

Letter to the Editor

**Successful treatment with cyclosporine of pure red cell aplasia induced
by Obinutuzumab Bendamustine therapy**

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Dear Editor,

Anti-CD20 antibody combined with chemotherapy is frequently used as a standard treatment for symptomatic stage IV follicular lymphoma (FL) patients. Rituximab or obinutuzumab (GA101, G) plus bendamustine (B) or CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) are often selected as the chemotherapy component. Although several drugs are known to induce pure red cell aplasia (PRCA), there have been no reported cases of bendamustine-induced PRCA. Here, we report the first case of bendamustine-associated PRCA successfully treated with cyclosporin.

A 48-year-old woman with pemphigus was admitted due to a giant mass in the abdomen. The size of the mass was more than 10 cm along the major axis, and the mass ranged from the retroperitoneum through the right kidney, the abdominal aorta and the bilateral iliac artery. Needle biopsy from the retroperitoneum confirmed the diagnosis of FL (grade 1–2) in stage IVA. Because the patient was considered to have high tumor burden based on either the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria[1] or the British National Lymphoma Investigation (BNLI) criteria[2], she received obinutuzumab plus bendamustine (GB) therapy. The laboratory data just before the third cycle of GB therapy were as follows: white blood cell (WBC) count $67.1 \times 10^9/L$

(reference range [r.r.] 33–86) with 81% neutrophils, 2.5% lymphocytes, red blood cell count $2.60 \times 10^{12}/L$, hemoglobin 7.5 mg/dL (r.r. 11.6–14.8), hematocrit 23.7% (r.r. 35.1–44.4), reticulocyte count 1.8‰ (r.r. 7–20) and platelet count $610 \times 10^9/L$ (r.r. 158–348). Human parvovirus B19 was negative. WBC and platelet counts were recovered from the previous cycle of chemotherapy. However, anemia progressed during the GB therapy. Bone marrow aspiration revealed almost complete absence of erythroblasts but normal myeloid cells and megakaryocytes, and thus she was diagnosed with PRCA. We stopped sulfamethoxazole trimethoprim, acyclovir, and vonoprazan fumarate because they were considered possible causes of PRCA. Following the start of anemia progression, she received 4 units of red blood cell transfusion, and cyclosporin was started 2 months after the last administration of bendamustine. One month after the start of cyclosporin, her anemia began to gradually improve, and she was able to withdraw from transfusion. Three cycles of GB therapy induced complete remission of FL, as judged by positron emission tomography-computed tomography. She has continued to receive rituximab monotherapy with adjunctive cyclosporin.

Secondary PRCA has been reported as a complication of underlying diseases such as lymphoma[3] and plasma cell disorder[4], viral infection such as human parvovirus B19[5], autoimmune disease[6, 7], and various medicines[7, 8]. In the present case there was no PRCA at the diagnosis of lymphoma, and the patient had no history of autoimmune disease. Human parvovirus B19 was negative when her anemia occurred. However, PRCA occurred after 2 cycles of GB therapy, suggesting that one or more of the chemotherapeutic drugs were the cause of PRCA. The drugs commonly implicated in the induction of PRCA are antimicrobials, anticonvulsants and myelosuppressive agents. The underlying mechanisms of PRCA induction include IgG-mediated destruction in the

1 presence of the offending drugs and a direct effect on DNA synthesis[9]. Previous reports
2 have pointed out the possible involvement of clonal T cells in the pathogenesis of
3 PRCA[10, 11]. However, we have not analyzed the T cell clonality in the present case
4 because of her lymphopenia before cyclosporin therapy. According to the drug package
5 insert of bendamustine, leukocytopenia, anemia and thrombocytopenia are seen in 69.8%,
6 24.5%, and 38.3% of cases, respectively. Because bendamustine belongs to the alkylating
7 agents and is structurally similar to purine analogs[12], we speculate that bendamustine
8 may lead to PRCA via a mechanism similar to that of PRCA induction by purine analogs,
9 such as fludarabine. Withdrawal and reduction criteria have been established for patients
10 on GB therapy who develop neutropenia or thrombocytopenia, but not for those with
11 anemia. Thus the important lesson from the clinical point of view is that we need
12 reduction or withdrawal criteria for anemia. When anemia progresses during
13 bendamustine-containing chemotherapy, it is important to consider PRCA, a rare side
14 effect of bendamustine.

Conflict of Interest

All the authors declare no conflicts of interest.

Financial disclosure

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Author contributions

Yutaka Shimazu performed the research, collected data, analyzed data, and wrote the paper; Yuta Hanyu, Kazuhisa Chonabayashi, Junya Kanda, and Chisaki Mizumoto performed the research and collected data; Akifumi Takaori-Kondo critically reviewed the paper; All authors reviewed and revised the paper and approved the submitted version.

Ethical approval

All procedures performed in this study involving the patient were in accordance with the ethical standards of our institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from the patient in this study.

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Figure Legends

Figure 1. Histopathology of the bone marrow biopsy.

(A) Erythroblasts were completely absent in the bone marrow (Hematoxylin-eosin staining). **(B)** Immunohistochemistry shows that CD71-positive cells were absent in bone marrow.

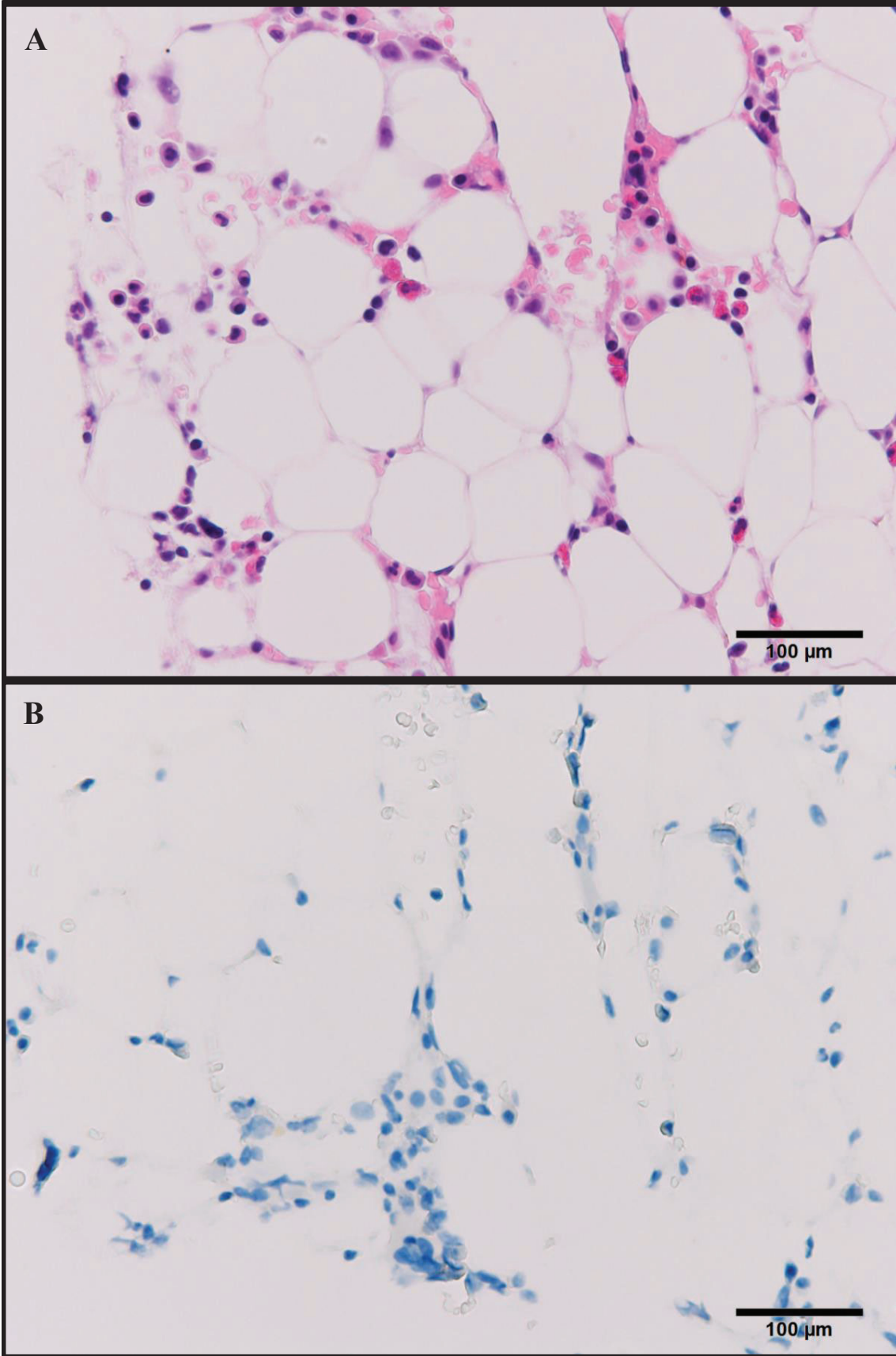


Figure 1