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S-100 protein-positive Langerhans cells in various human lung cancers, especially in peripheral adenocarcinomas

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Summary. The appearance of S-100 protein-positive Langerhans cells was studied in 90 cases of various lung cancers by an immunohistochemical method. S-100 protein-positive dendritic cells were frequently observed in many adenocarcinomas, especially in those subclassified as bronchiolar cell or type II alveolar cell type. However, no S-100 protein-positive cells were found in "goblet cell type" adenocarcinoma. In some cases of squamous cell carcinoma and large cell carcinoma, these dendritic cells were also observed though they were fewer in number. In all cases of small cell carcinoma, however, S-100 protein-positive dendritic cells were rare. Electron microscopic study of two adenocarcinomas clearly demonstrated many Birbeck granules in the cytoplasm of S-100 protein-positive dendritic cells and confirmed that S-100 protein-positive cells in lung cancer were identical with Langerhans cells.

Key words: S-100 protein – Langerhans cells – Lung cancer – Adenocarcinoma – Immunohistochemistry

Introduction

The Langerhans cell, first described by P. Langerhans in 1868, is a peculiar dendritic cell of unknown nature. In early studies of Langerhans cells, many authorities believed that they were related to the peripheral nervous system or to melanocytes (Zelikson 1965). However, Breathnach et al. (1968) concluded that Langerhans cells did not belong to the melanocyte cell lineage, and that they did not stem developmentally from the neural crest. Although many theories concerning the origin of Langerhans cells have been proposed, the most convincing theory until recently was that Langerhans cells belonged to the mononuclear phagocyte system.

Langerhans cells were demonstrated not only to bear Fc and C3 recep-

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Table 1. Appearance of S-100 protein-positive Langerhans cells in various lung cancers

Classification of lung cancer	No. of cases			
	++[a]	+[a]	−[a]	total
Small cell carcinoma	0	0	22	22
Large cell carcinoma	1	4	8	13
Squamous cell carcinoma	2	9	5	16
Adenocarcinoma				
Goblet cell type	0	0	8	8
Bronchial gland type	1	0	0	1
Type II alveolar type	2	1	1	4
Non-ciliated bronchiolar cell type	8	4	4	16
Bronchial non-goblet cell type	1	0	4	5
Moderately or poorly differentiated	2	0	3	5
Total				90 cases

[a] The number of S-100 protein-positive cells observed. (++: over 10 cells, +: 2–9 cells, −: less than 1 cells/high power field of light microscopy)

tors (Stingle et al. 1977) and Ia-like antigen (Rowden et al. 1977) on the cell surface, but also to be positive for non-specific esterase, acid phosphatase and ATPase in the cytoplasm (Berman and France 1979). Furthermore, bone marrow transplantation experiments in the mouse confirmed that Langerhans cells originated from the bone marrow (Katz et al. 1979). These results strongly suggested that Langerhans cells were a subpopulation of mononuclear-phagocyte system.

However, the demonstration of S-100 protein in the cytoplasm (Cocchia et al. 1981; Nakajima et al. 1982a, b, c) and the presence of T6 antigen on the cell surface (Fithian et al. 1981) in human Langerhans cells contradicts the previous hypothesis. Both S-100 protein and T6 antigen have also been shown to be present in interdigitating cells of the lymphoid tissue and histiocytosis X cells (Takahashi et al. 1981; Nakajima et al. 1982b, c; Murphy et al. 1983), of which the cell lineage, including Langerhans cells, rarely shows any phagocytic activity, in contrast to ordinary macrophages which apparently belong to mononuclear phagocyte system.

We have investigated the distribution of S-100 protein in various human tumours (Nakajima et al. 1982b) and recently found that many S-100 protein-positive dendritic cells were present in certain human lung cancers. In this paper, we describe the appearance of S-100 protein-positive Langerhans cells in various human lung cancers and discuss the close relationship between certain types of lung cancer, particularly of peripheral adenocarcinomas, and Langerhans cells.

Materials and methods

Immunohistochemistry for S-100 protein. Ninety primary lung cancers of various histological types were collected from the pathology files of the National Cancer Center Hospital. Tumour

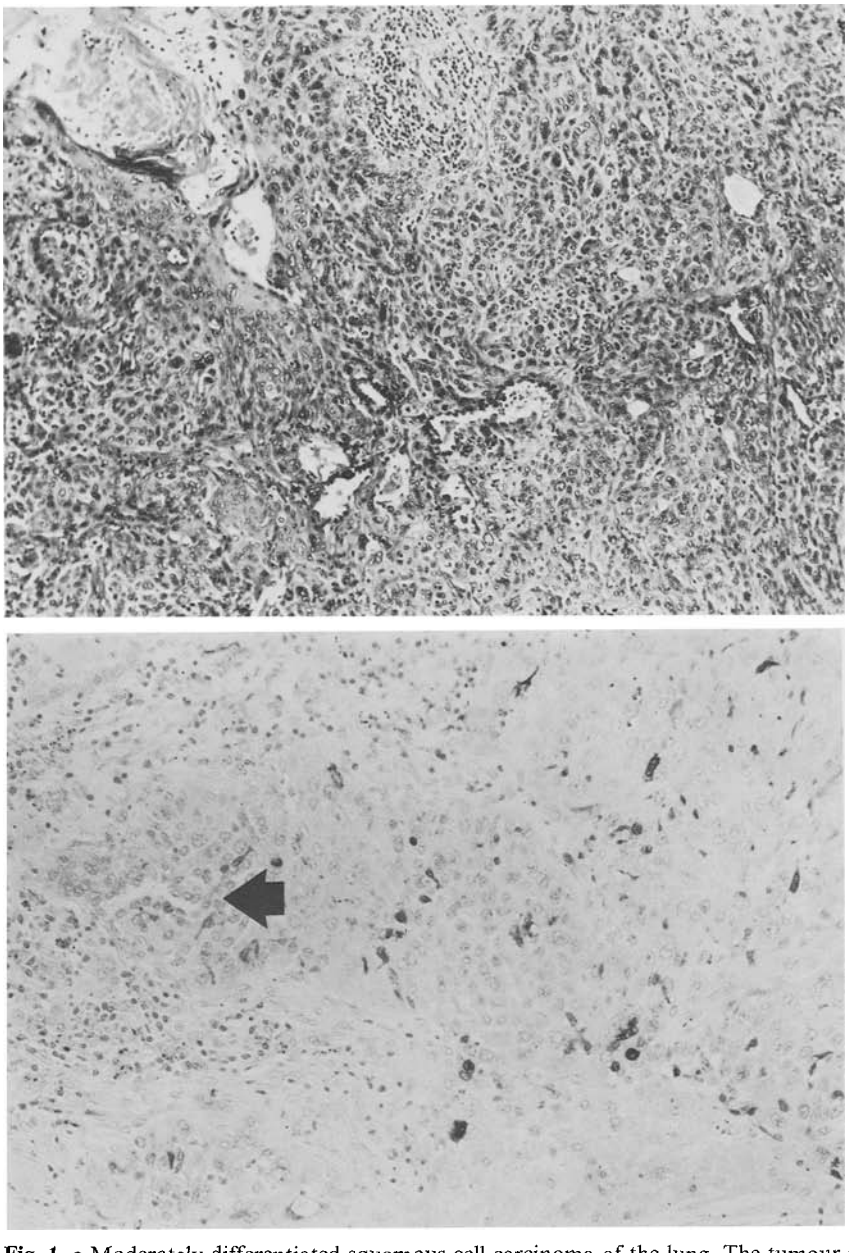
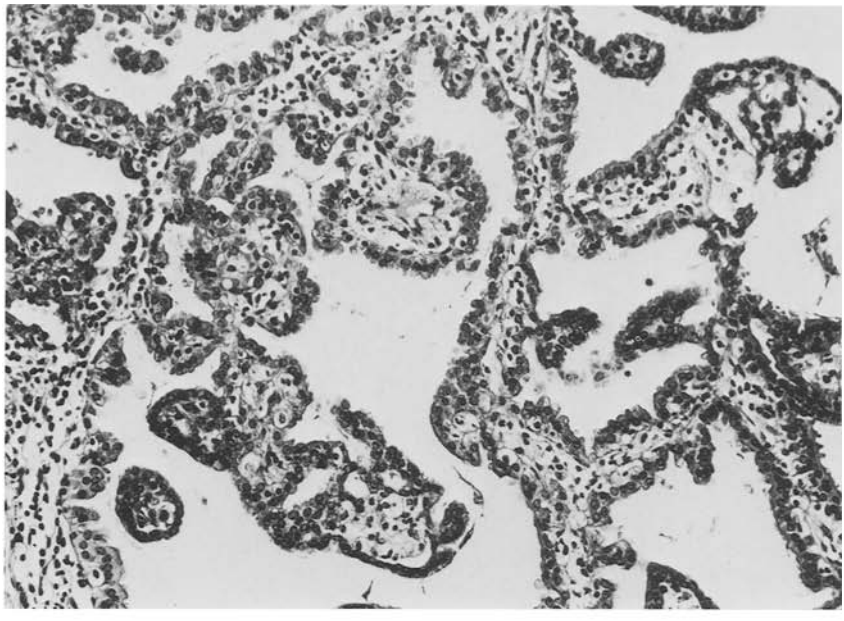
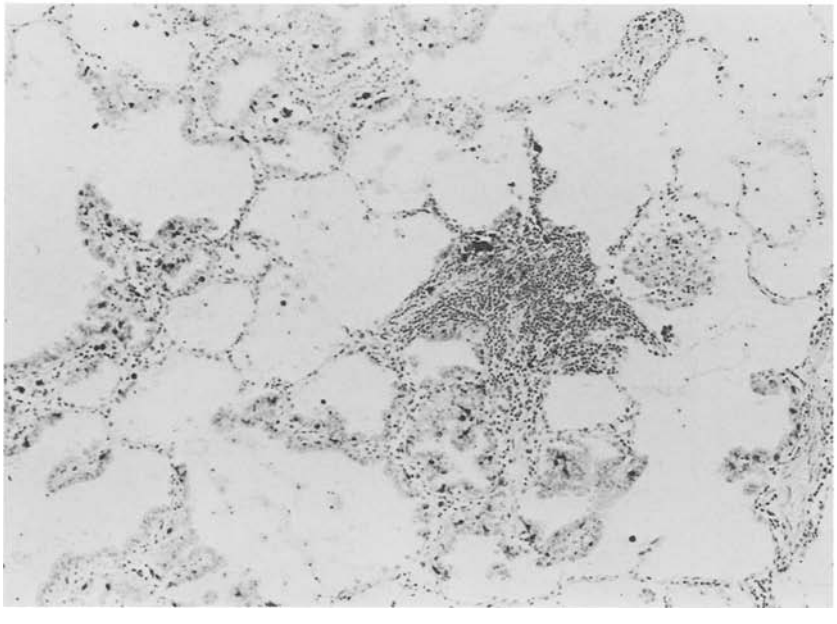


Fig. 1. a Moderately differentiated squamous cell carcinoma of the lung. The tumour involves much hyperplastic alveolar epithelium. Haematoxylin & eosin. × 75 **b** S-100 protein immunohistochemistry of squamous cell carcinoma. Several S-100 protein-positive dendritic cells are present in squamous cell carcinoma cells. The arrow indicates an area of involved hyperplastic cuboidal alveolar epithelium. Lightly counterstained with haematoxylin. × 150



a



b

Fig. 2. a Well differentiated adenocarcinoma subclassified as type II alveolar cell type. Haematoxylin & eosin. ×150. **b** In the periphery of the tumour, numerous S-100 protein-positive cells appear in the carcinoma cell invading alveoli, but not in the intact alveoli. Lightly counterstained with haematoxylin. ×75. **c** Higher magnification reveals that S-100 protein-positive cells are invading the carcinoma cells or are in the interstitium of the alveoli. Lightly counterstained with haematoxylin. ×300

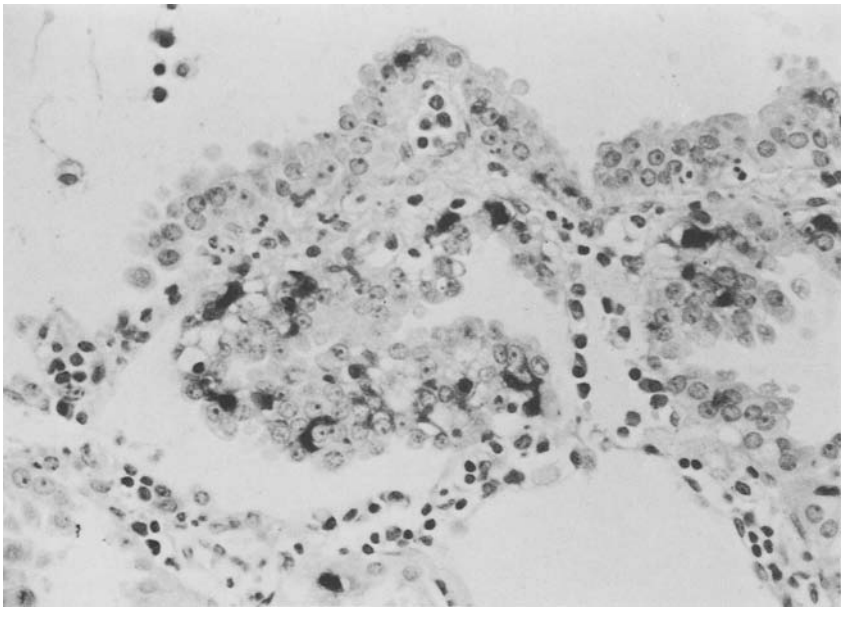


Fig. 2c

tissues were fixed in 15% formalin and embedded in paraffin for routine surgical pathology. Three micron thick paraffin sections were cut from each block from the 90 cases and used for light microscopy and immunohistochemical studies for S-100 protein.

After deparaffinization with xylene, the sections were soaked in absolute methanol solution containing 0.3% H_2O_2 for 30 min at room temperature to eliminate endogenous peroxidase activity. Subsequently these were treated with 10% normal goat serum in tris phosphate buffered saline, pH 7.6, for 30 min at room temperature before the first antibody reaction. Affinity purified anti-bovine S-100 protein rabbit IgG was detailed in a previous paper (Nakajima et al. 1982b) and was used as the primary antibody at a concentration of 0.5 μg/ml. The sections were reacted with the first antibody overnight at 4° C. Second antibody and avidin biotin peroxidase complex (ABC) were purchased from Vector Laboratory, USA, and the dilution and incubation time were as described by the staining procedure of the VECTASTAIN ABC KIT. Finally, the sections were colored with 0.05 M ammonium acetate citric acid buffer containing 30 mg/100 ml of 3,3′-diaminobenzidine tetrahydrochrolide and 0.005% H_2O_2 for about 5 min. To facilitate light microscopic observation, the sections were counterstained with haematoxylin and mounted in plastic embedding materials.

The method of the control study was the same as described in a previous paper (Nakajima et al. 1982b).

Simultaneous immunocytochemical light microscopic and ultrastructural study of S-100 protein-positive cells. Two adenocarcinoma cases containing many S-100 protein-positive cells by light microscopic immunohistochemistry were selected for electron microscopic study. Tumours were fixed with 2.5% glutaraldehyde for 1.5 h at 4° C and post-fixed with 1% OsO_4 for 1 h. Then they were embedded in Epon 812 after dehydration.

A semithin section (1–2 μm in thickness) and an adjacent ultrathin section of the same field were cut by LKB ultratome for simultaneous light and electron microscopic study of S-100 protein-positive cells. The plastic of semithin sections was removed by saturated potassium hydroxide and treated with 3% hydrogen peroxide for 10 min. They were then stained for S-100 protein by PAP immunohistochemistry for S-100 protein, for which detailed methods are described elsewhere (Tsumuraya and Kameya 1982). After observation and photography of the immunocytochemically stained cells in the semithin section, ultrathin sections were

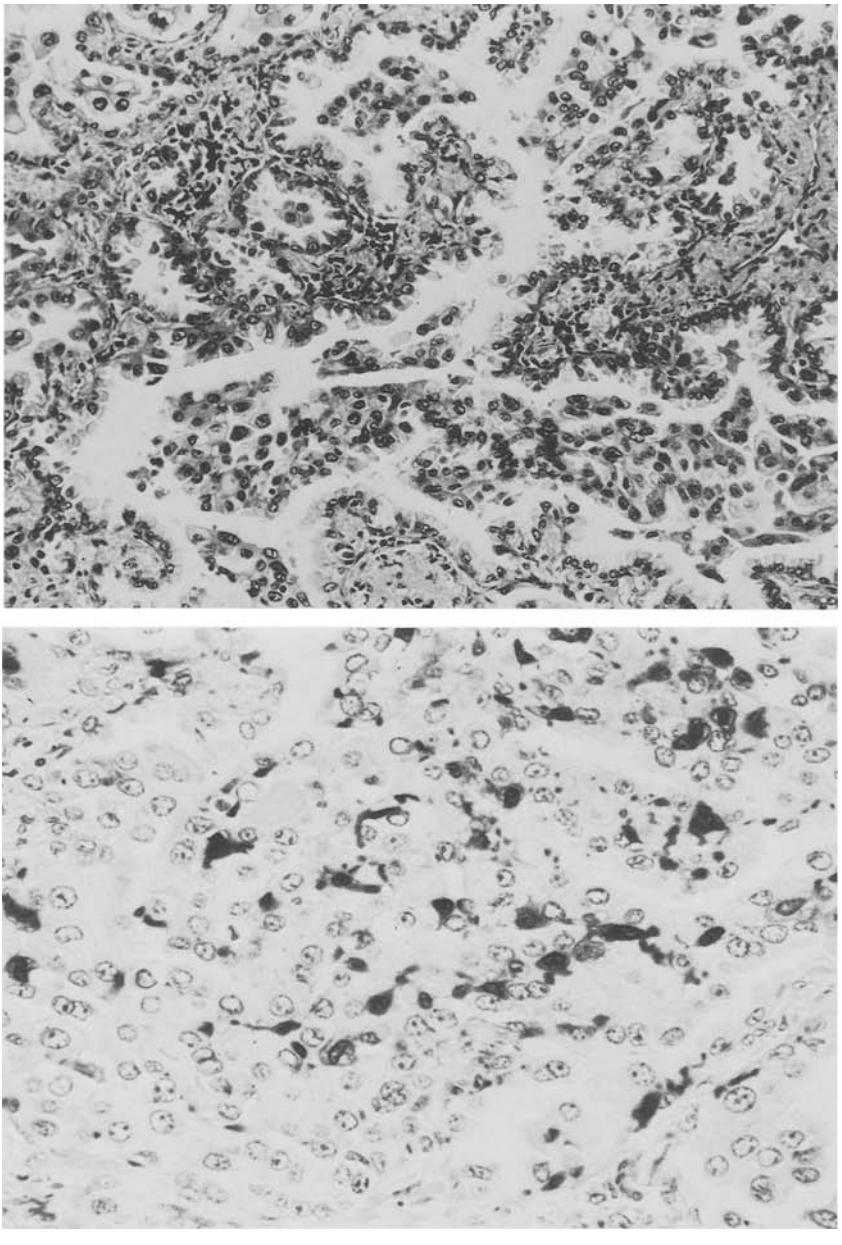


Fig. 3. **a** Well to moderately differentiated adenocarcinoma subclassified as bronchiolar cell type. Haematoxylin & eosin. × 150 **b** Numerous S-100 protein-positive cells extend cytoplasmic processes among carcinoma cells. S-100 protein immunoreaction product covers both nuclei and the cytoplasm. Lightly counterstained with haematoxylin. × 300

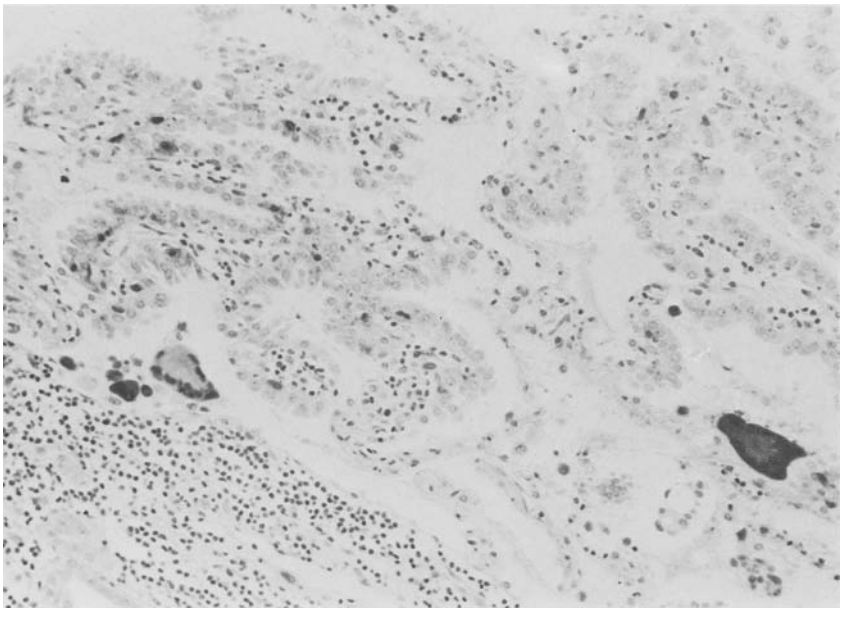


Fig. 4. S-100 protein positive-multinucleated giant cells are observed in a case of adenocarcinoma. The shape resembles Langhans type giant cells. Lightly counterstained with haematoxylin. ×150

doubly stained with uranium acetate and lead citrate and examined for positively immunostained cells in the photographed area by a Hitachi H-600 microscope.

Results

The lung cancers investigated in this study were classified histologically according to the WHO classification. In particular, adenocarcinomas were further subclassified by morphological similarities to the normal bronchial, bronchiolar and alveolar epithelia in accordance with Shimosato's classification (Shimosato et al. 1983). The large number of adenocarcinomata studied were well differentiated and were subclassified into the following classes; bronchial non-goblet cell type, goblet cell type, bronchial gland type, non-ciliated bronchiolar cell type (Clara cell type), type II alveolar epithelial cell type. Others were moderately or poorly differentiated type. The relationship between the histological type of lung cancer and the appearance of S-100 protein-positive cells is summarized in Table 1.

In small cell carcinoma of the lung, S-100 protein-positive cells were rarely observed in any fields of tumour nests. Chronic inflammatory cell reaction around the tumour cell nests was also rarely observed.

In large cell carcinoma and squamous cell carcinoma, S-100 protein-positive dendritic cells were frequently observed in one of 13 cases and two of 16 cases, respectively (Fig. 1). In general, S-100 protein-positive cells tended to appear less frequently in these types of lung cancer. No clear

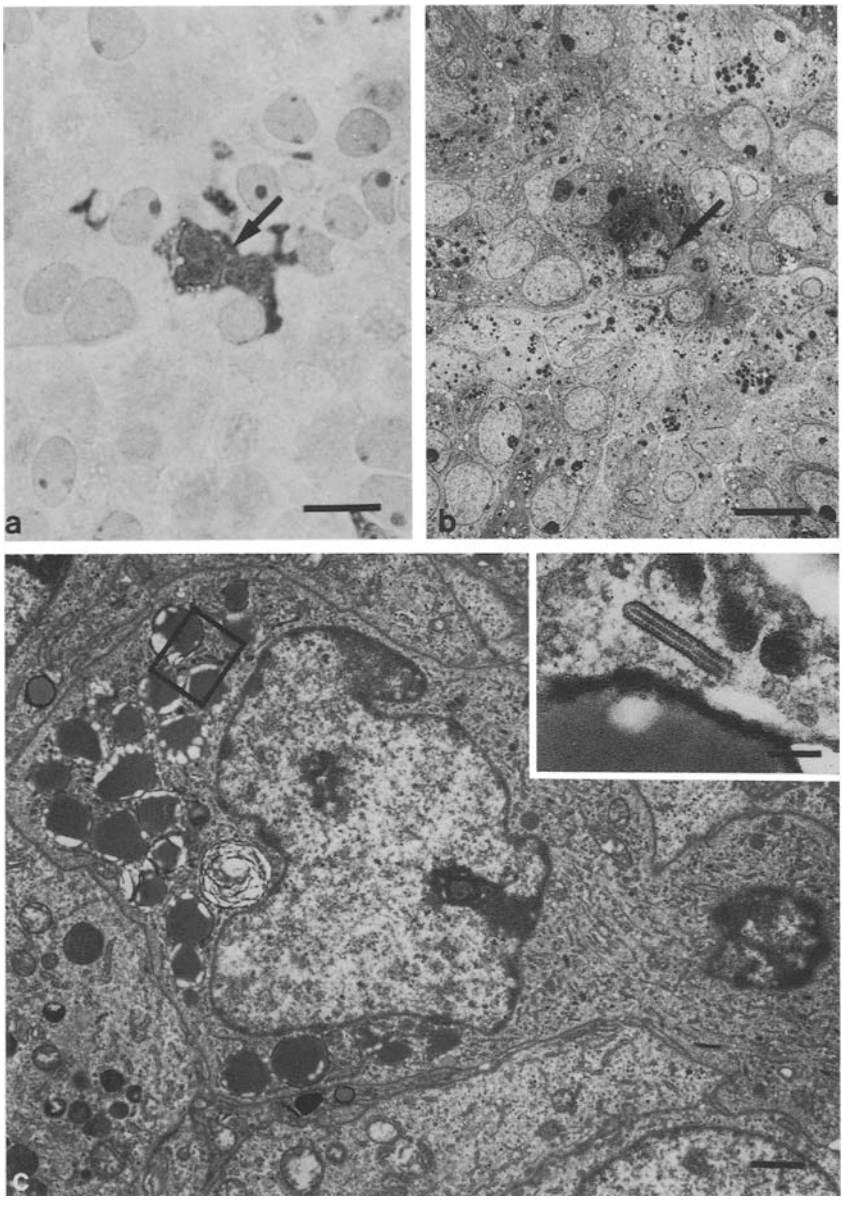


Fig. 5a–c. Simultaneous immunocytochemical and ultrastructural study of S-100 protein-positive cells in adenocarcinoma. **a** Light microscopic immunohistochemistry using Epon-embedded tumour tissue reveals S-100 protein positive cells (*arrow*) among carcinoma cells. The immunostain covers both nucleus and cytoplasm. (×1,000, Scale; 10 μm). **b** Using ultrathin section adjacent to the semithin section used for light microscopic immunohistochemistry, the same field is seen as shown in (**a**). The arrow indicate the S-100 protein positive cell as in (**a**). (×1,000, Scale; 10 μm). **c** Higher power view of the S-100 protein positive cell shows irregular nucleus with heterochromatin and many lipid droplets, several small mitochondria and microtubules in the cytoplasm. (×7,000, Scale; 1 μm). The *inset* is a higher magnification of the ares marked by a square and shows typical trilaminar Birbeck granule (×70,000, Scale; 0.1 μm)

relationship between the degree of keratinization and the appearance of S-100 protein-positive cells was noticed in squamous cell carcinoma.

In 10 out of a total of 20 cases of both non-ciliated bronchiolar cell type and type II alveolar cell type adenocarcinoma, numerous S-100 protein-positive dendritic cells appeared among tumour cells, in the interstitium of the tumour and in alveolar space (Figs. 2, 3). S-100 protein-positive cells were usually present in the periphery rather than the central part of the tumour. In a case of type II alveolar cell type adenocarcinoma, S-100 protein-positive cells were present in alveolar spaces and formed multinucleated cells resembling the Langhans type giant cell (Fig. 4). S-100 protein positive cells were also present in the inflammatory area in and outside the tumour, where lymph follicles were sometimes seen. Numerous S-100 protein-positive cells also appeared in several cases of bronchial non-goblet cell type, bronchial gland type and moderately to poorly differentiated adenocarcinoma. However, no S-100 protein-positive cells were found in adenocarcinomas of the goblet cell type.

S-100 protein-positive cells present in lung cancers were usually dendritic in shape and extended several long cytoplasmic processes among cancer cells. The nuclei of S-100 protein-positive cells were characteristically tortuous or irregular and usually showed deep nuclear indentation. By immunohistochemistry, S-100 protein staining covered both cytoplasm and nuclei diffusely. However, some cells lacked nuclear staining. The staining intensity varied from cell to cell.

Comparison of electron microscopy and light microscopic immunohistochemistry for S-100 protein was performed on adjacent sections of two non-ciliated bronchiolar cell type adenocarcinomas. These were selected by previous immunohistochemistry for S-100 protein. The semithin section cut from Epon embedded tumour materials revealed well-preserved antigenicity of S-100 protein and S-100 protein-positive dendritic cells were clearly demonstrated as in previous immunohistochemistry studies using paraffin sections (Fig. 5a). Electron microscopic observation of the ultrathin section adjacent to the immunostained semithin section revealed that S-100 protein-positive cells in the semithin sections were slightly electron lucent when compared with nearby carcinoma cells, and extended long cytoplasmic processes (Fig. 5b, c). In their cytoplasm, many rod-shaped trilaminar granules were observed and were morphologically identical to Birbeck granules (Fig. 5c, inset). They also contained many lipid droplets, well-developed Golgi apparatuses, and occasional microtubules and centrioles in the cytoplasm. No cell attachment devices were found.

Discussion

Since the Birbeck granule is a hallmark of Langerhans cells (Birbeck et al. 1961) electron microscopy has been greatly utilized for the study of these cells. Langerhans cells are now known to be distributed not only in the epidermis (Birbeck et al. 1961; Zelickson 1965) and various lymphoid tissues (Jimbow et al. 1969; Vernon et al. 1973; Thorbecke et al. 1980), but also

in various other organs and tissues of the human body such as the oesophagus (Yaassin and Toner 1976), cornea (Sugiura and Matsuda 1969), uterus (Younes et al. 1968), and others (Tobe et al. 1982). Furthermore, these cells were found in histiocytosis X (Basset et al. 1965), adnexal tumours such as spiradenoma (Castro and Winkelmann 1977) and dermal cylindroma (Headington et al. 1977), pleomorphic adenoma of submandibular gland (David and Buchner 1980), and even in cancer cells diagnosed as malignant fibrous histiocytoma (Tsuneyoshi and Enjoji 1979) and squamous cell carcinoma (Lonig et al. 1982).

In 1974, Basset et al. first reported that large numbers of Langerhans cells were present in a bronchiolar-alveolar tumour of the lung and suggested that the presence of Langerhans cells in the normal lung might render more explicable the characteristic features of the pulmonary lesions of histiocytosis X. Later, Hammer et al. (1980) observed Langerhans cells electron microscopically in 7 out of 37 cases of bronchio-alveolar carcinoma of the lung. Previous studies attempting to detect these cells in lung cancer consisted only of electron microscopy to find Birbeck granules as a hallmark of Langerhans cells. However, recently T6 monoclonal antibody has been used to identify Langerhans cells and their probable precursors in lung cancer (Watanabe et al. 1983).

In this study, S-100 protein-positive dendritic cells were observed in many lung cancers and were recognized to be morphologically similar to Langerhans cells of the epidermis. In human epidermis, Langerhans cells have been already shown to be positive for S-100 protein (Cocchia et al. 1981; Nakajima et al. 1982a, b, c). Our electron microscopic observation of S-100 protein-positive cells in human lung adenocarcinomas clearly demonstrated many characteristic Birbeck granules in the cytoplasm, indicating that the S-100 protein-positive cells in lung cancer were identical to Langerhans cells of the epidermis. S-100 protein immunohistochemistry has great advantages in the detection of Langerhans cells in paraffin-embedded human tissues, as has T6 and HLA-DR antigen immunohistochemistry using frozen sections (Watanabe et al. 1983; Long et al. 1982).

Our study added several new findings to the appearance of Langerhans cells in lung cancers. Firstly, well differentiated adenocarcinoma, subclassified as non-ciliated bronchiolar cell type and type II alveolar cell type, contained many Langerhans cells, these results corroborating previous electron microscopic findings. Kimula et al. (1978) reported that the majority of bronchio-alveolar cell carcinomas were identical to adenocarcinoma of non-ciliated bronchiolar cell type, but some were classified as bronchial gland type and bronchial goblet cell type. It is noteworthy that no Langerhans cells were present in goblet cell type adenocarcinoma, a cell type of bronchiolo-alveolar carcinoma. Secondly, the appearance of Langerhans cells was not an unusual phenomenon in large cell carcinoma and squamous cell carcinoma. Lastly, Langerhans cells were rarely found in small cell carcinomas investigated in this study.

Reports concerning the distribution of Langerhans cells in non-neoplastic lung tissue are few in number. Basset et al. (1976) reported that Langerhans cells were scattered in alveolar interstitium, generally below or between

hyperplastic type II pneumocytes in biopsied lung tissue from patients of usual interstitial pneumonia and desquamative interstitial pneumonia. Kawanami et al. (1981) investigated many fibrotic lung disorders electron microscopically and also found Langerhans cells in the proliferating epithelial layer of bronchioles and alveoli and in association with cuboidal epithelial cells of bronchioles and type II alveolar cells in normal lung. Summarizing these data, Langerhans cells are usually present in the bronchiolo-alveolar level and any closely related to type II alveolar cells or bronchiolar cells in normal and damaged lung tissue. Thus, in the neoplastic condition, it is easily comprehensible that Langerhans cells appear frequently in peripheral type adenocarcinoma of the lung subclassified as bronchiolar or type II alveolar cell type.

In this study, the appearance of Langerhans cells seemed to be related to the presence of chronic inflammation. The frequent appearance of Langerhans cells has already been described in a certain type of pneumonia and in fibrotic lung disease (Basset et al. 1976; Kawanami et al. 1981). Furthermore, rare Langerhans cells were observed in all cases of small cell carcinoma in this study, in which inflammatory cells were rare. Lonig et al. (1982) showed that Langerhans cells in the epidermis or oral mucosa changed in number and arrangement not only in neoplastic conditions, but also in inflammatory conditions, using the immunohistochemistry for T6, HLA-DR antigen and vimentin filament. These facts indicate Langerhans cells are carried by the blood stream from the bone marrow as previously confirmed by Katz's experiment (1979).

The nature of Langerhans cell is still obscure. The major function of this cells is now thought to be the antigen presentation and the detection of alloantigen (Green et al. 1980; Stingle et al. 1980). They also have a close relationship to T-lymphocytes (Rausch et al. 1977). Our previous study showed that S-100 protein-positive cells were mainly distributed in the paracortical area of various lymphoid organs, indicating a close relation to T-lymphocyte (Nakajima et al. 1982c).

In conclusion, the present study shows that Langerhans cells have a more intimate affinity to adenocarcinoma of the lung, especially of the non-ciliated bronchiolar cell type and type II alveolar epithelial cell type, than to the other histological types of lung cancer. It is necessary to investigate the mutual interaction between Langerhans cells and the bronciolo-alveolar epithelium, and such study will be helpful to clarify the true nature of Langerhans cells.

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