Nivolumab Effective for Gastric and Lung Cancers but Not for Multiple Myeloma in a Multiple Primary Cancer Patient

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1. Introduction

Multiple myeloma (MM) is a hematological malignancy for which survival has been prolonged through the development of new agents such as proteasome inhibitors, immunomodulators, and antibody drugs [1–3]. The median survival of patients with MM has increased from 3 to 8 years in the last 15 years. However, second primary cancers have created problems with the long-term survival of patients with MM [4]. It has been reported that the risk of developing solid tumors remains unchanged, but the risk of developing hematological malignancies is significantly higher, especially in patients treated with immunomodulators such as lenalidomide [5–7]. In addition, the prognosis of patients with second primary cancers has been reported to be worse than that of patients without them [8, 9].

Nivolumab is classified as a checkpoint inhibitor that is a monoclonal antibody drug against programmed cell death-1 (PD-1). The indications for PD-1 antibody drugs have been expanded to various cancers, and it has become available from the second line for unresectable advanced or recurrent gastric cancer and the first line for unresectable advanced or recurrent non-small cell lung cancer [10, 11]. In contrast, unfortunately, pembrolizumab, a similar PD-1 antibody, was found not effective for MM in combination with lenalidomide [12], so the PD-1 antibody drugs are not approved for MM in the United States and Japan.

A rare case, in which a patient who had been treated with new agents for MM developed multiple primary cancers (gastric cancer and lung cancer) and was treated with nivolumab, which was effective for gastric and lung cancers, but not for MM, is presented.

2. Case Report

A 76-year-old man noticed melena and had a medical examination. He was found to have renal dysfunction 6 years earlier, and further evaluations showed serum albumin, 2.2 g/dL; urinary protein, 4+; urinary Bence Jones protein- (BJP-) λ-type M protein positivity; decreased serum IgG,
IgA, and IgM levels; and an increased serum IgD (516 mg/dL) level. In addition, bone marrow aspiration showed clonal proliferation of plasma cells, so he was diagnosed with MM (IgD-λ type, BJP-λ type, International Staging System III). He was treated with 7 courses of bortezomib dexamethasone (BD) therapy, but due to recurrence, his therapy was changed to lenalidomide dexamethasone (Ld), and he was undergoing his 36th course. On upper gastrointestinal endoscopy, a type 1 tumor with a diameter of 30 mm was seen at the posterior wall of the corpus of the stomach, and the histopathological diagnosis of the tumor was tubular adenocarcinoma (Figures 1(a)–1(c)). And, the HER2 status of gastric cancer was negative, and MSI status of that was not examined. In addition, computed tomography (CT) showed liver metastasis of gastric cancer, so the gastric cancer was diagnosed as clinical stage IV (T3N2M1). Furthermore, CT showed a pulmonary nodule with a diameter of 20 mm in the upper lobe of the left lung, and the diagnosis of the nodule was primary lung cancer clinical stage IA2 (T1bN0M0) based on the imaging findings (Figure 2). Transbronchial lung biopsy could not be performed because the lesion of the lung cancer

Figure 1: (a) Upper gastrointestinal endoscopy findings. A type 1 tumor with a diameter of 30 mm is found on the posterior wall of the gastric body. The tumor is easily bleeding. (b) Histopathologic findings of the biopsy specimens of gastric cancer. Findings of well-differentiated adenocarcinoma. Hematoxylin and eosin staining, ×100. (c) Hematoxylin and eosin staining, ×400.

Figure 2: Clinical courses of the patient after gastric and lung cancers are diagnosed. The solid line indicates serum IgD level. Computed tomography (CT) shows the lung nodules and stomach. At the time of appearance, a pulmonary nodule with a diameter of 20 mm is found in the upper lobe of the left lung. The tumor grew over time, and a new intrapulmonary lesion appears after DOC treatment, but after nivolumab treatment, the new lesion almost disappeared and the primary lesion reduced. The gastric cancer could not be identified by CT at the start of treatment and had not changed since then. But 16 months after, gastric cancer increased. SOX: tegafur, gimeracil, oteracil potassium (TS-1), and oxaliplatin; DOC: docetaxel; Niv: nivolumab; Ld: lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide, and dexamethasone; CEA: carcinoembryonic antigen.
Table 1: Laboratory data at the time of diagnosis of gastric cancer and lung cancer.

|                      | Units          | Reference range |
|----------------------|----------------|-----------------|
| **Hematology**       |                |                 |
| WBC                  | 7.300          | µL              |
| Neut                 | 52             | %               |
| Eos                  | 2.0            | %               |
| Ba                   | 0.0            | %               |
| Mono                 | 8.0            | %               |
| Lymph                | 38             | %               |
| RBC                  | 329 × 10⁴/µL   |                 |
| Hb                   | 11.1           | g/dL            |
| Ht                   | 33.5           | %               |
| MCV                  | 89.6           | fl              |
| Platelets            | 20.1           | × 10⁴/µL        |
| **Biochemistry**     |                |                 |
| TP                   | 5.3            | g/dL            |
| Alb                  | 3.6            | g/dL            |
| T-bil                | 0.4            | mg/dL           |
| AST                  | 16             | U/L             |
| ALT                  | 27             | U/L             |
| LDH                  | 243            | U/L             |
| γ-GTP                | 106            | U/L             |
| BUN                  | 14.9           | mg/dL           |
| Cre                  | 0.86           | mg/dL           |
| Na                   | 142            | mmol/L          |
| K                    | 3.7            | mmol/L          |
| Cl                   | 110            | mmol/L          |
| Ca                   | 8.9            | mg/dL           |
| P                    | 3.1            | mg/L            |
| IgG                  | 453            | mg/dL           |
| IgA                  | 33             | mg/dL           |
| IgM                  | 21             | mg/dL           |
| IgD                  | 10.5           | mg/dL           |
| **Tumor markers**    |                |                 |
| CEA                  | 2.4            | ng/mL           |
| CYFRA                | 1.4            | ng/mL           |
| Pro-GRP              | 66.6           | pg/mL           |
| **Urinalysis**       |                |                 |
| Protein              | 0.22           | g/gCr           |
| RBC                  | (—)            |                 |
| WBC                  | (—)            |                 |

WBC: white blood cells; Neut: neutrophils; Eos: eosinophils; Ba: basophils; Mono: monocytes; Lymph: lymphocytes; RBC: red blood cells; Hb: hemoglobin; Ht: hematocrit; MCV: mean corpuscular volume; TP: total protein; Alb: albumin; T-Bil: total bilirubin; AST: aspartate transaminase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; γ-GTP: gamma-glutamyl transpeptidase; BUN: blood urea nitrogen; Cre: creatinine; Na: sodium; K: potassium; Cl: chloride; Ca: calcium; P: phosphorus; IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; IgD: immunoglobulin D; CEA: carcinoembryonic antigen; CYFRA: cytokeratin-19; Pro-GRP: progastrin releasing peptide.

A rare case, in which nivolumab treatment was administered for primary gastric cancer and primary lung cancer that developed during treatment for MM, and the gastric cancer and lung cancer responded, but the MM did not, was reported. Patients with second primary cancers that develop after treatment for MM have been reported to have a 2- to 6-fold increased risk of death compared to those without second primary cancers [8, 9]. In particular, patients treated with lenalidomide have a high incidence of secondary carcinogenesis, which is estimated to be 5–8% [5–7]. In addition, older age is also considered to be a significant risk factor for the development of secondary primary cancers [13]. According to a Swedish report, 1,547 of 26,627 patients with MM developed second primary cancers, but the rate of gastrointestinal cancers was low (364 patients, 1.4%) and that of respiratory cancers was also low (68 patients, 0.25%). A study of 2,732 patients with MM treated with lenalidomide found no gastric cancers, 5 (0.18%) lung cancers, and only 3 multiple primary solid cancer cases [13]. It is considered that cases such as the present one in which gastric cancer and lung cancer developed as second primary cancers are extremely rare. The present patient was an elderly patient who had been receiving long-term lenalidomide and dexamethasone treatments with relapse of MM after proteasome inhibitor treatment. Because the risk of death from MM is much higher than the risk of death from second primary cancers, lenalidomide treatment should be given aggressively for MM, but it is necessary to always keep in mind the onset of second primary cancers, especially in elderly patients receiving long-term lenalidomide treatment.
Nivolumab is classified as a checkpoint inhibitor that is a monoclonal antibody drug against PD-1. This drug can be used in first-line, second-line, and third-line treatments for unresectable gastric cancer and lung cancer [10, 11]. In the present case, there was no pathological proof of lung cancer, but the pulmonary nodule was likely to be primary lung cancer based on the CT findings. Gastric cancer and lung cancer were evaluated as stable disease and partial remission, respectively, based on clinical and imaging findings. However, nivolumab was not effective for MM, so daratumumab was also used, but it was also ineffective, and the patient died. Pembrolizumab, a PD-1 antibody similar to nivolumab, also failed to show efficacy against MM [12], which led to the discontinuation of clinical trials with nivolumab. Therefore, PD-1 antibody drugs are not indicated for MM. PD-1 antibody drugs have been reported to be effective for MM in some cases [14], but not in the present case. Other therapeutic approaches may be needed for MM, but in the present case, treatment for MM alone was associated with a high risk of exacerbation of other multiple cancers, so further approaches may have been difficult.

With the development of treatment for MM, the diagnosis and treatment of multiple primary cancers become very important issues. The present case was treated with nivolumab, but it was ineffective for MM. With the accumulation of more such multiple primary cancers cases, more effective treatments might be developed.

Data Availability
The figure data used to support the findings of this study are included within the article.

Conflicts of Interest
The authors have no conflicts of interest to disclose.

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