

1 **Successful treatment of Hodgkin Lymphoma-like EBV-associated post-transplant**
2 **lymphoproliferative disorder following allogeneic hematopoietic stem cell**
3 **transplantation with nivolumab**

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36 Dear Editor,

37 Epstein-Barr virus (EBV)-associated post-transplantation lymphoproliferative
38 disorders (PTLD) represent a heterogeneous group of EBV-driven abnormal lymphoid
39 proliferations occurring after allogeneic hematopoietic stem cell transplantation [1-3].

40 Although several therapeutic strategies, such as reduction of immunosuppressive agents,
41 rituximab monotherapy, multiagent chemotherapy, and infusion of EBV-specific
42 cytotoxic T-lymphocytes (CTLs) have somewhat improved the outcome of patients with
43 PTLD, there is a concern that PTLD is still significantly associated with high mortality.
44 The use of immune checkpoint inhibitors (iCPIs) has emerged as a promising strategy
45 because of its potential effectiveness in enhancing anti-tumor immunity.

46 Recently several case reports have been published describing the use of iCPIs to treat
47 patients with aggressive hematological malignancies such as Hodgkin lymphoma [4-6].

48 However, there is a paucity of data on the safety and efficacy regarding the use of iCPIs
49 before or after allo-HSCT. Although iCPIs can induce an anti-tumor immune response,
50 there is also a risk of graft-versus-host disease (GVHD). Ijaz A et al. have reported that
51 14% of the patients who receive iCPIs after allo-HSCT develop acute GVHD and 9%
52 develop chronic GVHD [7]. Therefore, development of GVHD should be considered
53 while applying these agents in the pre- or post-allo-HSCT settings. Despite the

54 abundant data on the use of iCPIs for the treatment of cHL, only one pediatric case
55 report is available on the use of iCPIs for PTLD [8]. Here we report the first case of
56 successful iCPI use for the treatment of an adult patient with cHL-like PTLD following
57 allo-HSCT.

58 A 58-year-old woman was diagnosed with myelodysplastic syndrome and refractory
59 cytopenia with multilineage dysplasia (MDS-RCMD) with complex karyotype in June
60 2013. She received bone marrow transplantation from an HLA8/8 allele-matched
61 unrelated donor in March 2014. In March 2018, ¹⁸F fluorodeoxyglucose-positron
62 emission tomography (¹⁸F-FDG-PET) revealed left supraclavicular and abdominal
63 paraaortic lymphadenopathies (Figure 1a and b). Biopsy of the supraclavicular lymph
64 node was performed for diagnosis, and the histology showed EBV-associated cHL-like
65 PTLD with the presence of CD15, CD30, and EBER-positive tumor cells.

66 We started administering brentuximab vedotin (BV) every three weeks. After six
67 courses of BV, ¹⁸F-FDG-PET/CT showed complete remission. After four months,
68 follow-up CT study showed paraaortic lymphadenopathy of 20 mm in diameter. The
69 CT-guided biopsy of the lymph node demonstrated the relapse of cHL-like PTLD.
70 ¹⁸F-FDG-PET/CT revealed no other lymph node involvement (Ann Arbor stage I).
71 Following the regulatory approval, biweekly administration of nivolumab was started.

72 The starting dose was set to 240 mg/every other week. After four courses, liver toxicity
73 (grade 3) developed, thus we postponed the next course. One month later, the liver
74 function was improved. Therefore, we restarted administering nivolumab at the same
75 dose. After six courses, cutaneous pruritus developed as an immune-related adverse
76 event (irAE) of nivolumab, and thus we started administering 15mg prednisolone. Final
77 evaluation with ¹⁸F-FDG-PET after ten courses of nivolumab administration showed
78 complete remission of PTLD (Figure 1c, d).

79 Although nivolumab is considered as a rational treatment option in cHL-like PTLD, to
80 the best of our knowledge, this is the first case report of its use in an adult patient of
81 EBV-associated PTLD after allo-HSCT. Ijaz A et al have demonstrated the high risk of
82 acute and chronic GVHD among patients who received iCPIs after allo-HSCT [7]. In
83 fact, a treatment for skin rash and liver damage after using iCPIs is needed, although it
84 is difficult to distinguish between GVHD and irAE.

85 In conclusion, this case report shows the effectiveness of iCPIs on EBV-associated
86 cHL-like PTLD after allo-SCT. However, the high risk of GVHD and irAE should be
87 carefully considered while treating with iCPIs. To evaluate the efficacy and safety of
88 iCPIs for PTLD, further analysis with a larger number of patients must be conducted.

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92 departments for their contributions to this study.

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94 **Compliance with ethical standards**

95 **Ethical approval:** All procedures performed in studies involving human participants
96 were in accordance with the ethical standards of the institutional and/or national
97 research committee and with the 1964 Helsinki declaration and its later amendments or
98 comparable ethical standards.

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100 **Conflict of interest:** The authors declare no conflicts of interest.

101 **Informed consent:** Informed consent was obtained from the patient included in the
102 study.

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127 **Figure. 1**

128 Response to nivolumab in a patient with Hodgkin lymphoma-like PTLD after alloSCT.

129 ¹⁸F-FDG-PET obtained before (a and b) and after 10 courses of nivolumab

130 administration (c and d). The maximum intensity projections (a and c) and axial

131 reconstructions of the CT/PET fusions (b and d) are shown. The pre-treatment images (a

132 and b) show a metabolically active lymph node in the left inner hilum of the kidney.

133 The post-treatment scans (c and d) reveal the complete resolution of the metabolic

134 activity in the lesion.

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