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CASE REPORT

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Surgical treatment of lung cancer associated with Werner's syndrome: A case report and review of the literature

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Abstract

Werner's syndrome is a rare progressive disorder that is characterized by a variety of clinical manifestations which mimic features of advanced ageing. Malignancy is one of the most problematic complications of Werner's syndrome. Lung cancer associated with Werner's syndrome is rare. A 54-year-old woman with Werner's syndrome was referred to our department because an abnormal shadow had been detected on routine chest radiography. Chest computed tomography revealed an abnormal nodule in the left upper lobe. Bronchoscopic examination revealed the presence of squamous cell carcinoma. Other imaging studies showed no metastatic lesions; therefore, the patient was diagnosed with stage IA3 squamous cell carcinoma. She underwent left upper lobectomy and lymph node dissection without major complications, and no recurrence was found for 2 years postoperatively.

KEYWORDS
complications, lung cancer, progeria, surgery, Werner's syndrome

INTRODUCTION

Werner's syndrome, a type of progeroid syndrome, is an autosomal recessive disorder caused by a mutation in the *WRN* gene, which encodes a DNA helicase.[1] The incidence of this disease is higher in Japan than elsewhere in the world.[2] It is characterized by early ageing phenotypes, including greying and loss of hair, juvenile cataracts, skin ulcers, insulin-resistant diabetes, and neoplasms.[3] Lung cancer is extremely rare in patients with Werner's syndrome, and it is rarely treated surgically because of poor postoperative wound healing.[4] We herein present a case of surgical management of lung cancer in a patient with Werner's syndrome in which a successful outcome was achieved with no major complications.

CASE REPORT

A 54-year-old woman was noted to have an abnormal lesion on chest computed tomography (CT). Her height was 144.6 cm, and her weight was 50.4 kg. She had an aged, bird-like face, greying and thinning hair, a high-pitched and hoarse voice, and atrophied skin and muscles. The patient had undergone bilateral cataract operations at the age of 23 years. She had been treated for diabetes, dyslipidaemia, arteriosclerosis obliterans, and bilateral foot ulcerations beginning in her 30s. Foot radiography revealed calcification of the Achilles tendon (Figure 1). Although she refused to undergo mutation analysis, she was diagnosed with Werner's syndrome based on the presence of all cardinal signs and symptoms. None of her family members had Werner's syndrome.

The patient underwent annual screening CT for neoplasms, which showed a 2.9-cm-diameter mass in the left upper lobe (Figure 2A). The hilar and mediastinal lymph nodes were not enlarged. On positron emission tomography, the mass showed abnormal uptake (maximum standardized uptake value of 15.9). A bronchoscopic biopsy revealed squamous cell carcinoma. The tumour tested positive for epidermal growth factor receptor (EGFR) mutation (exon 19 deletion) and showed high expression of programmed

death ligand 1 (PD-L1), with a tumour proportion score of 60%. Based on these examination results, we diagnosed the patient with pulmonary squamous cell carcinoma, clinical stage IA3 (cT1cN0M0). The patient had several preoperative comorbidities associated with Werner's syndrome, but her general condition was good. Her forced vital cavity (FVC) and forced expiratory volume in 1 second (FEV1) were 2.12 L (90.2% of predicted value) and 1.80 L (90.5%), respectively; and her FEV1/FVC ratio was 84.91%; and her ejection fraction was 66% on echocardiography. Therefore, we considered that the patient could tolerate thoracic surgery.

After the patient had provided informed consent, we performed left upper lobectomy with regional lymph node dissection via thoracotomy with a 10-cm anterolateral incision aiming to shorten the operative time and ensure the patient safety. The operative time was 179 minutes, and the blood loss volume was 60 mL. She developed postoperative drug-induced liver injury, but this resolved upon stopping nonsteroidal anti-inflammatory drug therapy and beginning administration of a hepatoprotective agent. The patient developed no skin-related complications and was discharged 12 days after surgery.

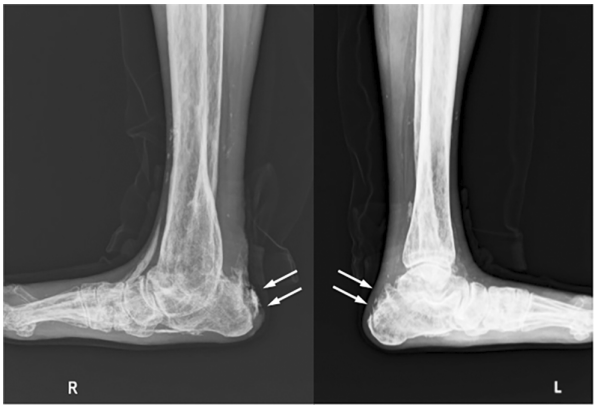

FIGURE 1 Radiograph of the foot showed calcification of the Achilles tendon (arrows).

The resected left upper lung lobe contained a solid tumour measuring 2.9 cm in its greatest diameter. Histopathological examination of the tumour revealed squamous cell carcinoma (Figure 2B). No metastatic lesions were observed in the lymph nodes or other lung tissue; therefore, the pathological stage was IA3 (pT1cN0M0). In the preoperative examination, thoracic CT revealed a left breast mass, and the patient was diagnosed with breast cancer. Total mastectomy was performed for the left breast, and the postoperative course was uneventful. The patient had no recurrence of lung cancer for 2 years after surgery.

DISCUSSION

Werner's syndrome, an autosomal recessive premature ageing syndrome, is rare. The most critical complications of Werner's syndrome are arteriosclerosis and malignant tumours, and the most common cause of death in recent years has been the development of non-epithelial tumours.[5] In one study of Japanese patients, the frequency of malignant tumours was 20.7% (85 of 411 reported cases), and 25 patients (6.1%) died of malignant tumours.[6] In patients with Werner's syndrome, the incidence of malignancies of mesenchymal origin (sarcomas) was higher than that of epithelial cancer.[3] Moreover, lung cancer has been very rarely observed in patients with Werner's syndrome, probably because they have a shorter lifespan. To the best of our knowledge, four cases of surgery to remove lung cancer in patients with Werner's syndrome, including the present case, have been reported to date.[4,7,8] These cases are summarized in Table 1. All the patients were in their fifth decade of life, and lobectomy was performed. No patients developed major postoperative complications, including skin-related problems. Recent data have revealed that the lifespan of Japanese patients with Werner's syndrome has been significantly prolonged by approximately 10 years.[5] This longer life expectancy of patients with Werner's syndrome might be due to the improved long-term control and better treatment modalities for metabolic risk factors

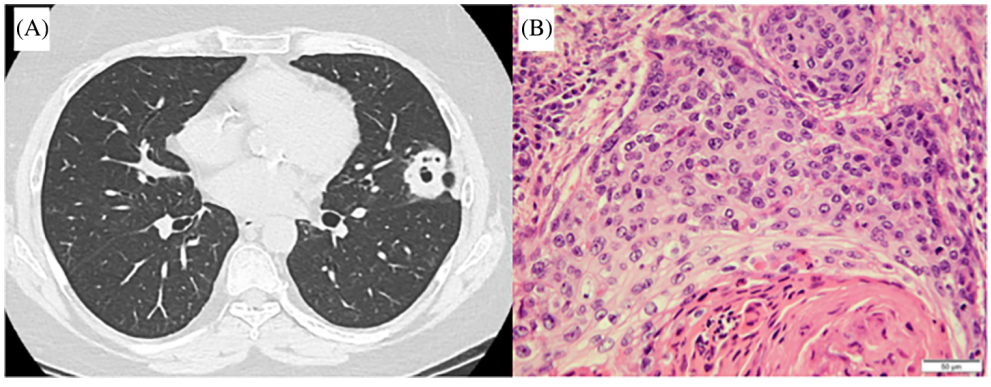

FIGURE 2 (A) Chest computed tomography showed a solid tumour in the left upper lobe. (B) Histopathological examination of the lung tumour revealed squamous cell carcinoma (haematoxylin and eosin staining, ×200).

TABLE 1 Reported surgical cases of lung cancer in patients with Werner's syndrome.

	Naramoto et al.[7]	Yamanaka et al.[8]	Ohnishi et al.[4]	Present case
Age/Gender	55/Male	52/Male	52/Male	54/Female
Consanguinity of parents	First cousins	First cousins	None	None
Mutation of *WRN*	N/A	N/A	Positive	N/A
Other malignancies	Osteosarcoma of the left upper limb	None	Pharyngeal cancer	Left breast cancer
Histopathology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma
Surgical procedure	Left lower lobectomy	Right upper lobectomy	Left upper lobectomy	Left upper lobectomy
Pathological stage	Stage IA2	Stage IA3	Stage IA3	Stage IA3
Postoperative complication	None	None	None	Drug-induced liver injury
Outcome	47 months alive with disease	44 months doing well	24 months died	24 months doing well

Abbreviation: N/A, not available.

such as dyslipidaemia, hypertension, and diabetes that have developed in recent decades.[9] As the life expectancy of patients with Werner's syndrome continues to increase, the incidence of cancer might also increase, and effective screening and treatment strategies should therefore be required.

The mechanism underlying the development of neoplasms in patients with Werner's syndrome remains unclear. Mutation of *WRN*, which contributes to DNA repair and telomere maintenance, may partly explain the characteristic tumour spectrum of patients with Werner's syndrome.[10] A recent study showed that *WRN*-mutant colorectal cancer had a higher frequency of PD-L1–positive expression than did *WRN*-wild-type colorectal cancer.[11] In the present case, the tumour was positive for PD-L1 and EGFR expression. However, the correlation between Werner's syndrome-associated lung cancer and biomarkers for immunotherapy, including the prevalence of PD-L1 expressed on tumour cells, is under discussion, and the association between Werner's syndrome and EGFR mutation also remains unknown. Currently, immunotherapy alone or in combination with chemotherapy is standard therapy for advanced lung cancer, and immunotherapy in a patient with Werner's syndrome-associated lung cancer has been reported.[12] As their lifespan increases, immunotherapy may become a treatment option for lung cancer in patients with Werner's syndrome.

In conclusion, we safely performed lobectomy for primary lung cancer in a patient with Werner's syndrome. Surgeons tend to hesitate to recommend standard treatment for patients with Werner's syndrome because of the higher perioperative risks and the uncertainty of long-term benefits. However, patients with Werner's syndrome who develop lung cancer should not be denied resection on the grounds of the disease. A malignant tumour is the most problematic complication and an important risk factor for a poor prognosis, but we consider that the diagnosis of and timely surgery for early-stage lung cancer can contribute to a satisfactory long-term outcome and low mortality rate. Further case series are required to establish the efficacy and safety of surgery for lung cancer in patients with Werner's syndrome.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the case report. Fumihiro Ishibashi wrote and drafted the manuscript. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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