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Immunohistochemical study of so-called sclerosing haemangioma of the lung

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Summary. To elucidate the histogenesis of sclerosis haemangioma of the lung, we examined 7 cases with the immunoperoxidase method using antibodies against several useful marker antigens; secretory component (SC), cytokeratins, epithelial membrane antigen (EMA) for epithelial cells, factor VIII related antigens (factor VIII) for endothelial cells, vimentin and desmin for mesenchymal cells. The results were compared with those of histologically normal lung tissues. Both the characteristic round cells arranged in sheets, which are present predominantly in the solid area and are reported to be neoplastic, and the flattened cells lining blood lakes show positive staining for EMA only, with negative staining for the other marker antigens. These observations suggest that these cells are derived from epithelium rather than mesothelium or from endothelium, and are analogous to type I pneumocytes. This conclusion is supported by their immunohistochemical characteristics, in comparison with the localization patterns of the marker antigens in normal lung tissues. However, the lining epithelial cells of papillary projections in the papillary area and of ducts in the solid area stained for SC and cytokeratins as well as EMA, and their immunohistochemical characteristics are analogous to those of bronchiolar epithelial cells or type II pneumocytes in normal lung tissues.

Key words: Sclerosing haemangioma – Lung – Immunohistochemistry

Introduction

Sclerosing haemangioma of the lung, an entity first described by Liebow and Hubbell (Liebow and Hubbel 1972), is an uncommon benign neoplasm found predominantly in middle-aged females. Although its histological pat-

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tern is distinct and well defined, the interpretation of the morphological findings is conflicting. Similar cases have been reported previously under different names, such as "fibroxanthoma", "histiocytoma", or "post-inflammatory pseudotumour" (Spencer 1977; Rosai 1981), expressing the authors' interpretations that the basic elements in the tumour are histiocytic and fibrous. Liebow and Hubbell interpreted the tumour by analogy with the sclerosing angioma of the skin, because of the predominance in this lesion of blood vessels and atypical epithelial proliferation accompanied by proliferation of fibrous connective tissue (Liebow and Hubbell 1972). The extraordinary variety of names reflects uncertainty about the histogenesis of the tumour. Several authors have proposed an epithelial or endothelial origin based on the ultrastructural findings (Haas et al. 1972; Hill and Eggleston 1972; Kennedy 1973; Kay et al. 1977; Koide 1979; Palacios et al. 1979; Alverez-Fernandez and Escalona-Zapata 1981).

Recently Katzenstein et al. have described four major histological patterns; solid, haemorrhagic, papillary and sclerotic, and they postulated that the neoplastic cells are considered to be round, relatively uniform blank cells with abundant eosinophilic cytoplasm which are found predominantly in the solid pattern (Katzenstein et al. 1980) and that they are derived from mesothelium, a conclusion based on glycosaminoglycan analysis (Katzenstein et al. 1983).

Although immunohistochemical techniques have an advantage in defining the cellular origin and characteristics of neoplasms in tissue sections, they have not been widely applied to sclerosing haemangioma of the lung. It has been suggested that secretory component (SC), epithelial membrane antigen (EMA) and cytokeratins are useful markers for epithelial cells (Poger et al. 1976; Schlegel et al. 1980; Sloane et al. 1981; Said et al. 1983; Nagura et al. 1983; Blobel et al. 1984), vimentin for mesenchymal cells (Altmannsberger et al. 1981; Gabbiani et al. 1981), desmin for smooth muscle cells (Altmannsberger et al. 1981; Gabbiani et al. 1981) and factor VIII related antigens (factor VIII) for endothelial cells (Mukai et al. 1980; Sehested et al. 1981).

In the present study, the aim was to gain more precise information on the origin of the cells of which these tumours are composed, using the immunoperoxidase method and antibodies against these marker antigens. The evidence obtained in the present study shows that the neoplastic cells in the sclerosing haemangioma of the lung are of epithelial origin, rather than endothelial or mesothelial origin.

Materials and methods

Materials. Seven cases which fulfill criteria for the diagnosis of sclerosing haemangioma of the lung were studied. Three cases (case 1, 2 and 3) were from the files of the Division of Surgical Pathology, Tokai University School of Medicine and four others (case 4, 5, 6 and 7) from Nagoya University Hospital. All specimens from the resected tumours were fixed in 10% formalin for one day, embedded in paraffin, and cut at 4 μm. In two cases (case 6 and 7), the specimens were promptly fixed in periodate-lysine-paraformaldehyde (PLP) (Mclean and Nakane 1974) for 6 h at 4° C, washed in increasing concentrations of sucrose in phosphate-

buffered saline (PBS, pH 7.2), and frozen in OCT compound (Lab-Tek products, Naperville, IL). Histologically normal lung tissues were obtained at the time of surgical removal for bronchogenic carcinoma at Nagoya University Hospital, and fixed in both PLP and 10% formalin.

Antisera. Antisera used as primary antibodies in the present study were summarized in Table 2. For secondary antibodies, horseradish peroxidase(HRP)-labeled goat IgG Fab fragments against rabbit IgG, HRP-labeled rabbit IgG Fab fragments against goat IgG and HRP-labeled rabbit IgG Fab fragments against mouse IgG were prepared in our laboratory as previously described (Shioda et al. 1984).

Immunohistochemistry. The indirect immunoperoxidase method after Nakane (Nakane 1975) was performed using both PLP-fixed, cryostat sections and formalin-fixed, paraffin-embedded sections. The sections were treated with 100% methanol and 0.3% hydrogen peroxide in PBS to inactivate endogeneous peroxidase, and they were then immersed in nonimmune goat serum or rabbit serum, washed in PBS, and reacted with primary antisera for 60 min. For control sections, nonimmune rabbit serum, goat serum or mouse serum was substituted for the primary antisera. After being washed in PBS, the sections were incubated with the HRP-labeled secondary antisera for 60 min. Rinsing with PBS, the sections were reacted with 0.25% diaminobenzidine (DAB) solution containing 10 mM hydrogen peroxide and 10 mM sodium azide, and then counterstained with methyl green. For the detection of cytokeratins and vimentin, paraffin-embedded sections were treated with 0.1% trpysin before the immune reaction with the primary antisera.

Results

General features

The pertinent clinical features and locations of the seven cases observed are summarized in Table 1. The patients were middle-aged females, ranging from 34 to 59 years old (mean age 46).

Grossly the tumours ranged from 1.0 to 5.0 cm in diameter. They were well circumscribed, and had variegated appearance characterized by friable haemorrhagic zones, which were spongy, fleshy and deep red in color, admixed with white and yellow areas. Tumours in six cases were located within the lung parenchyma, and a tumour in case 2 was in an interlobar fissure.

Light microscopic findings

The microscopic findings of each lesion showed a mixture of three or four different histological patterns: solid, haemorrhagic, papillary and sclerotic

Table 1. Clinical features and location

Case	Age	Sex	Symptom	Location	Follow-up
1	57	F	–	RUL	Alive, 7 years
2	41	F	–	Left Interlobar Fissure	Alive, 5 years
3	34	F	–	LUL	Alive, 4 years
4	39	F	–	RUL	Alive, 3 years
5	40	F	–	LUL	Alive, 1 year
6	59	F	–	RLL	Alive, 10 months
7	54	F	–	RLL	Alive, 5 years

RUL: Right upper lobe, RLL: Right lower lobe, LUL: Left upper lobe

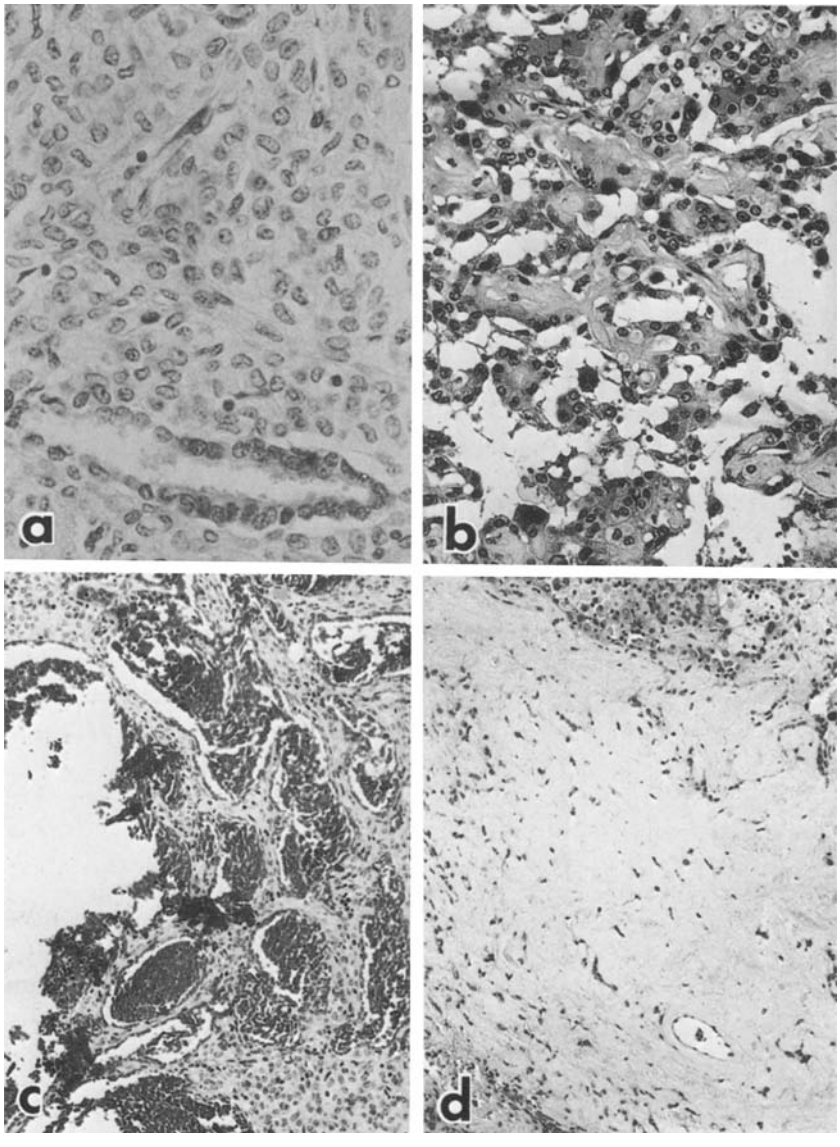

Fig. 1. Light micrographs showing variegated histological patterns of sclerosing haemangioma of the lung: **a** solid (case 2), **b** papillary (case 3), **c** haemorrhagic (case 7), and **d** sclerotic (case 5) patterns

(Fig. 1). The predominant cells, which were arranged in sheets in the solid areas and occasionally between blood-filled spaces or within papillary stalks had lightly stained, round or oval nuclei with abundant eosinophilic cytoplasm (Fig. 1 a–c). In the haemorrhagic areas, numerous blood-filled spaces with a variety of shapes and sizes were found and they were delineated by a single layer of flattened or cuboid or oval cells (Fig. 1 c). Numerous

Table 2. Antibodies used

Primary antibodies	Dilution	Second antibodies	Dilution
Anti-SC, Dako	1:100	HRP-anti-rabbit IgG	1:100
Anti-EMA, Sera-lab	1:200	HRP-anti-goat IgG	1:40
Anti-desmin, Dako	1:100	HRP-anti-rabbit IgG	1:100
Anti-cytokeratins			
Dako	1:300	HRP-anti-rabbit IgG	1:100
Transformation Research	1:100	HRP-anti-rabbit IgG	1:100
Monoclonal anti-cytokeratins			
Immunotech	1:500	HRP-anti-mouse-immunoglobulins	1:40
Labsystems	1:50	HRP-anti-mouse-immunoglobulins	1:40
Sanbio	1:50	HRP-anti-mouse-immunoglobulins	1:40
Monoclonal anti-vimentin			
Labsystems	1:100	HRP-anti-mouse-immunoglobulins	1:40
Transformation Research	1:50	HRP-anti-mouse-immunoglobulins	1:40
Sanbio	1:50	HRP-anti-mouse-immunoglobulins	1:40
Normal mouse serum	1:50	HRP-anti-mouse IgG	1:100
Normal rabbit serum	1:100	HRP-anti-rabbit IgG	1:100
Normal goat serum	1:100	HRP-anti-goat IgG	1:100

Dako: Denmark, Sera-lab: UK, Transformation Research: USA, Immunotech: USA, Labsystems: Finland, Sanbio: Holland

Table 3. Results of staining

Cells	EMA	Cyto-keratins	Vimentin	Desmin	F-VIII
Round cells in solid area	+	−	−	−	−
Lining cells of papillary projections & ducts	+	+	+	−	−
Lining cells of blood-filled spaces	+	−*	−*	−	−
Round or fusiform cells in sclerotic area	+	−	−	−	−

* Partly positive (see text)

papillary projections lined by cuboid or oval cells were seen in the papillary areas (Fig. 1b). Dense sclerotic foci composed of fibrous connective tissue were often found adjacent to the other areas (Fig. 1d). In addition, there was an infiltration of mast cells and haemosiderin- or lipid-laden histiocytes.

Immunohistochemical findings

The results of the immunohistochemical observations are summarized in Table 3. Both formalin-fixed, paraffin-embedded and PLP-fixed, frozen techniques employed in this study equally conserved antigenic reactivity,

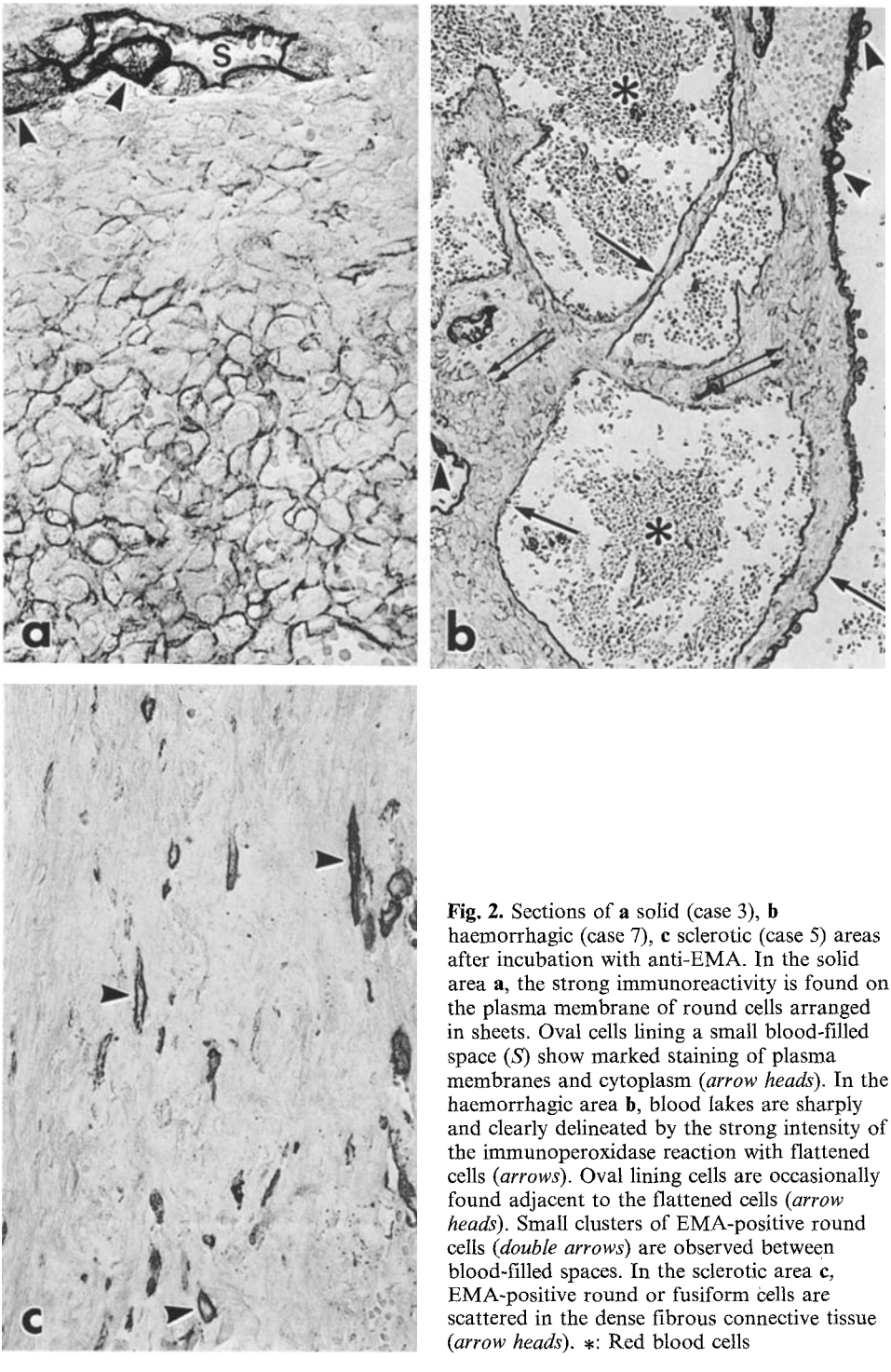

Fig. 2. Sections of **a** solid (case 3), **b** haemorrhagic (case 7), **c** sclerotic (case 5) areas after incubation with anti-EMA. In the solid area **a**, the strong immunoreactivity is found on the plasma membrane of round cells arranged in sheets. Oval cells lining a small blood-filled space (*S*) show marked staining of plasma membranes and cytoplasm (*arrow heads*). In the haemorrhagic area **b**, blood lakes are sharply and clearly delineated by the strong intensity of the immunoperoxidase reaction with flattened cells (*arrows*). Oval lining cells are occasionally found adjacent to the flattened cells (*arrow heads*). Small clusters of EMA-positive round cells (*double arrows*) are observed between blood-filled spaces. In the sclerotic area **c**, EMA-positive round or fusiform cells are scattered in the dense fibrous connective tissue (*arrow heads*). *: Red blood cells

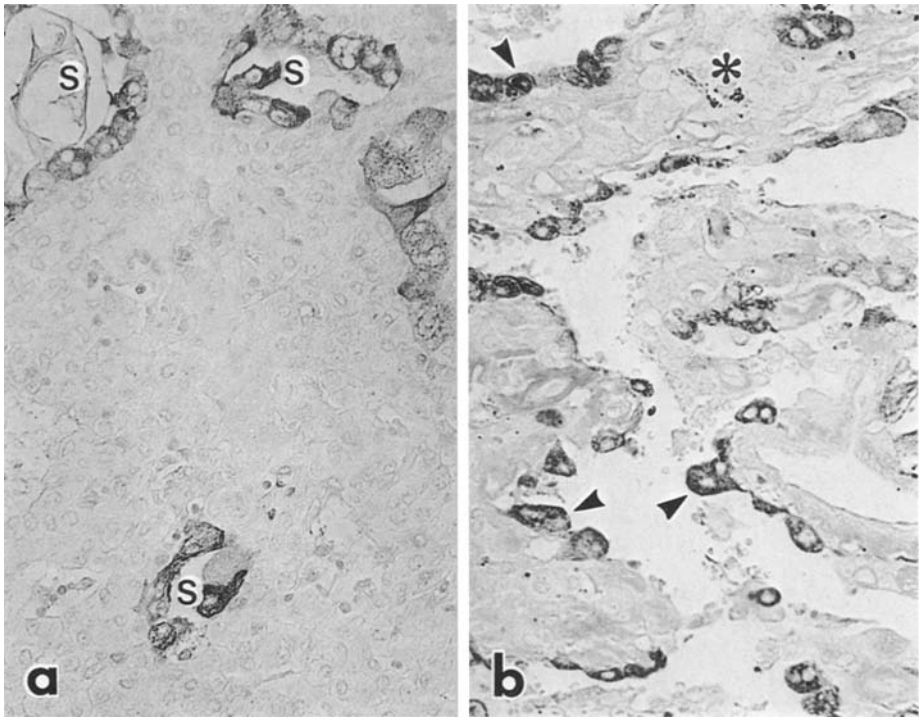

Fig. 3. Sections of **a** solid (case 4) and **b** papillary (case 5) areas after incubation with anti-SC. In the solid area **a**, there is marked staining of cytoplasm of oval or cuboid cells lining the ductal spaces (*S*). The round cells arranged in sheets do not exhibit immunoreaction with anti-SC. In the papillary area **b**, oval cells lining papillary projections show positive staining for SC (*arrow heads*). However, the adjacent round cells in the central stalks show negative staining. *: Granular deposits of haemosiderin

except for factor VIII and vimentin, the antigenecities of which were markedly reduced in formalin-fixed, paraffin embedded sections. Thus to make the immunoperoxidase method applicable for the localization of factor VIII and vimentin, PLP-fixed, cryostat sections were prepared.

Similar localization patterns of all the marker antigens used were obtained in the tissues from the seven examined cases. The neoplastic cells arranged in sheets in the solid areas and occasionally between blood-filled spaces or within papillary stalks exhibited striking staining for EMA only (Fig. 2a and b), but the other marker antigens were not detected in these cells (Figs. 3, 4, 5 and 6).

Although a single layer of flattened cells lining the blood-filled spaces possessed EMA only on the plasma membrane (Fig. 2b), cuboid or oval cells lining the blood-filled spaces showed positive cytoplasmic staining for SC and cytokeratins. They also stained positively for EMA (Fig. 2b). A small number of round or fusiform cells scattered in the sclerotic areas showed positive membranous staining for EMA only (Fig. 2c).

Cuboid or oval cells lining the papillary projections in the papillary

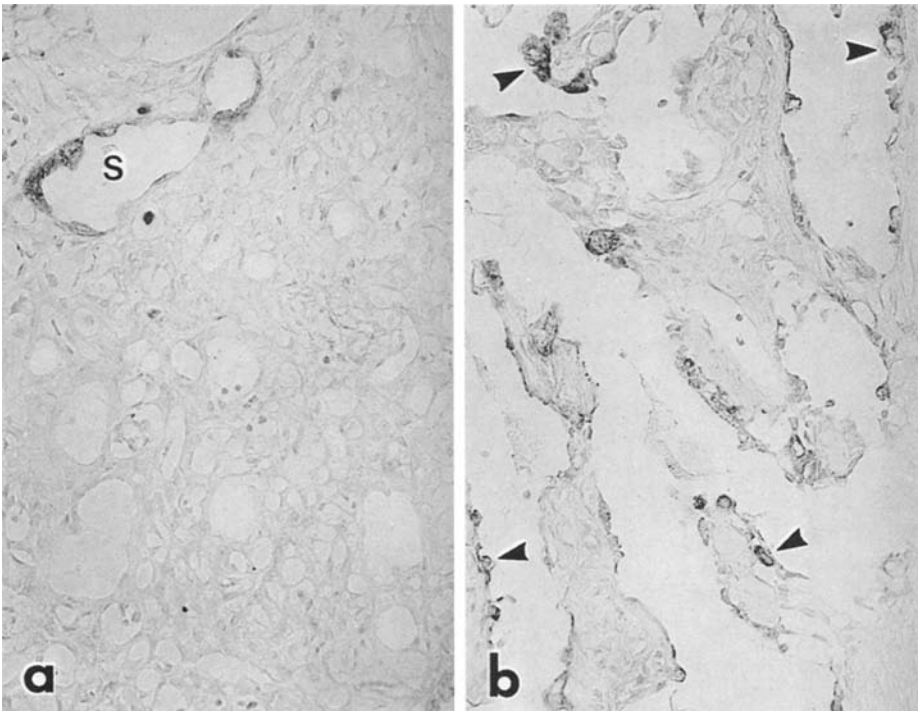

Fig. 4. Sections of **a** solid (case 6) and **b** papillary (case 5) areas after incubation with anti-cytokeratins. In the solid area **a**, there is marked staining of cytoplasm of oval cells lining the ductal spaces (*S*), whereas round cells arranged in sheets show an absence of cytokeratins. In the papillary area **b**, oval or cuboid cells lining the papillary projections show marked cytoplasmic staining (*arrow heads*), whereas small clusters of round cells in the central stalks show negative staining

areas and those of ductal structures in the solid areas exhibited consistent staining for SC, cytokeratins and EMA (Figs. 2a, 3 and 4).

Endothelial cells of the capillaries and small blood vessels in the tumour tissues stained positively for factor VIII (Fig. 5) and vimentin. Inflammatory cells also stained positively for vimentin (Fig. 6). Neoplastic cells with round or oval nuclei arranged in sheets were uniformly negative for factor VIII and vimentin (Figs. 5 and 6). No desmin-positive cells were detected in the tumour tissues.

In histologically normal lung tissues, bronchiolar epithelial cells and type II pneumocytes possessed SC, cytokeratins and EMA, whereas type I pneumocytes had only EMA. Hyperplastic mesothelial cells showed weak membranous staining for EMA and strong cytoplasmic staining for cytokeratins. Mesenchymal cells were positive for vimentin, and endothelial cells were positive for factor VIII. Smooth muscle cells of vessels positively stained for desmin.

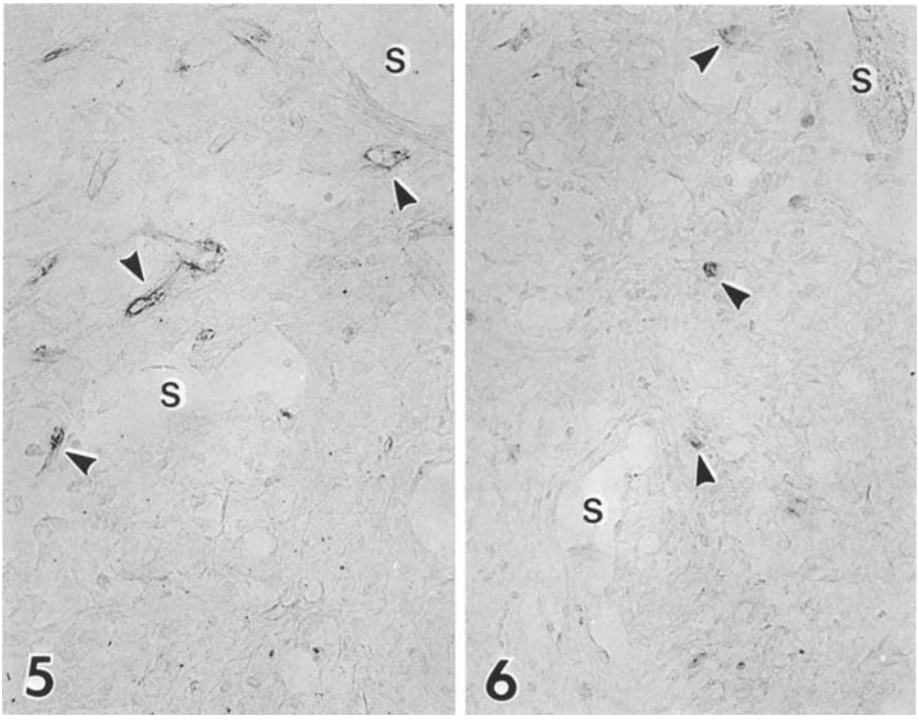

Fig. 5. Immunoperoxidase staining of the tumour (case 6) using a PLP-fixed, cryostat section with anti-factor VIII. Neither lining cells of blood or ductal spaces (*S*) nor round cells arranged in sheets possess factor VIII. However, endothelial cells of small blood vessels embedded in the tumour tissue show positive staining (*arrow heads*)

Fig. 6. Immunoperoxidase staining of the tumour (case 6) using a PLP-fixed, cryostat section with anti-vimentin. Neither round cells arranged in sheets nor lining cells of blood or ductal spaces (*S*) show an absence of vimentin. Inflammatory cells show positive staining (*arrow heads*)

Discussion

Sclerosing haemangioma of the lung is a distinct benign neoplasm with four characteristic histological patterns; solid, haemorrhagic, papillary and sclerotic in different proportions (Katzenstein et al. 1980). The common and predominant features in all cases observed were the presence of uniform round cells with pale or eosinophilic cytoplasm and round or oval nuclei (Haas et al. 1972; Hill and Eggleston 1972; Kennedy 1973; Koide et al. 1979; Palacios et al. 1979; Katzenstein et al. 1980; Alverez-Fernandez and Escalona-Zapata 1981). These cells are considered to be neoplastic (Koide 1979; Katzenstein 1980) and are found to be arranged in sheets in the solid areas, between blood lakes and within papillary stalks.

In spite of the distinction of the histological features and neoplastic nature of the round cells, previous ultrastructural studies of the tumour

have produced conflicting results; some authors favor an epithelial origin (Hill and Eggleston 1972; Kennedy 1973; Palacios et al. 1979; Koide 1979; Alverez-Fernandez and Escalona-Zapata 1981), while others favor an endothelial origin (Liebow and Hubbell 1956; Haas et al. 1972; Kay et al. 1977). Recently a mesothelial origin was also suggested based on glycosaminoglycan analysis in addition to ultrastructural observations (Katzenstein et al. 1983).

In our immunohistochemical study, the neoplastic cells in the tumour possessed EMA only, but no SC or cytokeratins marker antigens for epithelial cells, nor factor VIII for endothelial cells, nor vimentin and desmin for mesenchymal cells. EMA positivity of the neoplastic cells suggests epithelial derivation of sclerosing haemangioma of the lung (Sloane et al. 1981; Sloane et al. 1983) and does not favor endothelial derivation. Although there are a few reports describing EMA localization in lymphoma cells and plasma cells (Delsol et al. 1984; Sloane et al. 1983), no evidence for positive staining of endothelial cells is present. The neoplastic cells in question do not possess the characteristics of lymphoid cells according to the previous observations (Haas et al. 1972; Hill and Eggelston 1972; Katzenstein et al. 1983; Kay et al. 1977; Kennedy 1973; Koide 1979; Palacios et al. 1979). The negativity of vimentin and factor VIII also does not favor the endothelial derivation (Altmannsberger et al. 1981; Gabbiani et al. 1981; Mukai et al. 1980; Sehested et al. 1981).

In histologically normal lung tissues all epithelial cells including bronchiolar epithelial cells, respiratory bronchiolar cells, type I and type II pneumocytes showed striking positive staining for EMA (Sloane et al. 1981; Sloane et al. 1983). Hyperplastic mesothelial cells stained weakly for EMA (Sloane et al. 1981; Sloane et al. 1983) but exhibited strongly positive staining for cytokeratins as previous investigators have already shown (Schlegel et al. 1980; Corson and Pinkus 1982; Said et al. 1983). It is therefore doubtful that the neoplastic cells in sclerosing haemangioma of the lung are of mesothelial cell origin.

Several authors, in ultrastructural studies, suggested that sclerosing haemangioma of the lung is composed predominantly of epithelial elements and is derived from primitive respiratory epithelium (Hill and Eggleston 1972; Palacios et al. 1979). In the present study, the immunohistochemical characteristics of the neoplastic cells are identical to those of type I pneumocytes, and Koide has also reported that they possess the feature of type I pneumocytes at the ultrastructural level. However, they show little similarity to the characteristics of bronchiolar epithelial cells and type II pneumocytes because of the absence of SC and cytokeratins (Haimoto et al. 1984; Blobel et al. 1984). Thus, it is reasonable that the neoplastic round cells in question originate from primitive epithelial cells which are analogous to type I pneumocytes in immunohistochemical characteristics, although differentiation of type II pneumocytes as progenitor cells to type I pneumocytes in alveoli is now a generally accepted view (Adamson and Bowden 1974). Further immunohistochemical analysis of the development of the human embryonal lung and of lungs with alveolar damage should be performed.

In the haemorrhagic areas, numerous dilated blood lakes are lined by a single layer of flattened cells resembling type I pneumocytes in shape and possessing only EMA. Their immunohistochemical features are also similar to the neoplastic round cells and type I pneumocytes of normal lung tissues. Particularly in case 1, 5 and 7, the lining cells of dilated blood lakes show more proliferation when compared with the other three components. Therefore, they may also be thought to be neoplastic. However, a few oval cells intermingled with the flattened lining cells of blood lakes, superficial lining epithelial cells of the papillary projections and epithelial cells of the ductal structures in the solid areas showed positive staining for SC and cytokeratins as well as EMA. Recently these epithelial cells have been also reported to possess surfactant apoprotein by an immunohistochemical study (Singh et al. 1984). Accordingly we suggest that these cells are proliferated bronchiolar epithelial cells or type II pneumocytes, because of the similarity of the presence of marker antigens with bronchiolar epithelial cells and type II pneumocytes in the normal lung (Blobel et al. 1984; Haimoto et al. 1984; Sloane et al. 1983). In addition there are apparent ultrastructural differences between these cells and the neoplastic round cells as shown by other investigators (Kennedy 1973; Koide 1979; Palacios et al. 1979; Katzenstein et al. 1983). However, it is uncertain whether these components are neoplastic or not. If they are neoplastic, the cells are considered to possess a capability to differentiate toward bronchiolar epithelial cells or type II pneumocytes.

Based on our present study, which is the first systematic immunohistochemical survey of sclerosing haemangioma of the lung, it is reasonable to propose that the neoplastic cells in the tumour originated from epithelial cells and are analogous to type I pneumocytes in their immunohistochemical characteristics.

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