Case report

Antecedent presentation of aplastic anemia in a patient with diffuse large B cell lymphoma

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1. Introduction

Acquired aplastic anemia (AA) is an idiopathic disease manifested as unexplained bone marrow hypocellularity and peripheral cytopenia. Clinical response to immuno-suppressive therapy (IST)1 and HLA-DR15 restriction2, 3 manner both support an immune pathogenesis of idiopathic AA. It is caused by T-cell mediated autoimmune response against immature HLA-DR (+) hematopoietic progenitor cells. Rising evidence has shown that AA can also be a para-neoplastic phenomenon of lymphoid neoplasms.2, 4, 5 Lymphoid neoplasms may precede AA, or occur concomitantly or metachronously with AA. While some cases with AA and lymphoma can be para-neoplastic AA, some others may also be treatment related. Physicians might have dilemma in treating simultaneous AA and lymphoid neoplasms.2-5 For example, what is the aim of therapy? Would the marrow hematopoiesis recover or get worse after chemotherapy for lymphoid neoplasms? Here we present a female case of diffuse large B cell lymphoma (DLBCL) with antecedent presentation of AA. Recovery of AA was noted after complete response to lymphoma treatment. We also reviewed the literature regarding this issue.

2. Case report

A 50-year-old female presented with splenomegaly (24 cm) and pancytopenia in Mar. 2014. A bone marrow biopsy revealed hypocellular marrow (<5%). Biochemistry tests including ANA and anti-Ds-DNA were normal. Flow cytometry revealed no CD59/CD55 deficient clones. Aplastic anemia was diagnosed after serial workups. She initially received low dose prednisolone (10 mg/day). The hemogram improved but worsened again in Dec. 2014. On examinations showed white cell count (WBC) 810/ul; hemoglobin 7.0 g/dl; platelet count 64,000/ul, and lactate dehydrogenase 1041 U/L. An abdominal computed tomography revealed extensive lymphadenopathies mainly at retroperitoneum and massive splenomegaly, with biopsy proved DLBCL (Fig. 1).

Repeated bone marrow biopsy again showed remarkable hypocellular marrow (Fig. 2). Concerning for profound myelosuppression, we delivered chemotherapy with standard dose R-COP regimen (rituximab; cyclophosphamide; vincistine, and oral prednisolone), and we skipped anthracycline for the first 3 cycles due to concern for profound marrow suppression. Long-acting filgrastim (pegylated granulocyte colony stimulating factor, [G-CSF]) was given 24 h after chemotherapy. The patient stood 3 cycles of R-COP very well and there was no occurrence of neutropenia. Interestingly, her WBC recovered shortly after the 1st cycle of R-COP.

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Further 5 cycles of cytotoxic therapy with standard dose R-CEOP (rituximab; cyclophosphamide; epirubicin; vincristine, and oral prednisolone) regimen were given, and a follow-up abdomen CT showed marked decreased spleen size and resolution of previous lymphadenopathy (Fig. 4). PET-CT confirmed complete metabolic response (Fig. 5). We accomplished successful stem cell harvest after documented recovery of hematopoiesis (Fig. 6). Her HLA-DR typing revealed DRB1*12.

3. Discussion

Immunological manifestations occasionally develop concurrently with lymphoid neoplasms, including immune thrombocytopenia and autoimmune hemolytic anemia, but rarely acquired AA. Since Keisu et al noticed one third of patients with initial diagnosis of acquired idiopathic AA developed myelodysplastic syndrome (MDS) or Non-Hodgkin lymphoma (NHL),7 there have been more and more studies finding chronological associations between AA and NHL: some cases developed NHL during IST for initially diagnosed AA.8 In literature review, NHL tends to occur shortly after IST for antecedent AA, predominantly 2–4 months.
after IST.\textsuperscript{8,12,13} B-cell lymphomas are more likely. Dorr et al\textsuperscript{8} found withdrawal of IST plus radiotherapy attain complete remission. Suzuki et al\textsuperscript{13} used anthracycline-based chemotherapy to achieve a partial remission; while Saitoh et al reported a case that followed a more fulminant course and showed no response to IST withdrawal or chemotherapy, which might be the nature of a late stage relapsing lymphoma.\textsuperscript{12} On the other hand, NHL could also developed after a protracted use of IST, often 1.5 years later, in which T-cell\textsuperscript{4,15} or B-cell\textsuperscript{15,16} neoplasms evolved equally, and responded poorly to chemotherapy, carrying a grim prognosis.

HLA-DR15 might account for the paraneoplastic relationship between lymphoproliferative disease (LPD) and preceding AA: Nissen et al reported a case of NHL with tumor regression completely 10 days after diagnosis, accompanied with progressive pancytopenia, without treatment. The patient was positive for HLA-DR15; Jerez et al found a higher frequency of HLA-DR15 positivity (75\% vs 44\%, \(P = 0.02\)) in patient with concomitant AA and T large granular lymphocyte leukemia (T-LGL) than those who had no T-LGL clone.\textsuperscript{4} Though it is not HLA-DR15 in our case, whether other immunogenic HLA subtypes could predispose to both AA and LPD remains unclear. However, these evidences explained the paraneoplastic nature of AA as a collateral damage to hematopoietic progenitor cell while launching immune attack toward occult lymphoma cells.\textsuperscript{6} As occult lymphoma cells tolerate, escape immune surveillance mainly via IST, and re-expand as clonal evolution, it might be more aggressive than de novo lymphoma cells.\textsuperscript{2}

Reviewing the literature, we knew that in cases of AA, use of IST should be cautious, as IST might accelerate occult lymphoma

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**Fig. 4.** Spleen involvement and lymphadenopathy at diagnosis of DLBCL (A); remarkable remission after 6 cycles of chemotherapy (B).

**Fig. 5.** Complete metabolic response by PET-CT.

**Fig. 6.** Recovery of hematopoiesis after complete remission of lymphoma, obtained before stem cell harvest (HE stain, 200X).
There is also a possibility that this patient had both aplastic anemia and concomitant NHL, to choose cytotoxic chemotherapy or IST is an art. Depending on the intensity of immunogenic cytopenia and aggressiveness of NHL, physician might decide which aims should be treated first. In this case, splenomegaly at her first presentation is difficult to prove it lymphoma. However, lately lymphadenopathy and worsening splenomegaly confirmed lymphoma involvement. Her presentation of AA might be an immunogenic prodrome of DLBCL rather than hyper-splenism related. It should be noted that splenomegaly are not features of aplastic anemia; such findings suggest an alternative diagnosis such as a clonal myeloid or lymphoid disease, although there has been a rare case report of splenomegaly associated with AA.18 There is also a possibility that this patient had both aplastic anemia and diffuse large B-cell lymphoma. Aplastic anemia was refractory to steroid but responsive to rituximab. Medinger et al described two cases of concomitant AA and NHL, one case of multiple myeloma and concomitant AA. All of their hematopoiesis failed recovery after short course of chemotherapy, despite all attaining complete remission. The former two received IST and allo-HSCT respectively. Both restored hematopoiesis; the last one receiving IST, having temporary recovery, but still died of aplasia and infection. According to literature, hematopoiesis seldom recovers in cases of NHL with antecedent or concomitant AA despite remission of lymphoma. Nevertheless, here we provided a case report of DLBCL with initial presentation of AA. Hematopoiesis recovered after first cycle of chemotherapy, and later a successful stem cell harvest after complete remission of lymphoma.

Author contributions
All authors performed and/or designed the research study, analysed the data, contributed to the development and revision of the manuscript and approved the final version for submission.

Conflict of interest
The authors declare no conflict of interest.

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