Waldenström’s Macroglobulinemia Accompanying Systemic Amyloidosis: The Usefulness of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Detecting Amyloid Deposits

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Abstract

A 75-year-old man with a history of dyspnea lasting for three years presented to our hospital. Chest computed tomography showed bilateral pulmonary nodules, some of which were calcified, in addition to mediastinal/hilar lymphadenopathy and bilateral pleural effusions. Endobronchial ultrasound-guided (EBUS) transbronchial needle aspiration (TBNA) of the subcarinal lymph nodes showed amorphous acellular material compatible with λ-light chain amyloid deposits. Sternal bone marrow aspiration demonstrated increased small lymphocytes admixed with plasma cells and plasmacytoid lymphocytes. Serum immunoglobulin values were decreased with the exception of immunoglobulin M monoclonal peak. We subsequently diagnosed the patient as having Waldenström’s macroglobulinemia accompanying AL-type amyloidosis. In this case, EBUS-TBNA was useful for detecting AL-type amyloidosis.

Key words: Waldenström’s macroglobulinemia, amyloidosis, endobronchial ultrasound-guided transbronchial needle aspiration, lymph node

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Introduction

Amyloidosis is characterized by the pathological extracellular accumulation of the fibrous protein amyloid in various organs. Amyloid is biochemically classified into three major types: AL-type, AA-type, and hereditary amyloid. Although the fibrils of AL-type amyloid consist of monoclonal light chains, they rarely occur with immunoglobulin M (IgM) gammopathy (1).

We herein report a patient with Waldenström’s macroglobulinemia (WM) accompanying AL-type amyloidosis with mediastinal lymph node involvement. We initially suspected lung cancer on the basis of pulmonary nodules and swollen mediastinal lymph nodes. In this case, endobronchial ultrasound-guided (EBUS) transbronchial needle aspiration (TBNA) was useful for detecting amyloid in the lymph nodes, and a further evaluation led to the diagnosis of WM.

Case Report

A 75-year-old man presented to a local hospital with dyspnea that had developed three years earlier and subsequently deteriorated. He was diagnosed as having heart failure and was referred to our hospital in November 2013. The patient had smoked from 20 to 70 years of age; however, he had no alcohol habits or history of exposure to dust. On presentation, 8-mm-sized hard superficial cervical lymph nodes were palpable. Chest auscultation revealed no abnormal heart sounds or rales, and no peripheral edema was noted. An electrocardiogram showed Q waves in leads II,
III, aVF, and V1-V4. Left ventricular ejection fraction on echocardiography was 65% with restrictive cardiomyopathy, and a small pericardial effusion was noted. Blood gas analysis on O2 5 L/min (face mask) demonstrated a pH of 7.49, PaCO2 of 25.8 Torr, PaO2 of 58.6 Torr, and HCO3 of 19.3 mmol/L. Laboratory tests showed a white blood cell count of 7,000/mm³, hemoglobin of 16.1 g/dL, platelets of 22.3×10⁹/mm³ without abnormal smear findings, serum total protein (TP) of 6.3 g/dL, albumin of 2.6 g/dL, serum creatinine of 0.9 mg/dL, lactate dehydrogenase (LDH) of 297 IU/L, β2-microglobulin of 2.7 mg/L (normal range <2.0 mg/L), and troponin-T of 0.248 ng/mL (normal range <0.1 ng/mL). The results of immunochemical fecal occult blood test were negative, and tumor markers including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA), prostate specific antigen (PSA), pro-gastrin releasing peptide (ProGRP), and carbohydrate antigen 19-9 (CA19-9) were all within normal range.

Chest X-ray showed bilateral pleural effusions and cardiac enlargement (Fig. 1a). Plain computed tomography (CT) performed after drainage of the right-sided pleural effusion revealed mediastinal and bilateral hilar lymphadenopathy, bilateral pleural effusions, bilateral nodules, some of which were calcified (Fig. 1b), and intralobular septal thickening. CT did not show any findings suggestive of abdominal malignancy. The right-sided pleural effusion was transudative with TP 2.3 g/dL and LDH 145 U/L without malignant cells.

After admission, diuretics and oxygen were administered. On hospital day 5, the left-sided pleural effusion was aspirated and showed exudates with TP of 1.9 g/dL (serum TP of 4.8 g/dL) and LDH of 133 U/L (serum LDH 200 IU/L), without malignant cells.

Bronchoscopy performed on hospital day 12 showed no abnormalities in the bronchial lumens. EBUS-TBNA of the subcarinal lymph nodes using a 22-gauge transbronchial aspiration needle (NA-201SX-4022, Olympus, Tokyo, Japan) was performed without evident complications (Fig. 1c). Microscopic examination of the specimens obtained showed an amorphous acellular eosinophilic material. Under polarized light microscopy, Congo red-stained material showed the characteristic apple green birefringence of amyloid material with immunohistochemically positive staining for anti-ATTR antibody and negative staining for anti-Aκ, anti-AL, and anti-ATTR (transthyretin) antibodies (Fig. 2). Cervical lymph node and rectal biopsies also showed deposition of amyloid protein. Cardiac magnetic resonance imaging showed diffuse left ventricular thickening with linear gadolinium enhancement of the bilateral ventricular and atrial walls, suggesting cardiac amyloidosis (2). The BNP value on hospital day 14 had decreased to 127.6 pg/mL, but CT performed on hospital day 18 showed that bilateral pleural effusion and intralobular septal thickening persisted (Fig. 3). Sternal bone marrow aspiration performed on hospital day 18 revealed normocellular bone marrow with increased
small lymphocytes admixed with plasma cells and the presence of plasmacytoid lymphocytes positive for CD20, 79a, and surface and cytoplasmic IgM, and negative for CD5 and CD10. Serum electrophoresis showed λ-type monoclonal protein. The free light chain (FLC) κ/λ ratio was 0.05 (normal range 0.26-1.25) [κ FLC 7.3 mg/L (normal range 3.3-19.4)/λ FLC 156.0 mg/L (normal range 5.7-26.3)]. Serum immunoglobulin G (IgG) was 230 mg/dL, immunoglobulin A (IgA) 28 mg/dL, immunoglobulin E (IgE) 49 IU/mL, and IgM monoclonal peak 1,575 mg/dL. Urine protein was 0.99 g/day, and urinary electrophoresis also showed λ-type Bence-Jones protein. On the basis of these findings, we diagnosed the patient as having WM accompanying AL-type amyloidosis (3). We found no clinical signs of hyperviscosity syndrome.

On hospital day 26, blood gas analysis under ambient air improved to pH 7.45, PaCO₂ 31.4 Torr, PaO₂ 76.2 Torr, and HCO₃⁻ 21.5 mmol/L. Right-sided pleural effusion on discharge remained exudative with TP 2.6 g/dL (serum TP 5.9 g/dL) and LDH 143 IU/L (serum LDH 207 IU/L). He was transferred to another hospital for treatment.

**Discussion**

WM is a rare lymphoproliferative disorder of insidious onset and development of amyloidosis is considered an unusual complication of WM (4-6). It is important to recognize this entity, as the presence of systemic amyloidosis may affect survival. In a previous report, 50 patients with IgM monoclonal gammopathy, including WM, showed a poor prognosis, with an overall survival rate of only 24.6 months. Cardiac amyloidosis was responsible for 53% of the deaths, although several patients also died of progressive amyloidosis involving the kidneys, liver, gastrointestinal tract, and...
nodes are the most common site of thoracic involvement in systemic and systemic forms of amyloidosis and mediastinal lymph nodes are the most common site of thoracic involvement in systemic amyloidosis. Approximately 75% of patients with thoracic disease have mediastinal lymphadenopathy (7,9).

The leading causes of mediastinal lymphadenopathy include infectious, granulomatous, and neoplastic disease; however, in patients with unexplained lymphadenopathy, amyloidosis should also be included in the differential diagnosis.

Clinically, it is not possible to differentiate hilar and mediastinal lymphadenopathy due to amyloidosis from other causes, and a histologic examination of the involved lymph nodes is required for definite diagnosis. The use of CT-guided biopsy of the mediastinal lymph node has been reported (10); however, percutaneous biopsy of some lymph nodes is difficult for anatomical reasons. Although mediastinal lesions can be diagnosed by surgical methods such as mediastinoscopy, mediastinotomy, and thoracoscopy, these approaches are invasive. Mediastinoscopy, as one example, requires general anesthesia, carries a morbidity rate of 1-2%, and has the disadvantage that the posterior and hilar lymph nodes are inaccessible with this approach. TBNA is a widely available technique that can be used to make a specific diagnosis by sampling mediastinal adenopathy and other tissues in close proximity to airways. It has been proved useful in the diagnosis of granulomatous diseases, infections, and malignancies that affect mediastinal lymph nodes (11). Therefore, surgical biopsy can be avoided with use of TBNA (11, 12).

To our knowledge, only 3 cases of amyloidosis diagnosed by TBNA with (13, 14) or without (15) ultrasound guidance for mediastinal lymph nodes have been reported. TBNA via flexible bronchoscopy has value and bears consideration. However, the debate over the role of conventional TBNA in the era of EBUS remains unresolved. EBUS-TBNA offers a unique, safe, and minimally invasive way to image the airway and peribronchial structures (16). In the present case, we could reliably puncture lymph nodes under visualization with ultrasound guidance. Although conventional TBNA is a fairly blind technique that prevents target visualization, a randomized trial recently demonstrated that conventional TBNA is as effective as EBUS-TBNA in the subcarinal region (16). Furthermore, because EBUS-TBNA requires a dedicated bronchoscope designed for application only with this specific procedure, conventional TBNA should be considered as the first step in hospitals in which EBUS-TBNA is not available.

Most cases of lymph node involvement in patients with amyloidosis are associated with lung parenchymal disease (9). Pulmonary manifestation occurs in three major forms: tracheobronchial, nodular parenchymal, and diffuse parenchymal. In our patient, CT showed intralobular septal thickening and some calcified nodules. Although not histologically confirmed, nodular and diffuse parenchymal amyloidosis was suspected.

Pleural effusions appear to occur not infrequently in patients with systemic amyloidosis, (17), with the most frequent cause being congestive heart failure. Other explanations include liver failure, nephritic syndrome, and direct pleural deposition with amyloidosis (18). In our patient, the right-sided pleural effusion was transudative, whereas that of the left side was exudative. At patient transfer, the BNP level had decreased, and the right-sided pleural effusion had become exudative. We assume that the right-sided pleural effusion was transudative on admission due to heart failure but that exudates resulting from the pleural amyloidosis were also present in some areas.

In conclusion, EBUS-TBNA was useful for diagnosing the amyloidosis involving the mediastinal and hilar lymph nodes in a patient with WM accompanying systemic amyloidosis.

The authors state that they have no Conflict of Interest (COI).

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