

Letter to the Editor

# Potential mechanisms of spontaneous regression in patients with B-cell lymphoma; the significance of co-stimulatory molecules in lymphoma cells

**Keywords:** spontaneous regression, remission, lymphoma

## TO THE EDITOR

Spontaneous regression (SR) of malignant tumors has been observed in several types of tumors including lymphoma, kidney cancer, melanoma, and neuroblastoma.<sup>1</sup> SR is currently of interest for many clinicians because of an increased number of methotrexate-related lymphoproliferative disorders, and because SR is observed in many patients after withdrawal of methotrexate.<sup>2</sup> In terms of a mechanism, anti-tumor immune responses by host T lymphocytes reacting against tumor cells are believed to be involved in SR,<sup>3</sup> and several cases have recently been reported. In a recent issue of journal of clinical and experimental hematopathology (*JCEH*), Tanaka *et al.* described a case of diffuse large B-cell lymphoma (DLBCL) with SR.<sup>4</sup> A 35-year-old man had multiple mesenteric lymphadenopathy and a thickened small intestine wall, and was diagnosed with DLBCL (germinal center origin) without infection with Epstein-Barr virus (EBV) following laparoscopic lymph node biopsy. However, symptoms were improved and abnormal accumulation of fluorodeoxyglucose was disappeared 3 months after the biopsy. In addition, Abe *et al.* previously reported in *JCEH* a case of DLBCL harboring EBV infection with SR and reviewed some published SR cases of aggressive non-Hodgkin's lymphoma.<sup>5</sup> SR has also been seen in low-grade lymphoma. Matsuo *et al.* described a case of bilateral conjunctival extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue with SR.<sup>6</sup> Ye *et al.* just recently published four cases of SR in patients with mantle cell lymphoma.<sup>7</sup> SR is preferentially seen in extranodal lymphoma including in the intestinal tract.

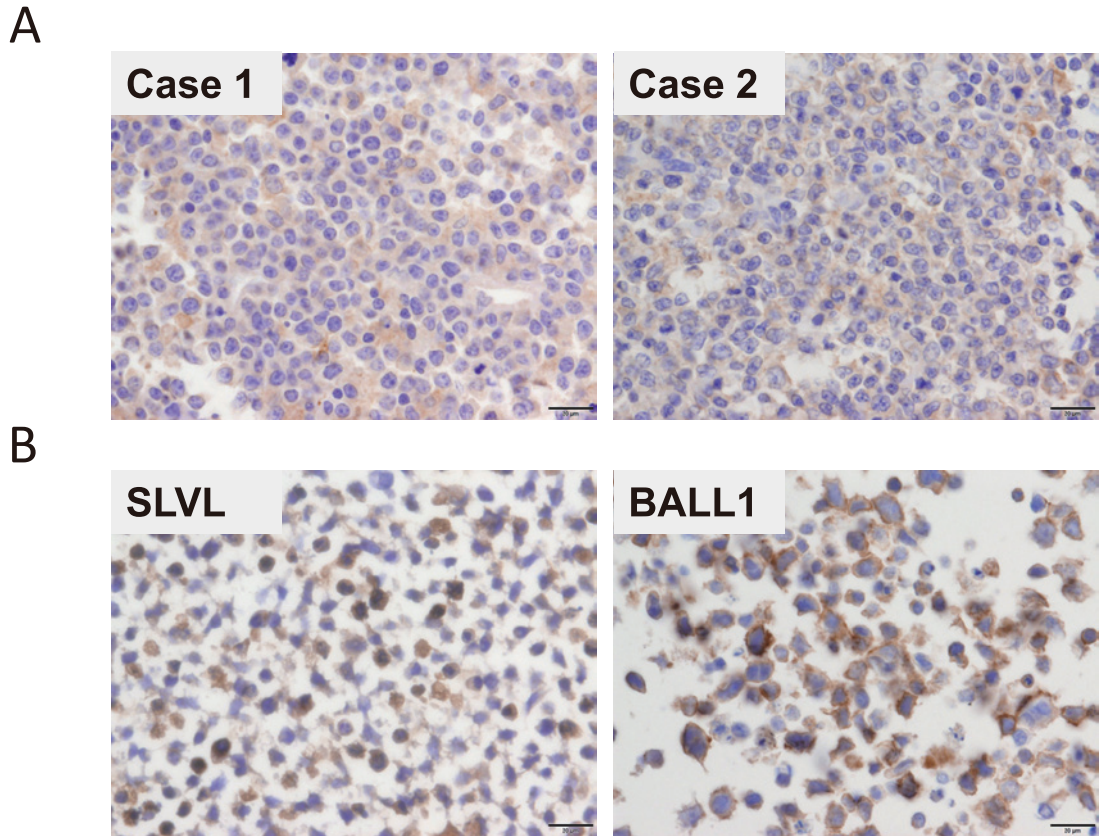
SR (also referred as "healing") is also observed in patients with non-hematological malignant tumors such as lung cancer, kidney cancer, breast cancer, and melanoma.<sup>8-11</sup> These solid cancers are known as immunogenic tumors because of increased expression of neoantigens, and anti-tumor therapy using immune checkpoint blockade antibodies and cytokines such as interferons have been used for these cancers.<sup>12,13</sup> However, mutation burdens of high-grade lymphomas are less than those of melanoma and lung cancers, indicating that unknown mechanisms are involved in SR in lymphoma cases.<sup>14</sup>

CD80 and CD86 are well-known co-stimulatory molecules expressed on antigen-presenting cells including B cells.

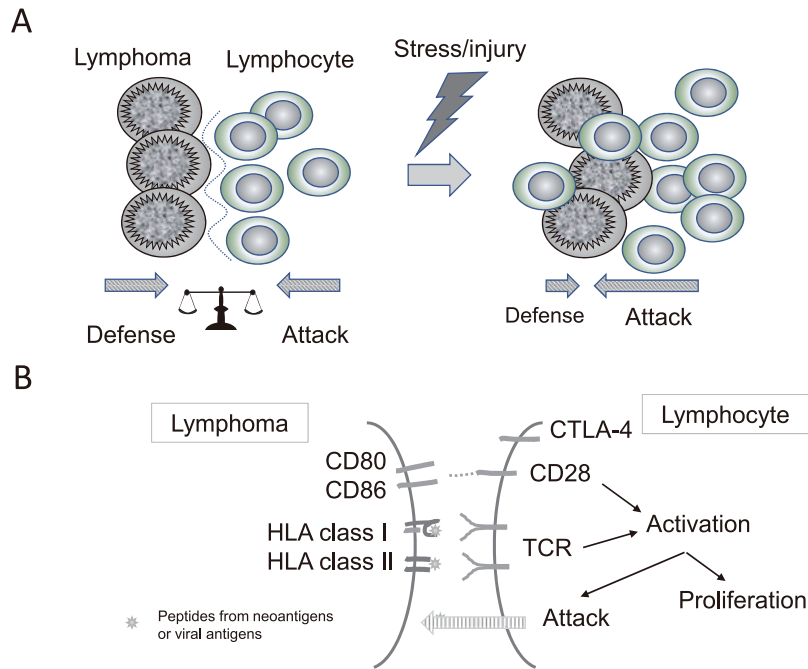
CD80 is expressed on lymphoma cells in 90% of DLBCL cases,<sup>15</sup> and the expression of both CD80 and CD86 is widely seen in leukemia or lymphoma cell lines in the NCI-60 cancer panel database [GEO data set, GDS4296]. As shown in figure 1, CD80 expression was observed in B-cell lymphoma and B-cell lymphoma cell lines. In addition, human leukocyte antigen (HLA)-DR, one of major histocompatibility complex (MHC) class II molecules, is also expressed in 65% of DLBCL cases, and HLA-DR-positive cases show a significantly better clinical course.<sup>16</sup> Given that lymphoma cells in DLBCL expressing co-stimulatory molecules such as CD80/CD86 and MHC class II molecules, lymphoma cells may have the higher immunogenic potential than other solid tumors. In support of this, Allison (received the Nobel Prize in 2018) *et al.* previously found that ectopic expression of CD80 on tumor cells induces T cell-mediated rejection in murine models by not CD4-positive T cells but CD8-positive T cells.<sup>17</sup> In addition, clinical trials with tumor cell vaccines using CD80-transfected autologous or allogenic tumor cells were performed for kidney cancer, lung cancer, and acute myeloid leukemia.<sup>18</sup> As a result, some patients who enrolled in these trials showed significant tumor reduction.<sup>19-21</sup> Although the overall response rate was limited, these findings indicate that CD80-expressing tumor cells could enhance anti-tumor immune responses. The interaction between CD80/CD86 and CD28 activates tumor-specific T cells to produce interleukin (IL)-2, which in turn triggers T cell proliferation in autocrine and paracrine manners in tumor micro-environment (Figure 2). Given that the interaction between CD80/86 and CTLA-4 results in T cell inactivation, therapies to block CTLA-4-mediated immunosuppression may improve this immune response.

Regarding EBV-infected lymphoma or lymphoproliferation, anti-EBV immune responses are believed to induce anti-lymphoma immune responses and SR.<sup>22</sup> However, EBV-transformed B lymphocytes and EBV-infected lymphoma cells produce IL-12, which is a cytokine to promote cellular immunity and is produced after CD40 ligation.<sup>23</sup> IL-12 production from lymphoma cells may be involved in SR in EBV-infected lymphoma or lymphoproliferative disorders.

Traumatic stress or injury including biopsy is considered to be a trigger for SR, and occasionally, administration of corticosteroids, anti-lymphoma drugs, or infection may cause the initiation of SR.<sup>1-3</sup> We propose a possibility that, after



**Fig. 1.** CD80 expression in lymphoma tissues and cell lines. (A) The immunostaining using anti-CD80 monoclonal antibody (clone EPR1157, Abcam) was performed as described previous methods.<sup>30</sup> Lymphoma cells were weakly positive for CD80 in diffuse large B-cell lymphoma (A), and strongly positive in two B-cell lymphoma cell lines (SLVL and BALL1) (B). Scale bar; 20µm.



**Fig. 2.** Scheme of the suggested mechanisms of spontaneous regression (SR). (A) In the growing phase of lymphoma, lymphoma cells are protected from microenvironment that includes cytotoxic T lymphocytes. Stress or injury disrupts the microenvironment, and immune reactions between T lymphocytes and lymphoma cells can be initiated. (B) Co-stimulatory molecules such as CD80/CD86 stimulate lymphoma-specific T cell response. Activated T lymphocytes proliferate and attack lymphoma cells, which present neoantigens or viral antigens with HLA class I or class II molecules.

lymphoma cells are exposed to anti-lymphoma T lymphocytes by physical disruption of the microenvironment, immune reaction between lymphoma cells and lymphoma-specific T lymphocytes may be initiated. Damage-associated molecular patterns are also considered to be involved in this immune reaction by activating the STING pathway in antigen-presenting cells.<sup>24</sup>

Recent advances of immunotherapy indicated the significance of programmed death-1 (PD-1) and its ligands such as PD-L1 and PD-L2. PD-L1-expression in lymphoma cells was seen in 11% of cases and reportedly associated to poor clinical course in DLBCL.<sup>25</sup> PD-L1 expression in lymphoma cells were potentially mediated by Stat3 activation which were suggested to be induced by macrophage-derived factors.<sup>26,27</sup> Indoleamine 2,3-dioxygenase (IDO) which has immunosuppressive functions due to enzymatic activities catalyzing the essential amino acid L-tryptophan was also expressed on 32% of B-cell lymphoma cases and IDO expression was associated to poor outcome.<sup>28</sup> These immunosuppressive molecules are also expressed on myeloid cells such as tumor associated macrophages.<sup>29</sup> Down-regulation of these factors might be linked to SR in lymphoma cases.

In conclusion, the expression of CD80/CD86 on lymphoma cells is potentially associated with activation of anti-lymphoma T cell responses and clinical SR. HLA-DR expression on lymphoma cells may also influence activation of lymphoma-specific CD4-positive helper T cells in the microenvironment. As a therapeutic strategy, anti-CTLA-4 antibody rather than anti-PD-1/PD-L1 antibody may be helpful to enhance anti-lymphoma T cell response in cases of CD80/CD86-positive lymphoma.

## CONFLICT OF INTEREST

All authors have no financial competing interests to declare.

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