Virchows Archiv A Pathol Anat (1990) 417:113–118

Virchows Archiv A
Pathological Anatomy and Histopathology
© Springer-Verlag 1990

So-called minute chemodectoma of the lung

An electron microscopic and immunohistochemical study

Chikao Torikata and Makio Mukai

Department of Pathology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan

Received January 19, 1990 / Received after revision March 3, 1990 / Accepted March 6, 1990

Summary. So-called minute pulmonary chemodectoma is a curious, small lung tumour found mainly in women. The nature and origin of the proliferating cells are still obscure. In the first report on the tumour, the component cells were described as resembling chemoreceptor cells and the tumour was named chemodectoma. However, electron microscopic studies of the tumour have revealed no evidence of neuronal characteristics and have shown a close resemblance to meningothelial cells. In this study, the electron microscopic findings were similar to those previously reported but in one of the two cases, tumour cells were filled with abundant cytofilaments, giving them an occasional dense, patch-like appearance. Immunostaining for myosin and vimentin was positive in all tumour cells, but epithelial membrane antigen staining was not seen. These findings indicate that the tumour might have its origin from muscle cells.

Key words: Minute chemodectoma – Lung – Ultrastructure – Immunohistochemistry

Introduction

So-called minute chemodectoma of the lung was first reported by Kohn et al. (1960) as multiple, minute pulmonary tumours resembling chemodectoma. The tumour is found in the periphery of any lobe of the lung in association with chronic lung disease, such as chronic pulmonary thromboembolism and diffuse pulmonary damage. It is seen predominantly in female patients (Spain 1964; Dail 1988). Most of the tumours are very small and are detected incidentally by light microscopic examination.

The first report of an electron microscopic observation of the tumour was that of Costero et al. (1972), who stated that the tumour is of pleural origin. Since then, only three reports of electron microscopic studies of so-called minute chemodectoma of the lung have been published (Kuhn and Askin 1975; Churg and Warnock 1976; Gaffy et al. 1988). They have all suggested that the tumour is unrelated to chemoreceptors and that the fine structure of the tumour resembles that of meningioma, characteristically showing a jigsaw puzzle-like arrangement of the cell membrane, numerous well-formed desmosomes and lack of a basal lamina. Recently, Gaffy et al. (1988) reported that the tumour is composed of meningothelial-like nodules in the lung on the basis of immunohistochemical staining for various types of cytoskeletal proteins and some cell markers. However, it is surprising to find "meningothelial" cells present so frequently in the interstitium of the lung in close relationship to the pulmonary veins.

The tumour is so small that it is difficult to obtain fresh material for electron microscopic and immunohistochemical study in order to determine the cell of origin, and this paper presents the results of immunohistochemical staining for vimentin, myosin and epithelial membrane antigen (EMA) in seven cases and electron micrograph in two. One of these showed quite different features from those previously reported. We discuss the possible nature of the proliferating cells of the tumour on the basis of the ultrastructural findings and the immunohistochemical study.

Materials and methods

All lung tissues examined in this study were fixed with 10% formalin solution and processed for routine histological examination. Sections from paraffin embedded tissues were cut (3 μm), deparaffinized and stained with haematoxylin-eosin (H&E), periodic acid-Schiff (PAS) with or without prior diastase digestion, Mallory stain, silver impregnation, Grimelius stain and Fontana-Masson stain. For immunohistochemistry, serial sections of minute chemodectomas were immunostained for actin (Amersham International, England; dilution 1:500), muscle actin (Enzo Biochem, New York; dilution 1:1500), vimentin (Dakopatts, Denmark; dilution 1:200), desmin (Bio Genex Lab. USA Kit dilution 1:1), cyto-keratin (Labosystem, Finland. dilution 1:200), EMA (Dakopatts, dilution 1:200), S-100 protein (Dakopatts, dilution 1:200), neuron specific

Offprint requests to: C. Torikata

Table 1. Clinicopathological data of the patients with so-called minute pulmonary chemodectoma

Case No.	Age	Sex	Pulmonary lesion	Major non-pulmonary disease	So-called minute chemodectoma	
					Location	Single/multiple
1	50	F	Lung carcinoma, large cell		l-LL	Single
2	54	F	Cryptococcosis		r-UL	Single
3	56	M	Lung carcinoma, squamous		l-UL	Multiple
4	78	F	Cryptococcosis; tumorlet in r-ML	Brain infarct	r-LL	Multiple
5	80	F	Bronchopneumonia	Diabetes mellitus	l-UL	Single
6	88	F	Emphysema; tumorlet in r-ML	Myocardial infarction	r-UL	2
7	94	F	PA thromboembolism	Brain infarct	All lobes	Multiple

Cases 1–3: surgically resected material
Cases 4–7: autopsy cases
Cases 3 and 7: studies by electron microscopy
UL, Upper lobe; ML, middle lobe; LL, lower lobe; r, right; l, left

Table 2. Immunohistochemical data of so-called minute pulmonary chemodectomas

	Case						
	1(1)	2(1)	3(7)	4(4)	5(1)	6(1)	7(9)
Cytokeratin	–	ND	–	ND	ND	ND	–
Vimentin	+	+	+	+	+	+	+
Desmin	–	ND	–	ND	ND	ND	–
Actin	ND	ND	–	–	ND	–	–
Muscle actin	–	ND	–	–	–	–	–
Epithelial membrane antigen	–	ND	–	ND	–	ND	–
Neuron-specific enolase	–	ND	–	ND	ND	ND	–
S-100 protein	ND	ND	–	ND	ND	ND	–
Myosin	+	ND	+	+	+	ND	+
Myoglobin	–	ND	–	ND	ND	ND	–

(); Number of foci examined for immunohistochemistry
+; positive in immunostain
–; negative in immunostain
ND; not immunostained

enolase (NSE) (IBL, Gunma, Japan. dilution 1:500), myosin and myoglobin (Bio Genex Lab. Kit dilution 1:1) using avidin-biotin peroxidase complex (ABC) (Vector Laboratories, USA) (Hsu et al. 1980) with or without pretreatment with 0.1% trypsin for 30 min at room temperature. Additionally, 10 meningiomas (5 of the meningotheliomatous type, 3 of the fibroblastic type, 2 of the angioblastic type), and 7 mesotheliomas (3 cases of the epithelial type and 4 of the fibrous type) were immunostained using the same procedures.

For electron microscopy, formalin-fixed, paraffin-embedded tissues of the 2 patients were used. One was from the left upper lobe of the lung of a 56-year-old man resected because of lung cancer; the other was from the lung of a 94-year-old woman who died of old age accompanied by brain infarction and multiple pulmonary thromboemboli. Two paraffin blocks of the lung tissues from each case were cut and deparaffinized with xylene, hydrated with graded alcohols and water, post-fixed with 1% osmium tetroxide for 1 h, dehydrated with graded alcohols and acetone, and embedded in Spurr's resin. After confirmation of the presence of so-called minute chemodectomas in these blocks, they were trimmed. Ultra-thin sections were cut and doubly stained with uranyl acetate and lead nitrate, and examined with a JEOL 100C electron microscope at 100 kV. Three cases of epithelial type and two cases of fibrous mesothelioma were also studied by electron microscopy.

Results

Small foci of so-called pulmonary chemodectoma were noted in H&E stained sections located in the interstitium at the periphery of the lung, in close relationship to the small pulmonary veins. Occasionally, tumour was situated in the interlobular connective tissue. The masses consisted of interstitial nests of cells, separated from air spaces by a rim of capillaries or fibrous connective tissue; the surface-to-air space was covered with cuboidal alveolar lining cells. The cell nests consisted of fairly large, bland cells with slightly indented nuclei and small, inconspicuous nucleoli. They were poorly defined and the abundant cytoplasm was finely granular and slightly eosinophilic in H&E stained sections. They were slightly positive with diastase-sensitive PAS stain, indicating the presence of glycogen, but never stained by Grimelius or Fontana-Masson stain. No mitoses were noted (Figs. 1, 2).

In immunohistochemistry, all nests of minute chemodectomas were diffusely and clearly stained for vimentin and myosin, but never for EMA, despite positive staining of the epithelial cell membranes (Fig. 3). In high power view, reaction products for myosin were noted diffusely in the cytoplasm of tumour cells (Fig. 4); however, the smooth muscle cells of the pulmonary vessels and of the interstitium were more strongly stained. In immunostaining for actin and muscle actin, tumour cells were negative in contrast to the stainability of smooth muscle cells of the pulmonary vessels. Immunostaining for S-100 protein, NSE and myoglobin was also negative judging from the control specimens.

In toluidine-blue stained sections from epon-embedded tissue, chemodectoma-like bodies were separated by capillaries and bundles of collagen and elastic fibres (Fig. 5). Ultrastructurally, they consisted of a single type of cells that had irregular cytoplasmic membrane processes showing a jigsaw puzzle-like arrangement and

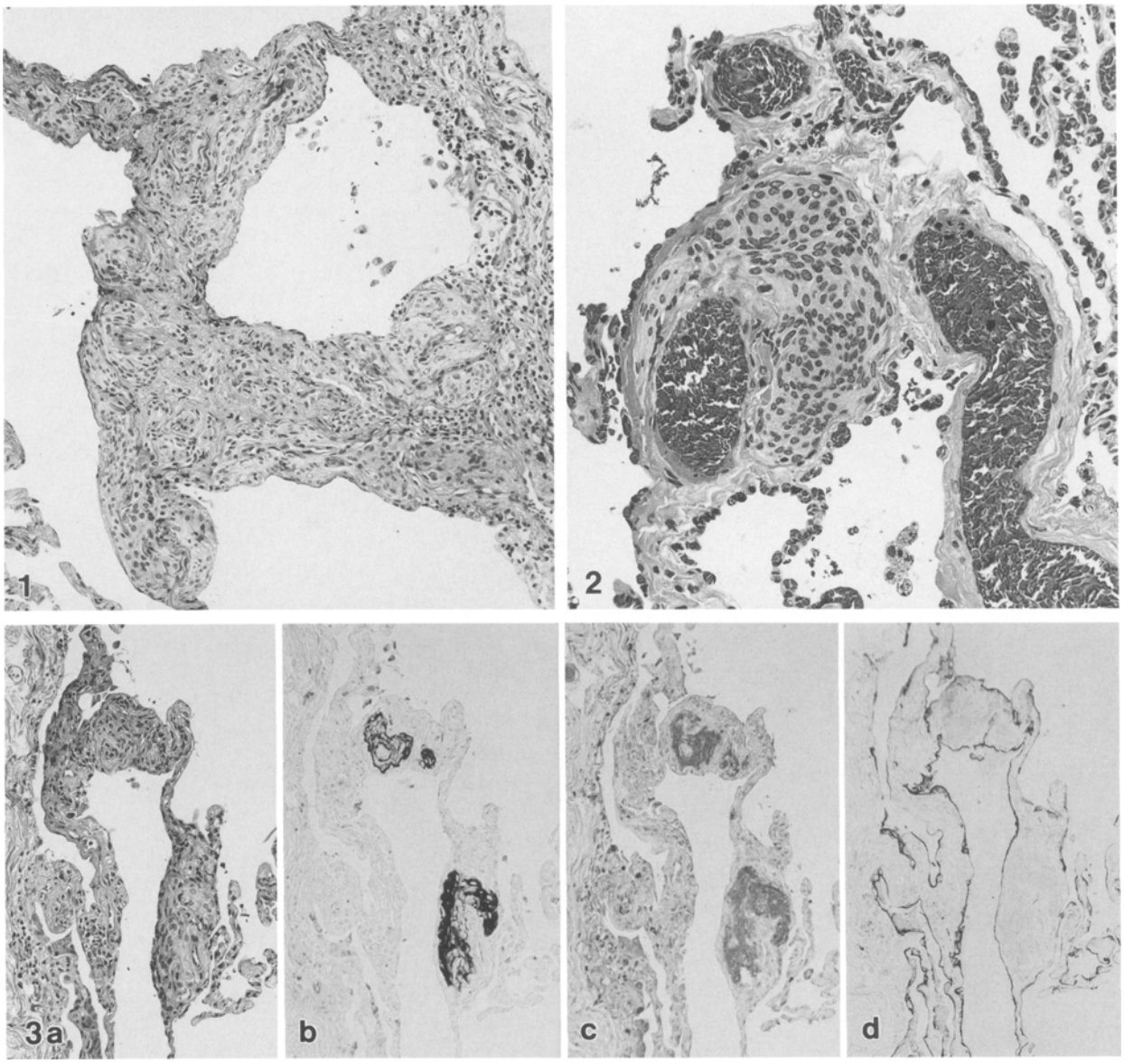

Fig. 1. So-called minute pulmonary chemodectoma. Numerous cells nests of so-called chemodectoma are noted in the fibrotic interstitium close to the visceral pleura. H&E ×100

Fig. 2. High-power view of so-called minute chemodectoma of the lung. Nests of the tumour are noted in the interstitium in close relationship to pulmonary veins. The tumour cells contain fairly large nuclei but inconspicuous cell membrane. Mitosis is not seen. H&E ×200

Fig. 3A–D. Immunohistochemistry for vimentin, myosin and EMA in serial sections. Small nests of so-called minute chemodectoma are noted around the pulmonary veins and they are strongly stained for vimentin (**B**) and diffusely for myosin (**C**), but completely negative for EMA despite positive staining of the epithelial cell membrane (**C**). **A** H&E; **B** immunostaining for vimentin; **C** for myosin; **D** for EMA. All ×100

were linked by numerous well-formed desmosomes and desmosome-like junctions (Fig. 6). In some areas, the junctions were very long and flocculent material was noted between the opposing cell membranes; this resembled a basal lamina (Fig. 7). Most of these cells contained abundant filaments in their cytoplasm, which were more clearly demonstrated in a surgical resection case. The tumour cells were filled with cytofilaments giving them an occasional dense, patch-like appearance, but typical actin-myosin complexes were not detected. Glycogen granules were scattered mainly in the periphery of the cells, sometimes forming aggregates (Fig. 8). No external lamina was noted around the tumour cells. Small trabecula of collagen fibres accompanied by elastic fibres were seen among the proliferating cells (Fig. 6), but no nerve was noted in or near the cell nests. Bundles of intermediate-sized filaments, probably vimentin filaments, inserted into the well-formed desmosomes between the opposing cells. Sometimes they showed dense aggregates of intermediate filaments just beneath the cell membrane when they were sectioned, tangentially (Fig. 9). These proliferating cells did not contain neuro-

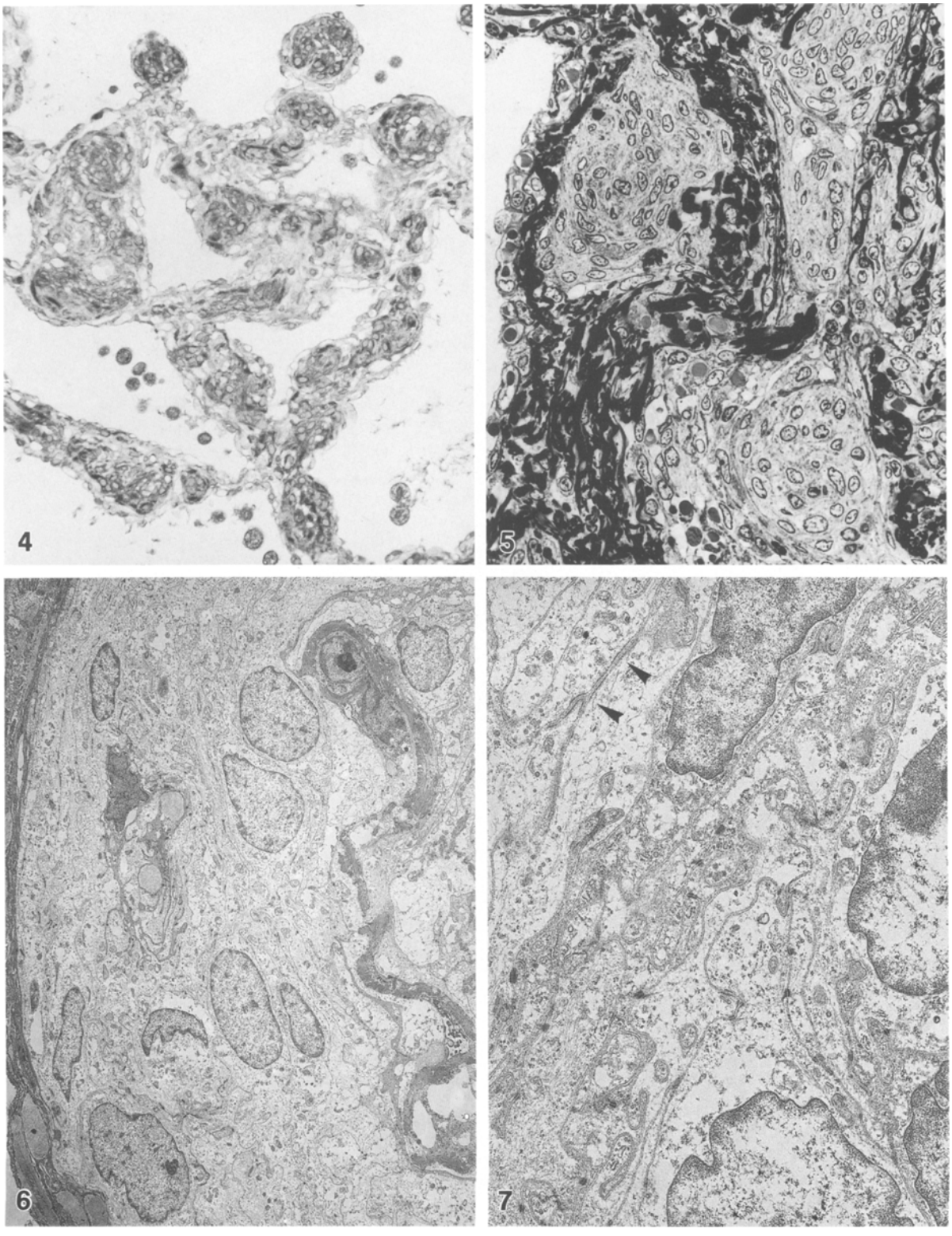

Fig. 4. Immunohistochemistry for myosin. Cytoplasm of proliferating cells of so-called minute chemodectoma in the interstitium are diffusely stained for myosin. ABC $\times 200$

Fig. 5. So-called minute pulmonary chemodectoma from epon-embedded tissue. The tumour is seen in the interstitium as cell nests surrounded by thin connective tissue and consists of a single type of cells which oval nuclei and poorly defined cytoplasm. Toluidine-blue stain. $\times 200$

Fig. 6. Low power electron micrograph of so-called minute pulmonary chemodectoma. The cell nests of the tumour are clearly identified by their fibroblastic cells and capillaries. Proliferating cells possess irregular cytoplasmic processes and numerous well-formed desmosomes between the opposing cells. $\times 2300$

Fig. 7. Cells from the central portion of so-called minute pulmonary chemodectoma. The tumour cells possess irregular cytoplasm and have numerous well-formed desmosomes and desmosome-like junctions. In some area, the junctions are long, and flocculent material between opposing cell membranes looks like a basal lamina (*arrowheads*). A typical external lamina is not seen around the tumour cells. $\times 7800$

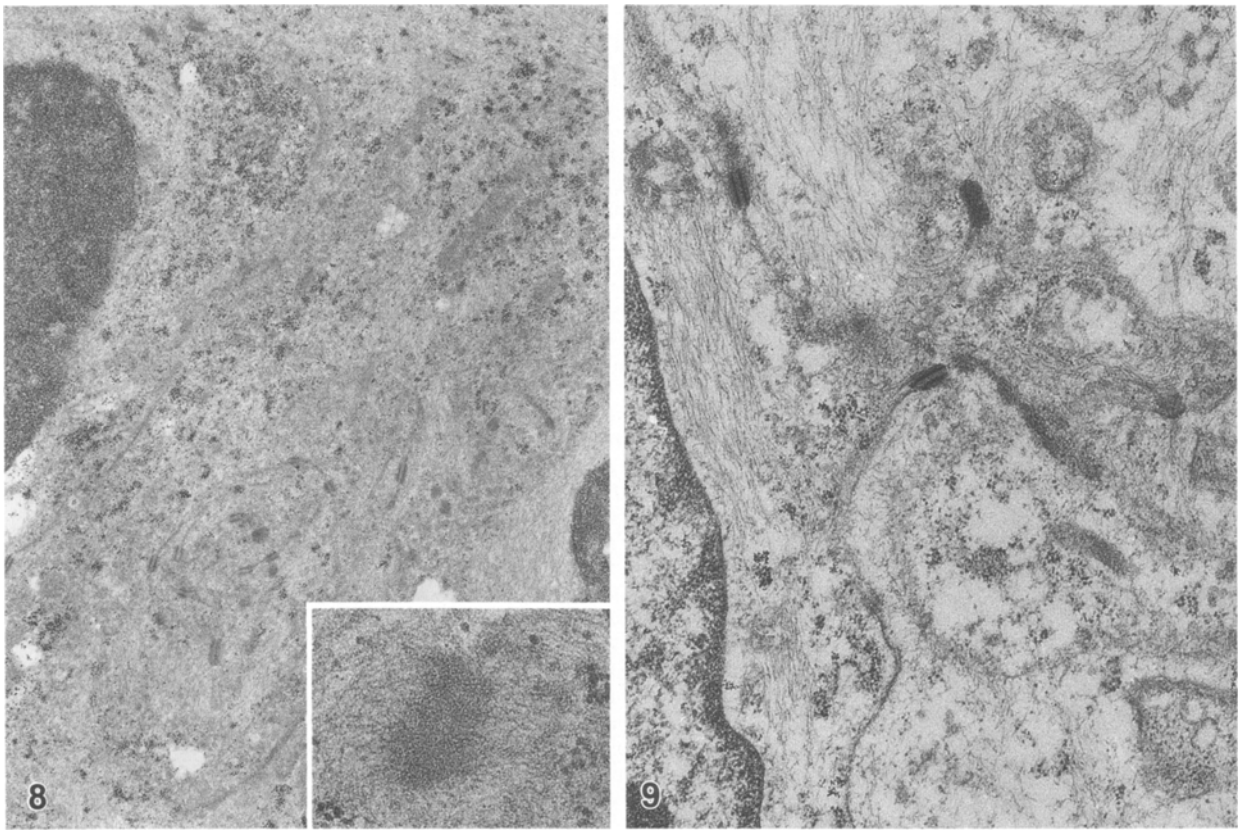

Fig. 8. High-magnification electron micrograph of so-called minute pulmonary chemodectoma. This photograph is of a paraffin-embedded surgical specimen, primarily fixed with 10% formalin solution. The proliferating cells have an inconspicuous membrane system including the cell and the nuclear membrane. However, they have abundant intracytoplasmic filaments and dense, patch-like structures consisting of accumulations of the filaments (*Inset*). Numerous well-formed desmosomes are noted along the cell membrane. Glycogen granules are scattered in the peripheral cytoplasm. ×14000. (*Inset*) ×60000

Fig. 9. High-magnification electron micrograph of so-called minute chemodectoma of the lung. The tumour cells show a jigsaw puzzle-like arrangement between opposing cells and contain abundant intermediate-sized filaments, which aggregate and insert into well-formed desmosomes. ×24000

endocrine granules or Weibel-Palade bodies, and no intercellular lumen formation was noted. No mitoses were detected by electron microscopy.

The clinicopathological and immunohistochemical data are summarized in the Tables.

Discussion

Minute pulmonary chemodectoma is a unique neoplastic lesion found predominantly in female lungs associated with chronic pulmonary thromboembolism and diffuse pulmonary damage. Hypoxic lung may stimulate formation of these tumours, but the sexual predominancy of this tumour is curious. The lesions are very small (usually less than 2 mm in diameter), and usually found incidentally by light microscopy. The pathological significance of minute pulmonary chemodectomas remains unclear. In contrast to the tumourlets of the lung (Torikata et al. 1975), the nature and origin of the proliferating cells is obscure and because of the difficulty of obtaining fresh material of so small a tumour, there is a lack of information about the proliferating cells.

In their report Kohn et al. (1960) described 19 cases in which the tumours were detected incidentally in the lung tissue and also the intimate relationship with veins seen in serial sections. In the first electron microscopic study of so-called minute pulmonary chemodectoma. Costero et al. (1972) commented on the absence of nerves and neuroendocrine granules and the presence of well-formed desmosomes. Since then, Kuhn and Askin (1975) and Churg and Warnock (1976) have published electron microscopic findings of the tumours and have seen irregular cytoplasmic membrane processes, well-formed desmosomes, cytoplasmic filaments and lack of both neuroendocrine granules and Weibel-Palade bodies. Both reports concluded that the tumour cells resembled meningeal-pia arachnoid cells. In this study, in addition to the characteristic findings previously reported, cells filled with intracytoplasmic filaments having a dense, patch-like appearance were seen, resembling smooth muscle cells despite their poor preservation.

For comparative purposes ten cases of various types of meningioma were stained for vimentin, and showed diffuse staining but were not stained for myosin and

EMA. Epithelial mesothelioma had quite different light and electron microscopic features and also showed a positive reactivity for keratin. Tumour cells of fibrous mesothelioma of the pleura showed positivity for vimentin but not for myosin, and had no desmosomes or jigsaw puzzle-like appearence of the cell membrane, so characteristic of minute chemodectoma of the lung.

In their immunohistochemical study, Gaffy et al. (1988) found that most of the tumour cells reacted positively for EMA and vimentin, but negatively for cytokeratin, S-100 protein, NSE and actin. On the basis of these and electron microscopic findings, they concluded that the tumours are minute pulmonary meningothelial-like nodules. However, in the current series, the tumour cells were diffusely positive for vimentin and myosin, but completely negative for EMA; these findings do not support similarity to meningothelial cells; the diagnostic value of EMA immunostaining of meningiomas has been emphasized (Schnitt and Vogel 1986). Immunostaining for actin and muscle actin was diffusely negative in this study and the literature on the anti-muscle actin antibody states that it does not react to normal pericytes. In immunostaining for actin, most epithelial cells, including the ciliated cells which contain considerable amount of actin, did not stain, suggesting that the amount of actin may be small or that preservation of immunochemical properties by fixation is poor.

Cases of meningioma in the lung have been reported (Kemnitz et al. 1982) and many more cases of haemangiopericytoma have been presented (Meade et al. 1974; Shin and Ho 1979; Yousem and Hochholzer 1987). Haemangiopericytic proliferation in meningroma has been studied by electron microscopy and a critical difference between the two cell types was the presence or absence of the basal lamina (Pena 1977; Mirra and Miles 1982). Normal pericytes can easily be recognized by electron microscopy; however, we do not know what is specific for the pericyte or how to distinguish pericytic neoplastic cells by means of immunohistochemistry. Furthermore, ultrastructural findings of haemangiopericytomas vary from case to case and the ultrastructural findings of so-called minute pulmonary chemodectoma are more likely to be those of meningioma than haemangiopericytoma (Eimoto 1977; Nunnery et al. 1981; Henderson and Papadimitriou 1982). However, some haemangiopericytomas of the soft tissue (Henderson and Papadimitriou 1982) and myofibroblastomas (Ghadially et al. 1983) have ultrastructural features similar to those of so-called minute chemodectoma of the lung, with numerous desmosomes and no basal lamina. We cannot find any cells in normal lung tissue that show the same ultrastructural morphology such as that of the proliferating cells in minute chemodectoma. However, the anatomical localization of the tumours containing myosin-positive cells in close association with the pulmonary veins is interesting.

We suggest that minute pulmonary chemodectomas show smooth muscle cell differentiation notably when closely associated with the small pulmonary veins. We do not see evidence of meningothelial cell differentiation, and note that myosin-like molecules have been detected in human non-muscle cells (Pollard and Weihing 1974).

References

Churg AM, Warnock ML (1976) So-called "minute pulmonary chemodectoma." A tumor not related to paraganglioma. Cancer 37:1759–1769

Costero I, Barroso-Moguel R, Martinez-Paloma A (1972) Pleural origin of some of the supposed chemodectomoid structures of the lung. Beitr Pathol 146:351–365

Dail DH (1988) Chemodectoma-like bodies and similar tumors. In: Dail DH, Hammar SP (eds) Pulmonary Pathology, Springer, New York Berlin Heidelberg, pp 903–910

Eimoto T (1977) Ultrastructure of an infantile hemangiopericytoma: a light and ultrastructural study. Cancer 47:2162–2170

Gaffy MJ, Mills SF, Askin FB (1988) Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 12:167–175

Ghadially FN, McNaughton JD, Lalonde JMA (1933) Myofibroblastoma: A tumor of myofibroblasts. J Submicrosc Cytol Pathol 15:1055–1063

Henderson DW, Papadimitriou JM (1982) Vasoformative tumours. In: Henderson DW, Papadimitriou JM (eds) Ultrastructural appearences of tumours. A diagnostic atlas. Churchill Livingstone, Edinburgh, pp 243–259

Hsu M, Raine L, Fangen H (1980) Use of avidin-biotin peroxidase complex (ABC) in immunoperoxidase technique: a comparison between ABC and unlabelled antibody (PAP) procedures. J Histochem Cytochem 29:577–580

Kemnitz P, Herman S, Heinrich P (1982) Meningioma of lung: first report with light and electron microscopic findings. Ultrastruct Pathol 3:359–365

Kohn D, Bensch K, Liebow AA, Castleman B (1960) Multiple minute pulmonary tumors resembling chemodectomas. Am J Pathol 37:641–672

Kuhn C III, Askin FB (1975) The fine structure of so-called minute pulmonary chemodectomas. Hum Pathol 6:681–691

Meade JB, Whitwell F, Bickford BJ, Waddington JKB (1974) Primary haemangiopericytoma of lung. Thorax 29:1–15

Mirra SS, Miles ML (1982) Unusual pericytic proliferation in a meningotheliomatous meningioma. An ultrastructural study. Am J Surg Pathol 6:573–580

Nunnery EW, Kahn LB, Reddick RL, Lipper S (1981) Hemangiopericytoma: a light microscopic and ultrastructural study. Cancer 47:906–914

Pena CE (1977) Meningioma and intracranial hemangiopericytoma. A comparative electron microscopic study. Acta Neuropathol (Berl) 39:69–74

Pollard TD, Weihing RR (1974) Actin and myosin and cell movement. CRC Crit Rev Biochem 2:1–65

Schnitt SJ, Vogel H (1986) Meningiomas: diagnostic value of immunoperoxidase staining for epithelial membrane antigen. Am J Surg Pathol 10:640–649

Shin MS, Ho KJ (1979) Primary hemangiopericytoma of lung. Radiology and pathology. Am J Radiol 133:1077–1083

Spain DM (1964) Intrapulmonary chemodectomas in subjects with organizing pulmonary thromboemboli. Am Rev Respir Dis 96:1158–1164

Torikata C, Kawai T, Yakumaru K, Kageyama K (1975) Histopathological studies on the tumourlets of the lung with special reference to the cytogenesis of proliferating cells. Acta Pathol Jpn 25:539–553

Yousem SA, Hochholzer L (1987) Primary pulmonary hemangiopericytoma. Cancer 59:549–555