Abstract

A 65-year-old man was admitted to our hospital because of dyspnea on exertion. He had oculocutaneous albinism innately and his parents were consanguineous. His chest roentgenogram on admission showed reticulo-nodular infiltrates and cystic changes throughout both lung fields, and 7 cm mass in the left middle field. Cytology of bronchoalveolar lavage fluid (BALF) revealed macrophages containing ceroid. The diagnosis of HPS was made clinically and the tumor was diagnosed as poorly differentiated adenocarcinoma of the lung. He died of respiratory failure. By autopsy, additional well-differentiated adenocarcinoma was detected. Cytology of BALF was useful to confirm ceroid accumulation in the lung.

Case Report

A 65-year-old male farmer was admitted to our hospital because of fever and dyspnea on exertion. His parents were married cousins. He had horizontal nystagmus and weakness of sight, and he had white hair innately. He had smoked a pack of cigarettes per day for 40 years. Since around the age of 50, cough with sputum and dyspnea on exertion had appeared, and he had been diagnosed as having interstitial pneumonia because of diffuse reticulonodular shadows in his chest roentgenogram. The difficulty in breathing had gradually increased and he had started home oxygen therapy at the age of 62. In September 2001, at the age of 65, he had a fever and severe dyspnea, and was referred to our department. On physical examination, he had white hair, whitish yellow sun-tanned skin, and light-brown irises. He had horizontal nystagmus and his vision was 0.02 in both eyes. Funduscopic examination revealed a lack of retinal pigment. Fine crackles were heard in both lower lung fields. The spleen was palpable 2fb below the costal margin. Peripheral blood count showed white blood cells 13,400/µl, red blood cells 500x10⁴/µl, and platelets 24.2x10⁴/µl. His blood examination showed lactic dehydrogenase 405 IU/l, C-reactive protein 5.9 mg/dl, KL-6 1,089 U/ml, SP-D 157.9 ng/ml, and rheumatoid factor was negative. The results of antinuclear...
antibody tests were positive, with a homogeneous pattern and nucleolar pattern at a titer of 1:640, but no singular antibody was found. Bleeding time was 1 minute. Pulmonary function tests showed a vital capacity of 2.75 l (89% of predicted value), FEV1/FVC of 73%, and diffusing capacity for carbon monoxide of 18.4% predicted. Arterial blood analysis in room air showed a pH of 7.459, Po2 of 56.5 mmHg, and Pco2 of 33.5 mmHg.

A chest X-ray revealed reticulonodular infiltrates and cystic changes throughout all lung fields and a 7 cm mass in the left lower lung (Fig. 1A). The infiltrates were diffuse and showed no predominance for the lower lobes or sub-pleural area. There was no reduction of lung volume. Chest computed tomography showed cystic changes predominantly in upper lung fields (Fig. 1B). Island-like normal lung structure was seen between the cysts. A 68×50 mm mass occupied the left S6 of the lung (Fig. 1C). Bronchoscopic examination showed the edema and stenosis left B6. After confirming no bleeding tendency, normal bleeding time, and normal coagulability, we performed brushing cytology, trans-
bronchial lung biopsy (TBLB), and BAL from left S6, but no malignant cell was observed in his TBLB and BAL specimen. The differential cell count of BALF showed 93.8% macrophages, 1.0% lymphocytes, and 5.2% neutrophils. Papanicolaou’s staining of BALF cells revealed macrophages filled with coarse brown granules (Fig. 2), and the amount of granules was variable in each cell. Because the granules were stained orange by Sudan’s stain and deep blue by Schmorl’s reaction, they were considered to be ceroid-like pigments. Similar pigments were not found in TBLB specimen. Bone marrow aspiration materials also showed macrophages containing similarly stained pigments. Considering his atypical interstitial pneumonia, his parents’ consanguinity, oculocutaneous albinism, and ceroid accumulation in BALF cytology, he was considered to be HPS. To made diagnosis of HPS, platelet function test and electron microscopic examination were performed. Platelet function studies showed a lack of secondary aggregation to collagen, in 1.25–2.5 μg/ml low concentration. Electron microscopic examination revealed severe reduction of platelet dense bodies, as compared with normal control (Fig. 3). Finally, we made the diagnosis of HPS.

The mass in the left lower lobe was suspected to be carcinoma, we proceeded with general diagnostic imaging. Ultrasonography of the abdomen revealed multiple liver tumors and splenomegaly. Bone scintigraphy revealed high uptake at the 9th dorsal vertebra, left 8th rib, and right hip joint. Moreover, there was a subcutaneous tumor in the chest and its biopsy sample revealed adenocarcinoma cells. It was thought to be subcutaneous metastasis from the pulmonary tumor. Despite glucocorticosteroid treatment, his pulmonary

Figure 2. Papanicolaou’s stain of BALF showed macrophages filling with brown granules (×400).

Figure 3. Ultrastructural analysis of platelet organelles. Ultra-thin frozen sections of glutaraldehyde-fixed platelets from a normal control and the patient were subjected to transmission electron microscopy. Organelles having a densely stained constituent (dense body, arrow) were present in platelets from a control (A). In contrast, dense bodies lacking a constituent (empty sack, arrow) were observed in patient’s platelets (B).
infiltrates and respiratory insufficiency progressed and he died in January 2002.

Autopsy revealed poorly differentiated adenocarcinoma in the left lower lobe, 110×80 mm in diameter (Fig. 4A). There was also a 7 mm diameter papillary type, well-differentiated adenocarcinoma in the right lower lobe (Fig. 4B). These carcinomas were different from each other in their differentiation status so that it was considered to be double adenocarcinomas. Pulmonary fibrosis was seen throughout both lung fields. Ceroid-like pigments in macrophages were found in the lung, bone marrow, liver, and spleen. Genetic analyses of HPS1-6 genes were performed for cDNA derived from patients, but no mutation was detected.

Discussion

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disease and vary rare in Japan. The triad is oculocutaneous albinism, bleeding tendency, and ceroid accumulation in lysosomes of macrophages (1, 2) and is considered to be due to a deficiency of lysosome-related organelles; such as melanosomes, platelet dense bodies, and so on (3–6). Patients will be diagnosed as having HPS based upon a paucity or deficiency of platelet dense bodies on whole mount electron microscopy or confirming ceroid accumulation under a microscope.

At least seven mutations; HPS1, ADTB3A, HPS3, HPS4, HPS5, HPS6, and HPS7 are known to cause HPS (6–11). ADTB3A codes for the beta 3A subunit of adaptor complex-3, known as a protein that assist vesicle formation from the trans-Golgi network. HPS1 and HPS4 proteins are considered being a part of BLOC-3 (biogenesis of lysosome-related organelles complex 3) and they play a central role in protein trafficking. The functions of other HPS gene products remain unknown but they are presumed to be transmembrane proteins.

In Japanese HPS patients, symptoms are usually mild and it is sometimes hard to make a proper diagnosis of HPS. The albinism is tyrosinase-positive and its phenotype expression is variable (12). As observed in this case, pigmentation increases with age and sun exposure. This makes it sometimes difficult to recognize the patient’s albinism. The bleeding tendency has a range of mild to severe and some cases show normal bleeding time. In some patients, platelet function tests show a lack of aggregation only to a low concentration of collagen (13). Therefore, in adult Japanese patients with HPS, dyspnea due to interstitial pneumonia often becomes the initial symptom.

Ceroid-like pigments accumulate in reticuloendothelial systems, like macrophages in the lung and skin, neural glia cells, Kupffer cells in liver. Ceroid is a yellow-green pigment with autofluorescence similar to lipofuscin. It is positive for Sudan’s stain and PAS reaction and stained deep blue by Schmorl’s reaction. Although ceroid accumulation is known to be age dependent, the process remains unknown. Ceroid is generated by lipid hyperoxydation of phagocytized foreign bodies and is cytotoxic. Macrophages with ceroid are suggested to be activated, produce superoxide and hydrogen peroxide, release lysosomal enzymes, and cause interstitial inflammation (10). Interstitial pneumonia is one of the most important complications of HPS, and is resistant to therapy, with a poor prognosis. Since clinical symptoms other than dyspnea are often not remarkable, patients are sometimes misdiagnosed as having idiopathic pulmonary fibrosis (IPF). However, pulmonary manifestation of HPS is somewhat different from IPF as seen in this case. The distribution of reticulonodular infiltrates on a chest roetogenogram is often different (14–16). In IPF, lower and subpleural areas are predominately affected. However, in HPS, it presents throughout all lung fields, and cystic changes are predominant in the upper lobe. Lung volume reduction is prominent in IPF, but it is not remarkable in HPS, probably due to additional cystic changes.
According to previous reports, the amount of ceroid varies in each case, and pulmonary macrophages obtained by BAL may not always show ceroid-like pigments. Some reports, open lung biopsies and TBLB are used to confirm ceroid accumulation. However, such biopsies are usually contraindicated because of the patient’s bleeding tendency. White and coworkers described the usefulness of BAL in diagnosis of HPS (17). BAL was useful also in the present case. In this case, since he had no bleeding tendency and showed normal bleeding time and coagulability, and we performed brushing cytology and TBLB to investigate the mass. However, as some Japanese HPS patients have a bleeding tendency, it is important to determine the indication of TBLB. We could also identify ceroid in macrophages obtained by BAL. Several types of granules could be seen in the macrophages: hemosiderin, asbestos, dust, and ceroid-like granules. With Papanicolaou’s stain, ceroid is recognized as a coarse brown pigment. Hemosiderin and asbestos are green-brown color but the cudgel shape of asbestos helps to identify it. Ceroid can also be stained orange by Sudan’s stain and deep blue by Schmorl’s reaction. We suggest the importance of careful examination of BALF cytology which is much safer than obtaining a tissue specimen by TBLB.

Moreover, the present case is unique in that it was complicated with double lung cancers. There have been some reports of HPS with malignant melanoma but only a few HPS cases with pulmonary carcinoma have been reported. Most HPS patients die in midlife of interstitial pneumonia. In the present case, two isolated cancers, poorly and well-differentiated adenocarcinomas, were detected. In Japan, only two HPS cases with lung carcinoma have been reported abstracts (18, 19); both died in their 40s of interstitial pneumonia and their adenocarcinomas, not recognized during lifetime, were detected by autopsy. These reports, as well as the present case, suggest that HPS itself may be a risk factor for lung cancer. The relation between HPS and carcinoma is unclear. However, it is known that IPF is one of the risk factors of lung cancer and some mutations of oncogenes and anti-oncogenes have been reported in IPF (20).

In conclusion, we described a case of HPS with pulmonary adenocarcinoma. This is the first precise case report of an HPS patient with pulmonary carcinoma in Japan. Careful examination of BALF confirmed ceroid accumulation in lung macrophages and helped us to make a proper diagnosis of HPS.

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References