Case report

Surgical removal of amyloid-laden lymph nodes: a possible therapeutic approach in a primary systemic AL amyloidosis patient with focal lymphadenopathy

Masayuki Matsuda[1)], Nagaaki Katoh[1)], Ko-ichi Tazawa[1)], Yasuhiro Shimojima[1)], Yoshito Mishima[2)], Shu-ichi Ikeda[1)]

1) Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan
2) Department of Plastic Surgery, Shinshu University School of Medicine, Matsumoto, Japan

***Key words**: lymphadenopathy, primary systemic AL amyloidosis, lymphadenectomy, high-dose melphalan, autologous peripheral blood stem cell transplantation*

***Abbreviations:** FLCs: free light chains, HDM/SCT: high-dose melphalan with autologous peripheral blood stem cell transplantation, VAD: vincristine, doxorubicin and dexamethasone*

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

We report a patient with primary systemic AL amyloidosis who suffered from remarkable bilateral cervical lymphadenopathy. Intensive chemotherapies, including 2 cycles of high-dose melphalan with autologous peripheral blood stem cell transplantation, were insufficiently effective for both the lymphadenopathy and amyloidogenic IgGλ–type M-protein in serum, but the patient showed complete hematological remission after extensive surgical removal of enlarged lymph nodes that had massive depositions of λ-type immunoglobulin light chain-derived amyloid. Lymphadenectomy may be a possible therapeutic approach with regard to both cosmetic and hematological aspects in primary systemic AL amyloidosis patients with focal lymphadenopathy

Introduction

Primary systemic amyloidosis is characterized pathologically by the deposition of amyloid derived from monoclonal immunoglobulin light chains (AL) and clinically by multiple organ involvement with no underlying disorders, such as multiple myeloma [1]. Lymphadenopathy occasionally develops as a main clinical manifestation of this disease [2], and intensive chemotherapies against plasma cell dyscrasia producing pathogenetic monoclonal light chains are usually employed for treatment [3]. Here, we report a primary systemic AL amyloidosis patient with marked bilateral cervical lymphadenopathy who was resistant to 2 cycles of high-dose melphalan with autologous peripheral blood stem cell transplantation (HDM/SCT) but was successfully treated with surgical removal of the enlarged cervical lymph nodes. Surgical intervention is occasionally employed for the treatment of a localized form of AL amyloidosis [4], but has not been considered hitherto in patients with primary systemic AL amyloidosis.

Case report

A 46-year-old woman noticed nodular swelling of the neck (Fig. 1A) and an epipharyngeal tumor with no precipitating cause as reported previously [2]. Briefly, she was diagnosed as having primary systemic AL amyloidosis [5] mainly manifesting with bilateral cervical lymphadenoapthy based on massive deposition of ALλ-immunoreactive amyloid in biopsied lymph nodes, positive IgGλ-type M-protein in serum (Fig. 2A) and plasma cell dyscrasia in bone marrow detected by flow cytometry [6]. No abnormal findings were found on either the electrocardiogram or echocardiogram, and there was no amyloid deposition in

the biopsied gastroduodenal mucosa. Quantitative assay of serum free light chains (FLCs) revealed an increase in λ-chain (48.7 mg/L, normal 5.7-26.3 mg/L) and a slight decrease in the κ/λ ratio (0.24, normal 0.26-1.65) [7]. At age 50 she received two courses of VAD (vincristine, doxorubicin and dexamethasone) and subsequent HDM/SCT [2, 8] because of a gradual increase in the size of the involved lymph nodes. Monoclonal subpopulations of plasma cells in bone marrow disappeared, and serum FLCs were normalized right after HDM/SCT. Nine months later additional HDM/SCT (dose of melphalan: 200 mg/m^2) was performed because serum M-protein remained positive (Fig. 2B) [9]. Despite the lack of monoclonal subpopulations of plasma cells in bone marrow with normal values of serum FLCs (κ: 12.3 mg/L, λ: 27.6 mg/L) and the κ/λ ratio (0.45), complete hematological remission was not achieved 1 year after the chemotherapy (Fig. 2C) and the bilateral cervical lymph nodes showed further enlargement.

At age 52 she underwent surgical removal of the involved lymph nodes. When the lymph nodes were neighboring or adjacent to large vessels in the neck, we left the capsule and removed the parenchyma alone. The operation was safely performed with no massive bleeding or injuries to other organs. The number of lymph nodes extirpated from the right and left side was 2 and 6, respectively. The patient was discharged from our hospital 1 week after the operation. The appearance of her neck improved remarkably with regard to reduction in size of nodular swelling (Fig. 1C), although several swollen lymph nodes were still seen on computed tomography (CT) (Fig. 1D). Histopathology of the removed lymph nodes demonstrated massive deposition of ALλ-immunoreactive amyloid, but revealed no abnormal findings in either HE staining or immunohistochemistry suggestive of lymphoproliferative

disorders (Fig. 3). Immunoglobulin rearrangement analysis showed no obvious monoclonality in the removed lymph nodes. Serum M-protein became negative 1 month after the lymphadenectomy (Fig. 2D). She has since been in good general health with no recurrence of enlargement of cervical lymph nodes or apparent involvement of visceral organs, including the heart and kidney.

Discussion

In primary systemic AL amyloidosis intensive chemotherapies targeting plasma cells have been reported to produce improvement in visceral organ dysfunction [3, 10] and also histological regression of amyloid deposits if complete hematological remission is achieved [11, 12]. Amyloid-laden lymphadenopathy can also show a decrease in size within several years after the disappearance of M-protein in response to intensive chemotherapies [13]. In our patient, however, amyloidogenic M-protein in serum remained positive even after VAD and 2 courses of HDM/SCT, and the size of the bilateral cervical lymph nodes enlarged further. Considering that the λ-chain band on serum immunofixation became slightly faint with no abnormal plasma cells in her bone marrow 1 year after the second HDM/SCT, these chemotherapies appear to have been effective in our patient but were probably not enough to completely eliminate the amyloidogenic M-protein produced from a different origin.

The most notable finding in the present patient is that M-protein in serum disappeared shortly after surgical removal of the bilateral enlarged cervical lymph nodes. This clinical finding suggests that the amyloid-laden lymph nodes themselves had produced an amyloidogenic M-protein, although there was no histological or laboratory evidence

indicating lymphoproliferative disorders with monoclonality even in postoperative examinations of the involved lymph nodes. It has been demonstrated that an amyloidogenic immunoglobuin light chain is usually secreted from lymphoplasmacytes with normal appearance located in close proximity to the site of amyloid deposition in a localized form of AL amyloidosis [14]. This pathogenetic mechanism seems to be applicable to the selective involvement of cervical lymph nodes with massive deposition of AL amyloid in our patient. The involved lymph nodes had been almost entirely replaced with amyloid deposits expressed as non-enhancement areas on CT. This massive amyloid deposition probably interfered with the infiltration of chemotherapeutic agents, such as melphalan, into the lymph nodes, leading to the survival of plasma cells producing pathogenic M-protein in the patient. In systemic AA amyloidosis associated with Castleman's disease, surgical removal of the causative lymph node tumor can halt the production of an amyloid precursor protein and improve clinical symptoms [15]. Lymphadenectomy may be beneficial too for primary systemic AL amyloidosis patients mainly showing focal lymphadenopathy, with regard not only to the cosmetic aspects but also as a radical treatment.

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Figures legends

Figure 1: The patient showed nodular swelling in the bilateral neck but mainly on the left side (A), confirmed as enlarged lymph nodes with centrally located non-enhanced areas on computed tomography (B, arrows). Three months after surgical removal of these lymph nodes there was no apparent recurrence (C, D).

Figure 2: Immunofixation demonstrated IgGλ-type M-protein before treatment (A, arrows). This protein remained positive 7 months after the first course of high-dose melphalan with autologous peripheral blood stem cell transplantation (B, arrows) and 1 year after the second one (C, arrows), but disappeared 1 month after lymphadenectomy (D). SE: serum electrophoresis

Figure 3: Macroscopic and histopathologic findings of an involved cervical lymph node.

A: The cut surface of an enlarged lymph node. Most of the parenchyma is filled by an amorphous material with a waxy appearance.

B: H&E, C: Congo red, D&E: Immunoperoxidase staining with anti-ALλ or ALκ antibody. F: Polarized view of the framed area in C (original magnification ×40), G: Higher magnification of the framed area in D (original magnification ×60). The amorphous material in the lymph node is eosinophilic (B) and congophilic (C), showing typical apple-green birefringence (F). This amyloid is positively immunolabeled by an anti-ALλ antibody (D) but not by an anti-ALκ antibody (E). Lymphoid follicles are sparsely distributed among heavy deposits of ALλ-immunoreactive amyloid (G) (Bars=1cm).

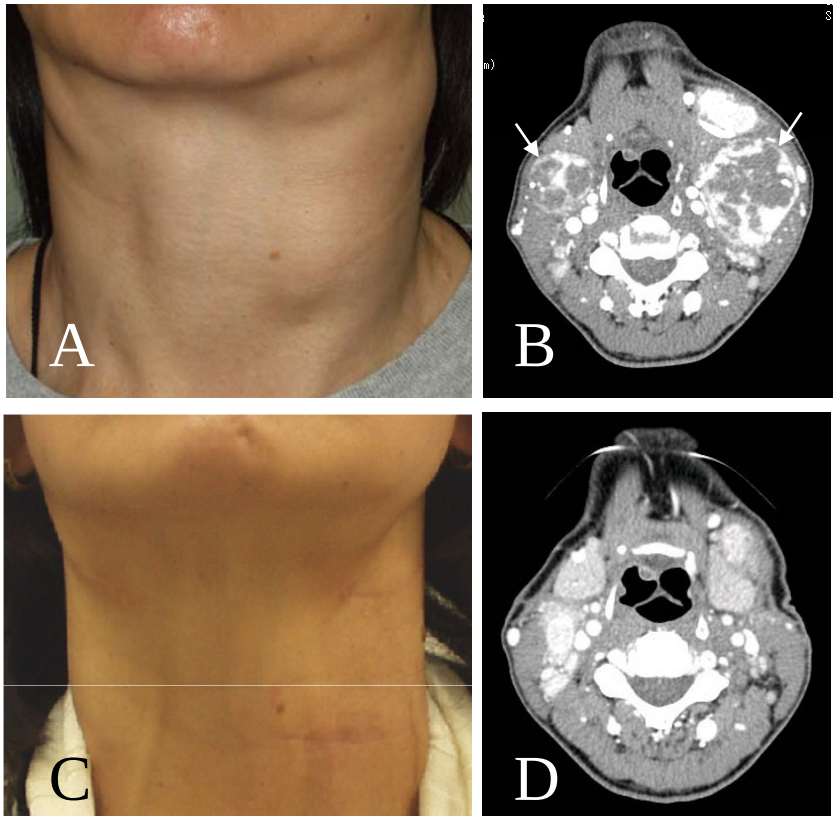

Fig. 1

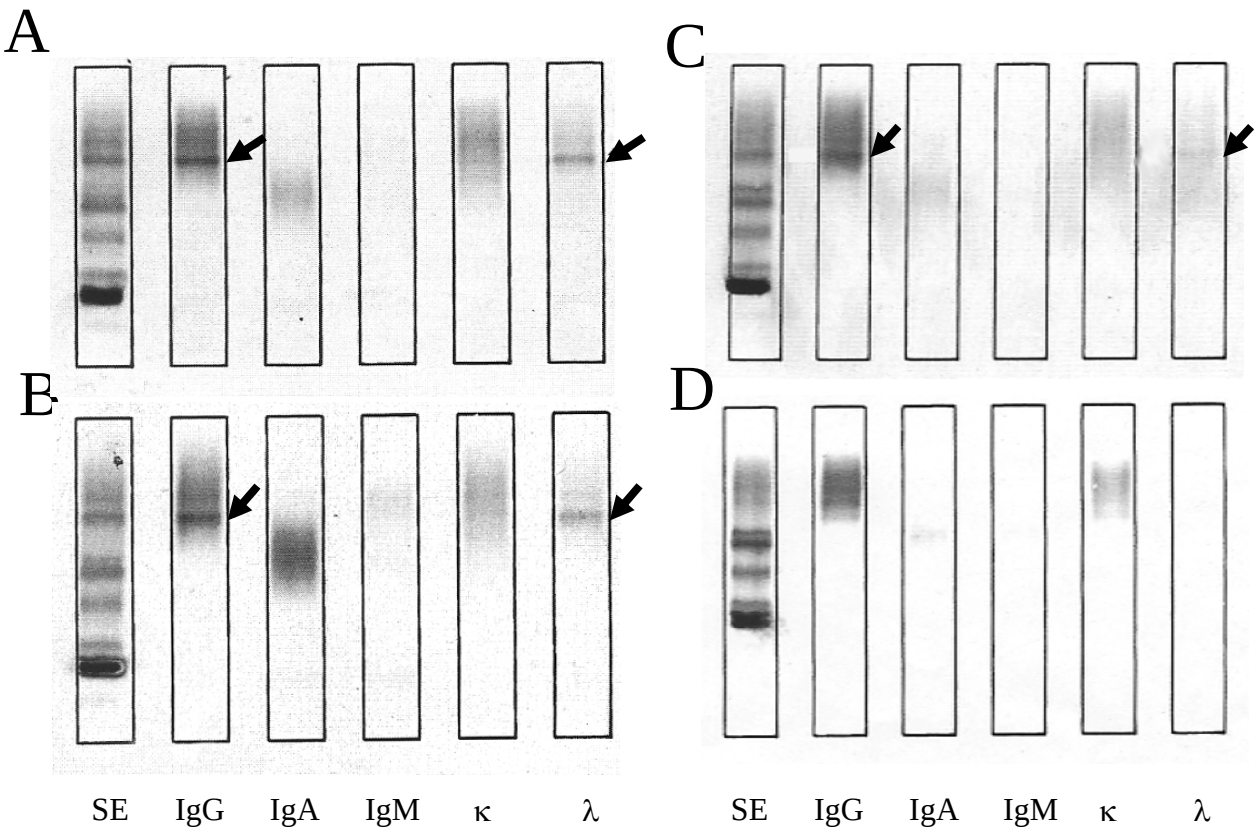

Fig. 2

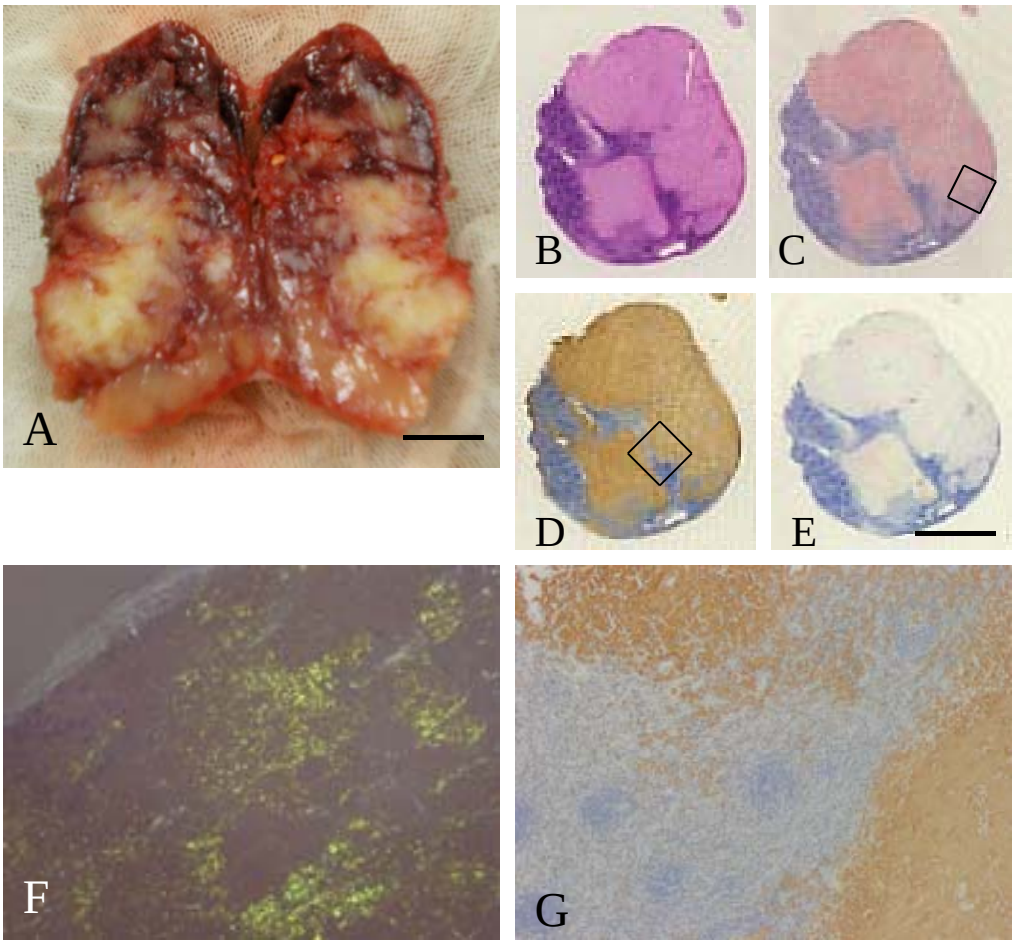

Fig. 3