Serum Soluble Interleukin-2 Receptor as a Possible Biomarker for the Early Detection and Follow-up of Nivolumab-Induced Pneumonitis

To the Editor:

Nivolumab, a programmed cell death protein 1 antibody, is one of the novel immune checkpoint inhibitors which have dramatically changed the landscape of cancer treatment in patients with advanced NSCLC. Despite their impressive benefits, immune checkpoint inhibitors have distinct immune-related adverse events as typified by pneumonitis. A recent study has shown that checkpoint inhibitor pneumonitis (CIP) occurred in 19.0% of patients with NSCLC, a higher rate than reported in previous trials, and that 48.7% of those were grade 3-4 and 12.8% were grade 5 in severity.[1] However, there is currently no biomarker for the early detection and follow-up of CIP. We herein present a case of CIP with a high level of serum soluble interleukin-2 receptor (sIL-2R) that reflected the disease process of CIP.

A 43-year-old man with stage IV (cT4N3M1c) NSCLC was admitted to our hospital because of dyspnea and dry cough. Six months before admission, he had been diagnosed with lung adenocarcinoma, and had been negative for EGFR mutation, ALK receptor tyrosine kinase (ALK), and ROS1 rearrangements with a programmed death-ligand 1 tumor proportion score of 2%. Since the patient showed no response to three cycles of first-line chemotherapy with carboplatin and paclitaxel, he subsequently received three cycles of nivolumab at a dose of 3 mg/kg, every 2 weeks. Eight days after the last nivolumab administration, he made an unscheduled visit because of progressive respiratory symptoms. Hypoxemia (partial pressure of oxygen/fraction of inspired oxygen ratio: 98) was present with diffuse ground-glass opacities, consolidation, septal thickening, and traction bronchiectasis in both lungs on chest computed tomography, suggesting CIP (Fig. 1). Laboratory tests have shown that the level of sIL-2R, together with other nonspecific inflammatory markers, increased with each course of nivolumab treatment from 1080 U/mL to 4430 U/mL (Fig. 1). The patient responded well to corticosteroid therapy (intravenous methylprednisolone 1000 mg daily for 3 days followed by oral prednisone 60 mg/day with subsequent tapering) with a remarkable improvement of pulmonary infiltrates and a reduction in the level of sIL-2R (1430 U/mL).

sIL-2R, a soluble form of IL-2–receptor derived from activated T lymphocytes, is widely recognized as a biomarker for disease activity in T-lymphocyte–mediated disorders, including, but not limited to, sarcoidosis and malignant lymphoma. In the present case, it is of interest to note that initial level of sIL-2R was increased and that those levels were correlated with the disease activity of CIP. Excessive T-cell activation may contribute to the increased levels of sIL-2R in CIP, as shown in the case studies of autoimmune diseases and interstitial lung disease, including hypersensitivity pneumonitis, cryptogenic organizing pneumonia, and idiopathic pulmonary fibrosis.[2-5] Further studies are warranted; however, our findings suggest that sIL-2R may have potential as a useful biomarker for predicting the occurrence and evaluating the disease activity of CIP.

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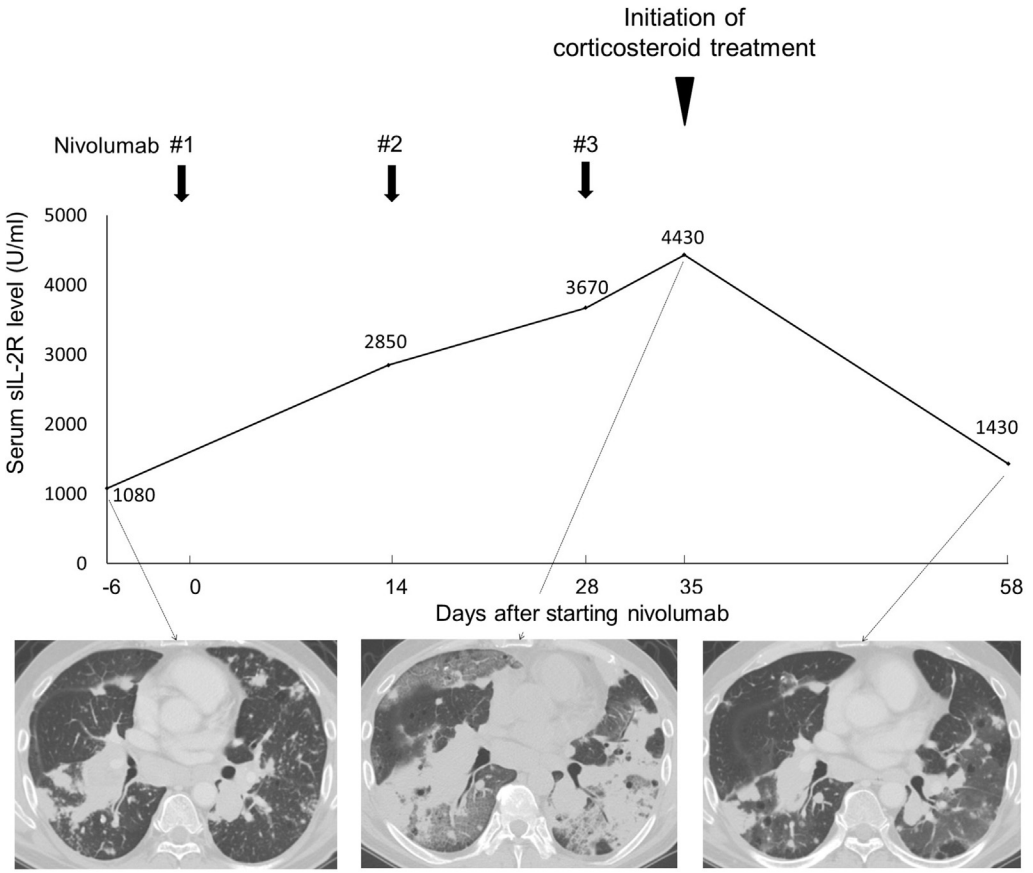

Figure 1. Clinical course. (*Upper*) The *solid line* indicates the level of soluble interleukin-2 receptor (sIL-2); *solid arrows* indicate time points of nivolumab administration; the *arrowhead* indicates initiation of corticosteroid treatment (intravenous methylprednisolone 1000 mg daily for 3 days followed by oral prednisone 60 mg/day with subsequent tapering). (*Lower*) Chest computed tomography images before starting nivolumab treatment, 8 days after the last administration of nivolumab, and 20 days after starting corticosteroid treatment.

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