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Case report

Severe autoimmune pancytopenia after autologous hematopoietic stem cell transplantation for Hodgkin lymphoma

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Autoimmune pancytopenia is rarely seen with Hodgkin lymphoma, and only one pediatric case of pancytopenia after autologous hematopoietic stem cell transplantation (HSCT) has been reported. We herein report a case of autoimmune pancytopenia that developed after autologous HSCT for nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). A 56-year-old Japanese woman underwent autologous HSCT for NLPHL. She developed autoimmune pancytopenia seven months after autologous HSCT. In this case, PSL was effective, and the blood cell counts normalized completely. However, the patient suffered from a fatal infection, probably because of immunosuppression caused by prolonged administration of PSL, as well as a history of several chemotherapies and autologous HSCT. To our knowledge, this is the first adult case of autoimmune pancytopenia after autologous HSCT for Hodgkin lymphoma. To further validate the optimal treatment strategy for autoimmune cytopenia after autologous HSCT, more cases are necessary.

Keywords: autoimmune pancytopenia, hematopoietic stem cell transplantation, Hodgkin lymphoma

INTRODUCTION

Evans syndrome is characterized by a combination of immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA). It accounts for around 7% of AIHA. Secondary Evans syndrome has been associated with various conditions, including systemic lupus erythematosus (SLE), lymphoproliferative diseases, drugs, and viral infections. Autoimmune neutropenia (AIN), which is usually seen in infancy, is caused by the autoantibody-induced destruction of neutrophils.[1] Adult-onset AIN is rare and most likely secondary to systemic autoimmune diseases, lymphoproliferative diseases, drugs, and viral infections. There have been few reports about autoimmune pancytopenia, a combination of AIN and Evans syndrome. Autoimmune pancytopenia has rarely been reported in patients with Hodgkin lymphoma or patients after hematopoietic stem cell transplantation (HSCT).[2] There are only five cases of Evans syndrome after autologous HSCT, and only one pediatric case of pancytopenia after autologous HSCT has been reported.[2-7] We herein report the first adult case of autoimmune pancytopenia that developed after autologous HSCT for nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).

CASE REPORT

A 56-year-old Japanese woman was diagnosed with stage IIA NLPHL. Physical examination and a computed tomography (CT) scan revealed that there were swollen lymph nodes in the right supraclavicular and axillary lymph node areas. The positron emission tomography (PET) -CT image is shown in Figure 1. There was one poor prognosis factor (age) as defined by the European Organization for the Research and Treatment of Cancer. She initially received four cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). Unfortunately, she had not achieved a complete response at the end of ABVD, and involved site radiation therapy 44 Gy (in 22 fractions) in the right supraclavicular and axillary lymph node areas was performed. After that, she achieved a complete response. However, nine months after the initial therapy, a follow-up CT scan detected recurrence of the lymphoma outside the irradiation areas, in which there were deep cervical lymph nodes and a hepatic hilar lymph node. Although the histological type was

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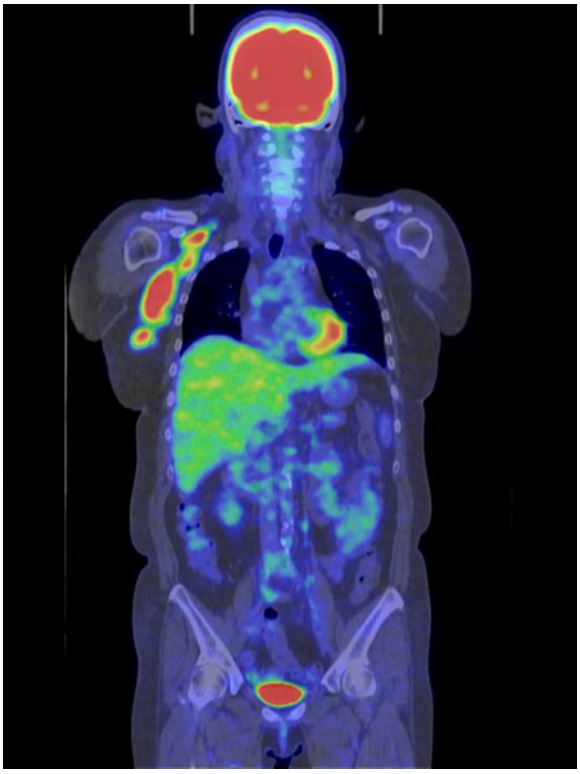

Fig. 1. PET-CT at the time of diagnosis of NLPHL.
PET-CT showed increased FDG metabolism of the right supraclavicular and axillary lymph node areas (SUVmax; 9.7).

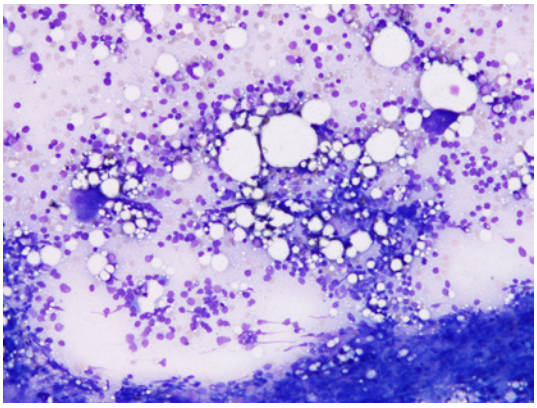

Fig. 2. Bone marrow aspiration at the time of diagnosis of autoimmune pancytopenia.

Table 1. Bone marrow aspiration at the onset of pancytopenia

NCC	4.8×10^4/μL	Lymph	24.0%
Blast	0.9%	Baso	0.1%
Promyelo	1.1%	Mono	4.6%
Myelo	20.8%	Plasma	0.4%
Metamyelo	16.8%	Macrophage	0.4%
Band	13.3%	Megakaryo	30/μL
Seg	2.3%	Erythroblast	13.1%
Eosino	2.1%	M/E	4.3

NCC: Nucleated cell count.

NLPHL, the tumor cells were positive for CD30 in the initial biopsy tissue, so we decided to administer brentuximab vedotin (BV) as a salvage treatment. Unfortunately, after five cycles of BV, she had not achieved a partial response. Subsequently, two cycles of GDP (gemcitabine, dexamethasone, and cisplatin) therapy successfully resulted in a partial response, and autologous HSCT was performed (CD34-positive cells: 5.58×10^6 cells/kg). The conditioning regimen included ranimustine, etoposide, cytarabine, and melphalan. Neutrophil and platelet engraftments were achieved on days 10 and 12, respectively. She was discharged on day 17 and achieved a complete response, finally.

Seven months later, the patient suddenly developed thrombocytopenia, and this was carefully followed up as an outpatient. However, severe pancytopenia progressed, and she was readmitted. Physical examination revealed petechiae on the extremities. There was no lymphadenopathy or hepatosplenomegaly. The white blood cell count was 1,900/μL, the absolute neutrophil count was 0/μL, the hemoglobin level was 8.4 g/dL, the reticulocyte count was 66,000/μL, the platelet count was 2,000/μL, the immature platelet fraction was 16.9%, and there was no erythrocyte fragmentation. Bone marrow aspiration and biopsy showed normocellular marrow (Figure 2). The numbers of myeloid precursors, erythroid precursors, and megakaryocytes were maintained (Table 1). The flow cytometry and karyotype analyses of the bone marrow were normal. There was no evidence of Hodgkin lymphoma or therapy-related myelodysplastic syndromes. No evidence of disease recurrence was observed on PET-CT (Figure 3). Monoclonal protein was not detected, and the free light chain ratio was normal. No clinical or laboratory evidence of other hematologic malignancies, splenomegaly, systemic lupus erythematosus, or autoimmune lymphoproliferative syndrome was observed. No evidence of any viral infections, including Epstein-Barr virus, cytomegalovirus, SARS-CoV-2, and human immunodeficiency virus was observed. In addition, the total bilirubin level was 1.0 mg/dL, the level of Lactate Dehydrogenase (LDH) was 247 IU/L, and the level of haptoglobin was 2 mg/dL. Direct Coombs tests, irregular antibodies (anti-E autoantibody), anti-HLA antibodies, antiplatelet antibodies, platelet-associated antibodies, and antineutrophil antibodies were all positive (Table 2). Taken together, the patient was diagnosed with autoimmune pancytopenia.

The clinical course is shown in Figure 4. The patient was treated with cefepime and filgrastim for febrile neutropenia on the day of admission. Prednisolone (PSL) of 40 mg (1 mg/kg) daily was started on day 3 postadmission. After starting the PSL, her blood cell counts gradually began to recover. On day 15, her neutrophil count had recovered to more than 500/μL. On day 26, her platelet count had recovered to more than 50,000/μL. Finally, her blood cell counts normalized, and she was able to be discharged from hospital with PSL of 20mg. However, four days later, she was readmitted with bacterial enteritis. She was treated with antibiotics and discharged on day 13. Unfortunately, she was read-

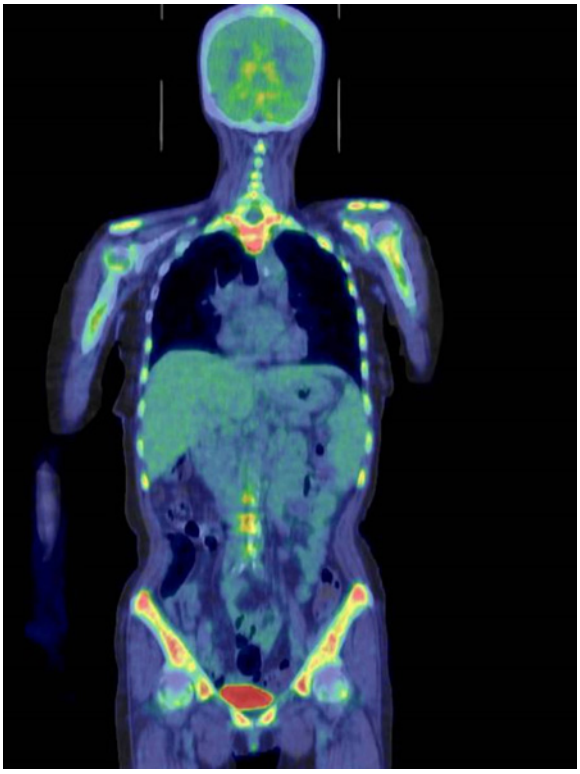

Fig. 3. PET-CT at the time of diagnosis of autoimmune pancytopenia. PET-CT showed diffuse increased metabolism of bone marrow, but there was no FDG uptake in any lymph nodes.

mitted ten days later with pneumonia. After starting PSL, prophylactic sulfamethoxazole-trimethoprim and fluconazole had been administered. *Pneumocystis* pneumonia was suspected, because no bacteria, fungus, or virus was detected, but β-D-glucan was 105.6 pg/mL. There was no relapse of autoimmune pancytopenia and lymphoma. She underwent endotracheal intubation, and was treated with several broad spectrum antibiotics and antifungal drugs. (PSL was increased to treat *Pneumocystis* pneumonia.) However, these treatments were unsuccessful, and she died 4 weeks later.

DISCUSSION

AIHA, ITP, and AIN are classified in autoimmune cytopenia (AIC). There have been several reports about AIC complicated by Hodgkin lymphoma. In Hodgkin lymphoma, AIHA and ITP have rarely been observed with a frequency of 0.5% and 0.4%, respectively.[8] AIN has even more rarely been observed in Hodgkin lymphoma, and there are few reports about cases of pancytopenia. AIC may occur before, concurrent with, or after treatment for lymphoma, and is triggered by paraneoplastic cytokine release or the production of autoantibodies. These events are considered results of the prominent relationship between Hodgkin lymphoma and immune dysfunction.[9]

It has been reported that AIC occurs after allogeneic HSCT.[10] The frequency of AIHA and ITP after allogeneic HSCT are 1-5% and 0.5-2%, respectively.[11,12] AIN after

Table 2. Laboratory data at the onset of pancytopenia

WBC	1,900/μL	T-Bil	1.0 mg/dL	C3	138 mg/dL
Band	0 %	AST	22 U/L	C4	9 mg/dL
Seg	0 %	ALT	7 U/L	CH50	56.4 U/mL
Eosino	3.0 %	LDH	247 U/L	ANA	×320
Baso	1.0 %	BUN	10.6 mg/dL	Anti-dsDNA Ab	< 15 IU/mL
Mono	31.0 %	Cre	0.47 mg/dL	Anti-Sm Ab	< 10 U/mL
Lymph	65.0 %	CRP	0.68 mg/dL	Anti-SS-A Ab	204.7 U/mL
RBC	254.7×10^4/μL	Fe	110 μg/dL	Anti-SS-B Ab	< 10 U/mL
Hb	8.4 g/dL	Ferritin	237 ng/mL	P-ANCA	< 3.5 IU/mL
MCV	98.4 fL	TIBC	317 μg/dL	C-ANCA	< 2 IU/mL
Reticulocyte	2.6 %	Vit.B12	319 pg/mL	PA IgG	857.5
Plt	0.2×10^4/μL	Folic acid	3.3 ng/mL	Anti-*H.pylori* IgG	< 3
IPF	16.9 %	IgG	2,645 mg/dL	LA	1.15
		IgA	395 mg/dL	Anti-β_2GPI IgG Ab	< 20 U/mL
PT-INR	1.11	IgM	395 mg/dL	Anti-CL IgG Ab	< 20 U/mL
APTT	27.5 sec	sIL2-R	2,427 U/mL	Irregular antibody	+
Fib	450 mg/dL	Haptoglobin	2 mg/dL	Direct Coombs	+
FDP	4.0 μg/mL			Indirect Coombs	+
D-dimer	1.4 μg/mL			anti-HLA antibody	+
				Antiplatelet antibody	+
				Antineutrophil Ab	+

IPF: immature platelet fraction, sIL2R: soluble interleukin-2 receptor, CH50: 50% hemolytic complement activity, ANA: antinuclear antibody, Anti-ds DNA Ab: anti-double stranded DNA antibody, Anti-SS-A Ab: anti-SS-A antibody, Anti-SS-B Ab: anti-SS-B antibody, P-ANCA: perinuclear antineutrophil cytoplasmic antibody, C-ANCA: cytoplasmic antineutrophil cytoplasmic antibody, PA IgG: platelet-associated IgG, LA: lupus anticoagulant, Anti-CL-β2GPI Ab: anti-cardiolipin β2- glycoprotein I complex antibody, Anti-CL IgG Ab: anti-cardiolipin antibodies-IgG, anti-HLA antibody: anti human leukocyte antigen antibody.

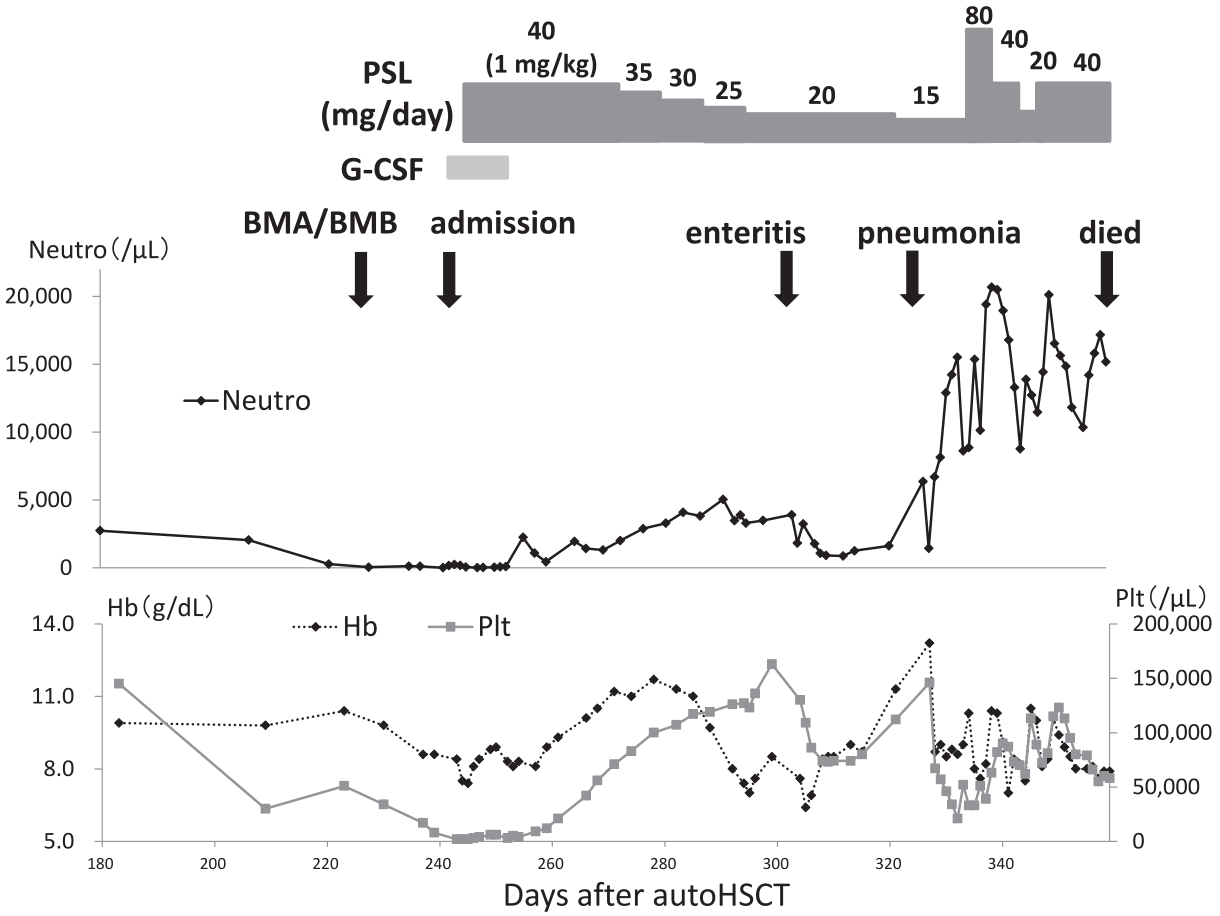

Fig. 4. Clinical course of the patient.
Pancytopenia was observed seven months after autologous HSCT. Her neutropenia was refractory to granulocyte-colony-stimulating factor but promptly responded to prednisolone (1mg/kg). Hemoglobin and platelets also recovered quickly after the starting of prednisolone.
PSL: prednisolone, G-CSF: granulocyte colony-stimulating factor, BMA: bone marrow aspiration, BMB: bone marrow biopsy.

allogeneic HSCT is rare, but there are several reports about it.[13,14] AIC also occurs after autologous HSCT, but is extremely rare. There are only five cases of Evans syndrome after autologous HSCT.[3-7] The mechanism of post-HSCT AIC is unclear but may be the result of impaired or altered immune reconstitution and failure or loss of self-tolerance. Immunological dysregulation can occur in both post-allogeneic and post-autologous HSCT cases. A thymic injury partly due to the conditioning regimen can impair central tolerance and therefore impair the negative selection of auto-reactive T cells. After HSCT, regulatory T cells have been described to be dysfunctional and reduced in number, and unable to suppress auto-reactive cells effectively.[12,15,16]

In our case, the patient developed autoimmune pancytopenia seven months after autologous HSCT. Unfortunately, we did not measure any cytokines and there is no evidence that immune abnormalities like classical HL occur in NLPHL. In addition, there was no evidence of lymphoma recurrence at the time of pancytopenia in our case. Therefore, we believe that AIC occurred as a complication of autologous HSCT rather than an immune abnormality caused by paraneoplastic cytokines. It is considered that immunological dysregulation due to several chemotherapies and autologous HSCT caused the autoimmune disorder. As mentioned, autoimmune pancytopenia is rarely seen in patients after autologous HSCT, and only one pediatric case of pancytopenia after autologous HSCT has been reported.[2] In that case, cytopenia occurred four months after treatment for HL was completed.

Corticosteroid is the first choice for AIHA and ITP. If the initial therapy fails and does not achieve a complete response, splenectomy or rituximab are the second-line treatments. Moreover, thrombopoietin receptor agonists are effective against refractory ITP. For refractory AIHA, other immunosuppressive drugs, such as cyclosporine, azathioprine, and mycophenolate mofetil (MMF), are used.[17,18] However, there is no standard therapy for autoimmune pancytopenia. Corticosteroid was the first choice in past case reports. If a patient is refractory to corticosteroid therapy, immunosuppressive drugs, such as cyclosporine, MMF, and azathioprine, can be considered.[2,10]

In summary, this is the first adult case of autoimmune pancytopenia after autologous HSCT. In the report of a similar pediatric case, treatments with steroid, intravenous

immunoglobulin, and immunosuppressive drugs were unsuccessful, and finally rituximab was effective.[2] In our case, PSL was effective, and the blood cell counts normalized completely. However, the patient suffered from fatal infections probably because of immunosuppression caused by prolonged administration of PSL, as well as a history of several chemotherapies and autologous HSCT. Therefore, it may be better to consider enrolling in clinical trials if possible, or the early administration of second-line agents, including rituximab and thrombopoietin-receptor agonists, when PSL cannot be reduced rapidly. To further validate the optimal treatment strategy for AIC after autologous HSCT, it is necessary to accumulate more cases.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

INFORMED CONSENT

Written informed consent was obtained from the patient.

REFERENCES

1 Akhtari M, Curtis B, Waller EK. Autoimmune neutropenia in adults. Autoimmun Rev. 2009; 9: 62-66.

2 Hsu WY, Chiou SS, Liao YM, *et al.* Successful management of multilineage autoimmune cytopenia complicated with severe infection and deep vein thrombosis in a patient with Hodgkin lymphoma post-autologous hematopoietic stem cell transplantation. Pediatr Transplant. 2016; 20: 168-171.

3 Keung YK, Cobos E, Bolanos-Meade J, *et al.* Evans syndrome after autologous bone marrow transplant for recurrent Hodgkin's disease. Bone Marrow Transplant. 1997; 20: 1099-1101.

4 Chihara D, Sakamoto T, Arimoto-Miyamoto K, *et al.* Refractory Evans syndrome after autologous stem cell transplantation for multiple myeloma: management with a second transplantation. Intern Med. 2010; 49: 683-687.

5 Kamezaki K, Fukuda T, Makino S, Harada M. Evans' syndrome following autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Clin Lab Haematol. 2004; 26: 291-293.

6 Gonzalez-Vicent M, Diaz MA, Garcia-Sanchez F, Molina J, Madero L. Early onset of evans syndrome following autologous peripheral blood progenitor cell transplantation in a child. Haematologica. 2002; 87: ECR17.

7 Kato I, Okada H, Nishida T, *et al.* Evans syndrome after autologous peripheral blood stem cell transplantation for recurrent Hodgkin lymphoma. Pediatr Int. 2016; 58: 933-936.

8 Xiros N, Binder T, Anger B, Böhlke J, Heimpel H. Idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia in Hodgkin's disease. Eur J Haematol. 1988; 40: 437-441.

9 Skinnider BF, Mak TW. The role of cytokines in classical Hodgkin lymphoma. Blood. 2002; 99: 4283-4297.

10 Holbro A, Abinun M, Daikeler T. Management of autoimmune diseases after haematopoietic stem cell transplantation. Br J Haematol. 2012; 157: 281-290.

11 Miller PDE, Snowden JA, De Latour RP, *et al.* Autoimmune cytopenias (AIC) following allogeneic haematopoietic stem cell transplant for acquired aplastic anaemia: a joint study of the Autoimmune Diseases and Severe Aplastic Anaemia Working Parties (ADWP/SAAWP) of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2020; 55: 441-451.

12 Baur K, Buser AS, Infanti L, *et al.* Immune cytopenia after allogeneic haematopoietic stem-cell transplantation: challenges, approaches, and future directions. Lancet Haematol. 2021; 8: e229-e239.

13 Shingai N, Taniguchi K, Kakihana K. Neutropenia associated with antihuman neutrophil antibodies following allogeneic hematopoietic stem cell transplantation. Transpl Int. 2014; 27: e21-e23.

14 Khouri IF, Ippoliti C, Gajewski J, Przepiorka D, Champlin RE. Neutropenias following allogeneic bone marrow transplantation: response to therapy with high-dose intravenous immunoglobulin. Am J Hematol. 1996; 52: 313-315.

15 Bohgaki T, Atsumi T, Koike T. Autoimmune disease after autologous hematopoietic stem cell transplantation. Autoimmun Rev. 2008; 7: 198-203.

16 Daikeler T, Tyndall A. Autoimmunity following haematopoietic stem-cell transplantation. Best Pract Res Clin Haematol. 2007; 20: 349-360.

17 Jäger U, Barcellini W, Broome CM, *et al.* Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020; 41: 100648.

18 Provan D, Arnold DM, Bussel JB, *et al.* Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019; 3: 3780-3817.