

Letter to the Editor

Marked shrinkage of amyloid lymphadenopathy after an intensive chemotherapy in a patient with IgM-associated AL amyloidosis

Ko-ichi Tazawa, Nagaaki Katoh, Yasuhiro Shimojima, Masayuki Matsuda,
Shu-ichi Ikeda

Department of Medicine (Neurology and Rheumatology), Shinshu University School
of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

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Running title: *Chemotherapeutic effects on AL amyloid lymphadenopathy*

Abbreviations: *VAD: vincristine, doxorubicin and dexamethasone, HDM: high-dose melphalan, SCT: autologous stem cell transplantation, CT: computed tomography, FLCs: free light chains*

Correspondence: Dr. Masayuki Matsuda, Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

Tel: +81-263-37-2673

Fax: +81-263-37-3427

e-mail: matsuma@shinshu-u.ac.jp

Abstract

A male patient with primary AL amyloidosis who had been suffering from systemic lymphadenopathy with IgM κ -type M-proteinemia received 2 courses of VAD and high-dose melphalan with *in vivo* elimination of CD20⁺ cells using rituximab followed by autologous peripheral blood stem cell transplantation. Four years after complete hematological remission he showed marked reduction in size of the amyloid-laden lymph nodes. Deposits of AL amyloid may regress from the tissue if the chemotherapy succeeds in persistent inhibition of the production of an amyloidogenic immunoglobulin light chain.

Primary systemic AL amyloidosis is caused by plasma cell dyscrasia and produces dysfunction of many visceral organs, the heart and kidney being most frequently involved [1]. Intensive chemotherapy, such as high-dose melphalan followed by autologous stem cell transplantation (HDM/SCT), has been recently reported to improve the function of the affected organs if complete hematological remission is achieved [2, 3]. Nevertheless, it remains unclear whether or not AL amyloid deposits regress from the tissue after the disappearance of M-protein in serum or urine. In this report we describe an IgM-associated AL amyloidosis patient with systemic lymphadenopathy who was treated with vincristine, doxorubicin and dexamethasone (VAD), and the following HDM/SCT. The patient showed remarkable reduction in size of swollen lymph nodes 4 years after this intensive chemotherapy.

Case report

A 49-year-old man developed progressive systemic lymphadenopathy, particularly in the neck and axilla (Fig 1-A). Computed tomography (CT) showed enlarged lymph nodes also in bilateral inguinal regions, but not in either the mediastinum or retroperitoneum. On the basis of IgM κ -type M-protein in serum, clonal expansion of CD20⁺ κ ⁺ cells in bone marrow and histopathology of lymph nodes showing massive deposition of A κ -immunoreactive amyloid (Fig. 2), he was diagnosed as having primary AL amyloidosis as reported previously [4]. The patient showed no abnormal findings in laboratory data suggestive of visceral organ involvement or amyloid deposition in other biopsied tissues, including the gastroduodenal mucosa and abdominal fat. Serum free light chains (FLCs) were 25.7 mg/L in κ (normal: 3.3-19.4 mg/L) and 11.6 mg/L in λ (normal: 5.7-26.3 mg/L), and the κ/λ ratio was 2.18 (normal: 0.26-1.65). At age 50 he achieved complete hematological remission after 2 courses of VAD and the following HDM/SCT according to our protocol [5] and *in vivo* elimination of CD20⁺ cells using rituximab. Serum IgM decreased to normal range (1,235 to 137 mg/dL, normal: 35-220 mg/dL) in conjunction with disappearance of M-protein on immunofixation and normalization of amyloidogenic κ -type FLCs (11.5 mg/L) and the κ/λ ratio (0.99). Lymph nodes gradually became smaller during the follow-up observation in the outpatient clinic. Serum IgM and FLC have remained in the normal range with negative results of serum M-protein on immunofixation for 4 years since achievement of complete hematological remission. At age 54 he appeared healthy and showed marked reduction in size of affected lymph nodes on CT (Fig. 1-B).

Discussion

Removal of amyloid fibrils from the affected tissues using chemotherapy is difficult and thus, radical treatments for underlying disorders or pathology producing amyloid precursor proteins have been employed for systemic amyloidosis. It has been recently noted that post-treatment regression of amyloid deposits certainly occurs in patients with some forms of systemic amyloidosis [6-9]. In primary systemic AL amyloidosis it has been shown that malfunction of visceral organs, including heart and kidney, remains stable and/or often improves after intensive chemotherapies targeting plasma cell dyscrasia [2, 3]. However, regression of AL amyloid deposits after these treatments remains controversial: some reports demonstrated a decrease in AL amyloid on the basis of histopathology of abdominal fat tissue or radiolabelled SAP scintigraphy

[10, 11], while in others serial renal biopsies failed to show histopathological regression of AL amyloid deposits even after improvement of renal function [12, 13]. Twenty to 30% of the patients with IgM-associated AL amyloidosis show systemic lymphadenopathy as seen in the present patient, but no improvement after the chemotherapy has been so far reported [14, 15]. The present patient showed marked reduction in size of involved lymph nodes on CT images 4 years after the intensive chemotherapy in conjunction with persistently negative M-protein in serum and normalization of serum FLCs. Considering that massive accumulation of AL amyloid caused remarkable lymphadenopathy before chemotherapy, cessation of the supply of an amyloid precursor protein may have led to regression of these amyloid deposits in the affected lymph nodes of this patient. The mechanisms by which amyloid is mobilized and cleared from the affected tissues are not known in any types of systemic amyloidosis.

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Figure legends

Figure 1: CT images of lymphadenopathy before and after chemotherapy.

A: At admission enlarged lymph nodes with positive contrast enhancement (indicated by arrows) are seen in the neck and axilla. B: 4 years after treatment they showed marked shrinkage, especially in left axillar area.

Figure 2: Histopathology of the biopsied cervical lymphnode.

Congo red staining shows extensive deposition of amyloid (A), which has characteristic apple-green appearance under polarized view (B).

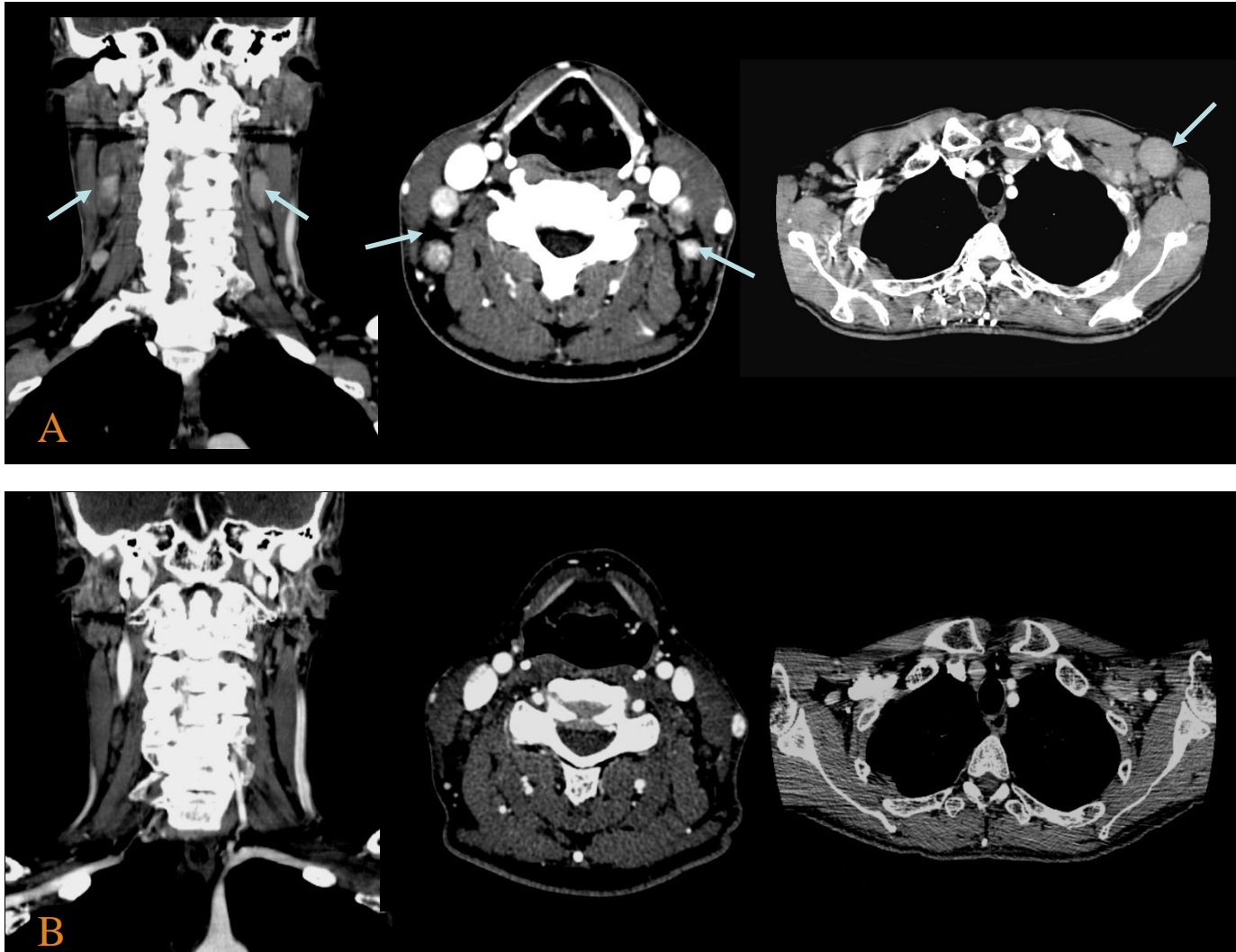


Figure 1

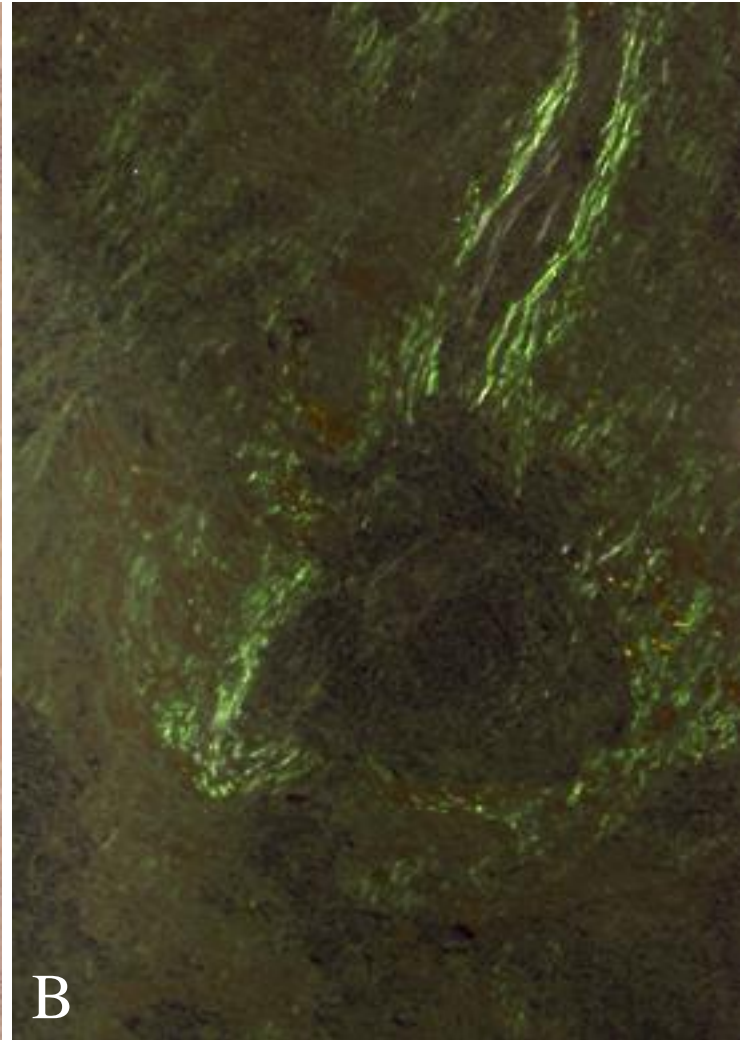
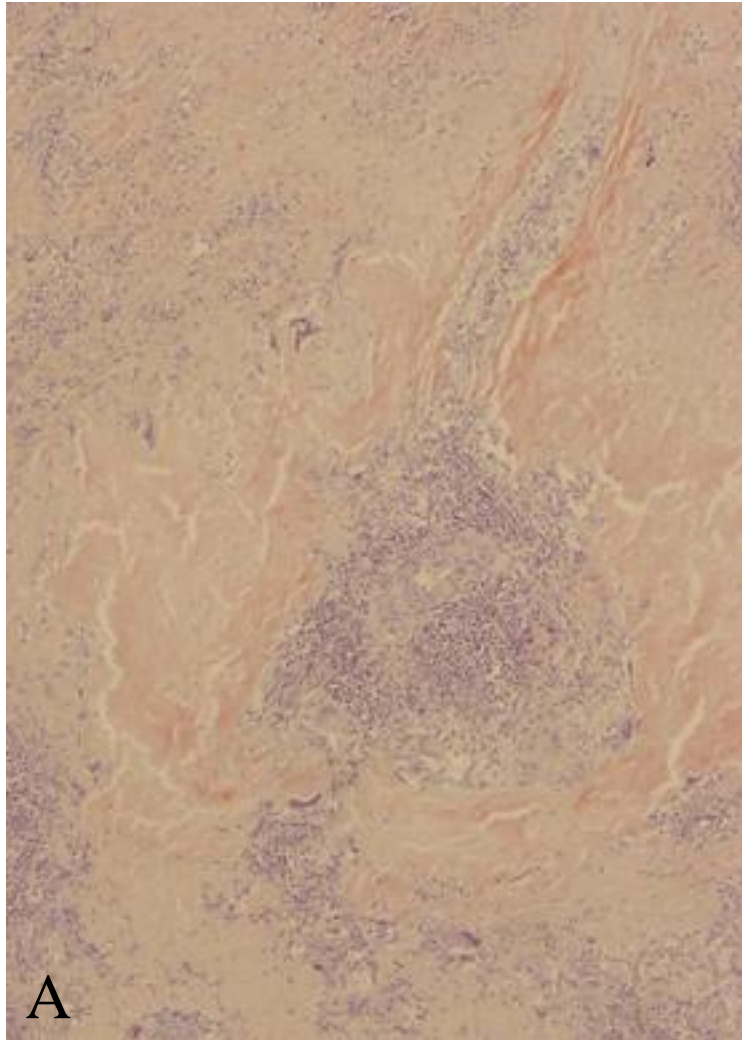


Figure 2