AA amyloidosis has been reported to be associated with chronic inflammatory diseases including rheumatoid arthritis, juvenile rheumatoid arthritis and chronic infection [1]. However, there have been only a few reports on patients with AA amyloidosis associated with hematological tumors [2–4]. In this report, we present a case of AA amyloidosis associated with macroglobulinemia in which combination chemotherapy was effective for amyloidosis and markedly improved the condition of the patient.

A 44-year-old man was admitted to our hospital because of a 3-month history of fever and lymphadenopathy. Hematological examination revealed a normal white blood cell (WBC) count (4.3 × 10⁹/L) with 17% lymphocytes and a normal platelet count (366 × 10⁹/L) but a slight decrease in hemoglobin concentration (12.6 g/dl). Laboratory examinations disclosed high levels of IgM (880 mg/dl), β₂-microglobulin (2.2 mg/l) and soluble interleukin-2 receptor (3,460 U/ml). Serum and urine immunoelectrophoresis demonstrated IgM-κ type of M-protein and Bence Jones protein-κ, respectively. CT scanning revealed hepatosplenomegaly as well as swelling of para-aorta lymph nodes. Histological examination of an excised cervical lymph node showed destruction of lymphatic follicles by plasma cell infiltration, which is not contradictory to lymphoplasmacytoid lymphoma. In addition, flow cytometric analysis of the lymph node sample showed 52.7% of CD20+ cells, 41.3% of IgM+ cells, 48% of κ+ cells and 9.2% of λ+ cells, indicating monoclonal proliferation of B cells with IgM-κ. Furthermore, a bone marrow aspiration sample showed hypercellularity with an increased number of mature lymphocytes (66%). Phenotypes of these lymphocytes are similar to those of the lymph node cells. Based on the results, we diagnosed this case as macroglobulinemia. Importantly, eosinophilic substances, which were positive for Congo-Red staining with green birefringence under a polarizing microscope, were also observed in the lymph node (Fig. 1a). These substances were stained with anti-AA antibody by immunohistological staining, whereas no staining was present with both anti-κ and anti-λ antibodies. Based on these findings, the substances were defined as AA amyloid (Fig. 1b). AA amyloid was also detected in biopsy samples of bone marrow, stomach and rectum. In addition to the deposition of AA amyloid in various organs, the level of serum amyloid A protein (SAA) was extremely high (99.9 mg/ml). The reason for the elevation of SAA was not clear; however, it is possible that macroglobulinemia itself induced inflammation, resulting in an increase in the level of SAA in this case. Based on these findings, the patient was diagnosed as having systemic AA amyloidosis. Since there was no evidence of tuberculosis or collagen diseases including rheumatoid arthritis, the AA amyloidosis was thought to be associated with macroglobulinemia.

The patient was treated with 30 mg prednisolone as an initial treatment. After 1 month of this therapy, both fever and lymph node swelling were improved. However, lymphadenopathy recurred with dose reduction of prednisolone. In addition, continuous increases in hepatomegaly and levels of alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GTP), probably due to infiltration of
lymphoplasmacytic cells or liver amyloidosis, were simultaneously observed (Fig. 2). At 7 months after the start of prednisolone treatment, the patient had severe pain in the lower jaw caused by amyloid deposition in the jawbone. Despite additional administration of cyclophosphamide, the patient’s condition did not improve. At that time, we thought that rigid control of macroglobulinemia was needed to inhibit the progression of systemic amyloidosis, and we performed eight courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) therapy. As a result, the levels of ALP and C-GTP were normalized and clinical features including fever, lymphadenopathy, hepatomegaly and lower jaw pain were all diminished (Fig. 2). Furthermore, SAA also rapidly declined to the normal level. Since then, the patient has remained in complete remission over a period of 1 year and no recurrence of macroglobulinemia as well as systemic amyloidosis has been observed.

Although standard therapy has not yet been established, immunosuppressive therapy is mainly used for AA amyloidosis. Recently, clinical trials of some reagents that directly inhibit the deposition of SAA in organs have been performed [5, 6]. Monoclonal antibodies against inflammatory cytokines or cytokine receptors, including IL-1 receptor, IL-6 receptor, TNF-α and TNF-α receptor, have also been evaluated for clinical application to AA amyloidosis [7]. However, good control of background diseases is also crucial to inhibit the progression of AA amyloidosis. Indeed, combination chemotherapy was effective for the complicated AA amyloidosis in our case.

AA amyloidosis associated with macroglobulinemia is very rare and only a few cases have been reported [4]. Our case suggests that aggressive treatment for background hematological diseases is needed for better control of AA amyloidosis in cases of AA amyloidosis associated with hematological tumors.
References