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Case report

Combination immunotherapy of nivolumab plus ipilimumab in a lung cancer patient with Werner syndrome; a case report

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ABSTRACT

Werner syndrome (WS) is a rare progressive disorder that is characterized by premature aging of all organs. Malignancy is a frequent complication of WS, however, lung cancer patients with WS are much rare. In patients with WS, the treatment for malignancy is often limited due to other complications of severe skin ulcer, diabetes mellitus and cardiovascular disease. Currently, immune-checkpoint inhibitors (ICIs) are standard therapy for several cancer patients and the combination of nivolumab plus ipilimumab has also been approved for the treatment of non-small cell lung cancer (NSCLC). Recent studies have also reported that serious immune-related adverse events (irAEs) induced by ICIs may correlate with elderly or more vulnerable patients. However, the efficacy and safety of ICIs in NSCLC patients with WS remain unclear. To the best of our knowledge, this is the first case describing a NSCLC patient with WS receiving the combination immunotherapy of nivolumab and ipilimumab. Our case showed objective response to ICIs, however, several immune-related adverse events (irAEs) including hypothyroidism, adrenal insufficiency, hard rash and interstitial lung disease occurred, thus resulted in early treatment discontinuation. Our case suggests that immunotherapy for NSCLC patients with WS could be effective, but physicians may be aware of the possibility of multiple irAEs undergoing immunotherapy for NSCLC patients with WS.

1. Introduction

Werner syndrome (WS) is a rare genetic disorder of accelerated aging caused by loss-of-function mutations in the WS RecQ helicase gene (WRN) [1]. It is also known that WS is hereditary cancer-prone syndrome and lung cancer complicating WS is much rare than other carcinomas such as thyroid follicular carcinoma and malignant melanoma or sarcoma [2]. In these patients with WS, the treatment for malignancy is often limited due to other complications of severe skin ulcer, diabetes mellitus and cardiovascular disease. Currently, immunotherapy alone [3] or in combination with chemotherapy [4] is standard therapy for lung cancer patients, and the combination of nivolumab plus ipilimumab has also been approved for the treatment of non-small cell lung cancer (NSCLC) [5]. However, none is known about efficacy and safety of these immunotherapies for NSCLC patients with WS. We hereby present a clinical

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case of NSCLC patient with WS who received combination immunotherapy of nivolumab plus ipilimumab.

2. Case presentation

A 54-year-old man was admitted to our hospital in February 2021 for the exploration of the mass in the right lower lung field. The patient's height was 157 cm and his weight was 43.9 kg. The patient was a former smoker (Brinkman Index 400; from age 20 to 40) and had a history of WS diagnosed in 2010 with all criteria of cardinal signs and symptoms: (i) progeroid changes of hair, (ii) cataract, (iii) intractable ulcer, (iv) achilles tendon calcification, (v) bird-like face, (vi) high pitched voice [6] (Fig. 1A). He was also being treated for hyperlipidemia, diabetes mellitus and chronic coronary triple-vessel disease with stent placement. His right lower limb and left foot were amputated before because of the hard skin ulcer (Fig. 1B). In his family history, there were no other members with WS.

He was asymptomatic and had an Eastern Cooperative Oncology Group performance status of 1. His laboratory test showed normal range of complete blood count (CBC), adrenal function (ACTH 31.9 pg/ml [reference range, 7.2–63.3 pg/ml] and cortisol 12.1 µg/dl [reference range, 7.07–19.6 µg/dl]), thyroid function (TSH 4.18 µIU/ml [reference range, 0.61–4.23µIU/ml] and free T4 0.75 ng/dl [reference range, 0.7–1.48µg/dl]) and hemoglobin A1c (6.0% [reference range, 4.9–6.0%]). Chest computed tomography (CT) revealed consolidation with interlobular septal thickening in the right middle lobe of the lung and multiple nodules in the bilateral lower lobe of lungs (Fig. 2A–C). A bronchoscopic biopsy of consolidation in the right middle lobe was performed for diagnosis and the histological examination revealed adenocarcinoma. Because of multiple metastasis in bilateral lungs, the patient was finally diagnosed with stage IV(cT4N0M1a) adenocarcinoma of the lung. Next-generation sequencing (NGS) of the tumor only detected positive for KRAS minor mutation (p.Gly12 Asp) and immunohistochemistry showed negative for programmed cell death-ligand 1 (PD-L1). Taking into account the hard skin ulcer on the left lower limb above the amputation (Fig. 1B), pressure sores and risk for febrile neutropenia induced by cytotoxic drugs, he received immune checkpoint inhibitors (ICIs) consisting of nivolumab (240mg/body, every 2 weeks) and ipilimumab (1mg/kg, every 6 weeks). After the first cycle of nivolumab and ipilimumab on day 34, he developed asthenia and anorexia. His blood test revealed adrenal insufficiency (ACTH 11.9 pg/ml and cortisol 0.96µg/dl) as well as hypothyroidism (TSH 8.715µIU/ml and free T4 0.64 ng/dl). Brain magnetic resonance imaging (MRI) showed no abnormal findings in his pituitary gland. He was started on hydrocortisone followed by levothyroxine replacement and showed clinical response with remission of symptoms. Free T4 and cortisol levels were also returned to their normal range, however, ACTH level gradually decreased (Fig. 3). He was diagnosed with primary hypothyroidism and late-onset secondary adrenal insufficiency induced by ICIs. After 2 cycle of ICIs on day70, he presented with fever, rash and dyspnea. CT revealed increased reticular opacities with ground glass opacities in the bilateral lower lobe of lungs, though shrinkage of primary lesion of tumor in the right middle lobe of the lung (Fig. 2D–F). Taking into account the immunotherapy-induced pneumonia and rash, the combination of ICIs was stopped and intravenous methylprednisolone, 1000mg for 3 days, was administrated. Thereafter, his clinical symptoms of rash and dyspnea were improved and treatment with 1mg/kg prednisolone was continued. Two weeks after high dose treatment of corticosteroid, chest pain and worsening of his senility suddenly occurred. His electrocardiogram showed ST segment depletion, and his blood test revealed elevated troponin level, thus, he was newly diagnosed with acute coronary syndrome. Because of multiple immune-related adverse events (irAEs) and chronic coronary triple-vessel disease with stent placement, coronary intervention was not carried out. The patient's general conditions deteriorated further and best supportive care was initiated for his comfort.



Fig. 1. (A) Characteristic features of the patient presenting with appearance of senility, bird-like face and progeroid changes of hair. (B) A hard skin ulcer on the patient's left lower limb near the amputation site.

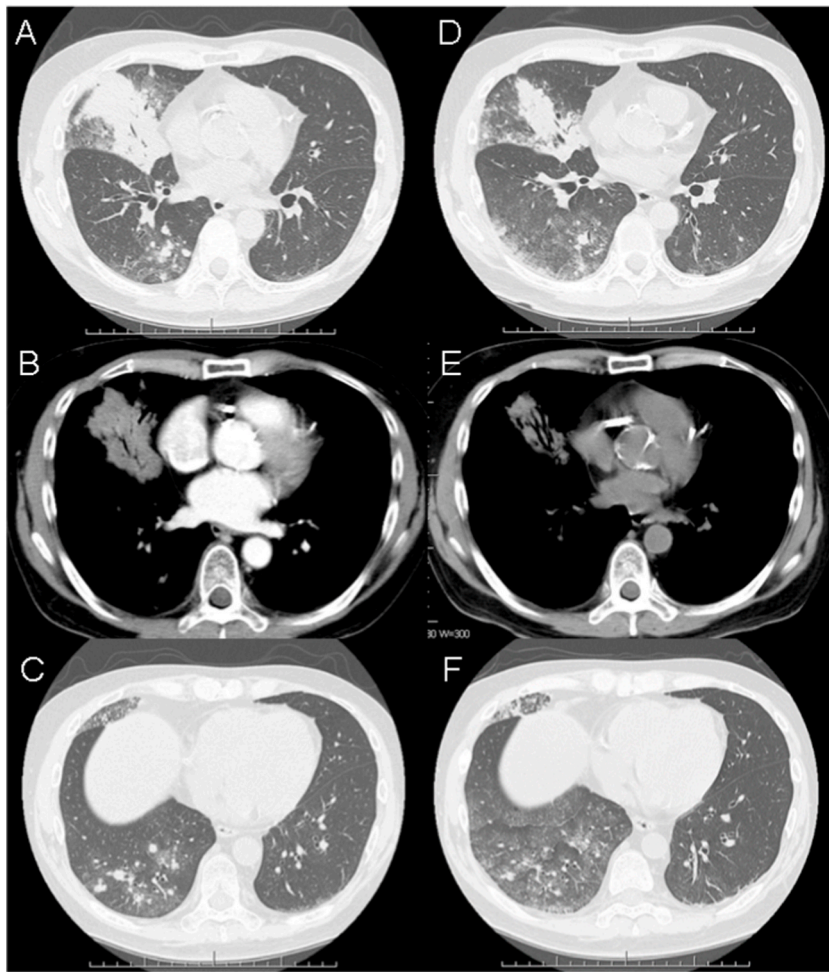


Fig. 2. Before treatment, CT revealed tumor consolidation with interlobular septal thickening in the right middle lobe of the lung and multiple nodules in the bilateral lower lobe of the lung (A–C). After 2 cycle of nivolumab and ipilimumab, CT showed shrinkage of primary tumor in the right middle lobe of lung (D and E), though increased reticular opacities with ground glass opacities in the bilateral lower lobe of lungs (F).

3. Discussion

Patients with WS, which is an autosomal recessive genome instability syndrome, and progeroid syndrome are at elevated risk for age-dependent disease such as cancer. Mutation of *WRN* which contributes to DNA repair and telomere maintenance may in part explain the characteristic tumor spectrum of WS patients [7]. Thus, *WRN* is a promising target in cancers with microsatellite instability (MSI). A recent study reported that higher prevalence of MSI-high (MSI-H) and higher tumor mutational burden (TMB) were observed in *WRN*-mutant colorectal cancer (CRC) patients than those in *WRN*-wild type of CRC patients (MSI-H:56% vs. 7%, and mean TMB: 49 vs 10.7 mutations/megabase, respectively), suggestive of a potential efficacy of ICI treatment in these patients [8]. Additionally, *WRN*-mutant CRC had a higher frequency of PD-L1 positive expression than *WRN*-wild type of CRC (13% vs. 4%, respectively). However, compared to MSI-H and TMB, positive PD-L1 expression was relatively few even in *WRN*-mutant CRC patients, and PD-L1 expression is still under discussion as a biomarker of response in regard to CRC patients [9]. Furthermore, the correlation between lung cancer associated with WS and biomarkers for immunotherapy including the prevalence of MSI-H, a high TMB, and PD-L1 expressed on tumor cells, also remains unknown.

Lung cancer patients with WS have rarely been reported. In previous case reports and the review, almost all of these cases were 50 years of age or more, operable, and well differentiated adenocarcinoma was predominant histology [2,10]. Except for unresectable and progressive stage of lung cancer, clinical characteristic of our patient was in accordance with that of previous cases. The precise mechanism of the development of lung cancer with WS has not been clear, but histopathological and immunohistochemical examinations suggested that adenomatous hyperplasia and degeneration in the progeroid lung might because of lung cancer associated with WS [2]. As far as we know, a case of NSCLC associated with WS to receive immunotherapy has not previously been described. In the present case, PD-L1 expression on tumor was negative, and the status of MSI and TMB were unfortunately unknown because the biopsy samples were not large enough to perform all of these tests. Checkmate 227 trial demonstrated that nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, particularly among patients with a

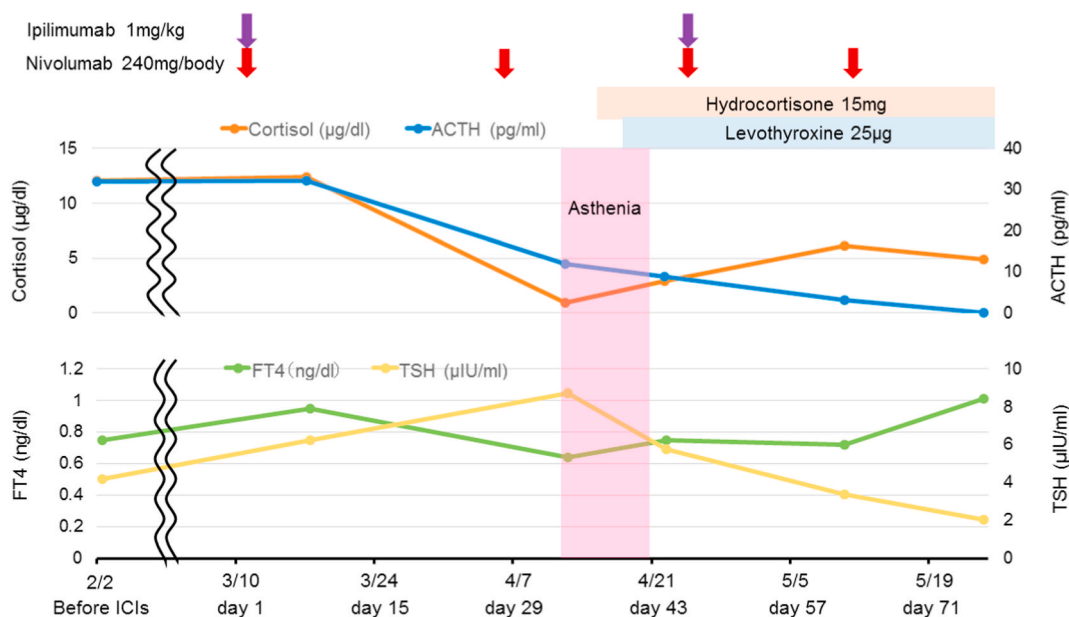


Fig. 3. Changes in blood levels of ACTH, cortisol, TSH and free T4 during hospitalization. The day of initial immunotherapy (nivolumab and ipilimumab) was defined as day1, and the patient developed adrenal insufficiency as well as hypothyroidism after the first cycle of nivolumab and ipilimumab on day 34. After the hydrocortisone and levothyroxine replacement, cortisol, TSH and free T4 levels were returned to their normal range.

high TMB, independent of the PD-L1 expression level [5,11]. Thus, PD-L1 status alone may not be a biomarker of reactivity to this immunotherapy. Therefore, it is interesting whether PD-L1 negative responder cases like our patient have high TMB or not. Other than PD-L1 and TMB, tumor infiltrating lymphocytes such as CD8⁺ T cells [12] and T cell receptor clonality can be predictive biomarkers for ICI [13]. Furthermore, peripheral blood test is also a non-invasive source of potential biomarker in patients receiving ICI. Previous report showed that a low absolute neutrophil count (<7500/ μ l), high absolute lymphocyte count (>1000/ μ l), and high absolute eosinophil count (>150/ μ l) on baseline blood test were significantly and independently associated with better overall survival in patients with NSCLC receiving nivolumab [14]. For ipilimumab study, low neutrophil to lymphocyte ratio (<3) and low absolute monocyte count (<650/ μ l) were also associated with improved overall survival and progression-free survival [15]. The present case was satisfied with all of these results of blood tests, which may be one of the reasons for the response to nivolumab plus ipilimumab.

On the other hand, from the viewpoint of side effects, our patient exhibited multiple irAEs including hypothyroidism, adrenal insufficiency, hard rash and interstitial lung disease also occurred. Combination therapy of nivolumab and ipilimumab is associated with an increased frequency of irAEs compared with each monotherapy [16]. Furthermore, previous observational studies suggested that elderly and vulnerable patients with cancer undergoing immunotherapy may be at a higher risk of irAEs [17]. In cancer patients with WS, cytotoxic drugs are often limited due to complications of WS such as skin ulcer and cardiovascular disease, however, physicians may be also aware of the possibility of multiple irAEs undergoing immunotherapy.

Additionally, the majority of irAEs are managed with corticosteroid as well as other immunosuppressive agents, thus physicians should also consider the exacerbation of complications including infection, diabetes mellitus and thrombosis for vessels which are life-threatening manifestations of WS.

4. Conclusion

Our case suggests that immunotherapy for lung cancer patients with WS could be effective, but can be associated with a high risk of irAEs regardless of patient age. Further investigation and case accumulation should be required to confirm the efficacy and safety of immunotherapy in lung cancer patients with WS.

Author contributions

Yuki Ikematsu: Conceptualization, Writing – original draft Preparation. Miiru Izumi: Writing - Review & Editing. Katsuyuki Katahira: Investigation. Tsuyoshi Ueno: Investigation. Yuki Moriuchi: Investigation. Mizuko Ose: Writing - Review & Editing. Naotaka Noda: Writing - Review & Editing. Makiko Hara: Writing - Review & Editing. Junji Otsuka: Writing - Review & Editing. Kentaro Wakamatsu: Project administration. Masayuki Kawasaki: Supervision.

Declaration of competing interest

None declared.

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