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Case of the month

Successful treatment of multi-agent chemotherapy with rituximab for IgM plasma cell leukemia

Satoko Oka [a,*], Taiji Yokote [a], Toshikazu Akioka [a], Satoshi Hara [a], Takeshi Yamano [a], Motomu Tsuji [b], Toshiaki Hanafusa [a]

[a] *First Department of Internal Medicine, Osaka Medical College, 2-7 Daigakumachi, Takatsuki City, Osaka 569-0801, Japan*
[b] *Division of Surgical Pathology, Osaka Medical College, 2-7 Daigakumachi, Takatsuki City, Osaka 569-0801, Japan*

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Abstract

A 67-year-old woman presented with impaired general performance, suffering from fatigue, dyspnea on exertion, and paresthesia of the finger tips. The laboratory findings showed increased white blood cells at 11.37×10^3 cells/μl with 26.5% abnormal cells, low haemoglobin and, elevated creatinine, although serum lactate dehydrogenase and calcium levels were normal. Serum immunofixation was positive for monoclonal IgM-kappa paraprotein. Total serum protein and the IgM component were elevated. X-ray examination of the skeleton was normal. Bone marrow aspiration showed 59.5% infiltration of abnormal cells that were characterized by typical mature plasmacytoid morphology. Abnormal cells expressed surface CD20, surface CD138, and cytoplasmic IgM, but not surface CD56 nor surface IgM by flow cytometric immunophenotyping with CD38 gating. Immunohistochemistry showed surface CD38, surface CD20, and cytoplasmic IgM. The clinical findings led to the diagnosis of the IgM Plasma cell leukemia (PCL). The patient recived multi-agent chemotherapy (VAD and EDAP with rituximab). The clinical symptoms disappeared, leading to the tumor load reduction.

To the best of our knowledge, this is the first report of successful treatment of multi-agent chemotherapy with rituximab for IgM PCL.
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Keywords: Plasma cell leukemia (PCL); Rituximab; IgM; Multi-agent chemotherapy

1. Introduction

Primary plasma cell leukemia (PCL) is a very rare acute leukemia considered as a variant of multiple myeloma and defined by more than 2000 mm^{-3} circulating plasma cells and plasmacytosis for >20% of the differential white cell count [1]. PCL is rare and it can occur either as a primary disorder or as a consequence of multiple myeloma. Primary plasma cell leukemia has features similar to multiple myeloma. However, in primary PCL, skeletal involvement is less pronounced, and histosplenomegaly and lymphoadenopathy are more common. Most primary PCLs involve IgG-producing cells and IgM and IgA PCL occur less frequently [2]. Response to therapy is usually poor and survival correspondingly brief. In this report we describe a patient with primary IgM PCL and successfully treated with multi-agent chemotherapy (VAD and EDAP) with rituximab.

2. Case report

A 67-year-old woman presented with impaired general performance, suffering from fatigue, dyspnea on exertion, and paresthesia of the finger tips in April 2004. Physical presentation revealed splenomegaly, but lymphadenopathy was absent. The laboratory findings showed increased white blood cells (WBC) at 11.37×10^3 cells/μl with 26.5% abnormal cells, low haemoglobin (67 g/l), elevated creatinine (1.53 mg/dl), and β-2-microglobulin (6.5 μg/ml), although serum lactate dehydrogenase and calcium levels were normal. Serum immunofixation was positive for monoclonal IgM-

* Corresponding author. Tel.: +81 72 683 1221; fax: +81 72 684 6531.
E-mail address: in1230@poh.osaka-med.ac.jp (S. Oka).

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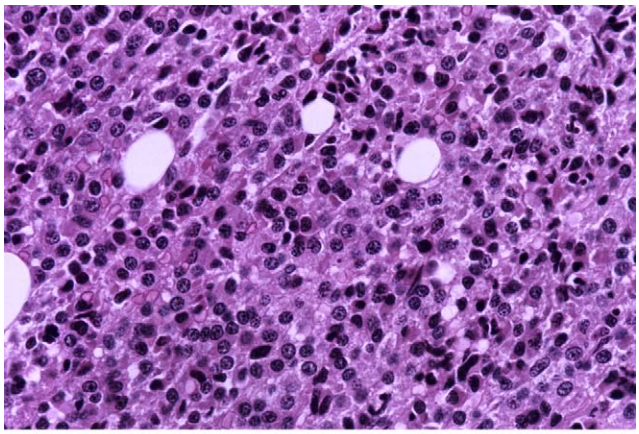
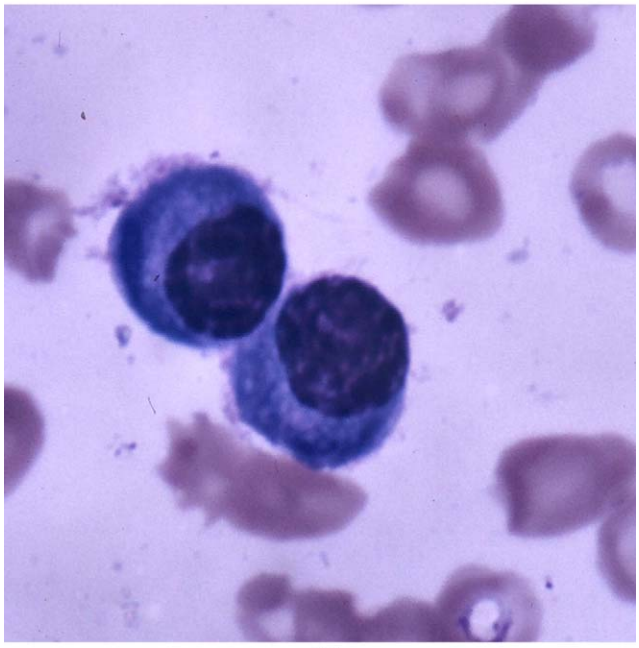


(a)



(b)

Fig. 1. (a) A biopsy of bone marrow shows infiltration of abnormal cells (hematoxylin and eosin ×100). (b) Histology of peripheral blood smear showing abnormal cells (May–Giemsa stain ×1500).

kappa paraprotein. Total serum protein was 106 g/l, and the IgM component accounted for 45.9 g/l. X-ray examination of the skeleton was normal. Bone marrow aspiration showed 59.5% infiltration of abnormal cells that were characterized by mature plasmacytoid morphology, exhibiting a nucleus with dense chromatin condensation, round nuclear contours, abundant cytoplasm, and a small nucleus to cytoplasm ratio (Fig. 1(a and b)).

Most of the abnormal cells expressed surface CD20, surface CD138, and cytoplasmic IgM, but not surface CD56 and surface IgM by flow cytometric immunophenotyping with CD38 gating.

Immunohistochemistory of bone marrow aspirate smears revealed positive staining in abnormal cells with cytoplasmic IgM, surface CD20, and surface CD38.

Southern blotting analysis showed rearrangement of monoclonal bands in the immunoglobulin heavy chain J gene region (J_H). Karyotypic analysis with Giemsa band staining of peripheral abnormal cells showed 45, X, −X, deletion (1)(q?), addition (7)(q11), addition (9)(q34), addition (12)(q24), −13, −14, −17, −20, +mar1, +mar2, +mar3, +mar4. The clinical findings led to the diagnosis of the IgM PCL, based on the clinical features, laboratory features, and immunophenotyping.

Two courses of VAD therapy [3], which consisted of vincristine 0.5 mg/m^2, continuous intravenous drip injection (div.) on days 1–4, doxorubicin 9 mg/m^2 div. on days 1–4, and dexamethasone 40 mg/body div. on days 1–4, were administered. Lenograstim 5 μg/kg/day by subcutaneous injection (s.c.) was then started from day 5 until the WBC count increased to above 10,000 μl^{-1}. One course of EDAP therapy [4], which consisted of etoposide 100 mg/m^2, cisplatinum 45 mg/m^2 div. on days 1–4, dexamethasone 40 mg div. on days 1–5, and cytarabine 1 g/m^2 div. on day 5, was administered and lenograstim 5 μg/kg/day by s.c. was started from day 6 until the WBC count increased to above 10,000 μl^{-1}. After multi-agent chemotherapies were administered, the clinical symptoms disappeared and the serum IgM level decreased to 21.4 g/l. However, abnormal cells in the peripheral WBCs remained and bone marrow aspiration showed 6.5% infiltration of abnormal cells. The VAD therapy following by EDAP therapy reduced the tumor load, but did not achieve a complete response (CR).

The therapy was changed to EDAP with rituximab, which consisted of rituximab 375 mg/m^2 div. on day 1, etoposide 100 mg/m^2, cisplatinum 45 mg/m^2 div. on days 2–5, dexamethasone 40 mg div. on days 2–6, and cytarabine 1 g/m^2 div. on day 6. Lenograstim 5 μg/kg/day by s.c. was started from day 7 until the WBC count increased above 10,000 μl^{-1}. Although the laboratory findings showed the WBC at 5.7×10^3 μl^{-1} with no abnormal cells, total serum protein was 75 g/l, serum IgM levels decreased to 18.0 g/l, and serious complications were not apparent after two courses; the patient declined any aggressive chemotherapy. Palliative therapy was then initiated on days 1–5 with 100 mg cyclophosphamide orally. Twenty months later the patient is alive and palliative therapy is ongoing.

3. Discussion

Plasma cell leukemia is a rare lymphoproliferative disorder characterized by a malignant proliferation of plasma cells in blood and bone marrow. The clinical signs of PCL are also seen in multiple myeloma (MM), although osteolytic lesions and bone pain are less frequent, and lymphoadenopathy and organomegary are more frequent. Two types of PCL are recognized. The primary PCL occurs in individuals without preceding MM and the clinical course is generally considered to be a rapid progressive disease and a short survival [5]. The second type evolves as a terminal event in 1–2%

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of MM [5]. The primary PCL occurs in individuals without preceding multiple myeloma and usually features a rapid clinical progression and a short survival. The mean survival of patients with PCL is about 2–6 months [6].

It was difficult to distinguish clinically Waldenström's macroglobulinemia (WM) from IgM PCL, because most primary PCLs involve IgG-producing cells and IgM and IgA PCL occur less frequently. Furthermore, the clinical course of WM is generally considered to be a slowly progressive disease [7], with a median average survival of 5 years.

Immunophenotyping has become one of the primary tools for the diagnosis of hematological malignancies. PCL cells generally express cytoplasmic monoclonal Ig, surface CD19, surface CD20, and lack surface CD3, surface CD10, surface CD56, and surface monoclonal Ig [8]. PCL cells from PCL displays a more immature phenotype than MM as assessed by the expression of CD20 antigen, which is usually absent in MM. In addition, PCL cells from PCL frequently lacked the CD56 antigen, which has been considerd to have an important role in anchoring PCL cells to the BM stroma. Therefore, we distinguish WM from PCL with immunophenotyping by flow cytometry and immunohistochemistry.

Rituximab, a chimeric mouse/human anti-CD20 monoclonal antibody, exhibits efficacy against B cell lymphomas [9]. As CD20 is expressed on most PCL cells, rituximab is considered one of the treatments. A partial response (PR) rate (30–75%) for single-agent rituximab has been reported [10–13,4] but complete responsiveness has not been reported. The combination of rituximab with chemotherapy can exhibit a benefit in both indolent and aggressive B-cell non-Hodgikin lymphoma. Moreover the addition of rituximab to chemotherapy results in superior benefit in both CR and PR rates compared with chemotherapy alone, without any significant toxicity [14,15].

In conclusion, this is the first report of IgM PCL that was diagnosed according to both the WHO and REAL classifications with immunophenotyping by immunohistochemistry and flow cytometry [16,17]. Multi-agent chemotherapy with rituximab is effective and well-tolerated.

References

[1] Pruzanski W, Platts ME, Ogryzlo MA. Leukemic form of immunocytic dyscrasia (plasma cell leukemia). A study of ten cases and a review of the literature. Am J Med 1969;47:60–74.

[2] Kosmo MA, Gale RP. Plasma cell leukemia with IgA paraproteinemia and hyperviscosity. Am J Hematol 1988;28(June (2)):113–5.

[3] Dimopoulos MA, Palumbo A, Delasalle KB, Alexanian R. Primary plasma cell leukemia. Br J Haematol 1994;88:754–9.

[4] Hovvenga S, de Wolf JT, Klip H, Vellenga E. Consolidation therapy with autologous stem cell transplantation in plasma cell leukemia after VAD, high-dose cyclophosphamide and EDAP courses: a report of three cases and review of the literature. Bone Marrow Transplant 1997;20:901–4.

[5] Costello R, Sainty D, Bouabdallah R, Fermand JP, Delmer A, Divine M, et al. Primary plasma cell leukaemia: a report of 18 cases. Leuk Res 2001;25(February (2)):103–7.

[6] Malhotra H, Dhabhar BN, Saikia TK, et al. Ifosfamide in plasma cell leukaemia. Am J Hematol 1992;40:226–8.

[7] Morel P, Monconduit M, Jacomy D, Lenain P, Grosbois B, Bateli C, et al. Prognostic factors in Waldenström's macroglobulinaemia: a report on 232 patients with the description of a new scoring system and its validation on 253 other patients. Blood 2000;96: 852–8.

[8] Garcia-Sanz R, Orfao A, Gonzalez M, Tabernero MD, Blade J, Moro MJ, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. Blood 1999;93(February (3)):1032–7.

[9] Campbell P, Marcus R. Monoclonal antibody therapy for lymphoma. Blood 2003;17:143–52.

[10] Dimopoulos MA, Zervas C, Zomas A, Kiamouris C, Viniou NA, Grigoraki V, et al. Treatment of Waldenstrom's macroglobulinemia with rituximab. J Clin Oncol 2002;20:2327–33.

[11] Ghobrial IM, Gertz MA, Fonseca R. Waldenstrom macroglobulinaemia. Lancet Oncol 2003;4:679–85.

[12] Dimopoulus M, Alexanian R, Gika D, Anagnostpoulos A, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinaemia with rituximab: prognostic factors for response and progression. Leuk Lymphoma 2004;45:2057–61.

[13] Mori A, Tamaru J, Kondo H. Effects of rituximab on a patient with Waldenstrom's macroglobulinaemia with deletion 13q14. Eur J Haematol 2002;69:321–3.

[14] Czuczman MS, Grillo-Lopez AJ, White CA, Saleh M, Gordon L, LoBuglio AF, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17: 268–76.

[15] Kewalramani T, Zelenetz AD, Nimer SD, Portlock C, Straus D, Noy A, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684–8.

[16] Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835–49.

[17] Harris NL, Jaffe ES, Stein H, et al. A revised European American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;82:3148–50.