Successful treatment of lung cancer coexisting with B-cell lymphoma with pembrolizumab following rituximab-included chemotherapy: A case report

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Received December 16, 2023; Accepted February 7, 2024

DOI: 10.3892/mco.2024.2731

Abstract. The combined occurrence of lung cancer and B-cell lymphoma, such as mucosa-associated lymphoid tissue (MALT) lymphoma, is rare. The efficacy and safety of immune checkpoint inhibitors (ICIs) remain unknown in this population of patients, and the occurrence of ICI-induced exacerbation of lymphoma is concerning. The present study describes a case of successful treatment with pembrolizumab following rituximab-containing chemotherapy for lung cancer complicated by MALT lymphoma. The patient was a 69-year-old woman diagnosed with MALT lymphoma based on a biopsy of stomach ulcerative lesions, and advanced lung cancer based on a biopsy of a lymph node in the left pulmonary hilum. Complete remission was achieved after one cycle of rituximab and bendamustine therapy for MALT lymphoma. Pembrolizumab monotherapy was subsequently initiated, resulting in a good response for lung cancer without recurrence or exacerbation of the lymphoma. In conclusion, the present study suggested that pembrolizumab, following rituximab-containing therapy, could be a treatment option for patients with lung cancer coexisting with MALT lymphoma.

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Abbreviations: ICI, immune checkpoint inhibitor; MALT, mucosa-associated lymphoid tissue; NSCLC, non-small cell lung carcinoma; PFS, progression-free survival; OS, overall survival; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; FL, follicular lymphoma; BR, bendamustine and rituximab; HP, *Helicobacter pylori*; CT, computed tomography; 18F-FDG, 18F-fluorodeoxyglycose; PET-CT, positron emission tomography-computed tomography; PR, partial response; CR, complete remission; ORR, overall response rate; r/r, relapse or recurrent

Key words: lung cancer, ICI, lymphoma, efficacy and safety

Introduction

Cases of non-small cell lung carcinoma (NSCLC) complicated by B-cell lymphoma are relatively rare. The majority of previous reports regarding such cases included accidental diagnoses or successful treatments through surgical resection (1). However, cases of advanced lung carcinoma and B-cell lymphoma being treated by immune checkpoint inhibitors (ICIs) have rarely been reported, except for two cases with conflicting results involving treatment with sintilimab and pembrolizumab (2,3).

The efficacy of ICIs has been demonstrated in various types of malignant tumors, including NSCLC. Some clinical trials have revealed that pembrolizumab improves progression-free survival (PFS) and overall survival (OS) in treatment-naïve patients with advanced NSCLC, particularly those with a high programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) (4,5). However, the efficacy of ICIs for malignant lymphomas is unknown, with the exception of Hodgkin's lymphoma and some types of B-cell lymphoma, such as mucosa-associated lymphoid tissue (MALT) lymphoma. In particular, in the case of indolent lymphomas, such as follicular lymphoma (FL) or MALT lymphoma, the efficacy of ICIs is controversial (6,7).

Moreover, the safety of ICIs in B-cell lymphoma has yet not been clarified. Some studies have reported the development of malignant lymphomas, such as FL, during or after treatment with ICIs (3,8,9); one study suspected that the development of lymphoma might be caused by ICIs (3). Thus, consensus on the commencement of ICI treatment for patients with advanced lung cancer in conjunction with B-cell lymphomas is not unanimous because of fear of lymphoma progression.

Herein, we present the case of successful treatment with pembrolizumab monotherapy following bendamustine and rituximab (BR) therapy for a patient simultaneously diagnosed with advanced NSCLC and MALT lymphoma, which could help determine the efficacy and safety of ICI treatment for this demographic.

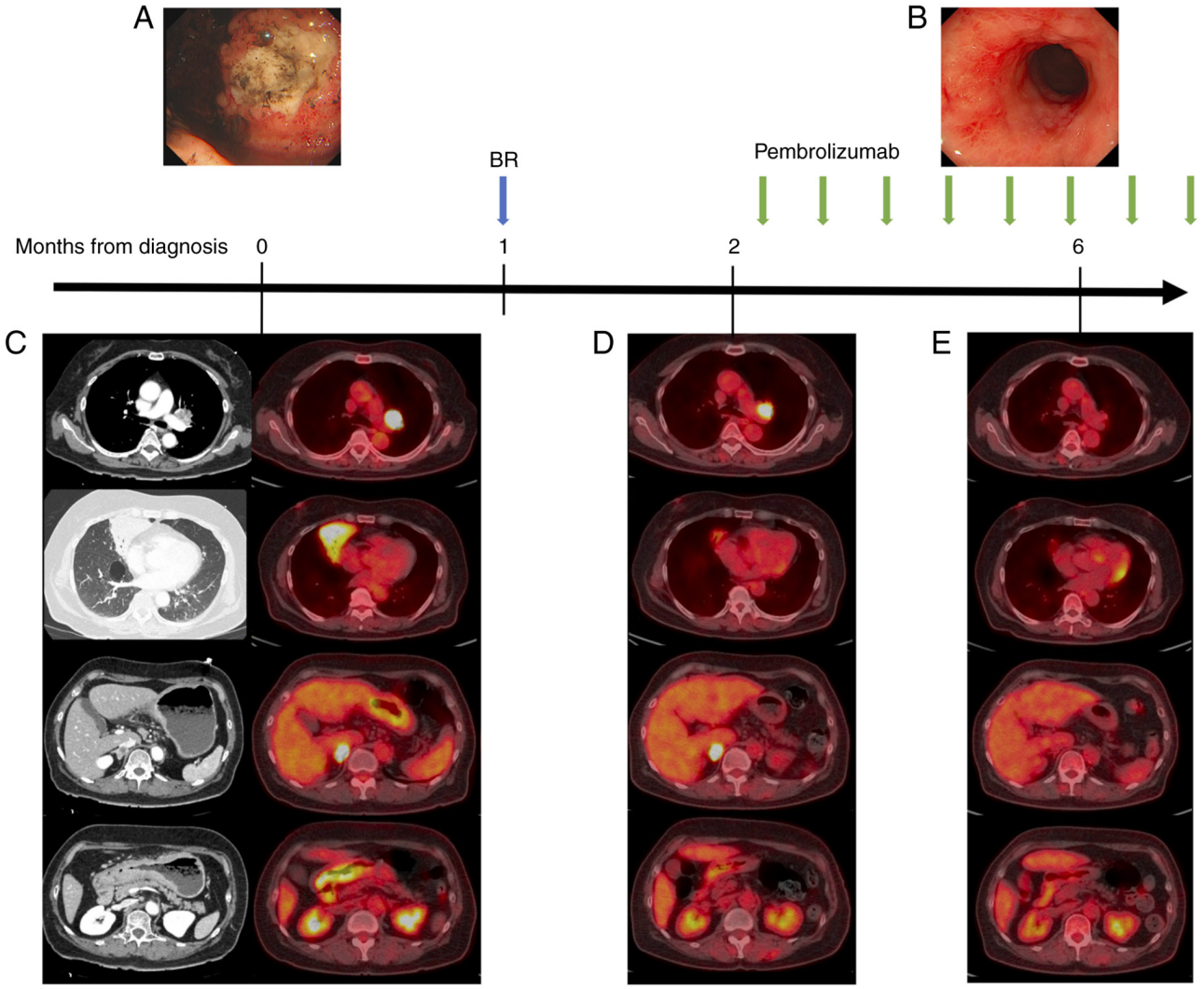

Figure 1. Clinical timeline and longitudinal change of tumor lesions in the PET-CT image and gastrointestinal endoscopy. (A) Ulcerative lesions formed by MALT lymphoma were found during gastrointestinal endoscopy. (B) After 4 months from the start of treatment, gastrointestinal endoscopy found an erosive lesion in the stomach wall and the biopsy of this lesion found no lymphoma cells. (C) At diagnosis, the CT image showed swelling of left pulmonary hilar lymph node and right adrenal gland in addition to atelectasis in the middle lobe of the right lung and thickness in the stomach wall. The PET-CT image showed 18F-FDG uptake in these lesions. (D) After one cycle of BR therapy, 18F-FDG uptake in the atelectasis and stomach wall reduced, leaving other lesions. (E) After 4 months from pembrolizumab commencement, 18F-FDG uptake in the swelling of the hilar lymph node and adrenal gland were reduced. PET-CT, positron emission tomography-computed tomography; MALT, mucosa-associated lymphoid tissue; CT, computed tomography; 18F-FDG, 18F-fluorodeoxyglucose; BR, bendamustine and rituximab.

Case report

A 69-year-old female patient visited Kyoto University Hospital (Kyoto, Japan) in March 2022 with an upper gastrointestinal hemorrhage. She had no history of smoking and a specific medical history, including *Helicobacter pylori* (HP) infection. Upper gastrointestinal endoscopy revealed ulcerative lesions in the stomach without active bleeding (Fig. 1A), and a biopsy of the lesions revealed MALT lymphoma (positive for cluster of differentiate 20 (CD20) and negative for CD3). Serological evaluation for immunoglobulin G (IgG) antibody against HP was negative, and MALT1 translocation was detected by fluorescence *in situ* hybridization. Bone marrow biopsy did not indicate malignancy. Computed tomography (CT) revealed stomach wall thickening, swollen lymph nodes around the stomach and left pulmonary hilum, and atelectasis in the middle lobe of the right lung, whereas the positron emission tomography-CT (PET-CT) image (Fig. 1C) showed right adrenal gland enlargement with 18F-fluorodeoxyglycose (18F-FDG) uptake. Magnetic resonance imaging showed no brain metastases. Although the stomach lesions were diagnosed as MALT lymphoma, the lesions in the lung and adrenal glands were suspected to be complicated by other diseases, such as lung cancer. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the left pulmonary hilum indicated NSCLC with suspected multiple distant metastases to the adrenal gland and the opposite side of the lung [cTxN1M1c, cStageIVB, no oncogenic driver mutations, PD-L1 TPS ≥75% (22C3)]. However, brush cytology detected atypical lymphoid cells, indicating that the atelectasis was caused by MALT lymphoma. Based on these findings, the patient was diagnosed with advanced NSCLC complicated with MALT lymphoma. Although NSCLS should be treated promptly, treatment for MALT lymphoma was prioritized,

Table I. B-cell lymphoma and other cancers treated with ICIs.

First author, year	Age/ sex	Lymphoma	Coexisting cancer	ICIs	Onset of lymphoma	Clinical course	Safety of ICIs for lymphoma	(Refs.)
Yuan, 2020	67/M	MALT lymphoma	LC (Ad)	Sintilimab	Before ICI induction	During chemotherapy with CBDCA, PTX, and bevacizumab, the MALT lymphoma was diagnosed and treated with rituximab and lenalidomide, resulting in CR. Sintilimab therapy for the progression of LC was initiated and stable condition was maintained	Maintained CR after the start of ICI treatment	(2)
Marumo, 2021	74/F	FL	LC (SQ)	Pembrolizumab	During ICI treatment	Following the commencement of pembrolizumab for LC, FL was developed and treated with rituximab. After achieving CMR and resuming pembrolizumab for LC, FL was exacerbated and R-CVP therapy was required to achieve CMR	Development and exacerbation of lymphoma might be induced by ICIs	(3)
Osumo, 2022	84/F	MALT lymphoma	Urothelial cell carcinoma	Pembrolizumab	During ICI treatment	Two years after the start of pembrolizumab, the MALT lymphoma was diagnosed in the right parotid gland. After the completion of rituximab therapy, pembrolizumab monotherapy was resumed	Good response was achieved after resuming ICI treatment	(9)

ICIs, immune checkpoint inhibitors; MALT, mucosa-associated lymphoid tissue; LC, lung cancer; Ad, adenocarcinoma; CBDCA, carboplatin; PTX, paclitaxel; CR, complete remission; FL, follicular lymphoma; SQ, squamous cell carcinoma; CMR, complete metabolic response; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone.

considering stomach bleeding. We initiated one course of bendamustine (90 mg/m^2) plus rituximab (375 mg/m^2) therapy. PET-CT showed reduced 18F-FDG uptake in the stomach wall and atelectasis in the right lung, except in other lesions (Fig. 1D). We initiated pembrolizumab (200 mg/kg body weight) therapy as a prognostic factor for NSCLC. Four months after pembrolizumab initiation, PET-CT showed no 18F-FDG uptake in any of the lesions (Fig. 1E). An erosive lesion was found in the stomach wall through gastrointestinal endoscopy and a re-biopsy of the stomach wall showed no residual lesions of MALT lymphoma, indicating pathological remission of the MALT lymphoma (Fig. 1B). The patient's best response was a good partial response (PR) for NSCLC and complete remission (CR) for MALT lymphoma. The treatment effect was maintained for more than 1 year without recurrence under continuous pembrolizumab monotherapy (cut-off date: April 25, 2023).

Discussion

Cases of lung cancers being complicated by B-cell lymphoma are relatively rare. To date, only a few cases of advanced lung

cancer with B-cell lymphoma have been reported. Two of these cases were successfully treated with alectinib or osimertinib (10,11) whereas the other cases reported partial efficacy of sintilimab treatment and exacerbation after pembrolizumab treatment in patients with advanced lung cancer and B-cell lymphoma (2) To the best of our knowledge, this is the first report of pembrolizumab treatment following one course of BR therapy for advanced NSCLC accompanied by MALT lymphoma, which resulted in good disease control.

The antitumor efficacy of ICIs has been demonstrated in many clinical trials. Pembrolizumab is a humanized IgG4 antibody against the PD-1 receptor, and its efficacy in lung cancer has previously been demonstrated. In particular, the Keynote-024 clinical trial revealed that pembrolizumab monotherapy for patients with NSCLC expressing PD-L1 ≥50% significantly improved the OS and PFS (4) The efficacy of ICIs for malignant lymphomas has not been determined, with the exception of Hodgkin's lymphoma. Clinical trials evaluating the efficacy of nivolumab for relapse or recurrent (r/r) lymphoma showed an overall response rate (ORR) of approximately 40% in r/r FL (6); however, phase 2 trials with nivolumab treatment for r/r FL showed an ORR of only 4% (7) In contrast, pembrolizumab plus rituximab therapy for FL showed relatively good ORR (67%) and CR (50%), with long-term remission (12).

The efficacy of ICIs in treating MALT lymphoma remains unknown, although a clinical study evaluating their efficacy is ongoing (NCT04268277). Three reports have investigated the treatment of B-cell lymphoma complicated with other solid cancers with ICIs (Table I). Two studies reported that MALT lymphoma with solid tumors was controlled by ICI treatment followed by rituximab monotherapy or rituximab-included chemotherapy (2,9) and one of which achieved CR for MALT lymphoma and PR for lung cancer by treatment with five courses of rituximab-included regimen, followed by sintilimab monotherapy (2). Another study reported CR for MALT lymphoma that developed during pembrolizumab treatment for urothelial cell carcinoma and was treated with four courses of rituximab (9) These cases suggest that ICIs with rituximab-containing regimens may be effective in these populations. However, the remaining patient reported the development and exacerbation of FL after pembrolizumab monotherapy, suggesting that lymphoma progression may be induced by ICI therapy (3).

However, the mechanisms underlying the development and exacerbation of B-cell lymphoma by ICI remain unclear. Two studies have reported the development of lymphoma after the cessation of ICI therapy (8,13) and one suggested that nivolumab treatment might inhibit the development of lymphoma (8) Moreover, the development of B-cell lymphoma after ICI treatment requires a long time. Previous studies have reported 80 cycles of treatment, 27 cycles of nivolumab, and approximately 2 years from pembrolizumab commencement (8,9,14) for the development of B-cell lymphoma, indicating that ICIs were not a direct cause of lymphoma development. However, the development and exacerbation of lymphoma during one case of pembrolizumab treatment suggested that the mechanism of exacerbation might be the depression of follicular helper T-cells and follicular regulatory T-cells induced by anti-PD-1 (3). Although the population at risk of lymphoma development and exacerbation is unknown, it is important to focus on this phenomenon during or after ICI treatment.

In our case, we observed CR for MALT lymphoma and good PR for lung cancer treated with one course of BR therapy, followed by pembrolizumab monotherapy. The efficacy of three courses of BR therapy for MALT lymphoma has been reported to be high, with an ORR of 100% and long-term response (15) One cycle of BR therapy may be effective enough to prevent relapse or recurrence after pembrolizumab initiation. Considering cases of MALT lymphoma with no relapse or exacerbation after ICI treatment (2,9) the initiation of ICI treatment may be safe after CR is achieved with a rituximab-containing treatment.

Pembrolizumab treatment following a rituximab-including regimen may be safely initiated in patients with MALT lymphoma and solid cancers, such as lung cancer.

In conclusion, cases of non-small cell lung cancer (NSCLC) simultaneously diagnosed with MALT lymphoma are rare. Pembrolizumab treatment following a rituximab-containing regimen could be a treatment option in such cases.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

DN wrote the original draft, and contributed to conception, design, data acquisition and data analysis. YS and HO contributed to supervision, writing, conception, design, data analysis, and reviewed and edited the manuscript. CM contributed to supervision, data acquisition, data analysis, and reviewed and edited the manuscript. KS, TN, HA, HY and TH contributed to data acquisition, conception, and reviewed and edited the manuscript. YS and HO confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written and oral informed consent to publish this report was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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