Case Report

Intravascular Bronchiolo-alveolar Tumor (IVBAT)
—Case Report with the Immunological Analysis—

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A case of intravascular bronchiolo-alveolar tumor, a rare lung neoplasm which is often found among women, is reported. Our ultrastructural findings and existence of factor VIII-related antigen support the hypothesis of vascular origin. The relationship between IVBAT and epithelioid hemangioendothelioma is discussed. We also examined whether immunological abnormalities existed in our patient, because tuberculin test gave negative result in many cases reported previously and our case. No specific immunological change was found except for negative tuberculin test.

Key Words: Intravascular bronchiolo-alveolar tumor, Factor VIII-related antigen, Weibel-Palade body, Epithelioid hemangioendothelioma.

In 1975, Dail and Liebow firstly reported twenty cases of a previously undescribed peculiar lung tumor as intravascular bronchiolo-alveolar tumor (IVBAT)1. Since their abstract, some cases have been described2-11. The histogenesis of this tumor has not been clearly settled, but recent electron microscopic studies by Corrin et al.2 and Weldon-Linne et al.6 have suggested that these tumors could originate from the endothelium of pulmonary vasculature. We report a characteristic case of this rare tumor with some immunological data and discuss the relationship between "IVBAT" and "Epithelioid hemangioendothelioma"12.

CASE REPORT

In 1983, a 40-year-old Japanese woman, a house wife, underwent a routine lung screening test and was found to have an abnormal shadow on her chest roentgenogram. In July 1983, she was admitted to Tokyo University Hospital with no symptoms for evaluation. She had no special past, family, smoking and occupational histories. Her chest roentgenogram showed multiple (about 80 in number) small nodules uniformly distributed throughout both lung fields (Figure 1). These nodules ranged from 0.3-0.5 cm in diameter. No calcification or hilar adenopathy was noted. Her physical examination was completely within normal limits. The erythrocyte sedimentation rate was 6 mm in the first hour. Other laboratory data including urinalysis, complete blood count, liver and renal function tests, electrolyte concentration and C-reactive protein value were all within normal limits. The serum level of angiotensin-converting enzyme was 41.5 nanomole/min/ml (normal, 22-40), and factor VIII-related antigen measured by rocket immunoelectrophoresis method was 60% (normal, 90-110).

Repeated sputum specimens yielded no acid-fast bacilli or pathological organisms. Upper gastrointestinal series, barium enema, echogram

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Fig. 1. Chest roentgenogram showing multiple nodules throughout both lung fields.

Fig. 2. The center of nodule is poor in cellularity and myxomatous, and at its marginal zone viable cells are more abundant. (hematoxylin and eosin stain: original magnification; x 40).

Fig. 3. At the periphery of the nodule, protrusions into the adjacent alveolar space are seen in polypoid manner through the Kohn’s pore. (hematoxylin and eosin stain: original magnification; x 100).

of abdomen including liver, pancreas and spleen, intravenous pyelogram, 67Ga-scintigram of whole body were all within normal limits. Arterial blood gas measurements and pulmonary function studies including FVC, FEV1.0, DlCO and flow-volume curve gave normal values. Fiberoptic bronchoscopy showed no abnormal lesions in the major bronchial system and transbronchial lung biopsies failed to reach the lesions and disclosed no pathological abnormalities.

Therefore, an open-lung biopsy was performed through a left thoracotomy. On the surface of visceral pleura, many delle were present occasionally with pleural anthoracosis, under which solid tumors were palpated. There were no lesions over the surface of the parietal pleura. No pleural effusion or hilar lymphadenopathy were present. Several lesions from the left lingula were removed by wedge resection.

**Gross pathologic findings:** The nodules were 0.3-0.5 cm in diameter, grayish-white touched with yellow, firm and cartilage-like in consistency. The shape of tumor was well demarcated and was not encapsulated. The surrounding pulmonary parenchyma appeared normal.

**Microscopic findings:** For light microscopy, tissue was fixed in formalin and stained with hematoxylin-eosin, PAS and elastica-van Gieson stains. The tumor nodules were located subpleurally showing pleural puckering and appeared homogeneously pink with hyalinous central part and cellular peripheral zone (Figure 2). The elastic stain showed that the original pulmonary lobular architecture, viz., bronchioles, alveolar ducts and sacs were preserved and embedded in the hyalinous myxomatous stroma. Pulmonary capillaries were apparently uninvolved but occasionally pulmonary arteries at the level of respiratory bronchioles were filled with tumor. At the peripheral zone, viable cells surrounded the rim
of the tumor stroma protruding into the adjacent alveoli in a micropolypoid manner via alveolar ducts as well as through the Kohn's pores (Figure 3). The alveolar septa was relatively normal though nearby the periphery of the tumor exhibited tumor invasion. The cellular aspect was difficult to discern at the peripheral zone of the tumor because of coexisting type II pneumocyte. In the central hyalinous portion, scantly present tumor cells had large irregularly shaped nuclei and frequently vacuolated, microcytic cytoplasm, which did not stain with PAS or alcian blue. The hyalinous stroma that contained faintly staining flocculent material, was weakly PAS and alcian blue positive.

**Electron microscopic findings:** For electron microscopic examination, fresh tissue was immediately fixed in sodium phosphate-buffered glutaraldehyde and post-fixed in sodium phosphate-buffered osmium tetroxide. Staining was done with uranyl acetate and lead citrate. Ultra-thin sections were examined with a transmission electron microscope—JEOL 100c. The central hyalinous portion of the lesion contained cell debris, collagen fibers and myofibroblasts embedded in amorphous material. The viable tumor cells were best seen in the peripheral proliferative zone. The tumor cells were located in the stroma immediately beneath the alveolar epithelial basement membrane and thinly extended endothelial cells containing multiple pinocytotic vesicles, with labyrinthine interdigititation at the border of the tumor cells. No desmosome or other junctional apparatuses were found. The nuclei were indented and bizarre, and the cytoplasm contained intermediate fibers, lysosomal granules and vacuolated mitochondria. Tubulovesicular Weibel-Palade granules were identified occasionally in cluster (Figures 4, 5).

**Immunological analysis:** Serum immunoglobulin levels, IgA, IgG, IgM and IgD were all within normal limits. Serum C3, C4 and C5 levels were also within normal limits. Serum CH-50 was 26.5 U/ml (normal, 30–40). Lymphocyte subsets examined by Leu-series monoclonal antibodies and lymphocyte stimulation tests by phytohemagglutinin, concanavalin A and pokeweed mitogen were all within normal limits. Tuberculin (PPD) skin tests (0.05 mcg/0.1 ml, 0.5 mcg/0.1 ml) gave negative results. But, DNCB (2,4-dinitrochlorobenzene) test was +++ positive.

**DISCUSSION**

This disease entity was first described by Dail...
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Fig. 5. Multiple Weibel-Palade bodies showing membrane bound granular or tubular structure. (original magnification; x 14500).

and Liebow in 1975 and subsequently isolated cases had been reported. Before Dail and Liebow's report, however, the same entity had been described by Farinacci et al. as "Pulmonary deciduosis" or Smith et al. as "Primary chondrosarcoma of the lung".

According to the summary of the previous reports including Dail and Liebow's large series describing twenty cases, prominent female preponderance is found in patients with this disease, these were 25 women (83%) and 5 men. The average age of the patients was about 35 years.

Concerning the histogenesis of this tumor, Dail and Liebow initially suggested an alveolar cell origin. But the ultrastructural observation by Corrin et al. showed that the cell of these tumors contained abundant microfilaments, moderate amount of rough endoplasmic reticulum, and characteristic microtubular bodies which were so-called Weibel-Palade bodies. In other words, the tumor cells exhibited features of smooth muscle, myofibroblast and endothelial cell differentiation and they concluded that those characteristic features were quite compatible with those of cells of vascular origin from precursor mesenchymal cells such as the vasoformative reserve cells.

Recently Dail and Liebow showed the same hypothesis based upon their studies by the immunoperoxidase technique using factor VIII-related antigen which is thought to be a marker for endothelial cell of the blood vessel and can be used to confirm the vascular nature of the neoplastic lesions. Our present case also showed positive staining of this antigen as well as numerous Weibel-Palade bodies, findings which support their hypothesis.

It was noteworthy that liver metastases were found in some of the reported cases, and similar lesion was reported as "Hepatic tumors of long duration with eventual metastasis". As a matter of course, in some autopsy cases lungs were the sole organ invaded by the tumor. The uniform dissemination of this tumor throughout both lung fields, however, rather suggests metastatic nature than a primary lung tumor. Weiss and Enzinger have advocated a new concept on such lesions giving a name of epithelioid hemangioendothelioma. These tumors share a property of a distinctly epithelial appearance, a frequent angiocentric location, and a conventional angiosarcoma, composed of short cords or clusters of rounded or polygonal cells embedded in a myxohyaline matrix, whose features are similar to those of IVBAT. Ultrastructurally, the cell of epithelioid hemangioendothelioma has Weibel-
Palade bodies. Factor VIII-related antigen can also be demonstrated in this tumor. Weiss suggested that when this tumor arose as a primary tumor in the lung, it might be designated as "intravascular bronchiolo alveolar tumor." It may be appropriate that these tumors are labeled as epithelioid hemangiendothelioma of the lung.

To date, 7 cases have been reported in Japan, and two of them were reported in detail. In these cases, negativity of the tuberculin test appears characteristic, since more than 80% of adults have positive tuberculin reaction in Japan. Similarly, cases in English literatures had also negative tuberculin reaction. But the analysis of other immunological data revealed no other abnormalities. Negativity of tuberculin test might be thought to be rather anergy than disturbance of cell mediated immunity.

The prognosis of this disease is not so clear. Currently this tumor is thought to be not so malignant, showing slowly progressive course beyond five or ten years. In Dail and Liebow's series, ten of twenty died and most of them were due to respiratory insufficiency subsequent to wide extension of the tumor. In the present case, liver lesion was not recognized in spite of serial examination, but our two other unpublished cases had liver lesions, and died of hepatic failure. Unlike highly malignant angiosarcoma, this endothelial tumor shows very insidious growth and can kill the sufferer in a time to come. Some therapeutic measures should be undertaken in an attempt to curb the progress of the disease. Considering its high propensity for women, anti-estrogen drug such as tamoxifen can be a candidate as a chemotherapeutic agent, if estrogen receptor exist on the tumor cells.

REFERENCES