Pulmonary Meningothelial-like Nodules

A Genotypic Comparison With Meningiomas

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Background: Minute pulmonary meningothelial-like nodules (MPMNs) are incidental interstitial pulmonary nodules. They share histologic, ultrastructural, and immunohistochemical features with meningiomas (MGs).

Design: Sixteen cases yielding 33 separate MPMNs and 10 cases of benign MG were studied. Immunohistochemical studies and mutational analyses were performed on microdissected tissue using 20 polymorphic microsatellite markers targeting 11 genomic regions in an effort to identify genetic similarities of MPMN and MG.

Results: A total of 96.6% of MPMNs stained positive for vimentin, 33.3% for epithelial membrane antigen, 3% for S-100, and all were negative for cytokeratin and synaptophysin. Loss of heterozygosity (LOH) was identified in 25% of single MPMN affecting 3 genomic loci. No solitary MPMN had more than 1 LOH event. Multiple LOHs were seen only in MPMN-omatosis syndrome, where 33.3% of MPMNs showed LOH affecting 7 genomic loci. MG showed the highest frequency of LOH with major events seen at 22q (60%), 14q (42.8%), and 1p (44.4%) that were not shared by MPMN.

Conclusion: Isolated MPMN lacks mutational damage, consistent with a reactive origin. MPMN-omatosis syndrome might represent the transition between a reactive and neoplastic proliferation. MPMNs are different from MG based on the major molecular genetic events seen in their formation and progression.

Key Words: pulmonary chemodectoma, meningothelial-like nodule, loss of heterozygosity, meningioma, genetics

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Minute pulmonary meningothelial-like nodules (MPMNs) are asymptomatic, small (100 μm to 3 mm) nodules often representing incidental microscopic findings in lung specimens. Clinically, MPMNs are seen in patients 12 to 91 years of age, mostly in the seventh decade.[7] The majority of the cases are seen in women (84%),[7] and in some studies they are seen three times more often in the right lung than left.[6] Microscopically, the lesions consist of nests or whorls of moderately sized cells (Zellballen) centered on small veins. The cells are elongated or spindled, with oval nuclei, finely granular chromatin, and inconspicuous nucleoli. Cytoplasm is abundant, granular, and eosinophilic, with indistinct cell borders. By their architecture, cytologic characteristics and relationship with blood vessels, chemodectomas were thought to have an oxygen-monitoring function as chemoreceptors and were initially called "minute pulmonary tumors resembling chemodectomas," although no endocrine granules or nerves fibers were identified by electron microscopic analysis.[10] These studies, as well as those done by Churg and Warnock in 1976,[5] questioned the chemoreceptor-like nature of chemodectomas and described ultrastructural features that suggest a meningothelial rather than neuroendocrine differentiation of these cells. On the basis of immunohistochemical stains, Gaffey et al[9] demonstrated further similarities with meningothelial cells: reactivity with vimentin and epithelial membrane antigen (EMA) and lack of reactivity with cytokeratin, actin, S-100, and neuron-specific enolase. Based on these latter observations, the name "minute pulmonary meningothelial-like nodules" was proposed in 1988. In contrast, Torikata and Mukai[30] found pulmonary menigothelial-like nodules to be EMA negative and vimentin and myosin positive, suggestive of a myogenic rather than meningothelial origin of these curious tumors. As of today, the phenotype and histogenesis of pulmonary meningothelial nodules remain unclear.

In 1963, Zak and Chabes also described the presence of multiple MPMNs in 6 cases and called this condition chemodectomatosis (minute pulmonary meningothelial-like nodulomatosis, MPMN-omatosis).[34] Very little is known about this rare syndrome; only one case of association with deteriorating lung function and the necessity for aggressive chemotherapy is described in a literature in a 15-year-old adolescent.[4]

In the current study, we compared isolated and syndromatic MPMNs with cases of benign intracranial and spinal menigiomas using genotypic analysis to assess the reactive versus

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the neoplastic nature of MPMN and their molecular genetic relationship with meningiomas.

MATERIALS AND METHODS

Patients and Tissue Preparation

Thirty-five cases of MPMN and 10 cases of benign meningiomas were gathered from the paraffin block archives of the University of Pittsburgh Medical Center and the consultation files of one of the authors (S.A.Y.) after obtaining the approval of the Institutional Review Board (IRB# 020979). Cases were limited to those occurring between 1997 and 2003 based on the availability of the histologic slides and paraffin blocks. Histology slides on each case were reviewed, and the diagnosis of MPMN was confirmed. Cases of metastatic meningiomas were carefully excluded. Fifteen serial sections (4-μm thickness) were obtained from tissue blocks of MPMN. Five sections were used for a panel of immunohistochemical stains (vimentin, EMA, cytokeratin, S-100, and synaptophysin) to confirm the diagnosis of MPMN. Eight to 10 unstained histologic sections were microdissected as previously described under stereomicroscopic visualization for the lesion and corresponding normal lung parenchyma[20] (Fig. 1). Microdissection of normal lung tissue was carefully performed to be no larger in size than that of any MPMN sample for a given case. In view of the fact that normal lung is relatively less cellular than lung tumor, this ensured that all microdissected normal samples were equally or less cellular.

Cases of benign meningiomas were reviewed and reclassified upon the current World Health Organization histologic classification of meningiomas adopted in 2000. In 8 of these cases, the tumor was intracranial. The other two meningiomas were located in the spinal cord and the ethmoidal and nasal sinuses. Four serial sections were obtained, and in each case one normal and one area of the tumor was microdissected using the aggregate material from three to four 4-μm-thick unstained histologic sections. Microdissected tissue from both MPMN and meningiomas was collected in appropriately labeled Eppendorf tubes containing 50 μL of buffer (Tris-HCL, pH 7.0) and digested with proteinase K as described previously.[20]

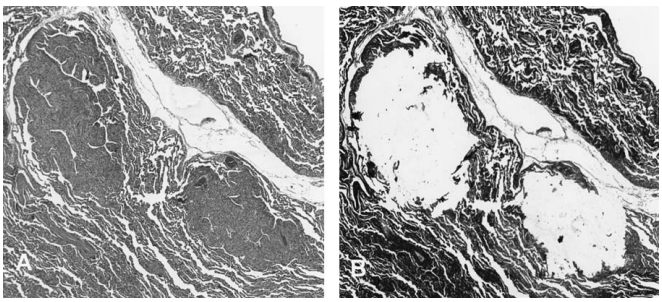

FIGURE 1. Tissue microdissection performed under stereomicroscopic visualization for the lesion and corresponding normal lung parenchyma. Two MPMNs before microdissection (**A:** hematoxylin and eosin, original magnification ×10) and after microdissection (**B:** unstained slide, original magnification ×10).

Nineteen cases of single MPMN were excluded from the study due to the loss of the minute lesion on deeper levels. Cases with multiple MPMNs were identified, and the number of lesions ranged from 1 to 46 per case. Four cases with a minimum of 4 pulmonary nodules identified by the CT scan and confirmed by microscopic examination as MPMN (in the absence of other explanatory pathology) were classified as MPMN-omatosis syndrome. These patients were asymptomatic and had bilateral lesions measuring <1 cm seen on the CT scan. Their main diagnosis and reason for lung surgery was carcinoid tumor in 2 cases, hypersensitivity pneumonitis in 1 case, and metastatic carcinoma in another case.

PCR Amplification and Loss of Heterozygosity (LOH) Analysis

Aliquots of the sampled tissue were used in individual PCR amplification reactions with fluorescent-labeled primers flanking tetranucleotide and pentanucleotide microsatellite repeat polymorphisms situated in proximity to specific genes of interest. PCR amplification products were analyzed for LOH by capillary gel electrophoresis using a multicolor fluorescence-based DNA analysis system (ABI Prism 3100 Genetic Analyzer, Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. Migrating allelic bands were detected by a laser-induced fluorescence system, which was digitally interfaced with a central processing unit. The acquired data were downloaded and analyzed by the GeneScan software (ABI Prism 3100 Genetic Analyzer, Applied Biosystems).

Individual electropherograms were plotted, indicating allelic peaks in relative fluorescence units (RFU) with a peak height range of 150 to 6000 RFU. The size in basepairs of the PCR products was determined by accompanying peaks of Rox size-standards (ROX-standards, Applied Biosystems).

Mutational genotyping was based on allelic loss using polymorphic microsatellites situated within or adjacent to known tumor suppressor genes or genomic sites potentially involved in human pulmonary and brain carcinogenesis.[11,14,16–19,23–25,28,29] Twenty different microsatellite markers located on 1p, 3p, 5q, 7q, 8q, 9q, 9p, 10q, 14q, 17p, 18q, 19q, and 22q were used as detailed in Table 1. The use of more than one microsatellite marker ensured a higher yield of information for each genomic locus.

All MPMNs and benign meningiomas samples were run with corresponding normal tissue samples to determine microsatellite informativeness, exclude the effect of allelic drop-out, and assess allelic imbalance in tumor samples. Microdissected, normal appearing, nonneoplastic tissue also served as

TABLE 1. Locations of Microsatellite Markers and Adjacent Genes

Chromosome	Genes	Microsatellite Markers
1p	MYCL1	D1S.1172, D1S.407, MYCL
3p	VHL	D1S.1539, D1S.2303
5q	APC/MCC	D5S.592, D5S.615
9q	PTCH	D9S.252
9p	P16	D9S.251, D9S.254
10q	PTEN	D10S.520, D10S1173
17p	P53	D17S.1289, D17S.974
14q	DAL	D14S555
18q	DCC	D18S391
19q	Not known	D19S400, D19S559
22q	NF2	D22S.532, D22S.417

an internal control for formalin fixation and tissue processing effect on DNA. Allelic dropout was evaluated by imposing a requirement that all normal samples must show equal or nearly equal microsatellite intensity bands in informative subjects. Any case failing to meet this rigorous criterion was rejected for assessment of tumor allelic loss. A case was informative for a particular allele if the maternal and paternal alleles migrated differently and deemed noninformative if they overlapped (Fig. 2A).

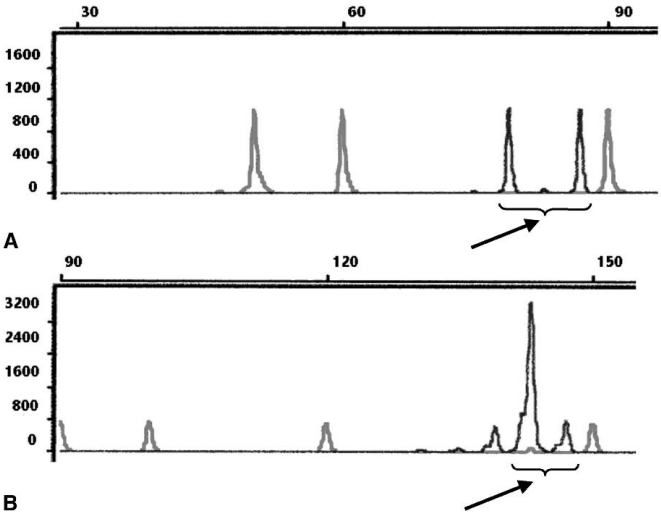

FIGURE 2. Graphic representation of an informative case. **A:** The case was informative for a particular allele if the maternal and paternal alleles migrated differently and deemed noninformative if they overlapped. **B:** Graphic representation of a case with LOH. The ratio between the two heights was defined as the allelic imbalance factor. The lesion samples were considered to have LOH if the allelic imbalance factor for the specific microsatellite marker was <0.6 or >1.5.

For informative subjects with respect to a specific marker, alleles were assessed as being in balance when the ratio of the individual allele peaks fell within the range of 0.6 to 1.50. Values beyond this range were classified as being allelic imbalance with two categories. Low-level allelic imbalance was said to exist when the microsatellite allelic peak height ratios fell into the range from 0.50 to 0.66 or from 1.50 to 2.00. High level allelic imbalance was present when the allele ratios fell below 0.50 or above 2.00 (Fig. 2B). To afford a conservative assessment of the presence of mutation, in this study only high-level allelic loss was classified as indicative of mutation. Using these criteria, it would be necessary for no less than 50% of the cells in any given microdissection target to be mutated in order for the microdissection genotyping approach used here to detect this alteration. Two observers (E.S. and P.A.S.) evaluated the presence or absence of LOH independently. At the final step of evaluation, the concordance ratio of positive LOH between two observers was 100%. Fractional allelic loss (FAL) was defined as the number of chromosomal arms on which allelic loss was observed divided by the number of chromosomal arms for which allelic markers were informative.

Determination of LOH in Each Patient

In each case, the presence or absence of LOH in each nodule was determined separately. For each nodule, LOH was determined as positive when any of the microdissected samples showed LOH.

Determination of FAL

FAL was defined as the ratio of chromosomes affected by LOH in the informative chromosomes and calculated for every microdissected sample. Average FAL was calculated for each of the studied groups.

Statistical Analysis

Paired Student *t* test was used for the comparison of FAL values between single MPMNs, MPMN-omatosis syndrome, and benign meningiomas. Other data were analyzed using Fisher exact test. A P (two-tailed) <0.05 was taken as the level of significance.

RESULTS

The study cases were grouped as single MPMNs (12 cases, 12 nodules), MPMN-omatosis syndrome (4 cases, 21 nodules), and benign meningiomas (10 cases, 10 tumors) (Fig. 3). The mean age at the time of lung surgery for the patients with single and multiple MPMN was 60 years and 57.5 years, respectively. These patients were 3 males and 9 females for the single MPMN group (male:female ratio 1:3) and all 4 were females in the cases of MPMN-omatosis syndrome. The mean age at the time of brain surgery of the 3 males and 7 females (male:female ratio 3:7) from the meningioma group was 60.9 years.

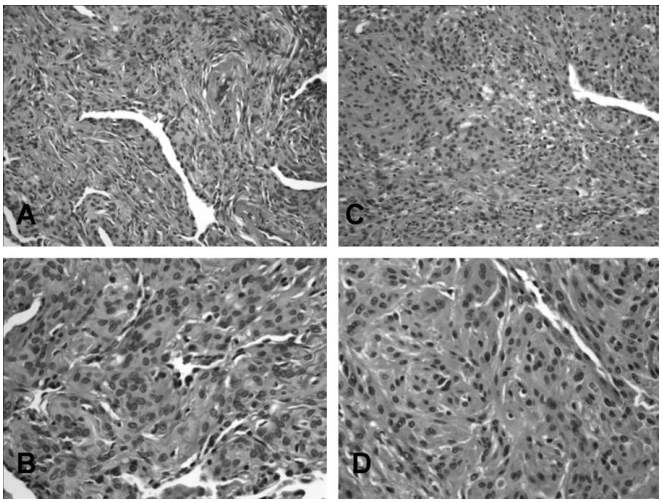

FIGURE 3. Comparison of minute pulmonary meningothelial-like nodules and meningioma. Pulmonary meningothelial-like nodules (**A**, **B**) have a histologic appearance similar to benign meningioma (**C**, **D**). The cells are arranged in nests centered on small veins ("Zellballen"). Cytologically, the nuclei are bland, oval, with inconspicuous nucleoli and the cytoplasm is abundant, eosinophilic, and granular. A and C, hematoxylin and eosin, original magnification ×4; B and D, hematoxylin and eosin, original magnification ×20.

In cases of single MPMN, these nodules were derived from specimens resected for primary lung carcinoma in 25% of the cases (3 of 12), metastatic sarcoma in 16.6% of the cases (2 of 12), lung transplantation in 16.6% of the cases (2 of 12), and with other miscellaneous diagnoses (emphysema, interstitial pneumonia, interstitial lung disease, and pulmonary vascular malformation) in the remainder of the cases (5 of 12).

Single MPMNs were identified mostly in the right lung (58.33%); 80.95% of MPMN in the MPMN-omatosis syndrome were identified in the right lung. The size of MPMN varied from 0.05 to 0.2 cm.

To confirm the diagnosis of MPMN, we performed a panel of 5 immunohistochemical stains. All MPMNs stained negative for cytokeratin (AE1/E3) and synaptophysin and 97% stained negative for S-100 (32 of 33). The majority (96.9%) of MPMNs showed reactivity with vimentin, but only 33.3% of them were positive for EMA (11 of 33). EMA staining was weak and focal in some of the positive cases, and this staining pattern was seen in single MPMN (41.66%; 5 of 12) as well as in MPMN-omatosis syndrome (28.57%; 6 of 21).

All cases were investigated for the occurrence of LOH with 20 microsatellite markers from 11 different chromosomal loci (1p, 3p, 5q, 9p, 9q, 10q, 14q, 17p, 18q, 19q, and 22q) (Table 1). The informative rate was between 70% and 100%. The data indicated infrequent occurrence of LOH in cases of single MPMN (Table 2). Only sporadic LOH was identified in 4 of 12 cases (33%) and was seen in 3 different chromosomal loci (3p, 17p, and 22q). Two cases (16.6%) had LOH identified at different chromosomal loci (17p and 22q). For the other 2 cases (16.6%), LOH was identified at 3p.

Table 3 summarizes the LOH results for the cases of MPMN-omatosis syndrome. The number of analyzed MPMN in the 4 cases investigated varied from 4 to 7. In the MPMN-omatosis syndrome, all cases showed LOH in at least one site and 14.28% (3 of 21) of the individual nodules showed LOH in two or more chromosomal loci. From a total of 8 LOH-positive nodules (8 of 21), 5 nodules showed LOH at one single chromosomal locus, two nodules (16.6%) had 2 LOH at different loci, and only one nodule (4.76%) had LOH identified at 3 different loci. Single LOH was seen at 1p, 9q, 9p, 10q, 19q, and

TABLE 2. Summary of LOH by Chromosomal Locus in 12 Cases of Single MPMNs

Case No.	1p	3p	5q	9p	9q	10q	14q	17p	18q	19q	22q
1	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—
4	—	—	—	—	NI	—	—	—	—	—	—
5	—	—	NI	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—	—
7	—	—	—	NI	NI	—	F	LOH	—	F	—
8	NI	—	F	NA	—	—	—	NA	NI	—	NA
9	—	LOH	—	—	F	—	NI	—	—	—	—
10	—	LOH	—	NI	—	—	NI	—	NI	—	—
11	—	—	NI	NA	NA	—	—	NI	NA	NA	NI
12	—	—	NI	NI	—	—	NI	—	—	—	LOH

NI, noninformative; F, fail; NA, not available; LOH, loss of heterozygosity.

TABLE 3. Summary of LOH by Chromosomal Locus in 4 Cases (21 Nodules) of MPMN-Omatosis

Case No.	MPMN	1p	3p	5q	9p	9q	10q	14q	17p	18q	19q	22q
1	1	—	LOH	—	—	NA	—	NA	—	—	LOH	—
	2	LOH	—	—	—	—	—	—	—	—	—	—
	3	—	—	—	—	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—	—	—	—	—
	5	—	—	—	—	—	—	—	—	—	—	—
	6	—	—	—	—	—	—	—	—	—	—	—
2	7	—	—	—	NI	—	—	—	—	NI	—	—
	8	—	—	—	NI	—	—	NA	—	NI	—	NA
	9	—	—	—	NI	—	—	—	—	NI	—	—
	10	—	—	—	NI	LOH	—	—	—	NI	—	—
	11	—	—	—	NI	—	—	—	—	NI	—	—
	12	—	—	—	NI	—	—	—	—	NI	—	—
	13	—	—	—	NI	—	—	—	LOH	NI	—	—
3	14	—	—	—	—	—	—	—	—	—	—	—
	15	—	—	—	—	—	—	—	LOH	—	—	LOH
	16	—	LOH	—	—	—	LOH	NA	LOH	NA	—	NA
	17	—	—	—	—	—	—	—	LOH	—	—	—
4	18	—	—	—	—	NI	—	—	—	—	—	—
	19	—	—	—	LOH	NI	—	—	—	—	—	—
	20	—	—	—	—	NI	—	—	—	—	—	—
	21	—	—	—	—	NI	—	—	—	—	—	—

NI, noninformative; NA, not available; LOH, loss of heterozygosity.

22q (50%). At chromosomal locus 3p LOH was identified in 2 nodules from 2 different patients. p53 (17p) locus showed the highest number of mutations identified in 2 of the 4 cases.

Meningiomas were more genetically unstable (Table 4) than single MPMNs or those from the MPMN-omatosis syndrome (Fig. 4; Table 5). The informative rate in these cases varied from 50% to 100%. Eight of the 10 cases showed LOH (80%) at 1 to 4 chromosomal loci. Seventy-five percent of LOH-positive cases had mutations at 2 or more chromosomal loci. No LOH was identified at loci 5q, 17p, and 18q. The highest number of LOH was identified at chromosomal loci 22q (60%, 6 of 10), 14q (42.86%, 3 of 7), and 1p (44.4%, 4 of 9).

TABLE 4. Summary of LOH by Chromosomal Locus in 10 Cases of Benign MG

Case No.	1p	3p	5q	9p	9q	10q	14q	17p	18q	19q	22q
1	—	LOH	—	LOH	—	NI	LOH	NI	—	—	—
2	—		—	NI	—	—	—	NI	NI	—	—
3	LOH	LOH	—	—	F	LOH	LOH	—	—	—	—
4	LOH	—	NI	NI	NI	—	NI	NI	—	LOH	LOH
5	—	—	—	—	NI	—	—	—	—	—	—
6	—	LOH	—	NI	NI	—	—	—	—	NI	LOH
7	LOH	—	—	—	—	—	LOH	—	NI	—	LOH
8	LOH	—	—	—	LOH	—	NI	—	NI	—	LOH
9	NI	NI	—	NI	NI	—	NA	—	NA	NA	LOH
10	—	—	—	—	F	—	—	—	—	—	LOH

NI, noninformative; F, fail; NA, not available; LOH, loss of heterozygosity.

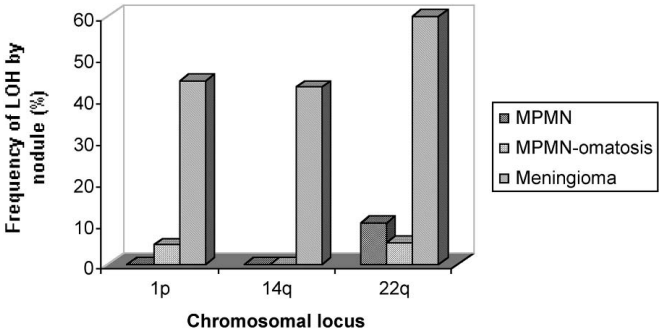

FIGURE 4. Frequency of LOH per nodule. Major genetic events at 1p, 14q, 22q, and 17p are different in single and syndromatic MPMN as compared with MG.

These findings are in concordance to the major genetic events described in the literature to play a role in the pathogenesis of meningiomas.[1–3,8,12,13,15,21,22,26,27,31–33] Single and multiple MPMNs showed LOH alterations at different chromosomal loci as compared with meningioma (Fig. 4), with distinguishing loci being 1p (0 and 4.76% vs. 44.44%), 9p (0 and 7.14% vs. 16.6%), 9q (0 and 6.25% vs. 25%), 14q (0 and 0% vs. 42.86%), and 22q (10 and 5.26% vs. 60%). Also different between MPMN and MG was LOH at 17p, with this locus being mutated in single MPMN (10%) and MPMN from MPMN-omatosis syndrome (19.04%), but not in MG (0%).

The mean FAL was calculated for MPMN, both single and multiple as well as meningiomas. The mean FAL of single MPMN (0.04 ± 0.06) was significantly different from that in meningioma (0.25 ± 0.15) ($P = 0.001$). MPMN-omatosis syndrome had a higher FAL (0.07 ± 0.10) than single MPMN, which was also significantly different from meningioma ($P = 0.004$).

DISCUSSION

MPMN was described more than four decades ago, but as of today the exact origin and pathogenesis of this curious lesion are still unknown. Currently, pulmonary meningothelial-like nodule is considered to be reactive and to have histologic, immunohistochemical, and ultrastructural features of meningioma. Molecular pathologic studies can provide valuable insights about the process of tumorigenesis and can help in identifying pathogenesis of several benign pathologic entities. We attempted to use these techniques to enhance our mor-

TABLE 5. Frequency of LOH in MPMNs, MPMN-Omatosis Syndrome, and Benign Meningioma

Chromosomal Locus	Single MPMN		MPMN-omatosis		Meningioma	
	Nodules	Cases	Nodules	Cases	Nodules	Cases
1p	0% (0/11)	0% (0/11)	4.7% (1/21)	25% (1/4)	44.4% (4/9)	44.4% (4/9)
3p	16.6% (2/12)	16.6% (2/12)	9.5% (2/21)	50% (1/2)	33.3% (3/9)	33.3% (3/9)
5q	0% (0/8)	0% (0/8)	0% (0/21)	0% (0/4)	0% (0/9)	0% (0/9)
9q	0% (0/8)	0% (0/8)	6.2% (1/16)	33.3% (1/3)	25% (1/4)	25% (1/4)
9p	0% (0/7)	0% (0/7)	7.1% (1/14)	33.3% (1/3)	16.6% (1/6)	16.6% (1/6)
10q	0% (0/12)	0% (0/12)	4.7% (1/21)	25% (1/4)	11.1% (1/9)	11.1% (1/9)
14q	0% (0/8)	0% (0/8)	0% (0/18)	0% (0/4)	42.8% (3/7)	42.8% (3/7)
17p	10% (1/10)	10% (1/10)	19% (4/21)	50% (2/4)	0% (0/7)	0% (0/7)
18q	0% (0/9)	0% (0/9)	0% (0/13)	0% (0/3)	0% (0/6)	0% (0/6)
19q	0% (0/10)	0% (0/10)	5.5% (1/18)	25% (1/4)	12.5% (1/8)	12.5% (1/8)
22q	10% (1/10)	10% (1/10)	4.7% (1/21)	25% (1/4)	60% (6/10)	60% (6/10)

phologic understanding by evaluating LOH in MPMN and by comparing MPMN with benign meningiomas using LOH-based genotyping analysis. Our study confirmed the reactive nature of MPMN, which is supported by the sporadic presence of LOH in our 12 cases of single MPMN. On the other hand, syndromatic MPMNs showed a greater genetic instability and multiple LOH per nodule than single MPMN, suggesting that this condition might represent the transition between a reactive and a neoplastic proliferation. These nodules are heterogeneous in their genetic alterations, and in only 1 of our 4 cases did nodules from the same patient share LOH positivity. In addition, 2 of these 3 nodules had additional mutations at 3p, 10q, and 22q.

Of particular interest in our study was the understanding that meningiomas have their own lineage-specific genetic pathways involving molecular genetic events on chromosomes 22q, 14q, and 1p, which are not shared by MPMN. The progression of meningiomas involves genetic alterations in the chromosome 22 (33%–60%) early in the process.[1,8,12,15,21,33] The second most frequently reported genetic abnormalities in meningiomas are deletions of 1p (11%–33%) and 14 q (0%–31%).[1–3,12,13,27,31] In our study, benign meningiomas showed mutation at 22q in 60% of cases, at 14 q in 42.86% of cases, and at 1p in 44.44%, which correspond clearly with results found in the literature. The LOH frequency in single and multiple MPMN was low at loci 22q and 1p (10%), and there was no LOH identified at 14q. The difference in genetic alterations seen in MPMN and meningioma suggests that they arise from different cells and have different histogenesis and that the documented genetic pathways for development of meningiomas are not common to MPMN.

Although benign meningiomas showed a high frequency of chromosomal aberrations, several studies have shown that these tumors lack mutation in the TP53 gene on chromosome 17.[32,33] This chromosomal locus, on the other hand, accounted for the highest rate of LOH in MPMN-omatosis syndrome (19.04%) and the second highest frequency of LOH in single MPMN (10%). TP53 mutations are not likely to be involved in the etiology of meningioma but may play a role in the pathogenesis of MPMN-omatosis syndrome.

New tools such as LOH-based genotyping analysis can help in characterizing MPMN and in proving that their histogenesis is different from that of meningioma. Further studies are necessary in searching for the cell of origin for these minute pulmonary nodules. The statement made in 1976 by Churg and Warnock[5] remains true today: "It is easy to rule-out a number of possible origins for the so called 'chemodectoma of the lung' but it is more difficult to assign a new one."

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