Lung Cancer Associated with Werner’s Syndrome: a Case Report and Review of the Literature

Akira Yamanaka¹, Takashi Hirai¹, Yohsuke Ohtake² and Masanobu Kitagawa³

Department of Chest Surgery, Fukui Red Cross Hospital, Fukui, ²Department of Chest Surgery, Chest Disease Institute, Kyoto University, Kyoto and ³Department of Pathology, Toyama Medical and Pharmaceutical University, Toyama, Japan

A 52-year-old male had an abnormal shadow on a chest X-ray film. His parents were first cousins. His father, brother and two sisters had been diagnosed with Werner’s syndrome. His lung lesion was diagnosed as lung cancer and right upper lobectomy was carried out. Histopathological examination of the resected specimen revealed bronchiolo-alveolar carcinoma with independent atypical adenomatous hyperplasia in the alveolar zone. The alveolar structures were those seen in aging lungs, suggesting a close relationship between Werner’s syndrome and cancer development.

Key words: Werner’s syndrome – lung cancer – bronchiolo-alveolar carcinoma – aging lung

INTRODUCTION

Werner’s syndrome is an autosomal recessive disorder characterized by progeroid syndrome. Its incidence is higher in Japan than elsewhere. It is well known that malignancy is a frequent complication of Werner’s syndrome. We present here a case of bronchiolo-alveolar carcinoma (BAC) which has a background resembling aging lung tissue. Lung cancer in patients with Werner’s syndrome is extremely rare. We review here the other three cases reported to date in Japan.

CASE REPORT

A 52-year-old male was being treated for fatty liver and hypercholesteremia. An abnormal shadow on a chest X-ray film was noted for the first time in April 1993. His parents were first cousins. His father, elder brother and two elder sisters had been diagnosed with Werner’s syndrome. His mother and one elder sister were normal. His height was 151 cm and his weight 44 kg. He had an old-looking face, atrophied auricles, a high-pitched, hoarse voice, atrophied skin and muscles and slender limbs (Fig. 1). The patient had had a cataract operation of the right eye when he was 26 and of the left eye when he was 27 years of age. His hair turned gray when he was about 40. He had been treated for bilateral foot ulcerations and osteomyelitis by resection of the first and fourth toes of the right and the second toe of the left foot after 44 years of age (Fig. 2). An adenomatous goiter was removed when he was 48.

His chest X-ray film and computed tomography (CT) revealed a homogeneous mass 2 cm in diameter in the peripheral upper lung field with an indefinite margin without calcification or pleural indentation. A bronchoscopic biopsy revealed adeno-carcinoma. Right upper lobectomy and mediastinal lymphnode dissection were carried out in July 1993. His postoperative course was uneventful and he was discharged in August.

The cut surfaces of the removed right upper lobe disclosed a subpleural tumor, measuring 25 mm at its greatest diameter, which contained coalescent white nodules of various sizes and a slight pleural depression (Fig. 3). There was no central scar or fibrosis. No metastases were formed in the lymph nodes. Histological examination showed BAC with tall columnar and small cuboid or flat cells lining the thickened alveoli and in other parts, with cuboidal clear cells lining the well preserved alveolar septa (Fig. 4). Several independent foci of atypical adenomatous hyperplasia (Fig. 5) were also identified on a background of atrophied lung parenchyma resembling aging lung with centrilobular emphysema (Fig. 6).

Histochemical and immunohistochemical studies showed only the tall columnar carcinoma cells to be partly positive for alcin blue (AB) and carcinoembryonic antigen (CEA) and negative for epithelial membrane antigen (EMA), whereas the other type cells, including those in the adenomatous hyperplasia, were positive for EMA only.
Werner’s syndrome is a rare, autosomal recessive disorder characterized by short stature and senile hoarseness and by premature aging of all the organ systems, atrophic skin, cataracts and early osteoporosis. Many cases of Werner’s syndrome have been reported since the first patients were described by Otto Werner (1) in 1904 and it is noteworthy that malignancy is a frequent complication with an incidence reported to be from 5.6% (2) to 10.3% (3). Tsuchiya et al. (4) listed 74 cases of Werner’s syndrome complicated by 82 malignancies; of these, 42 were Japanese patients who had 50 malignancies, i.e. more than half were Japanese. The locus of Werner’s syndrome has been found on the short arm of chromosome 8 in both Japanese (5) and non-Japanese subjects (6). One of the reasons for this relatively high incidence is considered to be custom of consanguineous marriages in local areas of Japan.
Carcinomas of the respiratory and digestive systems complicating Werner’s syndrome are much rarer than other carcinomas or sarcomas (4). Yokota et al. (7) reported that out of 52 malignancies complicating Werner’s syndrome in Japan, only six were epithelial cancers of the respiratory or digestive systems. As far as we know, only four cases of Werner’s syndrome with lung cancer have been reported, including the present case, and all are Japanese, three males and one female, all in the sixth decade. Well differentiated adenocarcinoma (including BAC) is the predominant histology (Table 1). As regards these findings, the results reported by Yoneyama (11) were suggestive. He showed that the mean age was 52.3 years and adenocarcinoma was the predominant histology in 42 patients with lung cancer whose parents had lung cancer. It might be guessed that hereditary or familial factors have an influence on a younger age distribution and a rising incidence of adenocarcinoma of lung cancer.

To investigate the carcinoma lesion and the background of the lung, we also performed histopathological and immunohistochemical examinations. Immunohistochemical studies have revealed that EMA is useful marker of alveolar origin (12). In the present case, the cells of BAC component and atypical adenomatous hyperplasia, which were positive for EMA but negative for periodic acid Schiff (PAS) and AB stains, are considered to be of bronchiolar or alveolar origin. The lung cancer in this patient showed various phenotypes, but we consider that it was of BAC origin in the progeroid lung and perhaps developed via adenomatous hyperplasia.

The mechanism of the development of malignancies in patients with Werner’s syndrome remains unclear. Hyperplasia or degeneration resembling those seen in aging patients might be the cause (13). A decrease in the replicative life span of skin fibroblasts from a patient with Werner’s syndrome has been demonstrated (14). Frequent chromosomal rearrangements (15) and an error of deoxyribonucleic acid (DNA) replication (16) in cultured skin fibroblasts from a patient with Werner’s syndrome support this hypothesis. From recent advances in chromosome studies, there are reports that DNA repair efficiency is lower in patients with Werner’s syndrome (17). Furthermore, it is considered that there are oncogenes or tumor suppressor genes localized on the short arm of chromosome 8. Loss of heterozygosity from the short arm of chromosome 8 is frequent in a variety of malignancies, including non-small cell lung cancer (18,19), suggesting the presence of tumor suppressor genes in this lesion. These findings may be more useful in explaining the occurrence of lung cancer in patients with Werner’s syndrome.

### Acknowledgements

We acknowledge with thanks the help of Drs Hidetoshi Suruta, Ritsuko Yoshioka and Atsuhiko Naramoto, who explained the details of the reported cases.

### References


