CASE REPORT

Immune pancytopenia after chemotherapy in a patient with diffuse large B-cell lymphoma

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Accepted 5 September 2016

SUMMARY

During treatment for malignant lymphoma, cytopenia can develop for several reasons. In the treatment of cytopenia, various possibilities should be considered because inadequate treatment causes exacerbation of cytopenia and can lead to fatal conditions, such as infection and bleeding. Herein, we describe immune pancytopenia 3 months after the last exposure to chemotherapy in a patient with diffuse large B-cell lymphoma (DLBCL). She suffered from severe pancytopenia after two courses of rituximab and bendamustine therapy for a second relapse of DLBCL. Immune pancytopenia was diagnosed with bone marrow tests and the presence of autoantibodies; it promptly resolved after initiation of prednisolone therapy. Clinicians should be aware of immune cytopenia and monitor for it carefully, even if patients have already finished chemotherapy treatment.

BACKGROUND

During treatment for malignant lymphoma, cytopenia can develop for several reasons, such as bone marrow invasion by lymphoma cells, myelosuppression due to chemotherapy, secondary myelodysplastic syndrome, viral infection, severe sepsis and disseminated intravascular coagulation. In the treatment of the cytopenia, various possibilities should be considered because inadequate treatment causes exacerbation of cytopenia and can lead to fatal conditions, such as infection and bleeding.

Autoimmune disorders, including autoimmune cytopenia, are common complications in chronic lymphocytic leukaemia (CLL). In non-Hodgkin's lymphoma, except for CLL, the prevalence of autoimmune haemolytic anaemia (AIHA) ranged from 0.23% to 6.2%,^{1–5} that of autoimmune thrombocytopenia (ITP) was 0.76%,⁶ and the prevalence of Evans' syndrome, concomitant AIHA and ITP, were 0.16%⁶ and 4%, respectively.⁷ Furthermore, autoimmune neutropenia (AIN) with malignant lymphoma is very rare,^{8–9} and only a few case reports have been published.^{10–13}

Here, we describe the development of immune pancytopenia 3 months after the last exposure to chemotherapy in a patient with diffuse large B-cell lymphoma (DLBCL).

CASE PRESENTATION

An 80-year-old Japanese woman was referred to our hospital with enlarged left cervical lymph nodes and worsening oedema on her lower extremities in January 2010. CT revealed enlarged cervical and mediastinum lymph nodes, and DLBCL was

diagnosed on lymph node biopsy. The patient received eight cycles of R-half dose CHOP therapy that included rituximab (375 mg/m² on day 1), doxorubicin (25 mg/m² on day 2), cyclophosphamide (375 mg/m² on day 2), vincristine (1 mg/body on day 2) and prednisone (50 mg/body on days 1–5) administered every 3 weeks. She achieved first complete remission (CR) in October 2010.

In August 2012, the recurrence of lymphoma in bilateral iliac lymph nodes was diagnosed by positron emission tomography (PET)–CT and laboratory findings. Low-dose etoposide (25 mg/body on days 1–21) and rituximab (375 mg/m² on day 1) therapy were administered every 4 weeks in October 2012, and the second CR was achieved in May 2014.

In March 2015, the second recurrence in the left cervical and axillary lymph nodes was diagnosed by PET–CT and laboratory findings. Rituximab (375 mg/m² on day 1) and bendamustine (60 mg/m² on days 2 and 3) therapy was administered every 4 weeks; however, this therapy had to be discontinued after two cycles because of complications of cytomegalovirus infection, atrial fibrillation and cardiac dysfunction. In July 2015, the patient developed dyspnoea on exertion and gradual worsening of oedema on her lower extremities and was immediately hospitalised.

INVESTIGATIONS

On physical examination at admission, she appeared to be well and was not in acute distress. Her temperature was 36.6°C, heart rate was 92 bpm, blood pressure was 123/81 mm Hg, and respiratory rate was 20 breaths/min; her oxygen saturation was 99% while breathing ambient air. Conjunctival pallor was observed; however, her sclerae were not icteric. The patient's jugular veins were distended, and cardiac examination was notable for holosystolic murmur at the apex. The lung sounds were bilaterally diminished at both bases; however, there were no crackles. There was severe pitting oedema on both lower extremities. The abdomen and skin were normal. Superficial lymph nodes were not palpable. The laboratory findings were as follows: white cell count $0.5 \times 10^9/L$ (63% neutrophils, 31% lymphocytes, 4.0% monocytes, 2.2% basophils and 1.0% eosinophils), red blood cell count $208 \times 10^9/L$, haemoglobin 6.7 g/dL, platelet count $55 \times 10^9/L$, reticulocytes 13.7/mL, lactate dehydrogenase 278 IU/L (normal range 124–226 IU/L), total bilirubin 1.7 mg/dL, indirect bilirubin 1.3 mg/dL and haptoglobin <10 mg/dL. The levels of complement proteins C3, C4 and CH50 were within the normal range. The

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To cite: Nagashima K, Tanaka H, Nagai Y, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-216880

polyspecific direct antiglobulin test was strongly positive. The monospecific direct antiglobulin test was strongly positive for IgG but not for complement C3. The cold agglutinin titre was <4. The platelet-associated IgG was 74 ng/10⁷ cells. The test for antinuclear antibody, antibodies to double-stranded DNA, and nuclear antigens Smith and cardiolipin indicated no increases. Soluble interleukin-2 receptor (sIL-2R) level was 4270 IU/mL. Bone marrow biopsy revealed mildly hypocellular marrow with an increased number of erythroid series and megakaryocytes; lymphoma cells were not observed. There were megaloblastic changes in a subset of erythrocytes. Chromosomal analysis of the bone marrow specimen using G-banding staining indicated 46XX, del(20)(q1) [5/20]; 46XX [15/20]. CT scans revealed bilateral pleural effusion, but there was no sign of lymphadenopathy. Despite the increase in sIL-2R levels, a recurrence of lymphoma was an unlikely diagnosis based on the bone marrow biopsy and CT scan results.

OUTCOME AND FOLLOW-UP

The patient was administered 60 mg of prednisolone, and 11 days later, pancytopenia markedly improved with a white cell count of $3.1 \times 10^9/L$, a haemoglobin level of 8.4 g/dL and a platelet count of $115 \times 10^9/L$ without blood transfusion. sIL-2R levels decreased to 1030 IU/mL without chemotherapy (figure 1). Cytomegalovirus antigenemia emerged after prednisolone initiation; however, it was improved immediately after ganciclovir administration. Prednisolone was tapered to 10 mg with no recurrence of either pancytopenia or lymphoma for 6 months. DLBCL recurred in January 2016, and the patient died of malignant lymphoma in May 2016.

DISCUSSION

Here we report a case with pancytopenia which developed 3 months after chemotherapy. Owing to the positive direct antiglobulin test with platelet-associated IgG positivity and the increased number of erythroid series and megakaryocytes in the bone marrow, pancytopenia caused by an autoimmune destruction was considered. Other autoimmune diseases, including systemic lupus erythematosus, were excluded by serological examination.

AIN includes primary AIN, which is usually diagnosed during the first few months and has a benign clinical course, and secondary AIN, which is a heterogeneous group of conditions that can be caused by several underlying factors, such as systemic

autoimmune diseases, infectious diseases, drugs, transplantation and haematological neoplasms.⁸ Diagnosis of AIN requires the exclusion of other diseases and confirmation of autoantibodies against neutrophils. In most cases of secondary AIN, however, the target of the autoantibodies is unknown.⁹ Although autoantibodies against neutrophils could not be confirmed in our case, the patient presented with immune thrombocytopenia and haemolytic anaemia and experienced a marked improvement in neutropenia after prednisolone administration without granulocyte colony stimulating factor. Patients with AIN quite commonly also present with thrombocytopenia and/or haemolytic anaemia.⁸ Some reports have described that secondary AIN with malignant lymphoma promptly improved with prednisolone administration.^{10 11}

It is a notable point that in our case, the autoimmune cytopenia presented after chemotherapy for DLBCL. A review of 108 cases of non-Hodgkin's lymphoma with AIHA reported 22 cases with AIHA and 2 cases with Evans' syndrome among those with DLBCL.⁷ However, among these patients, cold agglutinin disease was dominant, and AIHA after treatment of lymphoma was diagnosed in only 2 cases. In a review of 33 cases of non-Hodgkin's lymphoma with ITP (without CLL), there were 10 cases with an aggressive B-cell lymphoma, including 9 cases of DLBCL which was associated with ITP. ITP occurred before the diagnosis in three cases, concurrently with lymphoma in five cases, and after diagnosis and chemotherapy in two cases.⁶

Viral infection as the underlying cause of cytopenia should be considered. Our case suffered from recurrent cytomegalovirus infection. Although there have been no reports of autoimmune cytopenia due to cytomegalovirus infection in patients treated with chemotherapy, several reports showed haemolytic anaemia associated with cytomegalovirus infection in immunocompetent patients.^{14 15} However, it was unlikely to be an underlying cause in our patient because pancytopenia developed after the cytomegalovirus infection was completely resolved and did not worsen when cytomegalovirus antigenemia developed during prednisolone therapy.

Related to the drugs administered to our patient, there have been reports describing cytopenia induced by rituximab and bendamustine. Although rituximab is not a cytotoxic anticancer agent, the possibility of rituximab-induced cytopenia should be considered because there are several case reports and articles stating that rituximab-induced cytopenia. In a review of 16 cases with acute cytopenia following rituximab treatment, the potential risk factors are splenomegaly, bone marrow involvement and clinical manifestations that are compatible with the cytokine release syndrome.¹⁶ Regarding immune cytopenia induced by rituximab, there are articles of AIN induced by rituximab, which described that it occurred 2–9 months after the discontinuation of rituximab treatment.^{17 18} A few cases have been reported of concurrent drops in haemoglobin and platelet levels. One of the possible mechanisms of this is an aberrant process of B-cell reconstitution by disordered immunological status following rituximab administration. In our case, autoimmune cytopenia developed despite the fact that rituximab had been administered several times since disease onset. Bendamustine is a purine analogue/alkylator hybrid cytotoxic agent with good clinical efficacy and acceptable tolerability in patients with CLL and non-Hodgkin's lymphoma.^{19 20} Several recent cases with bendamustine-associated immune haemolytic anaemia were reported.^{21–23} An association between autoimmune cytopenia and these drugs cannot be denied in our case.

Figure 1 Clinical course. WBC, white cell count; Plt, platelet; Hb, haemoglobin.

If a patient has had treatment with various types of chemotherapy, the possibility of the complication of secondary myelodysplastic syndrome should be taken into consideration. In our patient, with regard to AIHA, the increase in reticulocyte count was relatively low and haemolytic findings were mild. Bone marrow examination revealed megaloblastic changes and deletion of chromosome 20 in G-banding staining, which is commonly observed in myelodysplastic syndrome.²⁴ Pancytopenia in our patient certainly influenced by myelodysplastic syndrome, although it could not entirely be explained by it.

In summary, we presented immune pancytopenia 3 months after chemotherapy in a patient with DLBCL. Clinicians should be aware of immune cytopenia and monitor for it carefully, even if chemotherapy has been finished.

Learning points

- During treatment for malignant lymphoma, cytopenia may develop for several reasons. In the treatment of cytopenia, various possibilities should be considered because inadequate treatment causes exacerbation of cytopenia and can lead to fatal conditions, such as infection and bleeding.
- Clinicians should be aware of immune cytopenia and monitor for it carefully, even if patients have already finished chemotherapy treatment.

Contributors KN and HT were responsible for analysis and interpretation. KN was responsible for writing of the article. HT, YN and SY were responsible for revision of the article.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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