Letter to the Editor



## **Rare concurrent indolent B-cell lymphoma and plasmablastic transformation of myeloma**

Keywords: concurrent; plasmablastic transformation; myeloma; B-cell lymphoma

## TO THE EDITOR

An 81-year-old woman presented to our hospital with leukocytosis and abnormal lymphocytes. Her white blood cell count was 8970/µl (abnormal cells, 34%). Abnormal cells were small, atypical nucleated lymphocytes with a high nucleus-to-cytoplasm ratio, round nuclei and basophilic cytoplasm, with short polar villi. Flow cytometry (FCM) with CD45-gating analysis revealed that the abnormal lymphocytes in the peripheral blood were positive for CD19, CD20, CD23, CD25, FMC-7, cytoplasmic CD22, cytoplasmic CD79a, immunoglobulin (Ig)M, and  $\lambda$ , and negative for CD5, CD10, CD103, CD138, and ĸ. No superficial lymph nodes were palpable. Mild anemia, a slight increase in total serum protein and soluble interleukin-2 receptor levels was detected, and mild splenomegaly was noted on ultrasonography of the abdomen. Neither protein electrophoresis, bone marrow examination nor systemic screening by computed tomography (CT) were conducted. Matutes' system of diagnosis for chronic lymphocytic leukemia (CLL) yielded a score of only 1 point (CD23 positive).<sup>1</sup> Cytomorphology and surface markers of abnormal lymphocytes in the peripheral blood were negative for characteristics of CLL or hairy cell leukemia (HCL). The patient was therefore followed without any treatment under a presumptive diagnosis of indolent B-cell non-Hodgkin lymphoma. Two years later, anemia worsened with elevation of the serum IgG level to 5440 mg/dl. Serum albumin, IgA and IgM were suppressed concurrently. Protein electrophoresis demonstrated an M spike in the  $\gamma$ -fraction and M protein of the IgG- $\kappa$  type was



**Fig. 1.** Abnormal lymphocytes and plasma cells in the bone marrow (May-Giemsa staining, original magnification, ×1000).

found by immune-electrophoresis, but the serum free-light chain ratio was within the normal range. Examination of bone marrow aspirate revealed the concurrent infiltration of abnormal lymphocytes (48.6%) and plasma cells (26.0%) Bone marrow biopsy was not conducted. (Fig. 1). Abnormal lymphocytes in the bone marrow were similar in morphology and surface markers by FCM CD45-gating analysis to those in the peripheral blood. By FCM CD38-gating analysis, a population of cells with high expression of CD38 was positive for cytoplasmic CD79a, CD138, and  $\kappa$ , whereas a population of cells with low expression of CD38 was positive for CD19, CD20, CD23, cytoplasmic CD79a, and  $\lambda$  (Fig. 2A, 2B). Chromosomal analysis by G-banding of the bone marrow demonstrated 47, XX, +3 and 47, XX, +3, t(2; 13) (q35; q14) in one-twentieth of the cells in the mitotic phase. Pathological findings of the bone marrow clots were mainly



**Fig. 2.** Flow cytometry CD38-gating analysis of bone marrow (*A*: population of cells with high CD38 expression; *B*, population of cells with low CD38 expression).

The population of cells with high CD38 expression is positive for  $\kappa$ . The population of cells with low CD38 expression is positive for  $\lambda$ .



**Fig. 3.** Histological findings for bone marrow (hematoxylin-eosin staining, original magnification:  $\times 250$ ;  $\times 960$ ;  $\times 1200$  and immunostaining).

Mature plasma cells occupy a large proportion of the bone marrow. Immunohistochemically, plasma cells are positive for CD138, cyclin-D1, and  $\kappa$ . The MIB-1 index is 20%. Plasma cells are negative for CD20 and  $\lambda$ .

infiltration of plasma cells with immature nuclei and cytoplasm, and Dutcher bodies. Immunohistochemically, plasma cells were positive for CD138, cyclin-D1, IgG and  $\kappa$ , and negative for CD20, CD56, CD79a, IgA, IgM and  $\lambda$  (Fig. 3). A mutation in myeloid differentiation primary response gene 88 (MYD88) L265P was negative in the peripheral blood specimen. Differential diagnoses of splenic marginal zone lymphoma (SMZL) and splenic diffuse red pulp small B-cell lymphoma were considered based on the splenomegaly and abnormal lymphocyte infiltration in the peripheral blood and bone marrow, but a diagnosis of B-cell non-Hodgkin lymphoma remained unconfirmed due to the lack of histology of spleen and bone marrow. Multiple myeloma was diagnosed by bone marrow infiltration of myeloma cells with serum M protein, and was categorized as stage II in the revised international staging system.<sup>2</sup> Formation of an osteolytic tumor in the left ilium was detected during systemic screening by CT (Fig. 4A). The patient was treated using THP-COP-VDS therapy (pirarubicin, cyclophosphamide, vincristine and vindesine) targeting malignant lymphoma. After the first course of THP-COP-VDS therapy, only minimal reduction of the pelvic tumor was observed. THP-COP-VDS therapy was

changed to BD therapy (bortezomib, dexamethasone) to target multiple myeloma. Although the serum IgG level decreased from 5440 mg/dL to 1348 mg/dL, the pelvic tumor enlarged after BD therapy (Fig. 4B). BD therapy was changed to VCD therapy (bortezomib, cyclophosphamide, dexamethasone), but this resulted in an increase in the serum LDH level to 1280 U/L. Biopsy of the pelvic tumor was conducted by CT-guided needle biopsy. Pathological examination of the pelvic tumor revealed abnormal cells with poor cytoplasm, anisokaryosis and pleomorphic nuclei infiltrating into skeletal muscles. Some were similar to plasmablasts. Immunohistochemically, the abnormal cells were positive for CD138, Cyclin-D1, IgG and  $\kappa$ , and negative for CD19, CD20, CD56, CD79a, Pax-5, ALK, human herpes virus (HHV)-8, IgA, IgM and  $\lambda$ . In situ hybridization for Epstein-Barr virus-encoded RNA was negative (Fig. 5). In addition, the MIB-1 index was 80% for abnormal cells in the pelvic tumor tissue, but only 20% for myeloma cells in the bone marrow (Figs. 3, 5). Cytogenetics of the pelvic tumor were not able to be examined because of the small specimen collected by needle biopsy. Extracavitary primary effusion lymphoma and ALK-positive diffuse large B-cell lymphoma were excluded due to the negative results for HHV-8 and ALK by immunostaining, and the negative result for human immunodeficiency virus (HIV) antibody in patient serum. Plasmablastic transformation of myeloma was diagnosed by exclusion of primary plasmablastic lymphoma (PBL) because



Fig. 4. Computed tomography of the pelvic tumor (*A*, at diagnosis; *B*; after BD therapy). *A*) An osteolytic tumor is detected in the left ilium. *B*) The pelvic tumor became enlarged following BD therapy. of the background of multiple myeloma. The pelvic tumor was resistant to radiation (total, 30 Gy/15 fractions), lenalidomide and iPAD therapy (bortezomib, adriamycin, dexamethasone). However, the serum IgG level remained low. Abnormal lymphocytes in the peripheral blood disappeared and splenomegaly improved. However, she died due to progression of the pelvic tumor 5 months after the start of chemotherapy.

Pantic et al. previously reported five patients with a biclonal origin of concomitant B-CLL and multiple myeloma.<sup>3</sup> The clonal relationship between B-CLL and multiple myeloma was resolved by the combination of single-nucleotide polymorphism mapping array and fluorescent in situ hybridization analyses. The present case was not resolved by such analyses, but we considered the relationship between indolent B-cell lymphoma and multiple myeloma to have a biclonal origin because of the different light chains. Pathologically, it is important to rule out other differential diagnoses for lymphoplasmacytic lymphoma (LPL), marginal zone lymphoma and CLL with plasmacytoid differentiation. CD56 and/or cyclin D1 expression by plasma cells was helpful for making a correct diagnosis.<sup>4</sup> Regarding LPL, the MYD88 L265P mutation exhibited high diagnostic significance because of positivity in the majority of LPL cases according to the 2016 WHO classification.<sup>5</sup> The negative result for the MYD88 L265P mutation was unable to completely exclude a diagnosis of LPL, but was helpful for differentiating LPL from lymphoid malignancy with primary infiltration to bone marrow associated with multiple myeloma. In the present case, myeloma cells of the pelvic tumor differed from those in the bone marrow in terms of both clinical and pathological features. Heterogeneous clonal groups are



**Fig. 5.** Histological findings for the pelvic tumor tissue (hematoxylin and eosin staining; original magnification: ×400; ×750 and immunostaining).

Abnormal cells with poor cytoplasm, anisokaryosis and pleomorphic nuclei infiltrated into skeletal muscle. Immunohistochemically, abnormal cells are positive for CD138 and  $\kappa$ . The MIB-1 index is 80%. Abnormal cells are negative for  $\lambda$ .

present within the same individual myeloma patient, and myeloma cells with acquired anaplastic characteristics are more likely to colonize extramedullary sites.<sup>6,7</sup> This may be one of the reasons for the clinical and pathological discrepancy between the myeloma cells of the pelvic tumor and those of the bone marrow. Multiple myeloma with aggressive tumors is often seen in the terminal phase after a heavy treatment history.<sup>8,9</sup> However, the tumor in the present patient rapidly progressed after initial chemotherapy. These clinical characteristics and histopathological findings resembled the clinical features of PBL. A background of immune suppression due to HIV or other causes is related to the development of PBL.<sup>10</sup> Low-grade B-cell neoplasms, such as CLL, SMZL and HCL, are associated with a frequent incidence of immune suppression or immune disorder.<sup>11-13</sup> Indeed, patients with concomitant B-CLL and multiple myeloma

often have a more unfavorable clinical course than those with multiple myeloma alone, presenting adverse prognostic features and early death due to myeloma progression. In addition, survival times with these pathologies are shorter than those with de novo plasma cell myeloma.<sup>3,4</sup> Consequently, the influence of complicated lymphoma may have led to the progression of the pelvic plasma cell tumor with original anaplastic characteristics. The immunosuppressive complications present in patients with low-grade B-cell lymphoma may enable neoplastic plasma cells to evade the mechanisms of anti-tumor immunity. The clinicopathological features of the reported cases of concomitant indolent B-cell lymphoma and multiple myeloma over the previous decade (2008 to 2017) are summarized in Table 1.<sup>3,4,14-17</sup> Twenty seven cases of concomitant indolent B-cell lymphoma and multiple myeloma were identified. One case of LPL (Case 26)

 Table 1. The clinicopathological features of the reported cases of concomitant indolent B-cell lymphoma and multiple myeloma in the previous decade (2008 to 2017).

Case	Age	Gender	Histology of lymphoma	Clonal identity	Light chain of lymphoma	M protein of myeloma	Aggressive manifestation of myeloma at diagnosis	Outcome	Reference
1	64	М	CLL	not resolved	λ	BJP-к	no	alive	3
2	76	М	CLL	biclonal	к	IgG-λ	no	deceased	3
3	73	М	CLL	biclonal	к	IgA-к	NA	deceased	3
4	73	М	CLL	biclonal	λ	IgG-к	no	deceased	3
5	62	М	CLL	biclonal	к	BJP-λ	NA	deceased	3
6	56	М	CLL	NA	к	IgG-к	no	alive	4
7	57	М	CLL	NA	к	BJP-κ	no	alive	4
8	58	М	CLL	NA	К	κ (no data on heavy chain)	no	alive	4
9	64	М	CLL	NA	λ	κ (no data on heavy chain)	no	alive	4
10	68	М	CLL	NA	к	λ (no data on heavy chain)	no	alive	4
11	71	М	CLL	NA	к	IgG-к	no	alive	4
12	74	F	CLL	NA	λ	κ (no data on heavy chain)	no	alive	4
13	78	М	CLL	NA	К	κ (no data on heavy chain)	NA	deceased	4
14	82	М	CLL	NA	λ	IgG-к	no	alive	4
15	85	М	CLL	NA	λ	IgG-λ	NA	deceased	4
16	91	М	CLL	NA	undetectable	IgA-λ	NA	NA	4
17	63	М	CLL	NA	λ	IgG-к	no	alive	4
18	77	F	CLL	NA	κ	BJP-λ	no	alive	4
19	77	М	CLL	NA	К	κ (no data on heavy chain)	NA	deceased	4
20	80	М	CLL	NA	no flow cytometry	IgG-λ	no	alive	4
21	67	F	CLL	NA	к	IgG-к	no	alive	14
22	60	М	CLL	NA	κ	IgG-к	no	alive	14
23	77	F	CLL	NA	К	λ (no data on heavy chain)	no	alive	15
24	55	М	CLL	NA	λ	κ (no data on heavy chain)	no	alive	15
25	66	F	CLL	NA	κ/λ (2 distinct clones)	κ (no data on heavy chain)	no	alive	15
26	73	М	LPL	NA	IgM-к	IgA-κ	yes (plasmablastic myeloma)	alive	16
27	76	М	LPL	NA	IgM-к	IgА-к	no	alive	17
28	81	F	indolent B-NHL	NA	λ	IgG-к	yes (plasmablastic myeloma)	deceased	our case

CLL, chronic lymphocytic leukemia; LPL, lymphoplasmacytic lymphoma; NHL, non-Hodgkin lymphoma; NA, not available.

demonstrated aggressive manifestations of myeloma at the diagnosis of myeloma. In conclusion, the present patient developed plasmablastic transformation of myeloma against a background of indolent B-cell lymphoma. On rare occasions, patients with concomitant indolent B-cell lymphoma and multiple myeloma may have a more unfavorable clinical course than those with multiple myeloma alone. More cases must be accumulated to clarify the etiological relationship between the aggressive clinical features of myeloma and indolent B-cell lymphoma.

## **CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

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Masuho Saburi,<sup>1)</sup> Masao Ogata,<sup>2)</sup> Kazuhito Itani,<sup>1)</sup> Kazuhiro Kohno,<sup>1)</sup> Yasuhiro Soga,<sup>3)</sup> Yoshiyuki Kondo,<sup>4)</sup> Yawara Kawano,<sup>5)</sup> Toshiyuki Nakayama<sup>1)</sup> <sup>1)</sup>Department of Hematology, Oita Kouseiren Tsurumi Hospital, Oita, Japan,<sup>2)</sup>Department of Hematology, Oita University Hospital, Oita, Japan,<sup>3)</sup>Department of Clinical Laboratory, Oita Kouseiren Tsurumi Hospital, Oita, Japan, <sup>4)</sup>Department of Diagnostic Pathology, Oita Kouseiren Tsurumi Hospital, Oita, Japan, <sup>5)</sup>Department of Hematology, Kumamoto University Hospital, Kumamoto, Japan. **Corresponding author**: Masuho Saburi, MD, Department of Hematology, Oita Kouseiren Tsurumi Hospital, 4333 Oaza Tsurumi, Beppu City, Oita 874-8585, Japan.

E-mail: masuho-saburi@oita-u.ac.jp

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