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LETTER TO THE EDITOR

Methotrexate-associated lymphoplasmacytic lymphoma complicated with type 2 cryoglobulinemia

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A 62-year-old female suffering from rheumatoid arthritis (RA) for 16 years was referred to our hospital with out of breath on slight exertion. She had been prescribed with methotrexate (MTX; 4 mg per week) and prednisolone for 10 years for the treatment of RA. Upon physical examination, tender liver and spleen that extended below the xiphoid were palpable with a protuberant abdomen. Computed tomography (CT) showed hepatosplenomegaly, bilateral pleural effusions and ascites in the absence of lung field abnormalities or lymphadenopathy. Bone marrow examination was performed to demonstrate an infiltration of clonal B cells confirmed by immunocytological analysis with flow cytometry. She was diagnosed as having MTX-associated lymphoproliferative disorder (LPD). The effusions in the body cavities and hepatosplenomegaly were dramatically improved only with the withdrawal of MTX.

She had been asymptomatic for 2 years until the current hospitalization. She presented herself in the outpatient department with a complaint of headache, vertigo and loss of vision and then she was readmitted because of extensive fluid retention in the chest, abdomen and lower extremities. A CT scan showed recurrence of the massive effusions in the body cavities and hepatosplenomegaly (Fig. 1a). Histological analysis for the liver specimen obtained by an ultrasound-guided needle biopsy showed a typical relatively monotonous appearance of lymphocytes, plasmacytoid lymphocytes and plasma cells (Fig. 1b). Proliferating cells were strongly expressed with CD20 (Fig. 1c). Immunocytological analysis with flow cytometry demonstrated that the atypical lymphocytes were positive for CD19, CD20 surface molecules with κ light chain-restricted surface immunoglobulin (Ig)-M and negative for CD5, CD10 and CD23 surface molecules. Bone marrow examination showed a lymphoplasmacytic infiltrate composed of lymphocytes with basophilic cytoplasm and plasmacytoid cells (Fig. 1d). Laboratory studies were remarkable for a white blood cell (WBC) of 2.8×10^9/L with normal differential, a hemoglobin of 9.9 g/dL, a platelet of 123×10^9/L, a lactose dehydrogenase (LDH) of 302 IU/L (normal range 120–260 IU/L), a creatinine of 1.36 mg/dL, an albumin of 2.7 g/dL, an IgM of 2,172 mg/dL, a rheumatoid factor (RF) of 16,150 IU/mL and a soluble interleukin-2 receptor (sIL-2R) of 3,270 U/mL. Serological marker for hepatitis C virus was negative. Precipitated proteins were displayed in the blood smears (Fig. 1e). These proteins precipitated at cold temperature and redissolved at normal body temperature. The serum test for cryoglobulins was positive. Immunoelectrophoresis with the serum samples at a room temperature showed abnormal precipitin arcs like a seagull on anti-IgG and anti-IgM reactions (Fig. 1f). The abnormal IgG precipitin arcs were not detected when the serum was pre-treated with 2-mercaptoethanol to cleave disulfide bonds between IgG and IgM (Fig. 1g). But it showed M-bows on anti-IgM and anti-κ reactions clearly. Thus, the cryoglobulins were considered to be composed of the monoclonal IgM bound to the polyclonal IgG. Taken together, she was diagnosed as having MTX-associated lymphoplasmacytic lymphoma complicated with type-2 cryoglobulinemia.

Chemotherapy with the 2-CdA/Cy (2-chlorodeoxyadenosine/cyclophosphamide) regimen was initiated. The regimen included 0.12 mg/kg of 2-CdA by intravenous

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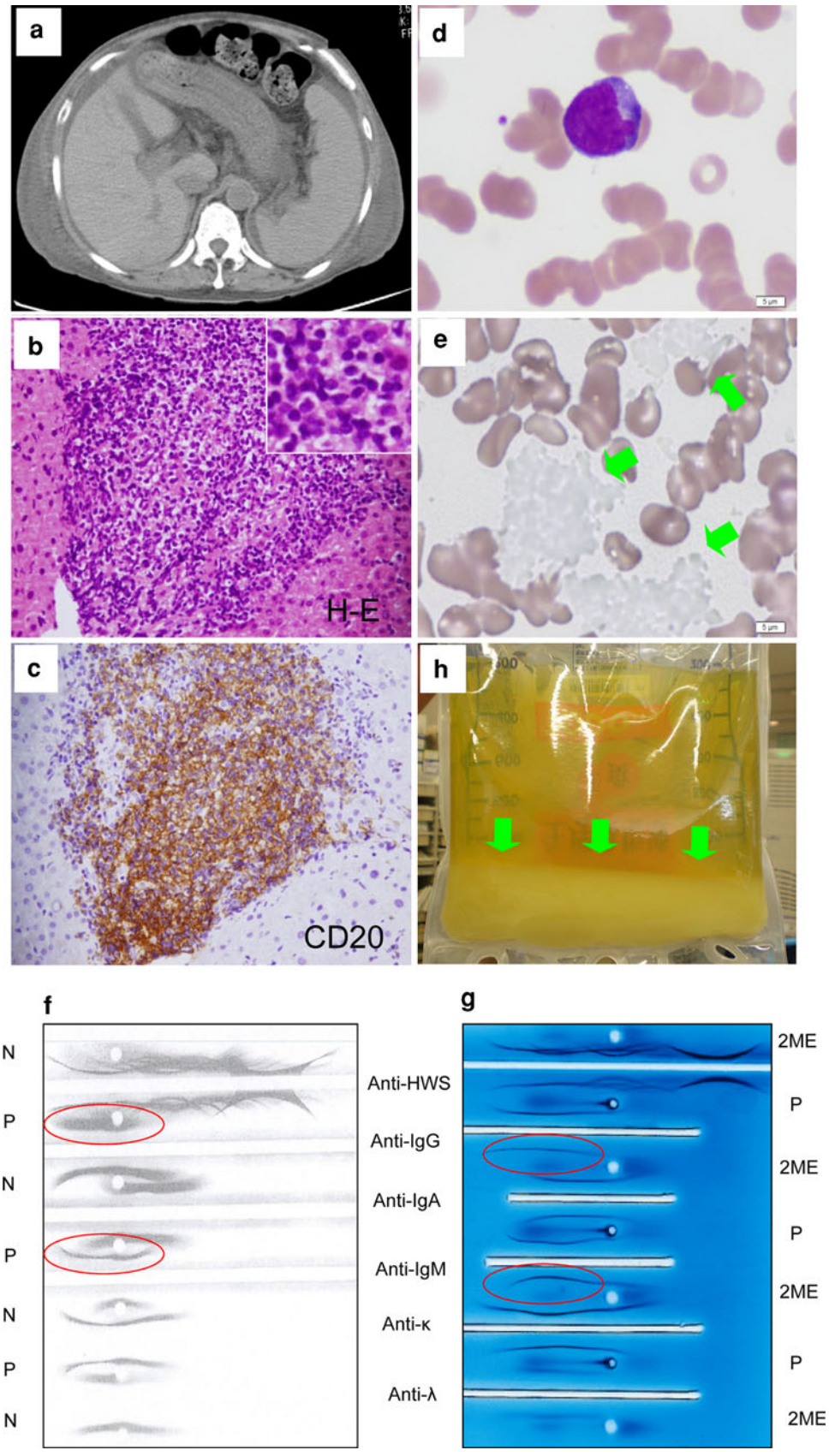

Fig. 1 **a** Computed tomography (CT) revealed massive effusions and hepatosplenomegaly. **b** Histological analysis on liver tissue specimen showed a typical relatively monotonous appearance of lymphocytes, plasmacytoid lymphocytes and plasma cells (×400). **c** Immunohistochemical staining demonstrated that CD20 was positive (×400). **d** Bone marrow examination showed a lymphoplasmacytic infiltrate composed of lymphocytes with basophilic cytoplasm and plasmacytoid cells (×1,000). **e** Precipitated cryoglobulins (*green arrows*) were found on the blood smear (×1,000). Immunoelectrophoresis with the serum samples at a room temperature showed abnormal precipitin arcs like a seagull on anti-IgG and anti-IgM reactions (**f**) and the M-bow on anti-IgG reaction was not detected when the serum was pre-treated with 2-mercaptoethanol (**g**), suggesting the presence of monoclonal IgM bound to the polyclonal IgG. *N* normal serum, *PS* patient's sample, *2ME* the serum pre-treated with 2-mercaptoethanol. **h** The cryocrits removed by the DFPP

infusion over 2 h for consecutive 3 days in combination with 40 mg/m^2 of Cy orally twice daily for consecutive 7 days. Although there was a gradual reduction of serum IgM level after the chemotherapy, the response was insufficient for the improvement of the hyperviscosity-associated symptoms such as weakness, and renal failure presumably due to the cryoglomerulonephritis (Supplemental Fig. 1). Therefore, the double-filtration plasmapheresis (DFPP) was applied which was followed by a systemic administration of rituximab (Rit). The plasma was replaced with an albumin and the cryocrits were removed (Fig. 1h). After the first DFPP, a striking clinical improvement was achieved in which the hyperviscosity-associated symptoms were apparently improved and a brisk diuresis was observed within 24 h. In addition, the parallel decrease in both IgM and RF was observed from 2,359 to 1,621 mg/dL and from 18,960 to 13,190 IU/L, respectively. After the addition of DFPP twice in combination with Rit, the effusions in the body cavities were reduced, resulting in a net negative fluid balance of 15 L over 10 days. Even after the therapeutic intervention was completed with 2-CdA/Cy regimen and three sessions of DFPP with Rit, there was a sustained reduction of serum IgM level for 2 months. She is in a good remission for 10 months.

The occurrence of LPD represents one of the major complications in RA patients treated with MTX [1]. MTX is administered to patients with autoimmune disease, especially RA, to suppress the hyperimmune state. This in turn may induce immunosuppression and provide a basis for the development of LPD. In the previous reports, it is demonstrated that most cases occurred in the MTX-associated RA patients are diffuse large B cell lymphoma (DLBCL) and LPL is extremely rare [2]. Although a significant proportion of patients with MTX-associated LPD have shown regression in response to drug withdrawal, in about half of these cases, the duration of remission is short (1–10 months) and subsequent chemotherapy is required [3]. However, a standard therapeutic strategy for the symptomatic or progressive LPL has not been yet established [4]. We show a case of MTX-associated LPL in which the 2-CdA/Cy/Rit regimen [5] was effective for the treatment of the disease and the DFPP was useful for the treatment of cryoglobulinemia.

The 2-CdA/Cy/Rit regimen was well tolerated and myelosuppression was mild and reversible. To avoid worsening renal dysfunction, the administration of 2-CdA was shorten to 3 days instead of 7 days. In addition, we applied plasmapheresis in advance of the administration of Rit since the "rituximab flare", a transient increase of serum IgM, may occur immediately after the administration of Rit [6]. Moreover, the DFPP was designed to remove the immunoglobulin fraction electively from the serum. We used the DFPP thermo-mode, called "DF Thermo". DF Thermo is a simple addition to plasmapheresis: after the patient's plasma is separated from the blood cells by plasmapheresis, the plasma is warmed in a chamber that controlled the temperature at 42°C to avoid decreasing degree of membrane fouling due to protein deposition. All the plasma retentate is recirculated to the inlet portion of the filter to increase the capacity of the plasma retentate, thus enabling the involvement of larger amount of serum IgM and minimizing the volume of substitution fluid [7]. Since serum viscosity is not linearly correlated with IgM levels, multiple exchanges were necessary and systemic therapy was accompanied with plasmapheresis for cytoreduction. We would suggest that the DF Thermo might be useful for the treatment of cryoglobulinemia, especially in a clinical feature showing apparent hyperviscosity-related symptoms.

The polyclonal B cell activation in a clinical setting of RA leads to the secretion of RF [8] and the presence of RF is associated with other autoantibodies. In our case, polyclonal IgG and monoclonal IgM were detected. We would speculate that the first event of lymphomagenesis was associated with the chronic stimulation of polyclonal B cells secreting RF at the site of the disease and that these polyclonal RF B cells might transform to monoclonal and disseminate into other organs when the disease relapsed. The IgM products of the neoplastic B cells seemed to be RFs because these titers changed quite similarly. The monoclonal secreted RF complexed with polyclonal IgG may cryoprecipitate. Additional cooperating events would be required, which would confer to these cells a low grade lymphoplasmacytic B cell lymphoma component.

In summary, MTX-associated LPL complicated with type 2 cryoglobulinemia was reported. The 2-CdA/Cy/Rit regimen in combination with the DFPP was effective for the treatment of LPL and cryoglobulinemia. Although a withdrawal of MTX needs to be considered before an initiation of systemic chemotherapy in any patient diagnosed or suspected of having MTX-associated lymphoma, appropriate administration of systemic chemotherapy supported by plasmapheresis needs to be considered.

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