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【 CASE REPORT 】

Nivolumab for Methotrexate-associated Classic Hodgkin's Lymphoma in a Rheumatoid Arthritis Patient

Keisuke Tanaka, Mai Kuboki, Satoshi Koi and Shigeo Toyota

Abstract:
Nivolumab exerts therapeutic activity in patients with classic Hodgkin's lymphoma (CHL) but may cause several types of immune-related adverse events. Some rheumatoid arthritis (RA) patients develop CHL during methotrexate therapy (MTX-CHL); however, the efficacy and safety of nivolumab for these patients remain unclear. A 68-year-old woman was diagnosed with CHL after six years of MTX therapy for RA. The disease did not respond to any type of chemotherapy. Nivolumab was then initiated, and the patient was successfully treated without the reactivation of RA. The reactivation of RA always needs to be considered with the administration of nivolumab.

Key words: classic Hodgkin's lymphoma, methotrexate, rheumatoid arthritis, nivolumab

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Introduction

The efficacy of immune checkpoint inhibitors as cancer therapy has been demonstrated. Programmed cell death-1 (PD-1) is a protein expressed on activated T cells, and the pathway of PD-1 and its ligands (PD-L1/L2), expressed on antigen-presenting cells, induces peripheral immune tolerance (1, 2). Some cancer cells also express PD-1 ligands and evade immune surveillance through this pathway, and the blockade of this pathway with anti-PD-L1 antibodies has been shown to enhance anti-tumor effects (3).

Nivolumab is a fully human IgG4 monoclonal antibody that targets PD-1 and exerts anti-tumor effects by blocking immune tolerance for cancer cells. It has already been approved in Japan for the treatment of melanoma, non-small cell lung cancer, and renal cell carcinoma based on its efficacy in the Japanese population (4-7). Its efficacy and safety for relapsed or refractory classic Hodgkin's lymphoma (CHL) were subsequently reported (8, 9), and it was approved for the treatment of relapsed or refractory CHL in Japan in December 2016.

However, nivolumab inhibits immune tolerance of not only cancer cells but also normal tissues and may cause several types of immune-related adverse events (irAEs) (10). Rheumatoid arthritis (RA) is an autoimmune disease, and patients treated with methotrexate (MTX) occasionally develop lymphoproliferative disorders (MTX-LPDs) several years after the initiation of its administration (11). The majority of MTX-LPDs are diffuse large B-cell lymphomas, among which CHL accounts for 10-30% (MTX-CHL) (12-15).

Since MTX-CHL patients have been excluded from clinical trials on nivolumab, its efficacy and safety in these patients remain unclear. To our knowledge, MTX-HL patients have yet to be treated with nivolumab.

Case Report

A 68-year-old woman had been diagnosed with RA in her 20s and treated with MTX. Six years after the initiation of MTX therapy, she developed lymphadenopathy, and MTX was discontinued without the initiation of other therapies for RA. After the withdrawal of MTX, her lymphadenopathy temporarily diminished, but systemic lymphadenopathy and splenomegaly were detected after two years. She developed a fever and fatigue that progressively worsened. A cervical lymph node biopsy was performed, and she was diagnosed with CHL (mixed cellularity type).

The histopathological findings are shown in Fig. 1. Hema-

Department of Hematology, Yokosuka Kyosai Hospital, Japan
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Correspondence to Dr. Keisuke Tanaka, keisukeaota@yahoo.co.jp

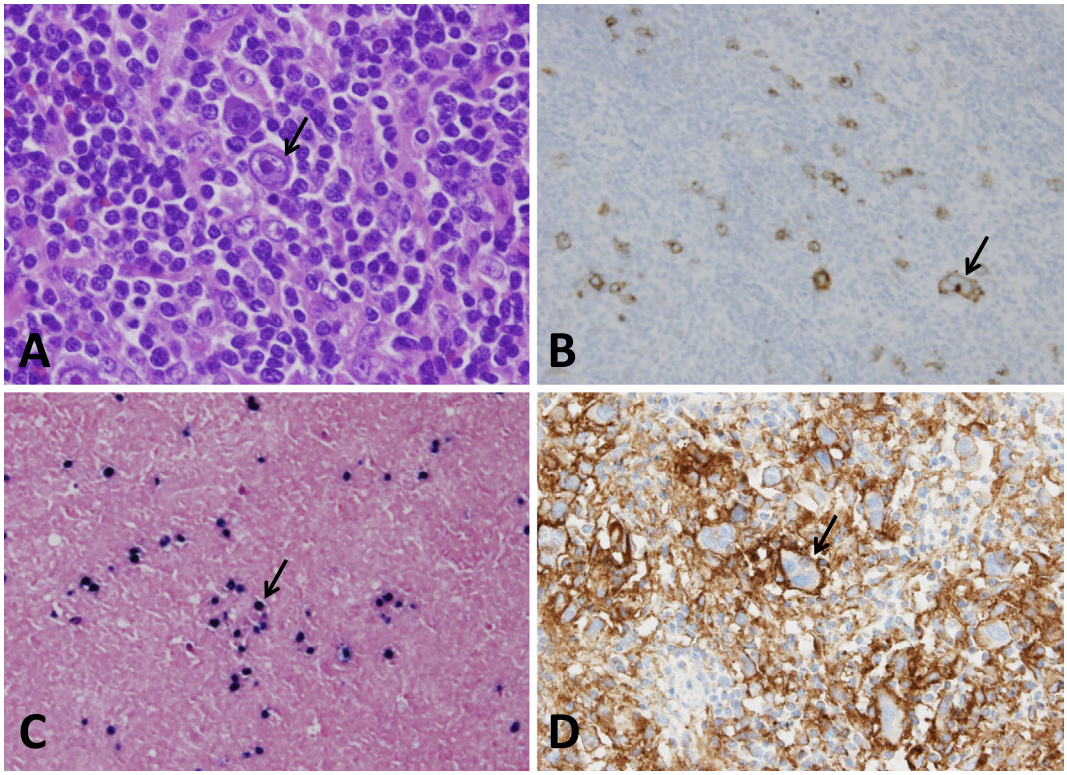

Figure 1. **The initial lymph node biopsy of the patient. A: Hematoxylin and Eosin staining (400×). B: CD30 immunostaining (100×). C: EBER immunostaining (100×). D: PD-L1 immunostaining (400×). Tumor cells are positive for CD30, EBER, and PD-L1 (arrows).**

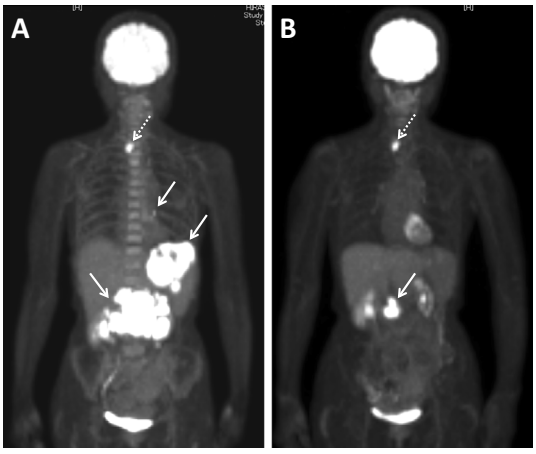

Figure 2. **FDG-PET. A: Before the introduction of nivolumab. B: After seven courses of nivolumab (3 mg/kg every 2 weeks). Solid arrows indicate lesions. The areas with an abnormal uptake (indicated with dotted arrows) are not lesions (proven by a biopsy).**

toxylin and Eosin staining revealed large tumor cells (Hodgkin's cells) that were positive for CD30, Epstein-Barr virus-encoded small RNA (EBER), and PD-L1 according to immunohistochemical staining. Between the cessation of MTX and diagnosis of CHL, RA flares were not observed despite the absence of any treatment.

At her diagnosis, the clinical stage was IIIB (systemic lymph node and spleen), the international prognostic score (IPS) was 4 (albumin <4 g/dL, hemoglobin <10.5 g/dL, age >65 years old, lymphocytes <8%), and the clinical disease activity index (CDAI) was 0. Serum lactate dehydrogenase (LDH) was 261 U/L (upper limit 229 U/L) and C-reactive protein (CRP) was 4.8 mg/dL (upper limit 0.3 mg/dL). She was treated with eight courses of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) but only had a partial response. Therefore, she was treated with ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisolone), and GDP (gemcitabine, dexamethasone, and cisplatin) as salvage therapies but did not respond to any of these treatments. Brentuximab vedotin (BV, 1.8 mg/kg every 3 weeks) was initiated; however, after 7 courses, fluorodeoxyglucose positron emission tomography (FDG-PET) showed the progression of mediastinal and abdominal lymph node and spleen lesions (Fig. 2A). Her performance status was not good (Eastern Cooperative Oncology Group performance status of 2) because of the subsequent complication of RA, and the patient refused to undergo allogeneic stem cell transplantation. Therefore, we decided to introduce nivolumab as a treatment for refractory CHL.

She had no other remarkable medical history or comorbidity apart from RA. Although some finger joints were deformed at the beginning of the nivolumab treatment, there was no active arthritis or symptoms (joint pain) in the absence of therapy for RA (CDAI:0). Blood tests were negative for rheumatoid factor and anti-cyclic citrullinated pep-

Table 1. Laboratory Findings with the Initiation of Nivolumab.

[Complete blood cell count]	
White blood cell	12,700 /μL
Neutrophil	87 %
Lymphocyte	5.5 %
Eosinophil	4 %
Monocyte	3.5 %
Basophil	0 %
Red blood cell	314×10⁴ /μL
Hemoglobin	10.2 g/dL
Platelet	19.6×10⁴ /μL
[Biochemistry]	
LDH	199 U/L
AST	32 U/L
ALT	59 U/L
γ-GTP	225 U/L
ALP	876 U/L
T-Bil	0.5 mg/dL
BUN	16 mg/dL
Cre	0.7 mg/dL
Na	133 mEq/L
K	4.0 mEq/L
Cl	97 mEq/L
Albumin	2.8 g/dL
Amylase	154 U/L
[Serology]	
C-reactive protein	28.4 mg/dL
[Autoantibody]	
Rheumatoid factor	<3 IU/mL
Anti-CCP antibody	<0.6 U/mL

LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma-glutamyl transpeptidase, ALP: alkaline phosphatase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine

tide antibody (Table 1). Laboratory data showed hemoglobin 8.6 g/dL (lower limit 11.3 g/dL), LDH 277 U/L, and CRP 21.76 mg/dL (Table 1). The copy number of serum Epstein-Barr virus (EBV) had increased to 2,000 copies/mL (≤200 copies/mL is undetectable).

After 2 courses of nivolumab (3 mg/kg every 2 weeks), an asymptomatic elevated serum amylase level appeared, and we diagnosed this event as a nivolumab-related irAE (16, 17) (Fig. 3). Nivolumab was therefore discontinued, and we started treating the patient with prednisolone (PSL). The serum amylase levels decreased after the initiation of PSL (starting at 20 mg/day and reduced to 10 mg/day), so nivolumab was restarted (3 mg/kg every 2 weeks). The serum amylase levels did not increase after the resumption of nivolumab. Serum EBV was not detectable after four courses of nivolumab, and FDG-PET showed that the mediastinal and spleen lesions had disappeared while the abdominal lesion had diminished (partial response) after seven courses (Fig. 2B). Nivolumab exerted strong effects on heavily treated refractory CHL. In addition, no active arthritis or joint pain was observed during the nivolumab treatment courses. Seven months after treatment initiation, she has shown no symptoms and is tolerating nivolumab.

Discussion

To our knowledge, this is the first case report of nivolumab therapy for an MTX-HL patient with RA. Retrospective studies have assessed the safety of anti-PD-1/PD-L1 therapy for other types of cancers with pre-existing autoimmune diseases; the findings of three of these studies are shown in Table 2 (18-20). A total of 126 patients were included (melanoma: 71, non-small-cell lung cancer: 56), with 124 receiving anti-PD-1 therapy and only two being treated with anti-PD-L1 therapy. One of the pre-existing autoim-

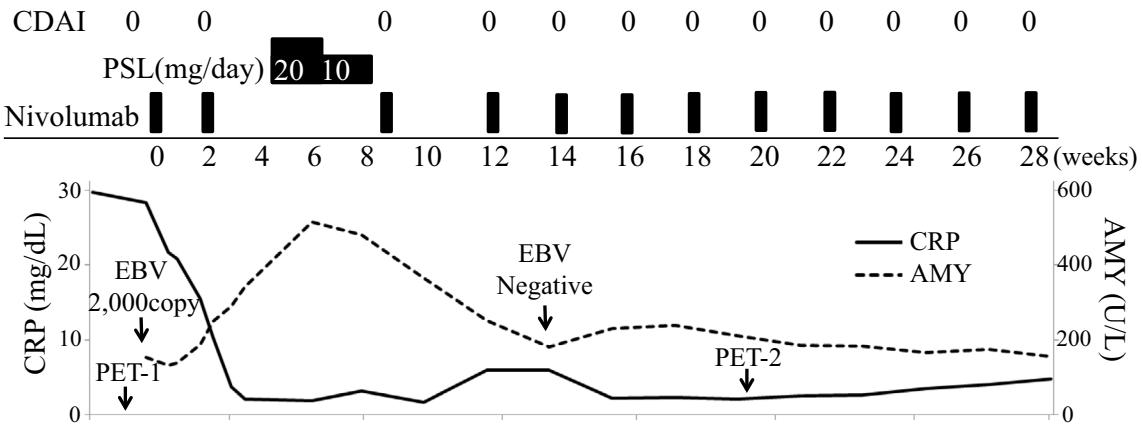

Figure 3. Clinical course of nivolumab treatment. PET-1: before the introduction of treatment, PET-2: after seven cycles of treatment (shown in Figure 2A, B). Serum EBV-PCR was positive before the initiation of treatment and became negative after four cycles. RA flares were not observed during the clinical course. CDAI: clinical disease activity index, EBV: Epstein-Barr virus, PCR: polymerase chain reaction, PET: positron emission tomography, PSL: prednisolone (mg/day)

Table 2. Findings of Three Studies on Patients with Pre-existing Autoimmune Diseases Treated with Anti-PD-1/PD-L1 Inhibitors.

Autoimmune disease	Patient, n	Flare, n (%)
Rheumatologic		
Rheumatoid arthritis	26	14 (53.8)
Other arthritis	10	4 (40)
Myositis	1	1 (100)
Vasculitis	2	0
Polymyalgia rheumatica	9	7 (77.8)
Sarcoidosis	5	2 (40)
SLE	3	1 (33.3)
Scleroderma	4	1 (25)
Sjögren's syndrome	3	2 (66.7)
Dermatologic		
Psoriasis	23	9 (39.1)
Others	4	0
Gastrointestinal		
Ulcerative colitis	6	0
Crohn disease	6	0
Celiac disease	1	0
Neurologic		
Guillan-Barré syndrome	3	0
Myasthenia gravis	2	0
Multiple sclerosis	3	0
Others	2	0
Endocrine (thyroiditis)	19	3 (15.8)
Respiratory (asthma)	2	0
Hematologic (AIHA or ITP)	3	2 (66.7)

SLE: systemic lupus erythematosus, AIHA: autoimmune hemolytic anemia, ITP: immune thrombocytopenic purpura

mune diseases was RA, and approximately 50% of patients showed the reactivation of RA after the introduction of anti-PD-1/PD-L1 therapy. The activity of pre-existing autoimmune diseases was identified as a risk factor for flares in these studies, and patients with rheumatic diseases were more likely to show reactivation than those with gastrointestinal diseases and neurological disorders. The safety of anti-PD-1 therapy for patients with pre-existing autoimmune diseases has not been investigated in detail and remains controversial; however, most flares in patients with RA were not severe and were easily managed without the termination of anti-PD-1 therapy. In the present case, RA did not reactivate during nivolumab therapy, which was thus continued safely.

Roemer et al. reported genomic alterations in PD-1 ligands (chromosome 9q24.1) in 108 CHL patients (21); 107 patients had genomic alterations, and a correlation was observed between the PD-L1 expression assessed by immunohistochemistry and relative genomic alterations. Amplification was associated with the stronger expression of PD-L1 than polysomy and copy gain, and the incidence of 9q24.1 amplifications was higher in advanced-stage CHL than in early-stage CHL. They also reported that the expression of PD-L1 was stronger in EBV-positive cases than in EBV-negative cases (shown in the appendix). These previous findings suggest that the tumor cells of advanced-stage EBV-positive HL may express PD-L1 more strongly than those of early-stage EBV-negative HL. In a phase II study of nivolumab for HL, a correlation was observed between the level of PD-L1 expressed on tumor cells and the efficacy of nivolumab (22). Since the majority of cases of MTX-CHL are positive for EBV (12-15, 23), nivolumab may be more beneficial as a treatment option for advanced-stage MTX-HL due to the stronger expression of PD-L1, than for early-stage disease. Clinical trials on nivolumab for EBV-positive lymphomas are ongoing (NCT03258567, NCT02973113), and this issue may be clarified based on the findings obtained therein.

Conclusion

We successfully treated a patient with nivolumab without RA flares. Refractory MTX-CHL patients are sometimes unable to receive high-dose chemotherapy or stem cell transplantation because of a poor performance status and elderly age. Thus, the treatment of patients with low-invasive therapy is important. BV is also a tolerable regimen for MTX-CHL patients with RA and is an important treatment option to be considered (24). The majority of RA flares induced by nivolumab are low-severity and thus manageable, and EBV may suppress the antitumor immunity by the PD-1/PD-L1 pathway in MTX-CHL cases. Nivolumab may therefore be suitable for these patients.

The authors state that they have no Conflict of Interest (COI).

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