MM with bortezomib, a proteasome inhibitor known for its remarkable efficacy in treating extramedullary MM.

Although the pathogenesis of MPE is unknown, it is theorized that it may be a direct extension of thoracic myelomatous involvement. A review of 57 cases [9] demonstrated that half of the patients with MPE had concomitant thoracic skeletal, lung parenchymal, or chest wall plasmacytomas, which would provide a source for MPEs. Similarly, both of our patients had a pulmonary nodule, which likely represented metastatic disease.

Genetic analysis showed that the patient in our first case had a trisomy at chromosome 3 and monosomy at chromosome 13. In addition to the t(4;14) translocation, this complex karyotype is associated with unfavorable prognosis [5]. Given that the median survival time for high-risk patients without malignant pleural effusions is 3 years, it is likely that the progression of the myeloma and development of the pleural effusions contributed significantly to the eventual death of the first patient. In our second case, the patient had no trisomy, but she did have monosomy of chromosome 13 in addition to the t(4;14) translocation. This chromosome 13 abnormality was also seen in 77.8% of patients in the Cho *et al.* [10] case series.

Although rare, more cases of MPE are being described in the literature, with evidence indicating its poor prognosis and lack of efficacious treatment [5, 12]. Because of the severity of MPE, we recommend that patients with pleural effusions and suspicion of myeloma undergo protein electrophoresis, flow cytometry, cytologic examination of the pleural fluid, or pleural biopsy examination to identify MPE and begin treatment promptly [12, 13].

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A rare case of diffuse large B cell lymphoma-associated hemophagocytic syndrome initially present in the bone marrow with a favorable clinical course

TO THE EDITOR: Lymphoma-associated hemophagocytic syndrome (LAHS) is a hematological disorder associated with malignant lymphoma. It is characterized by clinical features and laboratory findings associated with hemophagocytic lymphohistiocytosis (HLH), such as fever, cytopenia, hyperferritinemia, hypofibrinogenemia, and hemophagocytosis in the bone marrow (BM) [1]. The development of LAHS can be accounted for by various types of lymphoma,

but most of them are associated with T cell or natural killer (NK) cell lymphomas such as aggressive NK/T cell lymphoma, peripheral T cell lymphoma, anaplastic large cell lymphoma, or extranodal NK/T cell lymphoma [2-7]. Development of LAHS from B cell lymphoma is rarely reported, and occurs in old age with a low frequency of BM involvement at diagnosis [6, 7]. To date, seven cases of LAHS associated with large B cell lymphoma initially manifesting in the BM have been reported and the majority of these cases were of the non-germinal center (GC) type, with a complex karyotype and very poor prognosis [8]. We report here a rare case of diffuse large B cell lymphoma (DLBCL)-associated hemophagocytic syndrome initially manifesting in the BM and exhibiting a favorable clinical course.

In February 2015, a 73-year-old female was admitted with fever (body temperature, 38.1°C), poor oral intake, and general weakness, which had developed 2 weeks prior to admission. She was diagnosed as diabetes mellitus (DM) 8 years ago and had been on treatment with a hypoglycemic agent, but had no medical history related to hematological malignancy, including hepatosplenomegaly. The patient's hemogram results at admission showed pancytopenia (white blood cell [WBC] count 3.57×10^9/L [absolute neutrophil count 2.82×10^9/L], hemoglobin 7.6 g/dL, platelet count 32.0×10^9/L). Her peripheral blood smear showed the presence of atypical lymphocytes (3% of total nucleated cells). She underwent BM aspiration and biopsy due to pancytopenia with presence of atypical lymphocytes.

The patient's BM aspirates (Fig. 1A, B) and touch print (Fig. 1C, D) showed normocellular marrow with increased infiltration of large-sized neoplastic lymphoid cells with a frequency of 20.0% (indicated by the orange arrows).

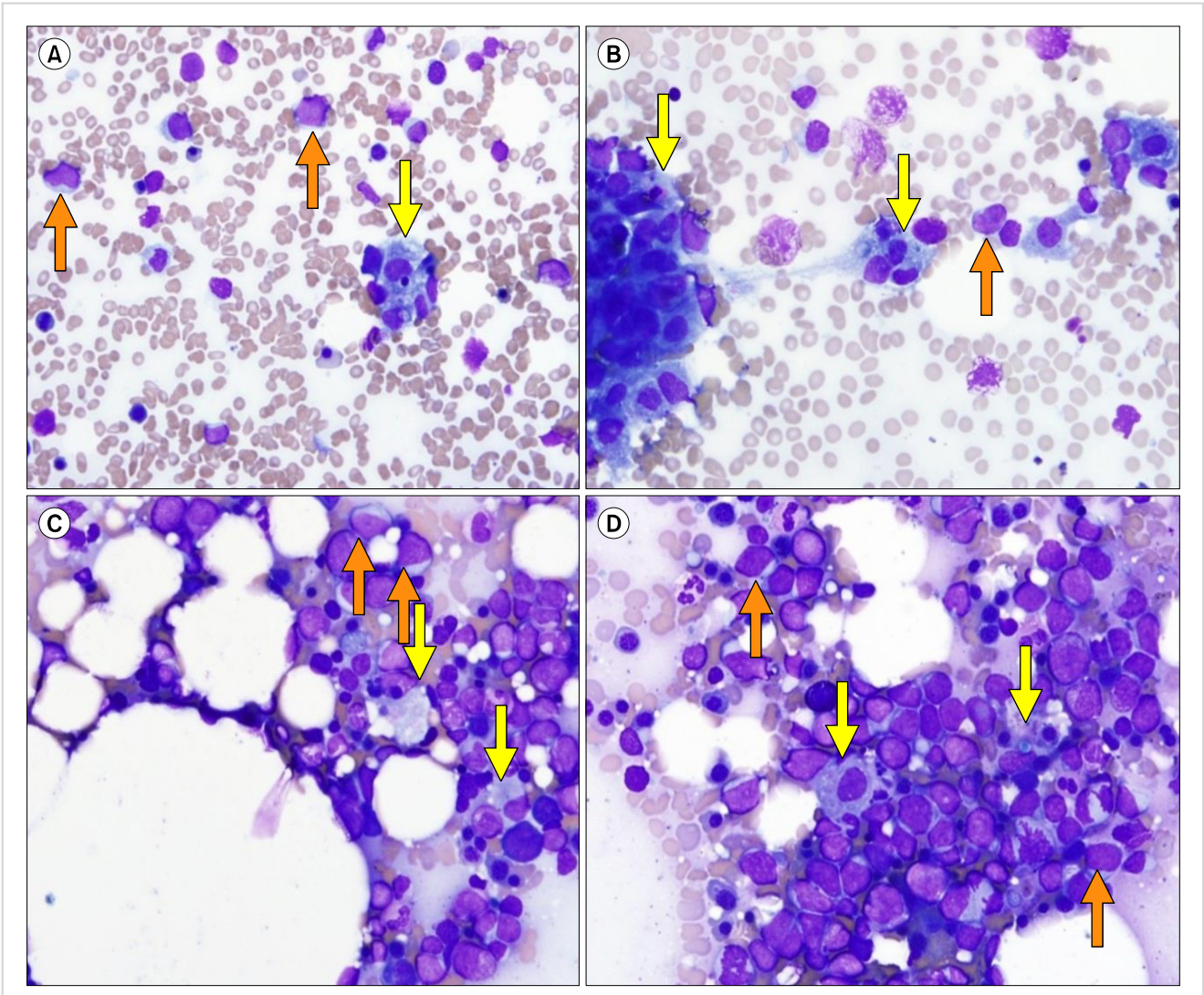

Fig. 1. Bone marrow aspirates (**A**, **B**, Wright stain, ×400) and touch print (**C**, **D**, Wright stain, ×400). The bone marrow aspirates and touch print show normocellular marrow with infiltration of neoplastic lymphoid cells (20.0% of total nucleated cells, orange arrows). In addition, hemophagocytic histiocytes (11.0% of total nucleated cells, yellow arrows) were identified.

In addition, histiocytes with active hemophagocytosis were occasionally identified with a frequency of 11.0% (indicated by the yellow arrows). Flow cytometric analysis results of BM aspirates demonstrated the presence of a clonal B lymphocyte population with kappa light chain restriction: 19.0% positivity for CD19, 22.6% positivity for CD20, 35.0% positivity for kappa light chain, and 5.2% positivity for lambda light chain. However, T-cell markers showed no evidence of clonality, with variable positivity for CD3, CD2, CD5, CD7, CD4 and CD8, (range, 10.9–48.1%).

The BM biopsy (Fig. 2A) showed that 65% of the marrow was cellular. Diffuse infiltration of CD20-positive neoplastic lymphoid cells (indicated by the orange arrows) and increased infiltration of CD68-positive hemophagocytic histiocytes (indicated by the yellow arrows) was demonstrated by immunohistochemical stains for CD3, CD20 and CD68 (DAKO, Glostrup, Denmark) (Fig. 2B–D, respectively). Serum ferritin, fibrinogen, triglyceride, and soluble interleukin-2 (IL-2) receptor levels were 1,198.0 ng/mL (reference range, 33–298 ng/mL), 300.5 mg/dL (reference range, 170–380 mg/dL), 149 mg/dL (reference range, 58–250 mg/dL) and 6,530.0 U/mL (reference range, 124–466 U/mL), respectively. The patient's karyotype analysis results showed 46–48,XX,add(1)(q25),add(1)(q42),add(2)(q33),del(4)(q21),del(5)(p13p15.3),add(6)(q21),del(8)(q22),+16,add(17)(q25),add(19)(p13.3),+20[cp11]/46,XX[9], indicating the presence of a complex karyotype in 55% of all analyzed cells. Based on these results, and because her clinical and laboratory findings fulfilled the 2008 diagnostic criteria of HLH (fever, cytopenia, hyperferritinemia, hemophagocytosis in BM, high soluble IL-2 receptor levels) [9], the patient was initially diagnosed with B cell LAHS which was finally revised as

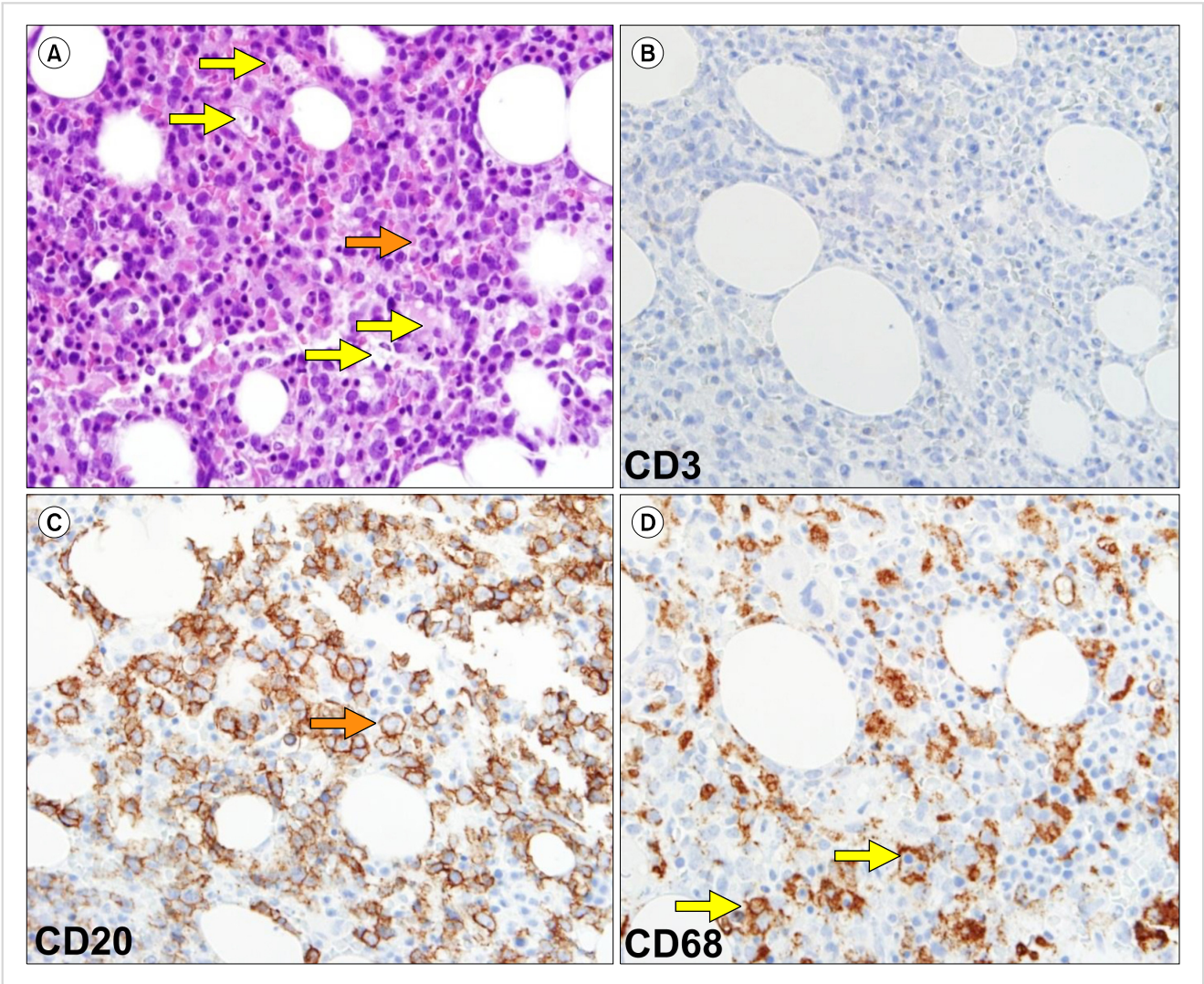

Fig. 2. Bone marrow biopsy (**A**, hematoxylin and eosin stain, ×400) and immunohistiochemical staining results for CD3, CD20 and CD68 (**B–D**, ×400, respectively). The bone marrow biopsy shows normocellular marrow with diffuse infiltration of CD20-positive neoplastic lymphoid cells (orange arrows) accompanied by an increase of CD68-positive histiocytes with occasional hemophagocytosis (yellow arrows), indicating the presence of B-cell lymphoma associated with hemophagocytic histiocytosis.

DLBCL (non-GC type)-associated hemophagocytic syndrome. She was treated with 5 cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab) chemotherapy. At follow-up after 3 months of chemotherapy, the patient's hemogram results had improved significantly (WBC 4.45×10^9/L, hemoglobin 10.7 g/dL, platelet count 148×10^9/L). In the BM study, residual neoplastic lymphoid cells were not identified and active hemophagocytosis was not observed, despite persistent histiocytic hyperplasia. The patient has been discharged in an improved condition and is waiting to undergo additional chemotherapy.

According to the literature, B cell LAHS cases are rather uncommon compared with T- or NK-cell lymphoma cases and the most common type is DLBCL, which occurs in older patients [6, 7]. To date, there have been seven reports of large B cell lymphoma initially manifesting in the BM, with consistent clinical features such as occurrence in old age (range, 54–80 yr), non-GC type (six cases), a complex karyotype, aggressive clinical course (four cases died before treatment), and no association with Epstein-Barr virus (EB) infection (all seven cases) [8]. The clinical features of our patient were generally similar to those of the previous cases: a complex karyotype, non-GC type of DLBCL, old age at diagnosis. However, our patient also demonstrated an uncommon clinical feature of B cell LAHS initially manifesting in the BM: a favorable clinical outcome after chemotherapy. Since our patient did not undergo serologic or molecular EBV studies, we could not confirm that EBV infection was not associated with B cell LAHS initially manifesting in the BM, which was suggested by the previous study [8]. Further studies will be required to confirm the clinical features of B cell LAHS initially manifesting in the BM.

In conclusion, we report a rare case of DLBCL-associated hemophagocytic syndrome initially manifesting in the BM and exhibiting a favorable clinical outcome. More extensive studies will be needed to investigate the clinical features of these patients.

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