Nivolumab for Methotrexate-associated Classic Hodgkin’s Lymphoma in a Rheumatoid Arthritis Patient: A Case Report

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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

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. Hematoxylin 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 de-
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                       | 31×10^12 /μL |
| Hemoglobin                           | 10.2 g/dL      |
| Platelet                             | 19.6×10^11 /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 IU/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

Formed 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 peptide 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

![Figure 3](image_url). Clinical course of nivolumab treatment. PET-1: before the introduction of treatment, PET-2: after seven cycles of treatment (shown in Figure 2A, 2B). 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)
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 autoimmune 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 reaction 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.

Margaretha 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-CHL 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).**

**References**

1. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 236: 219-242, 2010.
2. Boussiotis VA, Chatterjee P, Li L. Biochemical signaling of PD-1 on T cells and its functional implications. Cancer J 20: 265-271, 2014.
3. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 99: 12293-12297, 2002.
4. Yamazaki N, Kiyohara Y, Ubara H, et al. Efficacy and safety of nivolumab in Japanese patients with previously untreated advanced melanoma: A phase II study. Cancer Sci 108: 1223-1230, 2017.
5. Hida T, Nishio M, Nagami N, et al. Efficacy and safety of nivolumab in Japanese patients with advanced or recurrent squamous non-small cell lung cancer. Cancer Sci 108: 1000-1006, 2017.
6. Nishio M, Hida Y, Atagi S, et al. Multicentre phase II study of nivolumab in Japanese patients with advanced or recurrent non-squamous non-small cell lung cancer. ESMO open 1: e000108, 2017.
7. Tomita Y, Fukasawa S, Shinohara N, et al. Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study. Jpn J Clin Oncol 47.
8. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin’s lymphoma. N Engl J Med 372: 311-319, 2015.
9. Maruyama D, Hatake K, Kinoshita T, et al. Multicenter phase II study of nivolumab in Japanese patients with relapsed or refractory classical Hodgkin’s lymphoma. Cancer Sci 108: 1007-1012, 2017.
10. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol 8: 1-14, 2017.
11. Kamel OW, van de, Rijn M, Weiss LM, et al. Brief Report: Reversible Lymphomas Associated with Epstein-Barr Virus Occurring during Methotrexate Therapy for Rheumatoid Arthritis and Dermatomyositis. N Engl J Med 328: 1317-1321, 1993.
12. Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression. Eur J Hematol 91: 20-28, 2013.
13. Gion Y, Iwaki N, Takata K, et al. Clinicopathological analysis of methotrexate-associated lymphoproliferative disorders: Comparison of diffuse large B-cell lymphoma and classical Hodgkin’s lymphoma types. Cancer Sci 108: 1271-1280, 2017.
14. Tokuhira M, Saito S, Okuyama A, et al. Clinicopathological investigation of methotrexate-induced lymphoproliferative disorders, with a focus on regression. Leuk Lymphoma 59: 1143-1152, 2018.
15. Kurita D, Miyoshi H, Ichikawa A, et al. Methotrexate-associated lymphoproliferative disorders in patients with rheumatoid arthritis clinicopathologic features and prognostic factors. Am J Surg Pathol 43: 869-884, 2019.
16. Ikeychi K, Okuma Y, Tabata T. Immune-related pancreatitis secondary to nivolumab in a patient with recurrent lung adenocarcinoma: A case report. Lung Cancer 99: 148-150, 2016.
17. Friedman CF, Clark V, Raikhel AV, et al. Thinking critically about classifying adverse events: incidence of pancreatitis in patients treated with nivolumab + ipilimumab. J Natl Cancer Inst 109: 1-3, 2017.
18. Gutzmner R, Koop A, Meier F, et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmune or ipilimumab-triggered autoimmunity. Eur J Cancer 75: 24-32, 2017.
19. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol 28: 368-376, 2017.
20. Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. J Clin Oncol 36: 1905-1912, 2018.
21. Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin’s lymphoma and predict outcome. J Clin Oncol 34: 2690-2697, 2016.
22. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin’s lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicentre, single-arm phase 2 trial. Lancet Oncol 17: 1283-1294, 2016.
23. Mariette X, Hatem DC, Warszawski J, Liote F, Balandraud N, Sibilia J. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. Blood 99: 3909-3915, 2002.
24. Nakazato T, Takanashi S, Hirano M, et al. Brentuximab vedotin is effective for rheumatoid arthritis in a patient with relapsed methotrexate-associated Hodgkin’s lymphoma. Ann Hematol 97: 1489-1491, 2018.