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Case Report

Pembrolizumab as a Bridge to Autologous Stem Cell Transplantation in Refractory Gray Zone Lymphoma

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Abstract

Gray zone lymphoma (GZL), a rare type of B-cell lymphoma (BCL), has features between diffuse large BCL and classical Hodgkin lymphoma (cHL) and an unfavorable outcome. The expression of PD-L1, encoded by chromosome 9p24.1, has been positively correlated with the copy number alteration of 9p24.1, and it has been associated with a high response rate to anti-PD-1 treatment in cHL and primary mediastinal large BCL (PMBCL). GZL shares similar genomic alterations with cHL and PMBCL, and thus, it may also respond well to anti-PD-1 treatment. However, little is known about the efficacy of anti-PD-1 treatment and the predictive role of PD-L1 expression in GZL. Here, we present a case of GZL refractory to first-line chemotherapy. The patient had a high expression of PD-L1 and was successfully treated with pembrolizumab as a salvage treatment, followed by autologous stem cell transplantation (ASCT) in January 2018. The patient still had a complete metabolic response 42 months after ASCT.

Keywords: 9p24.1, anti-PD-1, autologous stem cell transplantation, gray zone lymphoma, PD-L1, pembrolizumab

Introduction

Gray zone lymphoma (GZL), a provisional entity first included in the WHO 2008 classification of B-cell lymphoma, has the features between primary mediastinal BCL (PMBCL), a subset of diffuse large BCL (DLBCL), and classical Hodgkin lymphoma (cHL). GZL can be further classified into mediastinal GZL (MGZL) and non-MGZL. GZL is characterized by high relapse rates and inferior outcomes compared to cHL and PMBCL.[1] Due to its relatively new classification and the paucity of clinical data, there is currently no standard treatment for newly-diagnosed GZL. Rituximab-based, DLBCL-specific regimens are generally recommended. For patients with relapsed/refractory GZL, however, the optimal therapy is undetermined. We present a case of refractory GZL who achieved a complete metabolic response after receiving

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pembrolizumab as a salvage treatment, which served as a bridge to autologous stem cell transplantation (ASCT).

Case Report

A 29-year-old female presented with progressive right neck swelling. Positron emission tomography/computed tomography (PET/CT) revealed lymphadenopathy over the bilateral neck; a right upper lung mass was abutting the anterior mediastinum, with a maximal diameter of 4.2 cm [Figure 1a and b]. An ultrasound-guided biopsy of the right neck lymphadenopathy revealed strips of lymphoid tissue with abundant small lymphocytes and giant Reed–Sternberg-like cells which were immunocytochemically positive for CD30, CD20, PAX5, and CD79a [Figure 2], variably positive for leukocyte common antigen, and negative for CD3 and CD15. The Epstein–Barr virus stain was negative. As the features were between DLBCL and cHL, GZL was diagnosed in January 2017.

The stage was Ann Arbor Stage IIE with neck, supraclavicular, mediastinal lymphadenopathy, and direct extension to the right upper lung. The IPI score was 0. Therapy was commenced with (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone [R-CHOP]) which achieved a partial response after the three cycles of treatment. However, follow-up PET/CT after six cycles of R-CHOP revealed a new mass in the right upper lung close to the hilum, along with complete response of the previous masses in the neck and right upper lung [Figure 1c and d]. A histopathology examination confirmed the diagnosis of refractory GZL in a repeat biopsy. Second-line salvage chemotherapy was recommended. However, the patient was reluctant to undergo chemotherapy due to concerns of the toxicity.

Immunohistochemistry (IHC) staining for the PD-L1 protein was assessed with the 22C3 antibody (Dako, Santa Clara, CA), which showed a high PD-L1 expression (tumor proportion score: 95%) in both the refractory [Figure 2d] and initial lymphoma sample. After thorough discussion and signed informed consent for off-label use, pembrolizumab (2 mg/kg every 3 weeks) was initiated following low-dose radiotherapy (10 Gy) in five fractions for the refractory tumor as immune modulation in September 2017. A PET/CT scan showed a complete metabolic response after six cycles [Figure 1e and f] in January 2018. The only immune-related adverse event was Grade 1 skin itching. Subsequently, peripheral blood stem cells were successfully harvested after mobilization with cyclophosphamide and granulocyte colony-stimulating factor. She then received autologous Hematopoietic stem-cell transplantation with the BEAM conditioning regiment (BCNU (carmustine), etoposide, cytarabine, and melphalan) and a transfusion of an adequate dose of stem cells (4.4 × 10^6/kg) on January 24, 2018. Engraftment occurred on day 9 after ASCT. The patient still had a complete metabolic response 42 months after the transplantation.

Discussion

The efficacy of anti-PD-1 therapy has led to it becoming the standard treatment for many types of cancer. Nivolumab demonstrated an objective response rate (ORR) of 66% (including a 9% complete response rate and 58% partial response rate) in 80 cHL patients after failure of both ASCT and brentuximab vedotin.[2] Similarly, pembrolizumab demonstrated an ORR of 69% (including a 22.4% complete response rate and 46.7% partial response rate) in 210 cHL patients with relapsed/refractory cHL.[3] Based on these studies, the U. S. Food and Drug Administration (FDA) approved the use of nivolumab and pembrolizumab for cHL patients with relapsed or refractory disease. Alterations in 9p24.1/PD-L1/PD-L2, which increase the abundance of PD-1 ligands, occur in almost all cHLs.[4] The overexpression of PD-L1 in cHL may facilitate immune evasion, and therefore, anti-PD-1 treatment has a remarkable response in cHL patients.[2,5]

The frequency of 9p24.1 aberrations has also been reported to be high in PMBCL.[6] The Keynote-170 study reported a 45%

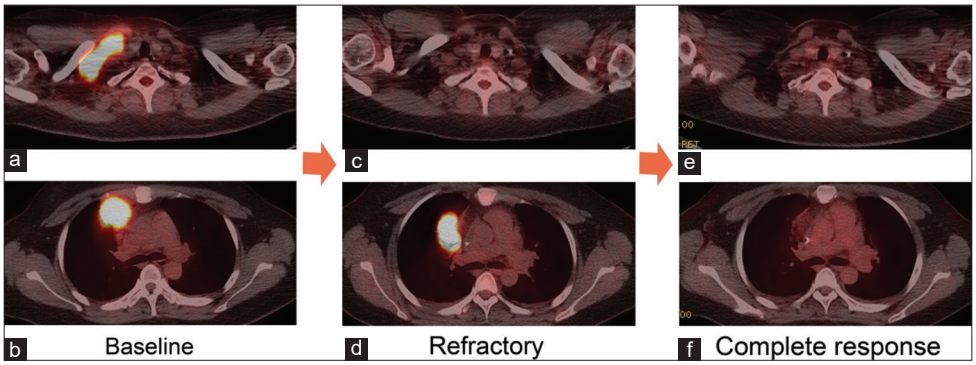

Figure 1: (a and b) positron emission tomography/computed tomography (PET/CT) at diagnosis showed hypermetabolic masses over the right supraclavicular fossa and right upper lung abutting the mediastinum. After six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone therapy, a restaging PET/CT scan showed a response in the right supraclavicular mass (c) but a new 2-[18F] fluoro-2-deoxy-D-glucose-avid mass was found (d) in the right upper lung, which was proven to be refractory lymphoma. After six cycles of pembrolizumab, positron emission tomography/computed tomography (e and f) showed a complete metabolic response

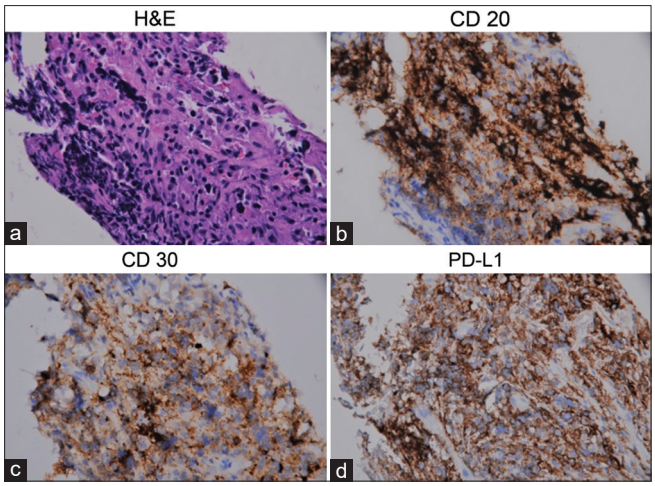

Figure 2: Hematoxylin and eosin, CD20, CD30, and programmed death-ligand 1 (PD-L1) expressions by immunohistochemistry of the lung tumor. (a) H and E stain showed scattered giant bizarre lymphoid cells and abundant small lymphocytes. These giant lymphoid cells were positive for CD20 (b) and CD30 (c). (d) The tumor proportion score of PD-L1 expression was 90%

ORR in relapsed or refractory PMBCL.[7] Therefore, the FDA granted approval for the use of pembrolizumab for relapsed or refractory PMBCL.

A study of genetic aberrations in a cohort of 27 cases with GZL identified alterations affecting 9p24.1 in 55% of the patients.[8] Sarkozy reported that the mutational profile of GZL involved in the anterior mediastinal masses was similar to that of cHL and PMBCL, suggesting a shared cell origin.[9] The biological similarities and clinical data in cHL and PMBCL suggest that anti-PD-1 therapy may also be an effective therapy for GZL. Melani *et al*. presented three cases with relapsed GZL who were treated with pembrolizumab or nivolumab and achieved a complete remission. One had a rearrangement of the genes encoding the PD-1 and PD-2 ligands (PD-L1/PD-L2) detected by fluorescence *in situ* hybridization (FISH) analysis. Another had amplification of PD-L1/PD-L2, and the third had focal membranous PD-L1 expression in IHC analysis.[10] Roemer *et al*. reported that 9p24.1 alterations were positively correlated with the expression of PD-L1.[4] Although we did not perform FISH analysis in our case, 9p24.1 amplification was speculated based on the strong expression of PD-L1 in IHC.

A greater understanding of the genetic abnormalities in GZL may lead to the greater use of anti-PD-1 as treatment. No consensus yet exists on the treatment of relapsed or refractory GZL. However, salvage chemotherapy regimens often cause severe treatment-related toxicity. Anti-PD-1 is a potential therapeutic agent in the treatment of refractory GZL with less toxicity. Clinical trials of anti-PD-1 for relapsed and refractory GZL are ongoing (NCT03255018, NCT04860674).

To the best of our knowledge, this is the first case of refractory GZL treated with anti-PD-1 as salvage therapy and successful bridge to ASCT. The clinical role of anti-PD-1 in GZL deserves further investigations.

Declarations

Ethics approval and consent to participate

The patient understood the intervention and had signed the informed consent before administration of the medication.

Consent for publication

The authors certify that the patient agrees with the publication and has signed the consent form. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal.

The patient understands that her name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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