

Generalized Primary Amyloid Lymphadenopathy

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Systemic amyloidosis is a disease that displays deposition of insoluble polymeric protein fibrils in tissues and organs. We report here on a case of a 64-year-old woman who initially presented with multiple enlarged lymph nodes. Computed tomography showed multiple enlarged lymph nodes in the mediastinal, lower cervical, supraclavicular, axillary and abdominal areas. Excision biopsy of the cervical lymph nodes and the subsequent histopathology showed amorphous eosinophilic material deposits, and these revealed apple-green birefringence on a polarizing microscopic examination on the Congo-red stained slide. The patient was diagnosed with amyloidosis and she received chemotherapy consisting of melphalan and dexamethasone. During chemotherapy, she was diagnosed with breast cancer. After modified unilateral radical mastectomy, the dexamethasone was restarted and this therapy resulted in stable disease. (*Korean J Hematol* 2009;44:320-324.)

Key Words: Systemic amyloidosis, Multiple lymph node enlargement, Chemotherapy

INTRODUCTION

Amyloidosis comprises diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. This disease can be divided into the systemic and localized types.¹⁾ Systemic amyloidosis can affect tissues throughout the body while the localized type is characterized by the deposit of amyloid proteins in a local/restricted area. Systemic amyloidosis is classified into three types: primary (AL), secondary (AA), and hereditary (ATTR). Primary amyloidosis occurs when a specialized cell in the bone marrow (plasma cell) starts to overproduce a particular protein portion of an antibody called

the light chain. To date, there are few published case reports regarding primary amyloidosis presenting with multiple lymphadenopathy.²⁾

CASE REPORT

A 64-year-old woman presented with stable angina. During follow-up, abnormalities were seen at chest X-ray. Computed tomography (CT) showed multiple mediastinal and hilar lymph node enlargements. The patient was recommended to be admitted for further diagnostic testing, but unfortunately she was lost to follow up. After a half year, the patient presented with swelling on the left side of the neck. Fine needle aspiration, showing chronic inflammation with extensive ne-

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crisis, did not yield a definite diagnosis. Under the presumptive diagnosis of tuberculosis lymphadenitis, she was given anti-tuberculosis medications consisting of isoniazid, ethambutol and rifampin.

Despite anti-tuberculosis medications for 4 months, the cervical swelling worsened. In addition, she developed a contra-lateral tumor-like mass. Simultaneously, she complained of pain in the lower back area. Magnetic resonance imaging of the spine showed extensive retroperitoneal soft tissue mass from the left renal hilar area to the presacral area, and direct tumor extension into L5/S1 disc and adjacent endplate. She was referred to our hospital.

Chest CT demonstrated lymph node enlargement of mediastinal, lower neck, supraclavicular

and both axillary areas. CT-abdomen showed multiple lymph node enlargements in the para-aortic, retroperitoneal, mesenteric, and right inguinal areas. There was thickening of mesorectal wall and multiple lymph node enlargements in mesorectum on the CT-abdomen (Fig. 1).

The obtained lymph node samples taken at other hospital were reviewed at our institution. The slides showed deposits of hyaline material in the extracellular matrix. This material did not reveal apple-green birefringence with polarizing microscope examination on the Congo-red stained slide. Also, the acid-fast bacilli (AFB) stain was negative. Therefore, we suspected that the biopsy specimens were not representative.

Routine laboratory tests demonstrated no abnormal findings except for an increase in IgG.

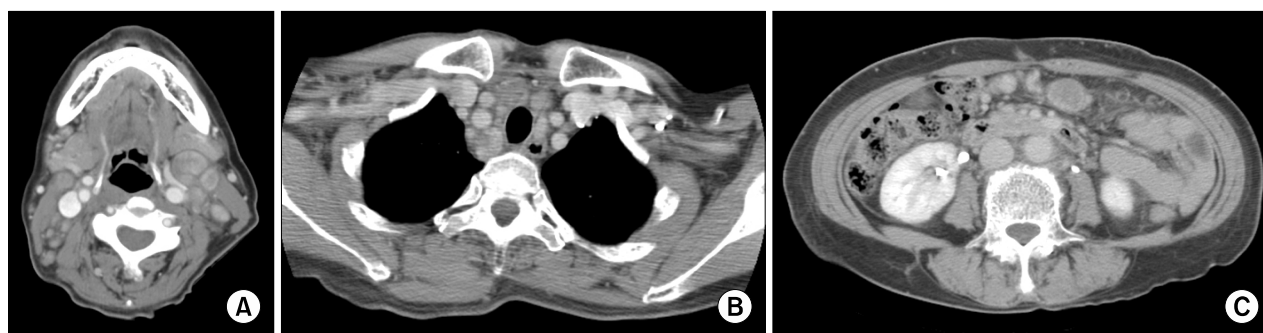


Fig. 1. Computerized tomography (CT) scans at diagnosis showing multiple lymph node enlargements with high enhancement in the cervical (A), mediastinal (B), and abdominal (C) area.

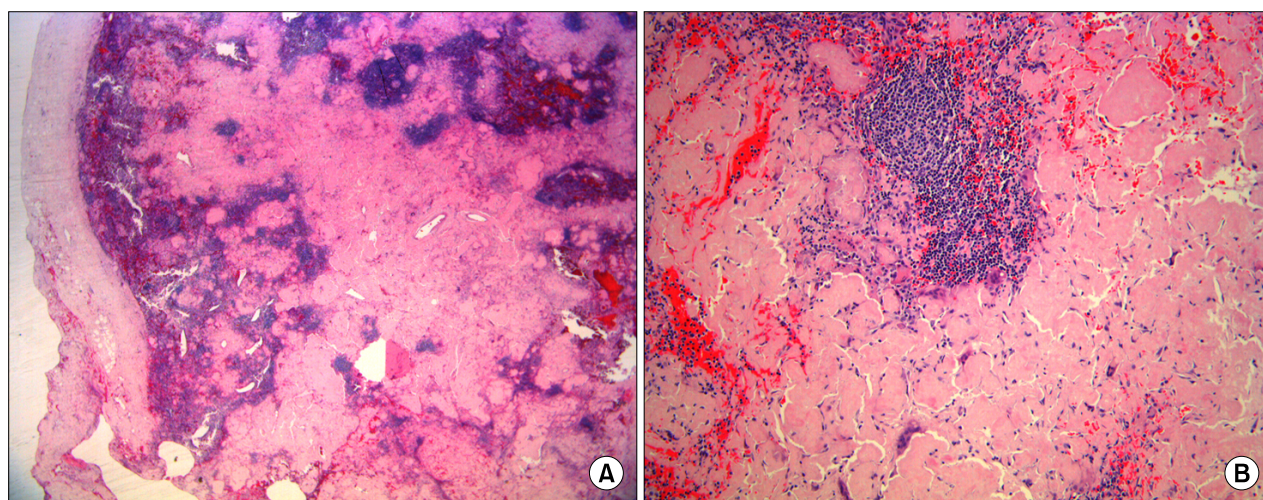


Fig. 2. Cervical lymph node biopsy specimens: H & E stain ($\times 10$) (A), and H & E stain ($\times 100$) (B) showing amorphous eosinophilic material deposits and chronic inflammation with multinucleated giant cells.

Immunofixation showed IgG-type M-proteins in the serum but no Bence-Jones proteins in the urine. Free kappa chains in the serum were not increased but free lambda light chains were increased. Free lambda chains were increased to 87.50 mg/L (normal 5.71~26.3 mg/L), with a kappa/lambda ratio of 0.12 (normal 0.26~1.65). The second excisional biopsy of cervical lymph nodes was performed with a bone marrow biopsy. The bone marrow aspirates showed a normocellular bone marrow with a slight increase of plasma cells of up to 3.5%, but there was no evidence of amyloid deposits. Histopathology of the

lymph nodes revealed diffuse amorphous eosinophilic material deposits and chronic inflammation with multinucleated giant cells (Fig. 2).

The Congo red stain slides were examined using polarized microscope, and revealed apple-green birefringence (Fig. 3). Immunohistochemical stain for lambda light chain was positive, but negative for kappa light chain (Fig. 4). The AFB stain and nested-PCR for *Mycobacterium tuberculosis* were both negative and the patient was finally diagnosed as amyloidosis involving multiple lymph nodes. She received chemotherapy consisting with 10 mg/m² of melphalan and 40 mg of dexam-

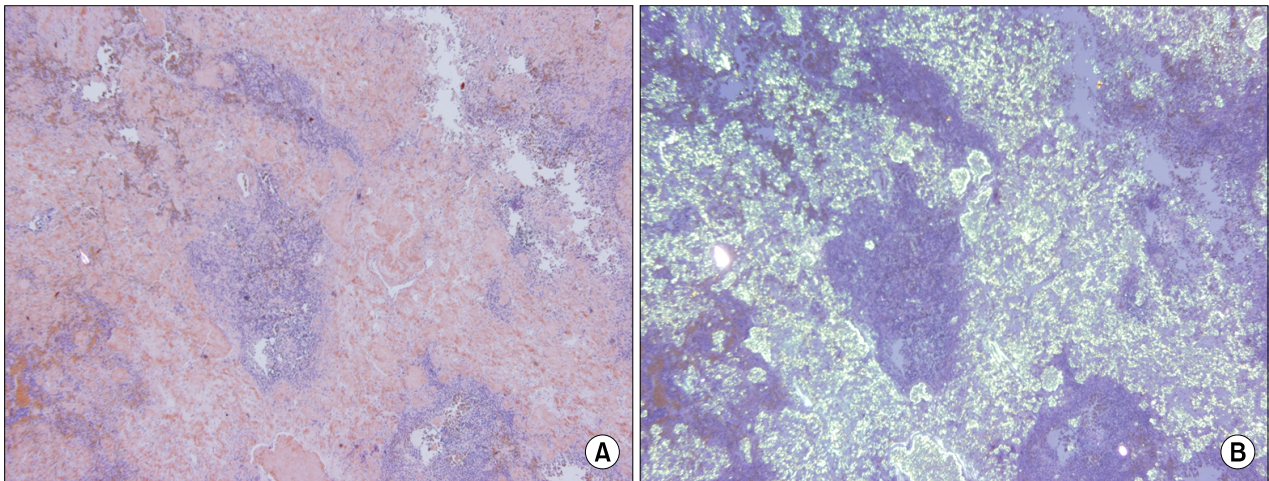


Fig. 3. Congo red stain ($\times 40$) of cervical lymph node: Amorphous eosinophilic material deposit (A) and apple-green birefringence (B).

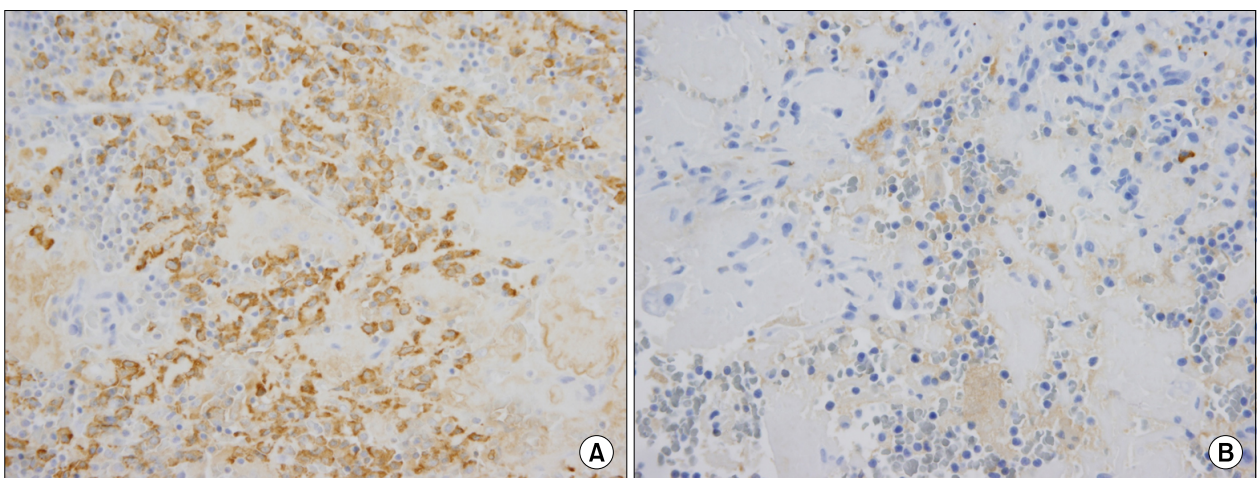


Fig. 4. Immunohistochemical stain for lambda light chain was positive (A), but negative for kappa light chain (B). (Polymer method, $\times 400$).

thasone for 4 days. After discharge, she received the same chemotherapy for 2 more cycles at an outpatient clinic. Even though the M-protein was no longer detectable, the patient's symptoms persisted, necessitating the addition of thalidomide. After one cycle of melphalan, dexamethasone, and thalidomide, the CT scan showed that the size of the lymph nodes had not decreased significantly. In addition, melphalan was withdrawn because of intolerance for drug.

At that time, a tumor of the right breast was detected. Histopathology showed ductal carcinoma in situ. The patient underwent modified unilateral radical mastectomy without complications. Simultaneously, axillary lymph node dissection was conducted and the pathologic result was consistent with amyloidosis. Ten days after the operation, the patient visited our clinic and dexamethasone was restarted.

DISCUSSION

The diagnosis of systemic amyloidosis relies on immunohistochemical or biochemical identification of amyloid deposits. The name of amyloid is attributed to the pathologist Virchow thought such deposits were cellulose-like material. Amyloid diseases are defined by the biochemical nature of the proteins in the fibril deposits and are classified according to whether they are systemic or localized, acquired or inherited, as well as their clinical patterns. In the nomenclature of *AX*, *A* means amyloidosis and *X* represents the protein in the fibril. AL is amyloid composed of immunoglobulin light chains, and is called primary systemic amyloidosis.

Patients with AL amyloidosis have an underlying clonal dyscrasia of plasma cells or B-lymphoid/lymphoplasmacytoid cells. The clonal cell burden in AL amyloidosis is usually small, and the plasma cell proliferation fraction is similar to monoclonal gammopathy of undetermined significance (MGUS). About 10~20% of patients diagnosed with AL amyloidosis meet the criteria

for multiple myeloma and conversely, minor amyloid deposits, frequently of no clinical significance, have been reported in up to 31% of multiple myeloma patients. Progression of the underlying monoclonal gammopathy to overt multiple myeloma disease is rare in systemic AL amyloidosis, which might be related to patients' relatively short overall survival.^{3,4)}

Our patient was diagnosed as AL amyloidosis on the pathological basis of amyloid deposits in biopsied cervical lymph nodes. In general, various presentations are possible. The most common presentation is nephrotic-range proteinuria with or without renal insufficiency, congestive cardiomyopathy, unexplained hepatomegaly, and sensorimotor and autonomic peripheral neuropathy. The most notable point of this case is that amyloid deposition occurred primarily in lymph nodes. Systemic amyloidosis affects lymph nodes in a frequency ranging from 17 to 37%,⁵⁾ but lymphadenopathy is rarely seen as an initial manifestation of this disease.

Treatment of AL amyloidosis is still controversial but median survival of AL amyloidosis with extensive multisystem involvement without treatment is usually about one year from the time of diagnosis. The conventional treatment is cyclic oral melphalan and prednisone to reduce plasma cell burden and improves survival up to a median of 2 years. High-dose dexamethasone substituted for prednisone demonstrated a higher response rate, though tolerability of dexamethasone was lower than prednisone, especially in patients with cardiac involvement or significant edema.⁶⁾ Moreover, high-dose melphalan followed by autologous stem cell transplantation showed a better prognosis.⁷⁾ However, the average cumulative 100-day treatment-related mortality in 4 centers was 21% because of organ failure.⁸⁾ Whether the conventional treatment regimen of AL amyloidosis should be modified in patients with AL amyloidosis involving multiple lymph nodes is not clear at present. Most of the patients with this type of amyloidosis show involvement of visceral organs

such as liver and lungs and have detectable M-protein in serum and/or urine. In general, this type of AL amyloidosis usually shows a good prognosis regardless of the presence of M-proteins. Nevertheless, some patients with AL amyloidosis with multiple lymphadenopathy die because of rapid progression despite aggressive treatment regimens.^{2,9)} According to these studies, intensive chemotherapy including high dose melphalan followed by autologous stem cell transplantation could be effective in patients with systemic AL amyloidosis presenting with multiple lymphadenopathy, particularly, in patients with rapidly progressive disease.¹⁰⁾

During follow-up of our patient, the level of M-protein in the serum decreased from 0.8 g/dL to 0.2 g/dL. However, the size of the lymph nodes did not change significantly, despite an aggressive treatment regimen. Although melphalan could not be continued because of side effects, the patient had a stable disease with treatment.

In conclusion, systemic amyloidosis presenting with multiple lymphadenopathy is a rare entity but should be included in the differential diagnosis of multiple lymphadenopathy. The standard treatment of this kind of presentation of primary systemic amyloidosis is unclear. Fairly intensive chemotherapy including melphalan and dexamethasone may improve the prognosis of these patients. The literature suggests that in patients with proper organ function and rapidly progressive disease, intensive chemotherapy including melphalan followed by autologous stem cell transplantation could improve the duration of survival.

요 약

전신성 아밀로이드증은 불용성 중합 단백질이 조직과 장기에 침착되는 질환이다. 우리는 처음 진단 시에 다발성 림프절 종대로 발현되어 아밀로이드증을 진단받은 64세 여자 환자의 증례를 보고하고자 한다. 환자의 전산화 단층 촬영술에서는 종격동, 목,

빗장뼈위, 액와 및 복강내 림프절의 종대가 발견되었다. 목림프절에 대해서 림프절 절제 생검을 실시하였고 병리 검사 결과 무정형의 호산구성 물질 침착이 관찰되었으며, congo red 염색에서는 apple-green 이중복굴절이 관찰되었다. 환자는 아밀로이드증으로 진단되어 melphalan과 dexamethasone을 포함한 전신항암화학요법을 시행받았다. 화학요법 시행 받던 도중 유방암을 진단받고 수술을 시행받았으며 stable disease 상태로 dexamethasone 투여를 다시 시작하였다.

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