis of PPM progresses along similar molecular pathways. Interestingly, 2 of the cases of MPMN also showed deletion of *NF2*, further consolidating the hypothesis that MPMNs and PPMs are closely related based not only on clinical and histologic characteristics but also on molecular evidence. Another compelling finding is the presence of polysomy in 2 cases of MPMN as well as 1 PPM. Polysomy of 22q has previously been reported in a subset of CNS ependymomas, which analogous to meningiomas often harbor *NF2* deletion, as well as in certain cases of meningothelial hyperplasia.[19,35] These chromosomal gains were interpreted to represent genomic instability possibly associated with a preneoplastic state or tumor progression, and similar deliberations may apply to our 3 polysomal cases. The fact that 2 of our MPMNs harvested from the same patient showed different molecular findings, deletion and polysomy of *NF2*, respectively, may provide further support of a stepwise accrual of genomic instability.

Apart from understanding the histogenesis of pleuropulmonary meningothelial lesions, unraveling the genetic factors underlying their development may also have implications for the use of novel targeted therapies. Although the majority of MPMNs and PPMs are benign lesions with an indolent clinical course, 1 of our patients presented with a more aggressive atypical meningioma that was characterized by widespread pleural dissemination. In future, such patients may benefit from the same targeted therapies or treatment approaches that have been recommended for patients with CNS meningiomas, such as regulation of major factors that are altered due to genetic aberration.[34]

In conclusion, using FISH to target *NF2* on chromosome 22q we have been able to demonstrate that pleuropulmonary meningothelial lesions develop along molecular pathways analogous to intracranial meningiomas. In addition, we believe there is also evidence on a molecular level to support the theory that MPMNs and PPMs are related conditions and derived from the same precursor cell. In future, novel treatment strategies similar to those proposed for patients with CNS meningiomas may also be explored for patients with more aggressive forms of PPM.

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