Immunohistochemical and Clonal Analysis of Minute Pulmonary Meningothelial-Like Nodules

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The histogenesis of meningothelial-like nodule or so-called minute pulmonary chemodectoma remains unclear, with various immunohistochemical analyses giving inconsistent results. We performed an immunohistochemical and clonal analysis of minute pulmonary meningothelial-like nodules. Thirty-one histologically defined meningothelial-like nodules in 14 cases were stained immunohistochemically. One case had multiple lesions with brown pigment granules, which were positively stained with Berlin blue method, indicating the presence of hemosiderin. All meningothelial-like nodules were positive for vimentin and epithelial membrane antigen (EMA), but not for S-100 protein, chromogranin A, or synaptophysin. Five of 13 cases (13 of 28 lesions) were positive for CD68 by KP-1. Ten cases (24 lesions) stained for CD68 by PG-M1 were weakly positive. All lesions were negative for lysozyme, myosin, actin, keratin, and melanoma-associated antigen. Alveolar macrophages were intensely positive for CD68 and lysozyme in all examined cases. We analyzed the clonality of 11 minute pulmonary meningothelial-like nodule lesions in two female cases based on an X-chromosome–linked polymorphic marker, the human androgen receptor gene (*HUMARA*). The *HUMARA* was found to be amplified with or without prior digestion by the methylation-sensitive restriction endonuclease *Hpa*II. Six of 11 lesions showed monoclonal expansion. Five lesions in a multiple case showed different patterns of monoclonality. Our findings showed that minute pulmonary meningothelial-like nodules have meningothelial-like and phagocytic characteristics but no muscular phenotype. Furthermore, some minute pulmonary meningothelial-like nodules may show monoclonal expansion, whereas others are polyclonal. Our data indicate that minute pulmonary meningothelial-like nodules are reactive rather than neoplastic. HUM PATHOL 30:425-429. Copyright © 1999 by W.B. Saunders Company

Key words: **meningothelial-like nodule, immunohistochemistry, CD68, clonality, human androgen receptor gene.**

Abbreviations: **MPC, minute pulmonary chemodectoma; MN, meningothelial-like nodule; EMA, epithelial membrane antigen; *HUMARA*, human androgen receptor gene; ABC, avidin-biotin complex; PCR, polymerase chain reaction; NSE, neuron-specific enolase; dGTP, deoxyguanosine triphosphate; AUC, area under the curve.**

So-called minute pulmonary chemodectoma (MPC) was first reported by Korn et al in 1960.[1] MPC consists of spindle-shaped cells with oval to indented spindle nuclei. The tumor was considered to be "miniature carotid body tumor" histologically because it was closely associated with pulmonary vessels.[2] Although this tumor had been proposed to be pulmonary microparaganglioma,[3] it has no endocrine granules and was not associated with nerves in electron microscopic analysis.[4] Ultrastructural studies showed that MPC cells closely resembled meningothelial cells.[5,6] A new term, *meningothelial-like nodule,* was proposed and has been accepted widely. Gaffey et al[6] reported that minute pulmonary meningothelial-like nodules (MN) were strongly immunoreactive for epithelial membrane antigen (EMA) and vimentin, and were negative for cytokeratin, S-100, neuron-specific enolase, and actin.[6] These findings were also similar to meningothelial cells. Accordingly, MPC has been more accurately named MN to reflect its ultrastructural and immunohistochemical characteristics. In contrast, Torikata and Mukai[7] described that immunostaining for myosin and vimentin was positive in all so-called MPC cells, and EMA staining was negative. They suggested a muscle origin for so-called MPC. Therefore, the histogenesis and phenotypes of MN remain unsolved.

Dail[8] described that small chemodectoma-like bodies may contain a scant amount of hemosiderin, which was demonstrated by Berlin blue staining.[8] We also experienced a case of multiple MN that contained hemosiderin. Therefore, we assumed that MN may have phagocytotic ability.

Monoclonality has been thought to be a fundamental characteristic of neoplasia.[9,10] One X chromosome is randomly and permanently inactivated at an early stage of embryogenesis in the female. This leads to somatic mosaicism of normal females with respect to X-linked alleles, with approximately half of the somatic cells expressing the maternal allele and the other half expressing the paternal allele. Tumors arising from a single cell will therefore express one of the two phenotypes. Recently, a highly polymorphic trinucleotide CAG repeat in the X-linked human androgen receptor gene (*HUMARA*) have been used to distinguish between the two X chromosomes[11] and to detect monoclonality in various neoplastic diseases.[12-17] We have reported the monoclonal nature of sclerosing hemangioma of the lung,[18] which supported a hypothesis that sclerosing hemangioma of the lung is a neoplasm.

The aim of this study was to better characterize MN by immunohistochemical analyses, including EMA, myosin, actin, and CD68, and clonal analyses based

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on an X-chromosome–linked polymorphic marker, the *HUMARA*.

MATERIALS AND METHODS

Patients

A total of 327 cases of primary lung cancer were resected at the National Cancer Center Hospital East from January 1996 to December 1997. Lungs were fixed with 10% formalin or 100% methanol and embedded in paraffin. Paraffin blocks were cut into 3-μm sections and stained with hematoxylin and eosin. In the cases in which MNs were identified, 3-μm serial sections were cut from the stored paraffin blocks.

Immunohistochemistry

We performed an immunohistochemical analysis by the avidin-biotin complex (ABC) method.[19] The primary antibodies used are listed in Table 1. Biotinylated secondary antibody and ABC reagent were purchased from DAKO Japan, Kyoto, Japan. Alveolar macrophages served as a positive internal control for immunostaining of CD68 and lysozyme. Appropriate positive and negative controls were used for each staining.

Strategy for Clonal Analysis

We conducted clonal analysis according to the method of Allen et al.[11] The strategy is based on random X chromosome inactivation by methylation. This random inactivation occurs early in embryogenesis, and remains conserved throughout cell division, even in tumors. The *HUMARA* on the X chromosome has a trinucleotide (CAG) repeat polymorphism. We used *Hpa*II, which cannot digest methylated DNA, to cut DNA before polymerase chain reaction (PCR), so that only the methylated allele was amplified. If the methylation pattern is uniform because of monoclonality, there is only one PCR product after *Hpa*II digestion, whereas if the methylation patterns differ (polyclonal), two PCR products are obtained for the trinucleotide repeat polymorphism. In monoclonal cases, if the longer or shorter allele was amplified after *Hpa*II digestion, we referred to it as the "l" or "s" pattern of monoclonality, respectively. The ratio of both alleles (allelic ratio) after *Hpa*II digestion was calculated by comparing the amount of PCR products after normalization with the undigested sample. Allelic ratio of each sample was divided by that of normal control, and called the corrected allelic ratio. If the corrected allelic ratio was less than 0.3, the sample was judged to be monoclonal.[20]

TABLE 1. Antibodies Used in the Study

Antibodies to	Clone	M/P	Source	Dilution	Antigen Retrieval
Keratin	AE1/AE3	M	DAKO	100:1	MW
Chromogranin A		P	DAKO	400:1	—
Synaptophysin		P	DAKO	200:1	MW
NSE	BBS/NC/VI-H14	M	DAKO	100:1	—
Vimentin	V9	M	DAKO	50:1	MW
S-100 protein		P	DAKO	1,000:1	—
EMA	E29	M	DAKO	100:1	—
Myosin		P	BG	50:1	—
Alpha-SrA	Alpha-Sr-1	M	DAKO	50:1	MW
Alpha-SMA	1A4	M	DAKO	50:1	MW
CD68	KP-1	M	DAKO	100:1	—
CD68	PG-M1	M	DAKO	100:1	trypsin
Lysozyme		P	DAKO	20:1	—
Progesterone receptor	1A6	M	NOVO	40:1	MW
Melanoma-associated antigen	HMB45	M	DAKO	50:1	—

Abbreviations: M, monoclonal antibody; P, polyclonal antibody; MW, microwave; NSE, neuron-specific enolase; DAKO, DAKOPATTS, Glostrup, Denmark; EMA, epithelial membrane antigen; BG, BioGenex Laboratories, CA; SrA, sarcomatic actin; SMA, smooth muscle actin; NOVO, Novocastra Laboratories, Newcastle, UK.

DNA Extraction

The paraffin blocks containing MN fixed with 100% methanol were cut into 5-μm sections and stained with hematoxylin and eosin. MN cells were microdissected under a micromanipulator (Olympus-Narishige, Tokyo, Japan). Adjacent normal lung tissue was scraped with a 27-gauge needle to provide a normal control. DNA was extracted with the DNA extractor WB kit (Wako Pure Chemicals, Osaka, Japan).

Polymerase Chain Reaction

DNA was digested with *Rsa*I and with or without *Hpa*II, and the *HUMARA* was then amplified by PCR as previously described.[21] Amplification of the *HUMARA* in exon 1 was performed using primers AR1 and AR2, essentially as described by Mutter and Bounton[22] with slight modifications. Six percent (w/v) dimethylsulfoxide and deoxyguanosine triphosphate (dGTP) instead of 7-deaza-2′-dGTP were added. AR 2 was labeled at the 3′ end with fluorescein. The *HUMARA* PCR products were analyzed with an automatic sequencer (ALFred, Pharmacia, Uppsala, Sweden), in which peaks represented PCR bands in the electrophoretic gel. Area under the curve (AUC) represented the amount of PCR products. AUC was calculated by the Fragment Manager software package (Pharmacia). To confirm the reproducibility of the experiment, all cases were examined at least twice by independently performed PCR and electrophoresis.

RESULTS

Thirty-four cases with MN were identified through the routine pathological examination of 357 cases of lung cancer (9.5%). Twenty-two of 214 adenocarcinomas (10%) and 3 of 84 squamous cell carcinomas (3.5%) had MN. The other five MNs were concomitant with two metastatic adenocarcinomas (from colon and breast), an adenosquamous carcinoma, a large cell carcinoma, and a typical carcinoid. Twelve cases were male (35%), and 22 cases were female (65%). Multiple MNs were detected in five cases (15%), in which four cases concomitant with adenocarcinoma and one with metastatic adenocarcinoma from colon. The size of the MN lesions ranged from less than 0.1 mm to 3 mm in diameter (median, 1.3 mm). Fourteen of 31 cases with MN were available for immunohistochemistry in the serial sections.

Small foci of the MN were found in the alveolar interstitium or subpleural region (Fig 1). The cells were arranged in an organoid pattern with cell nests of various sizes. Six of 14 cases had multiple MNs. Case 7 had multiple MNs, each with brown small granules that stained positive for iron demonstrated by Berlin blue method (Fig 2).

The results of the immunohistochemical analysis

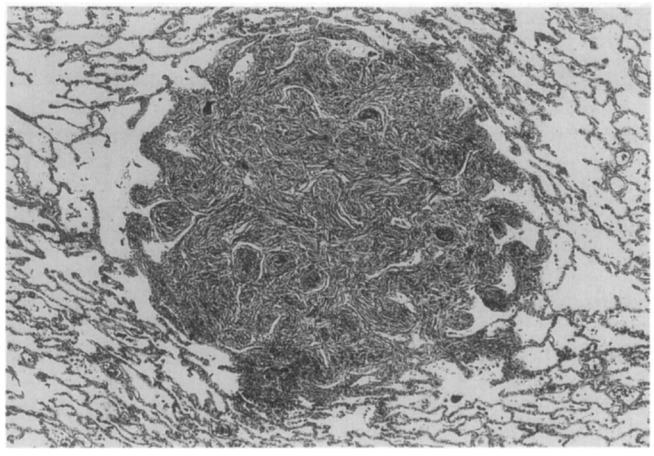

FIGURE 1. Microscopic features of a representative minute pulmonary meningothelial-like nodule. It showed organoid pattern with cell nests of various sizes, containing small brown granules. (H&E, original magnification ×47.)

are shown in Table 2. All MNs were strongly positive for vimentin. All cases were diffusely positive for EMA (Fig 3A), but not for myosin, alpha-sarcomatic actin, or alpha-smooth muscle actin. Three of seven cases (9 of 18 lesions) were clearly positive for progesterone receptor. Six of 13 cases (15 of 28 lesions) were strongly positive for CD68 by KP-1 (Fig 3B). Ten cases (24 lesions) stained by PG-M1 were weakly positive. All cases were negative for lysozyme. Alveolar macrophages were intensely positive for CD68 and lysozyme in all examined cases. Almost all lesions (25 of 29) were weakly positive for neuron-specific enolase (NSE) (positive in 25 lesions of 29), but were negative for chromogranin A, synaptophysin, and S-100 protein. All lesions were negative for keratin and melanoma-associated antigen (HMB-45).

Three female cases, in which resected lungs were fixed with 100% methanol, were analyzed for clonality (cases 11 to 13). Cases 12 and 13 were informative, with two PCR products of *HUMARA* (s and l) in the normal control. Six of 11 MN lesions showed monoclonal expansion, whereas normal lungs were polyclonal. Two of five lesions in one case showed an *s* pattern of monoclonality, whereas the other three showed an *l* pattern, indicating an independent origin (Fig 4).

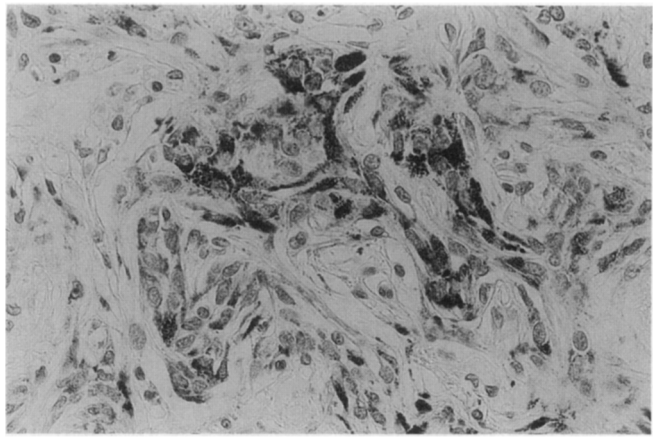

FIGURE 2. Minute pulmonary meningothelial-like nodule stained positive with Berlin blue method. Small granules were considered to be hemosiderin. (Original magnification ×426.)

DISCUSSION

Several immunohistochemical analyses of MN have been reported in the past decade. Gaffey et al[6] reported that minute pulmonary MN (so-called MPC) were positive for epithelial membrane antigen and vimentin, but negative for cytokeratin, NSE, S-100 protein, and actin. Conversely, Torikata and Mukai[7] reported that so-called MPCs were positive for myosin and vimentin, but negative for cytokeratin, desmin, actin, NSE, S-100 protein, and myoglobin.[7] They concluded that so-called MPC might originate from muscle cells. Our analysis also indicated that MNs were positive for vimentin, EMA, and progesterone receptor, but negative for myosin, actin, S-100 protein, keratin, and neuroendocrine markers such as chromogranin A and synaptophysin. Weak positiveness for NSE was considered nonspecific because normal alveolar epithelium was also weakly positive for this antigen. Our findings support the resemblance of MN cells to meningothelial cells reported by Gaffey et al.[6] Smooth muscle cell differentiation was not seen in our study.

Six of 13 cases (15 of 28 lesions) were positive for CD68 by KP1. Ten investigated cases were weakly positive for CD68 by PG-M1. Falini et al[23] compared KP1 and PG-M1 reactivity in paraffin sections.[23] They concluded that PG-M1 only labeled macrophages, whereas KP1 stained normal and neoplastic myeloid elements to various extents. KP1 was also reactive with a variable proportion of cases of malignant fibrous histiocytoma, malignant schwannoma, liposarcoma, leiomyosarcoma, cutaneous or metastatic melanoma, and renal cell carcinoma.[24] Therefore, KP1 is considered to be less specific as a histiocytic marker and to show a wide spectrum of immunoreactivity with malignant neoplasms of presumed nonhistiocyte origin.

The MN cells positive for CD68 were negative for lysozyme. Granulocytes and monocytes/macrophages stain positive for lysozyme. CD68 is expressed primarily as an intracytoplasmic molecule associated with lysosomal granules.[25] KP1 stains macrophages in a wide variety of human tissues, including Kupffer's cells and macrophages in the lung alveoli and bone marrow.[24] Kaiserling et al[26] reported that Schwann cells of the nerves with Wallerian degeneration and those in traumatic neuroma, neurofibroma, and granular cell tumor exhibited intracytoplasmic immunoreactivity with KP1 and PG-M1.[26] Those lesions were negative for lysozyme immunohistochemically. The reaction product was found to be located in phagolysosomes in granular cell tumor by electron microscopy. They concluded that immunoreactivity with CD68 by KP1 or PG-M1 could also be expected in cells that do not belong to the mononuclear phagocyte system even if they exhibited phagocytosis or autophagy. In our study, some minute

TABLE 2. Results of Immunohistochemical Study

	Case No.													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. of foci examined	1	4	2	3	2	1	1	1	1	1	1	6	4	1
Gender	f	m	f	f	f	f	m	m	f	f	f	f	f	m
Fixation	F	F	F	F	F	F	F	F	M	F	M	M	M	M
Keratin	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CGA	−	+*	−	−	−	−	−	−	−	−	−	−	−	−
SP	−	−	±	−	−	−	−	−	−	−	−	−	−	−
NSE	±	±	±	±	−	±	±	±	±	−	±	±	±	−
VIM	++	++	++	++	++	++	++	++	++	++	++	++	++	++
S-100	NE	−	−	−	NE	NE	−	NE	NE	NE	−	+	±	−
EMA	NE	+	±	+	NE	NE	+	NE	NE	NE	+	+	+	+
myosin	NE	−	−	±	NE	NE	−	NE	NE	NE	−	−	−	−
alpha-SrA	NE	−	−	−	NE	NE	−	NE	NE	NE	−	−	−	+
alpha-SMA	NE	−	−	−	NE	NE	−	NE	NE	NE	−	−	−	−
CD68 (KP-1)	−	−	±	±	+	±	±	±	+	NE	+	+	+	+
CD68 (PG-M1)	±	±	+	+	NE	NE	±	NE	±	NE	±	±	±	±
Lysozyme	−	−	−	−	−	−	−	−	−	NE	−	−	−	−
PgR	NE	NE	+	+	NE	NE	+	NE	NE	NE	−	−	±	−
MAA	−	−	−	−	−	−	−	−	−	NE	−	−	−	−

Abbreviations: f, female; m, male; F, formalin; M, methanol; CGA, chromogranin A; SP, synaptophysin; NSE, neuron-specific enolase; VIM, vimentin; EMA, epithelial membrane antigen; SrA, sarcomatic actin; SMA, smooth muscle actin; PgR, progesterone receptor; MAA, melanoma-associated antigen; NE, not evaluated because the lesions disappeared in the serial sections.

−: no staining; ±: faint staining; +: obvious staining; ++: dense staining.

*Positive for chromogranin A in one of four lesions.

pulmonary MNs were positive for CD68, and all were negative for lysozyme. Therefore, it is possible that some MNs do not belong to the mononuclear phagocyte system, yet have phagocytic ability. If so, this explains the presence of hemosiderin in MN cells.

Seven of 11 MN lesions showed monoclonality. The reason why some lesions were monoclonal and others were polyclonal remains unexplained. There were no particular histological differences between monoclonal and polyclonal MN. Because not all MN showed monoclonal expansion, MN is probably a reactive rather than neoplastic lesion. It is well known that some reactive lesions can show monoclonality, such as smooth muscle cells in atherosclerosis.[27] Thus, we speculate that some lesions arise from a single cell responding to proliferative stimuli, but when several cells proliferate simultaneously and compose one lesion, it becomes polyclonal. Therefore, the term *minute pulmonary chemodectoma* may not be appropriate for this lesion, as Gaffey et al[6] suggested. We also endorse the term *minute meningothelial-like nodules* coined by Gaffey et al for these lesions, to reflect their immunohistochemical and clonal characteristics.

In conclusion, MNs stained immunohistochemically positive for vimentin and EMA but not for myosin, actin, or S-100 protein. Some of them were immunoreactive for CD68 but not for lysozyme. Our findings indicated that MN has meningothelial-like and phagocytic characteristics, but no muscular phenotype. Furthermore, clonal analysis showed that some MNs showed

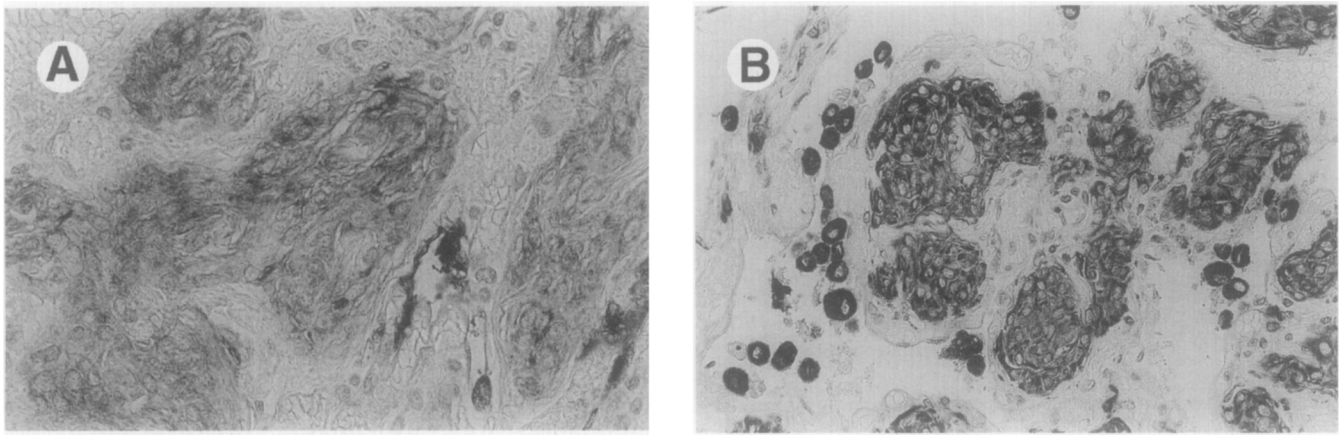

FIGURE 3. Immunohistochemistry of minute pulmonary meningothelial-like nodule. It was strongly positive in the cytoplasm for EMA (A) and CD68 (KP1) (B). (Immunoperoxidase, original magnifications: (A) ×333, (B) ×333). Pneumocyte cells and alveolar macrophages were also intensely positive for EMA and CD68, respectively.

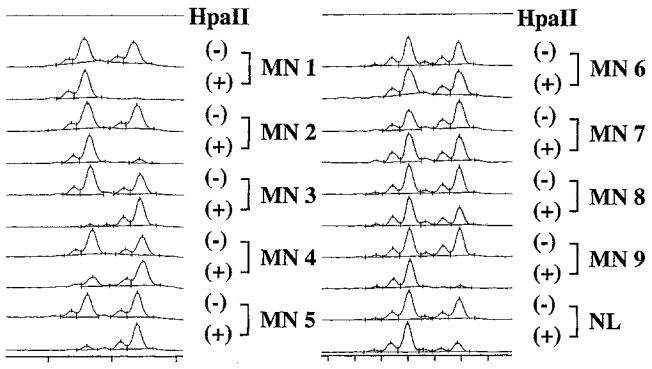

FIGURE 4. Clonal analysis of multiple minute pulmonary meningothelial-like nodules of case 13 by amplification of the human androgen receptor gene with or without *Hpa*II digestion. Corrected allelic ratio of MN 1 to 9 was 0, 0.34, 0.02, 0.13, 0.06, 0.31, 1.5, 1.7, and 0.21, respectively. MN 1 and 9 showed an "s" pattern of monoclonality, and MN 3, 4, and 5 showed an "I" pattern. Incontrast, MN 2, 6, 7, 8, and normal lung were polyclonal. MN, meningothelial-like nodule.

monoclonal expansion and others were polyclonal. Our data indicate that minute pulmonary meningothelial-like nodules are reactive rather than neoplastic.

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