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LETTER TO THE EDITOR

# γδ T cell clonal proliferation early after PD-1 blockade

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Dear Editor,

A recent study showed that programmed death 1 (PD-1) suppresses not only T cell-mediated immune responses but also overactivated T cell receptor (TCR) signaling, and its blockade can potentially promote T cell lymphomagenesis [1]. However, T cell lymphoma triggered by PD-1 inhibitors has not been reported previously. Recently, we encountered a case of secondary hepatosplenic T cell lymphoma (HSTCL) that developed early after PD-1 blockade therapy.

A 73-year-old man had been diagnosed with classical Hodgkin lymphoma (HL), mixed cellularity type, 2 years previously. He received nivolumab treatment (3 mg/kg every 2 weeks) for HL that relapsed after standard chemotherapy and brentuximab vedotin treatment. After two doses of nivolumab, the patient presented with high-grade fever, general fatigue, and bleeding tendency. Laboratory investigation showed acute-onset pancytopenia (white blood cell count, $1.0 \times 10^3/\mu L$; hemoglobin level, 9.2 g/dL; reticulocyte count, 0.5%; and platelet count, $47 \times 10^3/\mu L$) with increased serum levels of lactic dehydrogenase (12,313 IU/L) and ferritin (266,800 μg/L) suggesting hemophagocytic lymphohistiocytosis. Disseminated intravascular coagulation was also noted. Epstein–Barr virus (EBV) DNA levels in the peripheral blood were not elevated, and the patient showed neither infections nor autoimmune diseases. Whole-body computed tomography showed that the HL lesions had decreased in size compared to before nivolumab treatment. Bone marrow examination revealed clonal proliferation of atypical lymphocytes (Fig. 1a) that exhibited TCR-γδ restriction on flow cytometric analysis. Moreover, monoclonal rearrangements of the TCR-γ and TCR-δ genes were detected (Fig. 1b). Chromosomal examination showed abnormalities of 46,XY,add(17)(p13)[19/20]/46,idem,der(1)t(1:3)(p34:p13)[1/20]. Bone marrow biopsy specimen showed massive infiltration of neoplastic lymphoid cells, which were immunohistochemically positive for CD3, TIA-1, and granzyme B, but negative for CD4, CD5, CD8, CD10, CD20, CD30, CD79a, and EBV-encoded RNA on in situ hybridization. Despite intensive treatment, the patient's condition deteriorated rapidly, and he died 2 months after initiation of nivolumab. Autopsy showed massive infiltration of T cell lymphoma into the bone marrow, liver, and spleen. These findings were consistent with HSTCL, a rare subtype of extranodal T cell lymphoma. HSTCL has been reported in patients undergoing kidney transplantation or with a prior history of Crohn's disease, systemic lupus, rheumatoid arthritis, or malaria [2–4], suggesting that HSTCL is associated with immune dysregulation and chronic antigen stimulation. These reports also included two cases of HSTCL with a history of HL [2, 3]. An experimental model suggested that CD30 molecules, characteristic of Hodgkin–Reed–Sternberg cells, can potentially trigger clonal proliferation of γδ T cells [5]. In our case, blockade of PD-1 may have accelerated γδ T cell clonal proliferation occurring during prolonged HL-associated inflammation.

Another point of note in this case was that the neoplastic cells atypically showed expression of granzyme B with TIA-1, although HSTCLs usually have a non-activated cytotoxic phenotype without granzyme B expression [3]. We assumed that overactivated T cell-mediated immune responses triggered by PD-1 inhibitor led to the patient's severe inflammatory condition and aggressive clinical course. PD-1 blockade is a promising therapeutic approach for refractory

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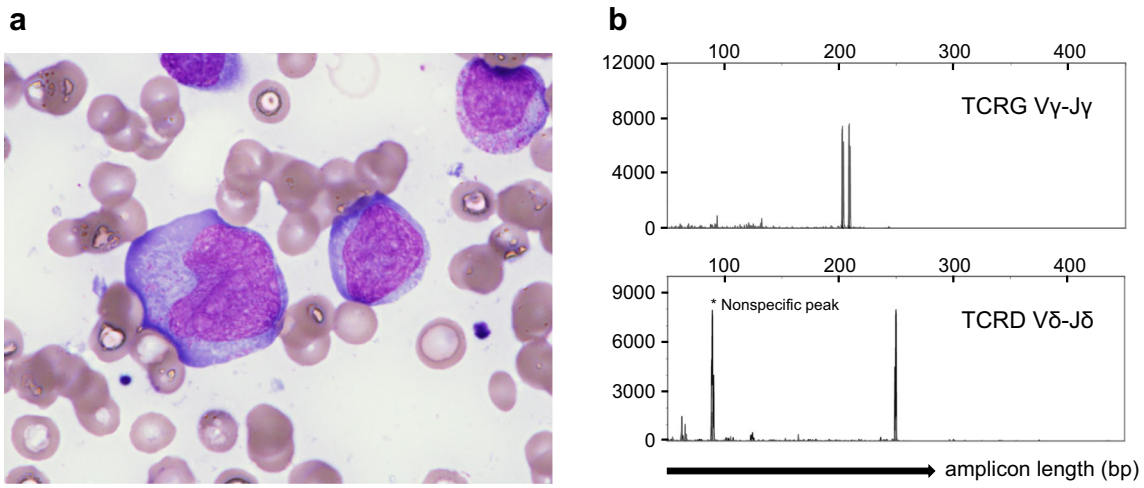


**Fig. 1** Hepatosplenic T cell lymphoma early after PD-1 blockade therapy. **a** Hematoxylin and eosin staining of bone marrow smear. Large atypical lymphocytes showed basophilic cytoplasm and irregular nuclei with dispersed chromatin and nucleoli. **b** T cell receptor (TCR) gene rearrangement analysis by polymerase chain reaction. Amplicon length is plotted against the fluorescence intensity (in arbitrary units). Monoclonal rearrangements of the TCR-γ and TCR-δ genes were detected

malignancies, but attention should be paid to secondary T cell lymphoma as well as autoimmune-related events.

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## Compliance with ethical standards

This single case study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** The patient provided informed consent.

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