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Primary isolated bone marrow diffuse large B cell lymphoma with long-term complete remission

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ABSTRACT

Secondary bone marrow involvement of non-Hodgkin's lymphoma (NHL) is relatively common. However, primary isolated bone marrow involvement in NHL which was successfully treated and remains in complete remission (CR) for a long-term duration without any relapse is extremely rare. We herein report a patient of primary bone marrow diffuse large B cell lymphoma (PBML/DLBCL) who presented a prolonged high-grade fever and systemic purpura due to severe thrombocytopenia. The patient was successfully treated with systemic chemotherapy by R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) and remains in CR at 8 years after the initial diagnosis. Review of the literature in PBML/DLBCL cases are also shown.

1. Introduction

Secondary bone marrow involvement of non-Hodgkin's lymphoma (NHL) is relatively common. However, primary isolated bone marrow involvement in NHL which was successfully treated and remains in CR for a long duration without any relapse is extremely rare. We herein report a patient of primary bone marrow diffuse large B cell lymphoma (PBML/DLBCL) with the initial presentation as severe thrombocytopenia who was successfully treated with systemic chemotherapy by R-CHOP (rixuimab, cyclophosphamide, doxorubicin, vincristine and prednisolone) and remains in complete remission (CR) at 8 years after the initial diagnosis. In addition, we reviewed 53 cases of PBML/DLBCL. PBML is a very uncommon lymphoma with particular clinical features and heterogeneous histology and its outcome is unfavorable. Its recognition is essential for establishing accurate diagnosis and adequate therapeutic strategies.

2. Case report

A 66-year-old woman was admitted to our hospital, because of a prolonged fever of unknown origin with a 5-week duration and general fatigue. No antibiotics were effective. She had a previous history of breast carcinoma; stage I, treated by only mastectomy without any adjunct chemotherapy or radiotherapy at 44 years old. On admission, she had high-grade fever; 39°C, pulse was 110 bpm and regular, and blood pressure was 125/75 mmHg. Physical examination revealed petechiae in the trunk and bilateral extremities, but neither lymphadenopathy, splenomegaly nor skin eruptions were present. Blood tests on admission showed the following: white blood cell (WBC) count 4100/μl (band + seg 78.0 %, mono 10.0 %, lymph 12.0 %); hemoglobin (Hgb) 11.0 g/dl; platelet count (Plt) 1.6 × 10^4/μl; lactate dehydrogenase (LDH) 735 IU/l (normal range 124–222 U/L); AST 121 IU/L; ALT 86 IU/l; total bilirubin (T-Bil) 0.44 mg/dl; triglyceride (TG) 200 mg/dl; C-reactive protein (CRP) 8.81 mg/dl; ferritin 1,150 ng/ml; and soluble interleukin-2 receptor (sIL2-R) 13,100 U/ml (Table 1). Routine tests including blood coagulation profile, kidney functions, serum iron, vitamin B_{12}, folic acid, and haptoglobin revealed normal. Tests for tuberculosis and viruses including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and cytomegalovirus (CMV) were negative. Epstein-Barr (EBV)-VCA IgG was 640x, EBV-VCA IgM was > 10x, and EBV-EBNA was 10x >, but the EBV DNA titer was within normal limits. Protein and immunoelectrophoresis, immunoglobulin, C3, C4 complement, anti-nuclear antibodies (ANA), lupus anticoagulant (LA), rheumatoid factor (RF), and thyroid function were normal or negative. Repeated blood cultures were also normal. A cervical, chest, abdominal and pelvic computed tomography (CT) scan and Gallium scintigraphy revealed no lymphadenopathy, hepatosplenomegaly or other abnormal findings. In contrast, bone marrow aspiration demonstrated widespread infiltration of medium to large sized atypical lymphoma cells with distinct nucleoli, basophilic cytoplasm,

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Table 1
Laboratory findings at the initial presentation, after the 1st cycle of chemotherapy and at 8 years after the initial diagnosis.

At the initial presentation	After the 1st cycle of chemotherapy		8 years after the initial diagnosis
WBC	4100/μl	7450/μl	7800/μl
band + seg	78%	93.0%	78.0%
lymph	12%	6.5%	17.0%
mono	10%	0.5%	5.5%
eosino	0%	0%	1.0%
baso	0%	0%	0.5%
RBC	352×10^4/μl	311×10^4/μl	356×10^4/μl
Hgb	11.0 g/dl	9.5 g/dl	11.4 g/dl
Hct	33.0%	28.8%	35.2%
Plt	1.6×10^4/μl	21.7×10^4/μl	18.9×10^4/μl
Ret	4.0‰	13.0‰	17.0‰
AST	121 IU/L	23 IU/L	23 IU/L
ALT	86 IU/L	47 IU/L	11 IU/L
LDH	735 IU/L	114 IU/L	180 IU/L
TB	0.44 mg/dl	0.88 mg/dl	0.78 mg/dl
BUN	13.2 mg/dl	22.9 mg/dl	10.1 mg/dl
Cr	0.60 mg/dl	0.42 mg/dl	0.57 mg/dl
TG	200 mg/dl	154 mg/dl	163 mg/
CRP	8.81 mg/dl	0.02 mg/dl	0.54 mg/dl
Feritin	1,150 ng/ml	150 ng/ml	33.0 ng/ml
sIL2-R	13,100 U/ml	1,470 U/ml	375 U/ml
ANA	(-)		
CMV Antigenemia	(-)		
HIV	(-)		
EBV –DNA	$<2\times10/10^6$ cell		

and cytoplasmic vacuoles, whose immunophenotyping revealed CD5-/CD10-/CD19+/CD20+/Igκ+ (Fig. 1(a): May-Giemsa stain x1000, Fig. 1(b): Immunophenotyping panel). The number of megakaryocyte was decreased. Bone marrow biopsy consistently revealed hypercellularity with widespread infiltration of large lymphoma cells positive for CD20 (L26), CD79α, BCL6, BCL2, MUM1, but negative for CD3 (Fig. 1, c: hematoxylin and eosin x200, d: CD20 x200, e: CD79αx200, f: BCL6 x400, g: BCL2 x400, h: MUM1 x400, i: CD3 x200). Pathologically, the proliferation of large lymphoma cells on the lumina of small vessels were not detected. In addition, EBV encoded small RNA (EBER) in situ hybridization was not detected on bone marrow tissues. Immunohistochemical analysis showed that these cells were negative for MPO, glycophorin C, CD34, c-kit, and terminal deoxyribonucleotidyl transferase (TdT). Cytogenetic analysis of the bone marrow cells demonstrated that 15 of the 20 cells analyzed showed complex chromosomal abnormalities; 47, XX, -1, add (3) (q11.2), add (4) (q31), t(6;14) (p21;q32), del (8) (q22q23), ?t(9;14) (p13b;q32), add(12)(p11.2), der (12)add(12)(p13), add (12) (q22), der(15)t(1;15) (q11;p11.1)del(1) (q23q25), der (16)add(16)(p11.2)add(16)(q22), +18, add(20) (q11.2), +der(?)t(?;1)(?;p22) (Fig. 1(j)). Based on these results, the patient was diagnosed as having PBML/DLBCL, non-germinal center B cell like (non-GCB type); stage IV_B (Age-adjusted International Prognostic Index: IPI score; high risk) and was immediately treated with R-CHOP chemotherapy (rituximab; 375 mg/m^2; day 1, cyclophosphamide; 750 mg/m^2; day 2, doxorubicin; 50 mg/m^2; day 2, vincristine 1.4 mg/m^2; day 2, prednisolone; 100 mg/body day 1 – day 5). She attained complete bone marrow response with no evidence of residual lymphoma cells in the bone marrow, assessed by immunohistochemistry on day 28 of the first cycle of the chemotherapy (Table 1, Fig. 2(a): hematoxylin and Eosin x200, b: CD20 x200) and chromosomal analysis showed normal karyotype (Fig. 2(c)). She had a normal platelet level of 21.7x10^4/μl. The level of LDH was 114 IU/l and sIL2-R was also decreased to 1470 U/ml. Baseline cerebrospinal fluid (CSF) examination was clear of atypical lymphoma cells, but prophylactic intrathecal methotrexate was given. She has remained in CR after receiving total 8 courses of R-CHOP chemotherapy. However, she had a prolonged low-grade fever, so she continued to be treated with moderate doses of prednisolone. After 6 cycle of R-CHOP chemotherapy, prednisolone was discontinued, and she has remained free of fever. During the clinical course, she suffered from a varicella zoster virus (VZV) infection once, but this was immediately resolved by the administration of aciclovir. She had moderate osteoporosis due to prednisolone treatment and continue to take regular check-up at orthopedic surgery in our hospital.

Currently, 8 years after the initial presentation, the patient has no signs of recurrence of lymphoma on the bone marrow survey including chromosomal analysis (Fig. 2(d)). Positron emission tomography (PET)/CT scan revealed slightly low 18F-FDG up-take which is considered to be associated with osteoporosis (Fig. 2(e)). She works every day, as she had before the diagnosis of lymphoma (Table 1).

3. Discussion

NHL presenting with primary isolated bone marrow involvement is rare, so a lack of uniform diagnostic criteria has made it difficult to define its clinical manifestation, histological findings, treatment and prognosis. Its diagnosis is currently based on bone marrow biopsy. The important points used to define PBML are; (1) its confinement to the bone marrow; (2) the absence of bone trabeculae destruction in the bone marrow biopsy; (3) the exclusion of any other leukemia/lymphoma entity known to arise primarily in the bone marrow; and (4) no evidence of lymph node, spleen, liver or other extra bone marrow involvement [1]. Review of 53 PBML/DLBCL cases presented in the literature suggested that common features at the initial presentation include advanced lymphoma stage (CS: IV), isolated bone marrow involvement with cytogenetic abnormalities, fever of unknown origin, cytopenia, and elevated LDH levels and showed a poor prognosis [1–7]. According to their histological features and immunohistochemical findings, several hematological malignancies arose primarily in the bone marrow. Kajiura et al. compared the Asian variant of intravascular large B-cell lymphoma (AIVL) with PBML [6]. Our case revealed no lymphoma cell infiltrations in the sinusoids of the bone marrow, so the diagnosis of AIVL was excluded. Another diagnostic possibilities, including acute lymphoblastic leukemia (ALL), lymphoblastic lymphoma (LBL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Burkitt's lymphoma (BL), Follicular lymphoma (FCL), splenic marginal zone lymphoma (SMZL), and Hairy cell leukemia (HCL) were also excluded. Furthermore, in order to exclude the overlap between primary bone lymphoma and PBML, a systemic CT scan showed normal findings. The mandatory absence of any localized bone tumor and the absence of evidence of trabeculae destruction in the bone marrow biopsy were consistently confirmed. Our case was also required to exclude the diagnosis of viral infections, such as EBV, CMV and HIV. Especially, the diagnosis of EBV associated hemophagocytic syndrome or EBV positive DLBCL of the elderly was highly suspected, however EBV DNA load in the peripheral blood was within normal limits and EBER in situ hybridization in the bone marrow tissue was negative, so finally diagnosis, related to EBV infection was excluded.

Recently, there have been significant advances in cancer imaging techniques. PET/CT becomes popular in the evaluation of patients with malignant lymphoma and has been shown to be more sensitive and specific than contrast-enhanced CT scan for the evaluation of nodal and extranodal involvements of lymphoma. Bone marrow involvement is one of the most important prognostic factors in patients with high grade lymphoma or intermediate grade lymphoma like our case and such cases are associated with significantly shorter survival. Currently, bone marrow biopsy is considered to be the method of the essential evaluation for the initial staging in patients with malignant lymphoma. However, bone marrow biopsy is an invasive procedure with a restrictive reliability, as only a limited area of the bone marrow is investigated, shown as a false negativity in up to 80% in a unilateral iliac crest biopsy, compared to bilateral iliac biopsies. Some of discordant rate was reported between bone marrow biopsy and FDG-PET/CT in

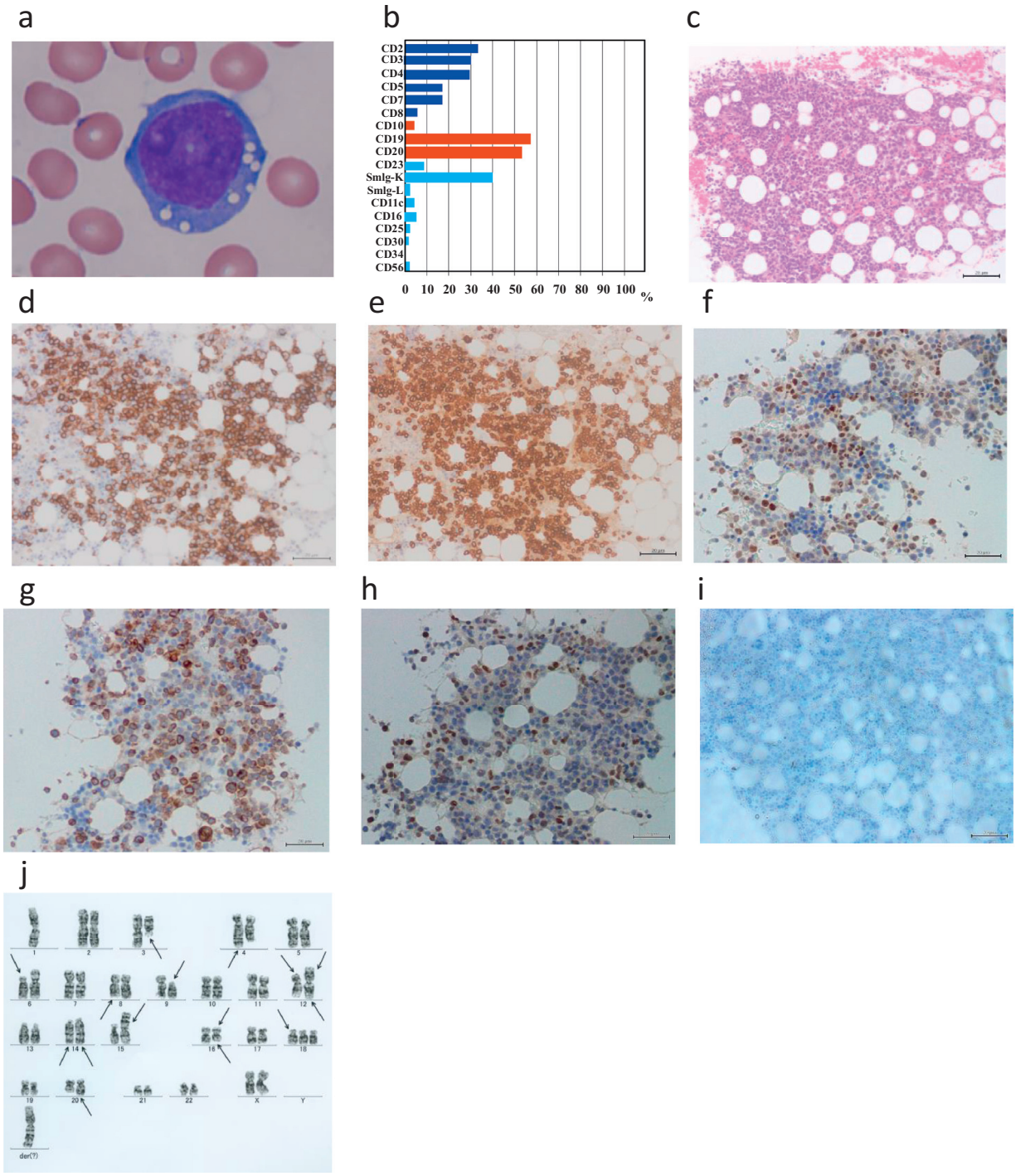

Fig. 1. (a) Bone marrow aspiration revealed medium to large sized atypical lymphoma cells with indistinct nucleoli, basophilic cytoplasm and cytoplasmic vacuoles (May-Giemsa staining x1000). (b) Immunophenotyping panel at the initial presentation. (c–i) Bone marrow biopsy at the initial presentation showed widespread infiltration lymphoma cells (c) hematoxylin &E eosin x200). Lymphoma cells are positive for (d) CD20 (L26) x200, (e) CD79α x200, (f) BCL6 x400, (g) BCL2 x400, (h) MUM1 x400, but negative for (i) CD3 x200. (j) G-Banding chromosomal analysis of the bone marrow cells at the initial presentation demonstrated that 15 of the 20 cells analyzed showed complex chromosomal abnormalities, including 47, XX, -1, add (3) (q11.2), add (4) (q31), t(6;14) (p21;q32), del (8) (q22q23), ?t(9;14) (p13b;q32), add)12)(p11.2), der(12)add(12)(p13), add (12) (q22), der(15)t(1;15)(q11;p11.1)del(1)(q23q25), der(16)add(16)(p11.2) add(16)(q22), + 18,add(20) (q11.2), + der(?)t(?;1)(?;p22).

detecting bone marrow involvement of DLBCL and although, there are no established guidelines to interpret bone marrow involvement by FDG-PET/CT in patients with newly diagnosed malignant lymphoma. However, patients with concordant bone marrow involvement had inferior survival compared to those with discordant marrow involvement. Therefore, an additional information on the role of FDG-PET/CT in detecting bone marrow involvement may be available and FDG-PET/CT may be used as a complementary rather than an alternative tool in detecting bone marrow involvement in patients with newly diagnosed DLBCL [8–10].

Review of 53 PBML/DLBCL cases presented in the literature suggests that most reported PBML cases have been DLBCL (Table 2) [1–7].

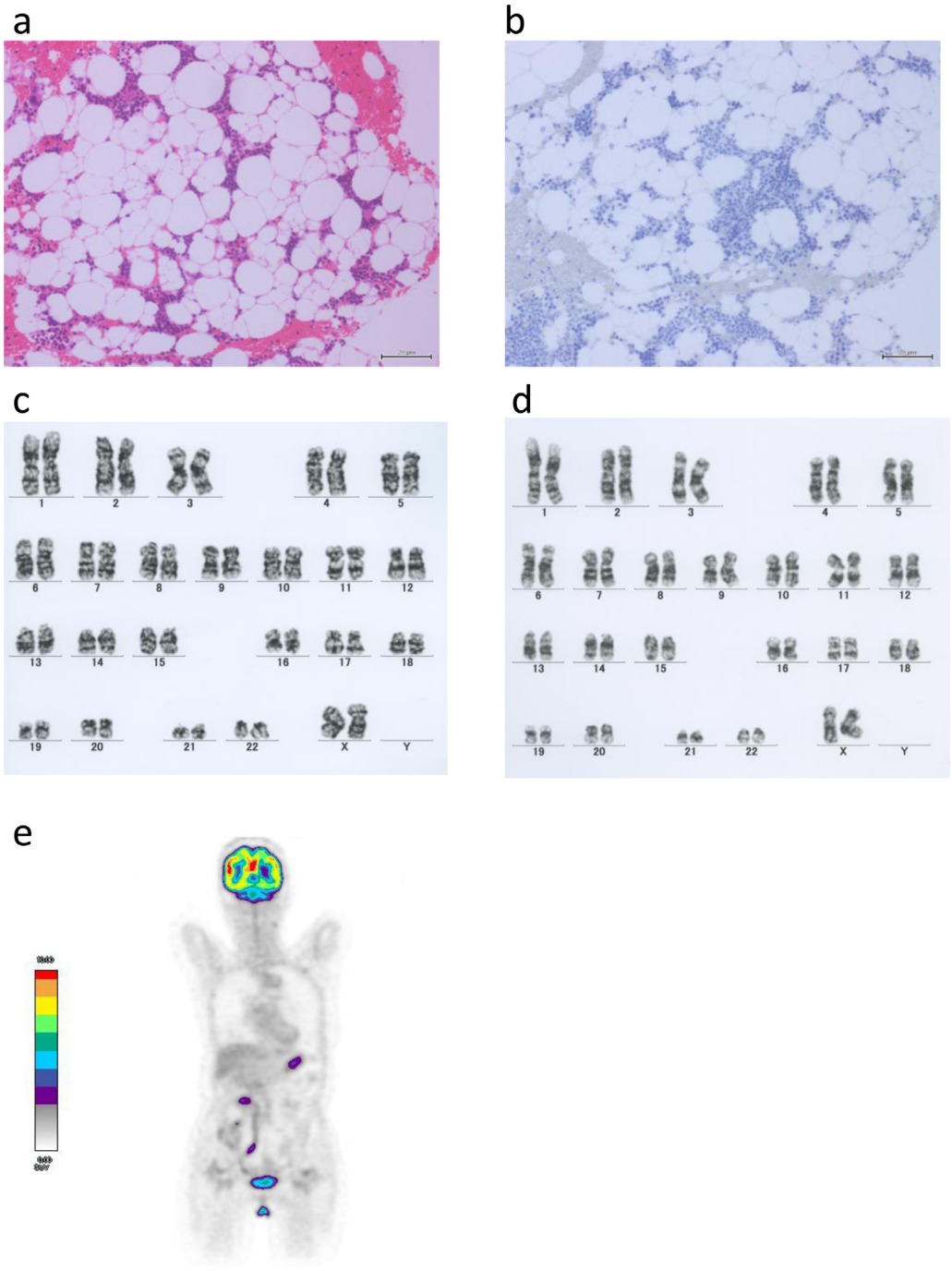

Fig. 2. (a)(b) Bone marrow biopsy at day 28 of the first cycle of R-CHOP therapy revealed complete clearance of CD20 positive atypical large lymphoma cells and commencement of resolution of the hemophagocytosis ((a) hematoxylin & eosin x200, (b) CD20 x200). (c) Chromosomal analysis at day 28 of the first cycle of R-CHOP therapy demonstrated 20 of the 20 analyzed cells showed normal karyotype and CR was attained. (d) Chromsomal analysis at 8 years after the initial presentation demonstrated 20 of the 20 analyzed cells showed normal karyotype and the patient has been in CR. (e) FDG/ PET at eight years after the initial diagnosis.

Martinez et al analyzed 21 PBML cases and found that 19 cases were B-cell lymphomas (4 cases; FCL, 15cases; DLBCL) and 2 cases were peripheral T cell lymphoma (PTCL) [1]. Furthermore, PBML/DLBCL cases that initially presented with severe thrombocytopenia, successfully treated without any relapse were extremely rare and had showed especially unfavorable outcomes, with a median overall survival (OS) of from 1 month to 2.4 years [1]. Changs, et al also reported these 12 cases and one of these cases reveals OS of 56 months with CHOP therapy, however this case relapsed [2]. In previous reports, in most cases, the first therapeutic option is R-CHOP therapy, however considering their unfavorable prognosis, intensive chemotherapy, including dose-modified R-ESHAP (rituximab, etoposide, cisplatin, cytarabine, prednisolone) or dose-modified R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) may be one of the therapeutic options even in the elderly patients without any organ dysfunctions or complications. Similarly, especially in younger patients without any organ dysfunctions or complications, up-front autologous stem cell transplantation may be one of the therapeutic options. In our case, chiefly due to bone marrow suppression after R-CHOP chemotherapy, it is impossible to repeat chemotherapy every 3 weeks. So, after confirming the recovery of neutrophil count in the peripheral blood, the next course of R-CHOP therapy was initiated, every 4 weeks. Our case belongs to high-risk group, according to IPI score and the presence of chromosomal abnormalities. Despite these backgrounds, our case has been in CR until now without any relapse signs, 8 years after the initial presentation. Several previous cases eventually developed extranodal recurrence including central nervous system (CNS) relapse, so we continued to take care of CNS involvement with the administration of prophylactic intrathecal methotrexate [1–3].

In conclusion, we reported unique case of PBML/DLBCL initially

Table 2
Summary of studies describing PBML/DLBCL with thrombocytopenia at the initial presentation.

Author	No. of cases	Thrombocytopenia at the initial Dx	Treatment	Outcome	Survival
Martinez A et al.	15	7/15	CHOP(3)R-CHOP(7)COP(1)HD-CHOP(1) CHOEP(1)VACOPB(1) Supportive care(1)	Dead(10)Alive(5)	<7days(Alive)-2.4years(Dead) <7days(Alive)-2.4years(Dead)
Chang H et al.	12	7/12	CHOP(3)R-CHOP(3)COP(1)R-COP(1) Auto-PBSCT(1)Supprotive care(1)	Dead(8)Alive(4)	<1month(Dead)-56months(Alive) <1month(Dead)-56months(Alive)
Alvares CL et al.	3	2/3	R-CHOP(1)CHOP(1) CHOP/COP + MIT + MTX(1)	Dead(2)Alive(1)	<1month(dead)-9months(Dead)
Hishizawa M et al.	1	ND	R-CHOP + Auto-PBSCT	Alive	12 month (Alive)
Barton JC et al.	7	0/7	VP/COP + Pro/ADR + Bleo + DTIC/COP + BCNU/L-asp(1) CBL-PSL(1)ADR + Bleo + DTIC/Bleo + DTIC(1), CBL + PSL/PSL(1), CBL + PSL/PSL/COP + Ara-C(1), PSL(2)	Dead(4)Alive(3)	2–54months(Alive)
Kajiura D et al.	9	ND		Dead(8) Alive(1)	1.5 weeks(Dead)-37 month (Dead)

MIT: mitoxantrone, MTX: methotrexate, Pro: procarbazine, ADR: adriamycin, Bleo: bleomycin, DTIC: dimethyl ariazeno imidazole, carboxamide, CBL: chrlorambucil, PSL: Prednisolone, Ara-C: cytosine arabinoside.

presenting with severe thrombocytopenia was successfully treated with systemic chemotherapy by R-CHOP and remains in CR for 8 years without any relapse signs. In cases with unknown fever and thrombocytopenia, PBML/DLBCL may be included in one of the differential diagnosis, and it is important to establish the exact diagnosis as quickly as possible and immediately initiate intensive chemotherapy.

Conflict of interests

The authors declare no competing conflict of interests to disclose.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.05.004.

References

[1] A. Martinez, M. Ponzoni, C. Agostinelli, et al., Primary bone marrow lymphoma: an uncommon extranodal presentation of aggressive non-Hodgkin lymphoma, Am. J. Surg. Pathol. 36 (2) (2012) 296–304.
[2] H. Chang, Y.S. Hung, T.L. Lin, et al., Primary bone marrow diffuse large B cell lymphoma: a case series and review, Ann. Hematol. 90 (2011) 791–796.
[3] C. Alvares, E. Matutes, M.A. Scully, et al., Isolated bone marrow involvement in diffuse large B cell lymphoma: a report of three cases with review of morphological, immunophenotypic and cytogenetic findings, Leuk. Lymph. 45 (4) (2004) 769–775.
[4] M. Hishizawa, K. Okamoto, K. Chonabayashi, et al., Primary large B-cell lymphoma of the bone marrow, Br. J. Haematol. 136 (2006) 351.
[5] J.C. Barton, M.E. Conrad, L.B. Vogler, et al., Isolated marrow lymphoma: an entity of possible T-cell derivation, Cancer 46 (1980) 1767–1774.
[6] D. Kajiura, Y. Yamashita, N. Mori, Diffuse large B cell lymphoma initially manifesting in the bone marrow, Am. J. Clin. Pathol. 127 (2007) 762–769.
[7] F.N. Ainle, O.P.R. Hamnvik, C. Gulmann, et al., Diffuse large B-cell lymphoma with isolated bone marrow involvement presenting with secondary agglutinin disease, Int. J. Lab. Hematol. 30 (2008) 444–445.
[8] J. Hong, Y. Lee, Y. Park, et al., Role of FDG-PET/CT in detecting lymphomatous bone marrow involvement in patients with newly diagnosed diffuse large B-cell lymphoma, Ann. Hematol. 91 (2012) 687–695.
[9] S. Muzahir, M. Mian, I. Munir, et al., Clinical utility of ^{18}F FDG-PET/CT in the detection of bone marrow disease in Hodgkin's lymphoma, Br. J. Radiol. 85 (2012) e490–e496.
[10] J.Y.Y. Ngeow, R.H.H. Quek, D.C.E. Ng, et al., High SUV uptake on FDG-PET/CT predicts for an Aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma, Ann. Oncol. 20 (2009) 1543–1547.