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CASE REPORT

Extramedullary hematopoietic pleural effusion in Waldenström's macroglobulinemia

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Abstract

Extramedullary hematopoietic effusion (EHE) is one of the extremely rare phenomena associated with extramedullary hematopoiesis, which is caused by serous effusions, including pleural effusion, and may be related to hematologic disorders and neoplasms. Herein, we present the case of an 81-year-old man with EHE accompanying Waldenström's macroglobulinemia (WM). The patient complained of anemia and dyspnea. The chest X-ray and computed tomography showed a massive left pleural effusion, and the aspirates revealed infiltration of the immature myeloid cells and megakaryocytes, in addition to the lymphoma cells. To our knowledge, this is the first report of EHE in WM.

KEYWORDS

6q deletion, extramedullary hematopoiesis, extramedullary hematopoietic effusion, Waldenström's macroglobulinemia

1 | INTRODUCTION

Serous effusions, such as pleural effusion, pericardial effusion, and ascites, may cause extramedullary hematopoiesis (EMH), which refers to the formation of normal blood cells outside the bone marrow (BM), usually involving the spleen, liver, and lymph nodes [1]. EMH that occurs in serous effusions is called extramedullary hematopoietic effusions (EHE) [2]. Most cases of EHE have been reported to result from hematologic malignancies, including myeloproliferative neoplasms (MPNs) or metastatic cancers [2, 3], whereas only a few cases of EHE accompanying a lymphoma diagnosis have been described [2–4]. To our knowledge, the current paper describes the first report of EHE accompanying Waldenström's macroglobulinemia (WM).

2 | CASE PRESENTATION

An 81-year-old man was admitted to our hospital in March 2021 because of anemia and dyspnea lasting for 1 month. A chest X-ray revealed a substantial pleural effusion in the left lung. Furthermore, computed tomography demonstrated marked pleural effusion in the left lung (Figure 1A), hepatosplenomegaly (long diameters of the liver and spleen were 21.6 and 11.6 cm, respectively), and a soft-tissue mass in the retroperitoneal. The following laboratory test results were obtained: white blood cell count, 5.0×10^9/L (neutrophil 77%, lymphocyte 17%); hemoglobin (Hb) level, 8.5 g/dl; platelet count, 230×10^9/L; total protein, 7.5 g/dl; albumin, 2.4 g/dl; lactate dehydrogenase (LDH), 193 IU/L (normal range: 124–222 IU/L); C-reactive protein, 6.46 mg/dl; immunoglobulin (Ig)G, 855 mg/dl; IgA, 79 mg/dl; and IgM, 2,928 mg/dl

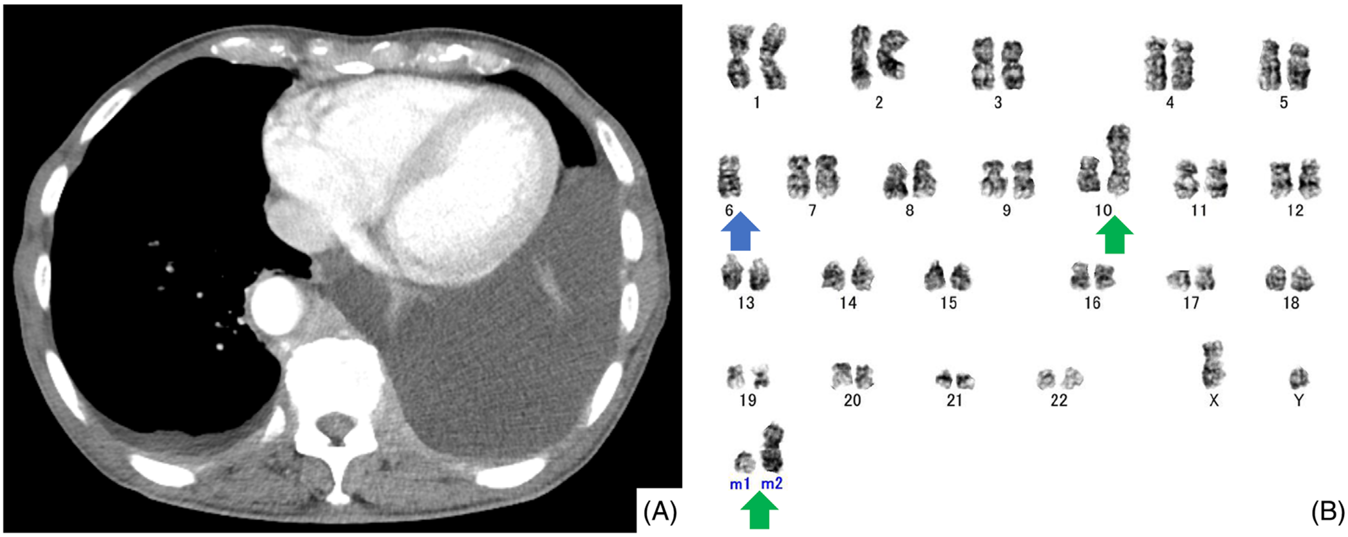

FIGURE 1 (A) The computed tomography obtained at diagnosis. Pleural effusion was observed in the left pleural cavity. (B) The conventional cytogenetic analysis of the bone marrow (BM) aspirate. The large blue arrow indicates monosomy 6. The green arrow indicates add(10)(p11.2), and m1 and m2 indicate marker chromosomes.

(normal range: 33–183 mg/dl). A serum immunofixation test revealed monoclonal bands of IgM and kappa. The BM aspirate revealed an abnormal increase in atypical small lymphocytes, lymphoplasmacytic cells, and plasma cells. The biopsied BM specimens exhibited 90% infiltration of small- to medium-sized atypical lymphocytes with plasmacytoid differentiation (Figure 2A,B). From immunohistochemical staining, the CD20 expression was positive in 50% of atypical small lymphocytes (Figure 2C), whereas the CD138 expression was positive in 10% of the atypical lymphocytes with plasmacytoid differentiation (Figure 2D). The fluorescence in-situ hybridization (FISH) analysis revealed monosomy 6, and the conventional cytogenetic analysis of the BM aspirate revealed 47, XY, +mar, −6, add(10)(p11.2), +mar2 [2] (Figure 1B). Thus, the patient was diagnosed with WM according to the World Health Organization classification [5].

After admission, 500 ml of pleural effusion was drained. The pleural effusion was exudative, with a total cell count of 2720/μl, LDH of 193 IU/L, and total protein of 4.2 g/dl. After May-Giemsa and Papanicolaou staining, the pleural effusion aspirate showed infiltration of immature myeloid cells (Figure 2E) and megakaryocytes (Figure 2F), in addition to the invasion of lymphoma cells. The immature myeloid cells were positive for myeloperoxidase staining (Figure 2G), whereas the megakaryocytes were positive for factor VIII [6] (Figure 2H). Thus, the etiology of the pleural effusion was EHE with lymphoma infiltration.

Oral tirabrutinib was administered once daily at 480 mg [7]. The treatment course of the patient is summarized in Figure 3. At 46 weeks, the pleural effusion completely disappeared, and the patient had a partial response according to the 6th International Workshop on WM response criteria [8].

3 | DISCUSSION

EMH refers to the production of hematopoietic stem and progenitor cells outside of the BM and usually occurs as a compensatory reaction in response to insufficient hematopoiesis of the BM [9]. EMH can be provoked by numerous pathological conditions: mainly hematologic disorders, including MPNs, leukemia, hemolytic anemia, thalassemia, and lymphoma; metastatic cancer; and cirrhosis [1]. The spleen and liver are the sites predominantly involved with EMH [1, 10]. In a case series of EMH without MPNs from Mayo Clinic, Fan et al. reported that EMH accompanied by lymphoma was observed in only 6% of the cases (19 of the 309 cases), and spleen or liver sites dominated 90% of the cases [1].

EMH has also been reported to occur in sites other than the spleen and liver [11]. For example, the para-vertebral body and lymph node were the next most frequently involved sites [9, 11], whereas the pleural cavity was rarely involved. In a retrospective study of 4,844 cases of pleural and peritoneal effusions over 22 years from the University of Michigan, only five cases of EHE were identified [3]. In previous studies, the conditions most commonly associated with EHE were myelofibrosis and metastatic cancers [2, 3]. EHE associated with lymphoma was reported in only a few cases [2–4].

WM is a low-grade B-cell lymphoma that originates from small lymphocytes, lymphoplasmacytic cells, and plasma cells, usually involving the BM, spleen, and lymph nodes [5]. Extramedullary and extra-nodal involvement was reported to occur in 4.4% of WM cases: the most common site of involvement is the pulmonary system (30%) [12]. However, determining a diagnosis of lymphoma infiltration into the pleural cavity is often challenging and requires cytopathological examinations, flow

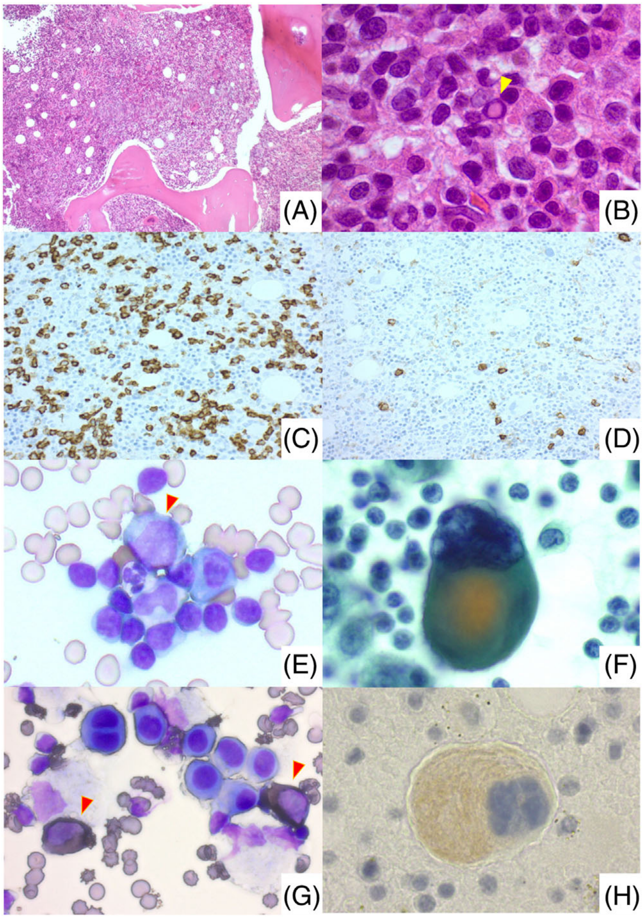

FIGURE 2 (A–D) Neoplastic cells in the bone marrow (BM) specimens. (A) The hematoxylin and eosin (H&E) staining. Diffuse infiltration of lymphocytes in the BM was observed (original magnification of 100x). (B) H&E staining using the highest magnification. Atypical lymphocytes, lymphoplasmacytic cells, and plasma cells were observed. The yellow arrowhead indicates the Dutcher body (640x). (C) Staining with CD20. Atypical small lymphocytes and lymphoplasmacytic cells were positive for CD20 (400x). (D) Staining with CD138. Lymphoplasmacytic cells and plasma cells were positive for CD138 (400x). (E-H) The aspirates or biopsied specimens from the pleural effusion. (E) May-Giemsa staining. The red arrowheads indicate immature myeloid cells among the lymphoid cells (400x). (F) Papanicolaou staining. Megakaryocytes were observed (400x). (G) Myeloperoxidase staining. The red arrowheads indicate immature myeloid cells, which were positive for myeloperoxidase (400x). (H) Staining with Factor VIII. The cytoplasm of the megakaryocytes was positive (400x).

cytometry, and cytogenetic analyses. In the present case, the detailed cytopathological examination of the pleural effusion helped to clarify the etiology of the pleural effusion and determine the treatment strategy after diagnosis.

Chromosome 6q deletion (6q del) or monosomy 6 is recognized as the most frequent cytogenetic abnormality in WM [13] and has been associated with a high tumor burden and a negative impact on survival [14, 15]. In the present case, the patient had monosomy 6 and exhibited a high tumor burden with diffuse infiltration of tumor cells into the BM,

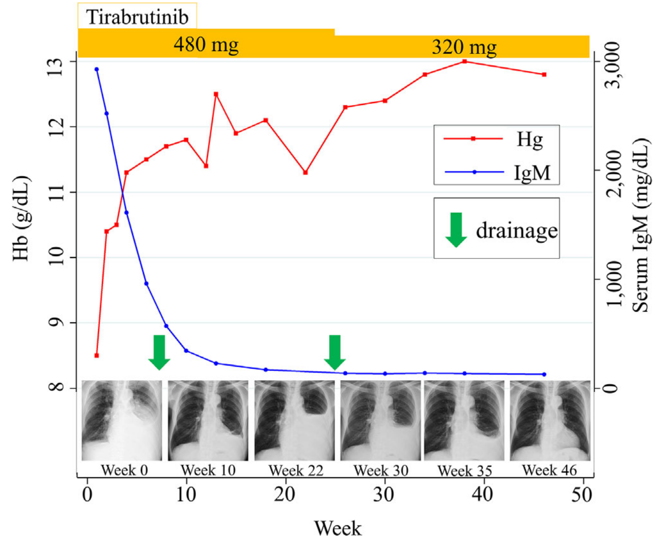

FIGURE 3 The clinical course of the patient. The blue lines show the chronological change of the serum immunoglobulin M (IgM) levels, whereas the red lines represented the hemoglobin (Hb) levels. The chest X-ray images show the chronological changes in the pleural effusion at each assessment point.

in addition to hepatosplenomegaly. We previously reported a case of EHE and follicular lymphoma (FL) associated with hepatosplenomegaly and diffuse infiltration into the BM [4]. The massive infiltration into the BM, liver, and spleen was observed in the previously reported FL case [4] and the present case; thus, this extensive infiltration may cause unusual sites of EMH, such as pleural effusion. Additionally, EHE disappeared in both cases after the lymphoma was successfully treated [4].

In summary, we reported a case of WM with high tumor burden, diffuse BM infiltration, and hepatosplenomegaly, accompanied by EMH in pleural effusion. To our knowledge, this is the first report of WM with EHE. The findings showed that a heavy tumor burden can cause EMH in unlikely sites.

AUTHOR CONTRIBUTIONS

Kenichi Ito analyzed and interpreted the data, and drafted the manuscript. Yoshihito Uchino and Kunihiko Harada acquired the data. Kazuhiko Hirano reviewed the pathological diagnosis and provided pictures for the figures. Naohiro Sekiguchi carefully reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Because this is a case report, ethical committee approval is not required for this study, in accordance with the ethical national guidelines in Japan.

PATIENT CONSENT STATEMENT

Written consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

CLINICAL TRIAL REGISTRATION

Not applicable.

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