http://dx.doi.org/10.4046/trd.2013.74.1.23
ISSN: 1738-3536(Print)/2005-6184(Online)
Tuberc Respir Dis 2013;74:23-27

Case Report

A Case of Multicentric Castleman's Disease Presenting with Follicular Bronchiolitis

Yup Hwangbo, M.D.[1], Seung-Ick Cha, M.D.[1], Yong Hoon Lee, M.D.[1], So Yeon Lee, M.D.[1], Hyewon Seo, M.D.[1], Serim Oh, M.D.[1], Minjung Kim, M.D.[1], Sun Ha Choi, M.D.[1], Tae In Park, M.D.[2], Kyung-Min Shin, M.D.[3]

Departments of [1]Internal Medicine, [2]Pathology, and [3]Radiology, Kyungpook National University School of Medicine, Daegu, Korea

Multicentric Castleman's disease (CD) is a rare atypical lymphoproliferative disorder, which is characterized by various systemic manifestations. Some patients with multicentric CD may have concomitant lung parenchymal lesions, for which lymphoid interstitial pneumonia (LIP) is known to be the most common pathologic finding. Follicular bronchiolitis and LIP are considered to be on the same spectrum of the disease. We describe a case of multicentric CD with pulmonary involvement, which was pathologically proven as follicular bronchiolitis.

Key Words: Bronchiolitis; Lung Diseases, Interstitial; Multi-centric Castleman's Disease

Introduction

Castleman's disease (CD), also known as angiofollicular or giant lymph node hyperplasia, is a rare atypical lymphoproliferative disorder[1-3]. Pathologically, CD was divided into hyaline-vascular, plasma cell, or mixed type. The hyaline-vascular type is characterized by hyperplasia of lymphoid follicles, and proliferation of capillaries with hyalinized walls surrounded by concentric layers of small lymphocytes and proliferative interfollicular vascular stroma[1,2,4]. The plasma cell type is characterized by sheets of dense plasma cells in the interfollicular spaces and a paucity of hyalinized capillaries in the lymphoid follicles[1,2,4]. Clinically, CD is classified into a unicentric or multicentric form by the extent of lymph node involvement. The pathologic types of the unicentric disease is more commonly the hyaline-vascular type, rather than the plasma cell type, whereas the multicentric form is mostly the plasma cell variant, and it frequently presents with systemic manifestations1. Most patients with CD have the unicentric form, whereas only 10% of the patients present with the multicentric form[5].

The most extensive study, regarding the pulmonary involvement in patients with multicentric CD, was performed by Johkoh et al.[4]. They demonstrated that intrathoracic multicentric CD typically exhibits bilateral hilar and mediastinal lymphadenopathy, poorly defined centrilobular nodular opacities, and systemic manifestations[4]. Of the 12 patients, 3 underwent open lung biopsy and were pathologically diagnosed with lymphoid interstitial pneumonia (LIP).

To our knowledge, reports regarding pulmonary involvement of multicentric CD are lacking in South Korea. Therefore, we describe a case of muticentric CD with an associated lung lesion, which was pathologically diagnosed with follicular bronchiolitis.

Address for correspondence: **Seung-Ick Cha, M.D.**
Department of Internal Medicine, Kyungpook National University Hospital, Kyungpook National University School of Medicine, 130, Dongdeok-ro, Jung-gu, Daegu 700-721, Korea
Phone: 82-53-200-6412, Fax: 82-53-426-2046
E-mail: sicha@knu.ac.kr
Received: May 8, 2012
Revised: May 23, 2012
Accepted: Jun. 11, 2012

Case Report

A 37-year-old human immunodeficienct virus-negative Korean woman was referred to our hospital for one year of cough with mucoid sputum. She had no hemoptysis, dyspnea, nor chest pain. She had lost 6 kg in the past 3 months. She was a nonsmoker and had no noteworthy specific family history. Physical examination on admission showed no abnormality. Laboratory data included a normochromic normocytic anemia with hemoglobin of 10.4 g/dL and elevated serum protein (11.5 g/dL) with hypoalbuminemia (2.8 g/dL). Serum protein electrophoresis showed polyclonal gammopathy and increased α 2-globulin level (1.3 g/dL). The levels of erythrocyte sedimentation rate (ESR, 120 mm/hr) and serum C-reactive protein (CRP, 7.1 mg/dL) were elevated, but serum lactate dehydrogenase level was within the normal range. On lung function test, no ventilator impairment was noted, but diffusing capacity for carbon monoxide corrected for hemoglobin was reduced (15.8 mL/mm Hg/min [69% pred.]). Chest radiography showed thickened bronchovascular markings and diffuse bilateral reticulonodular opacities in both lungs (Figure 1A). Enhanced chest computed tomography (CT) scan demonstrated multiple mediastinal and hilar lymph node enlargement (Figure 1B, C) and high-resolution CT scan showed the thickening of bronchovascular bundles, interlobular septal thickening, and poorly defined centrilobular nodules in both lungs (Figure 1D).

Bronchoalveolar lavage (BAL) fluid analysis demonstrated an increase in the total cell count (3.0×10^5/mL) with a normal distribution of differential cell count (98% alveolar macrophages, 1% lymphocyte, and 1% neutrophil). Flow cytometric analysis for BAL fluid disclosed a reduction of CD4+/CD8+ cell ratio (0.82). However, transbronchial lung biopsy did not give any useful diagnostic results, except for chronic inflammation. For a pathologic diagnosis, she underwent a vid-

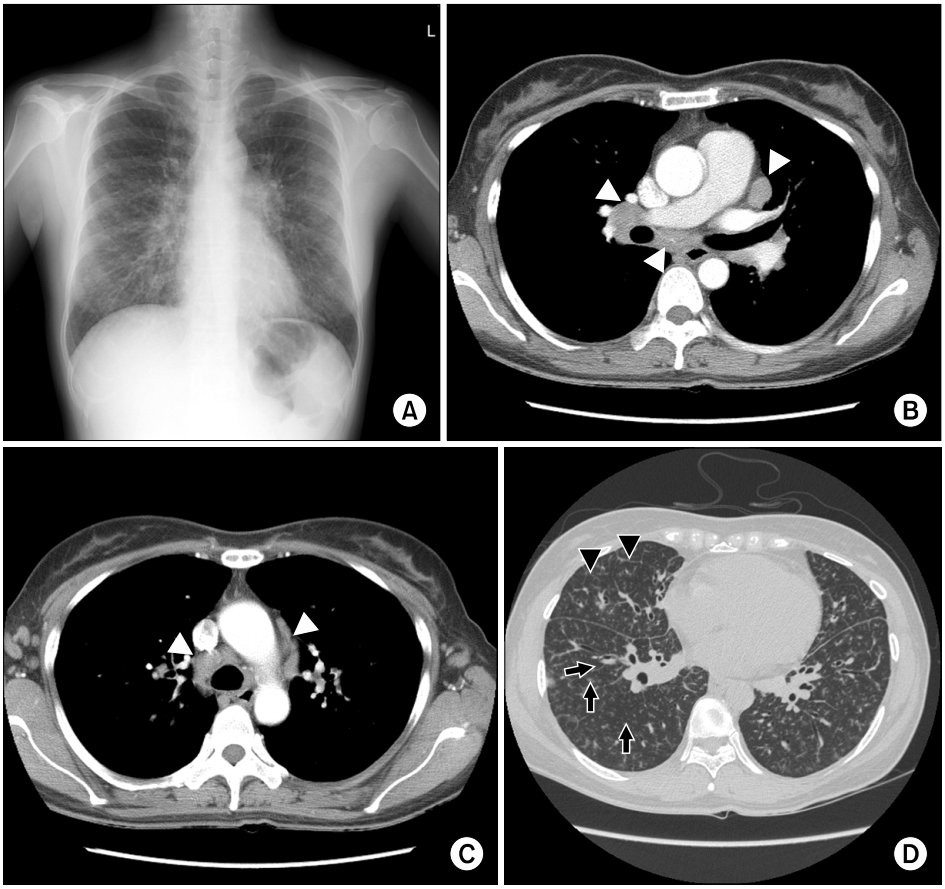

Figure 1. Chest radiography (A) shows prominent bronchovascular markings and diffuse reticulonodular opacities in both lungs. Chest computed tomography (CT) scan demonstrated multiple hilar and mediastinal lymphadenopathy on mediastinal window (B and C, white arrowheads). Poorly defined centrilobular nodules (black arrows) are diffusely scattered in both lungs and interlobular septal thickening (black arrowheads) are also noted in both lungs on lung window setting (D).

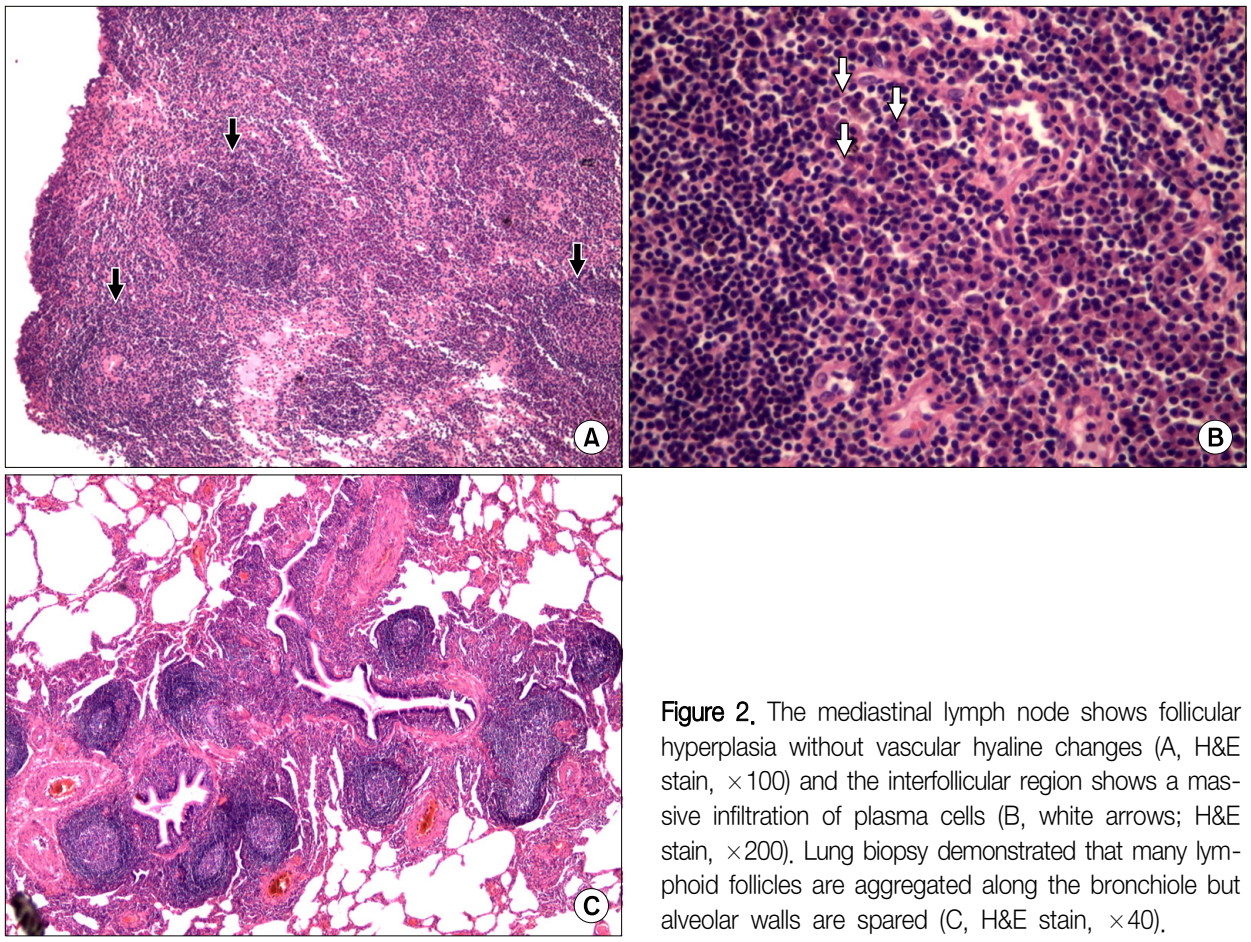

Figure 2. The mediastinal lymph node shows follicular hyperplasia without vascular hyaline changes (A, H&E stain, ×100) and the interfollicular region shows a massive infiltration of plasma cells (B, white arrows; H&E stain, ×200). Lung biopsy demonstrated that many lymphoid follicles are aggregated along the bronchiole but alveolar walls are spared (C, H&E stain, ×40).

eo-assisted thoracoscopic surgery (VATS) for lung tissues and mediastinal lymph nodes. VATS biopsy revealed typical findings of plasma cell type CD in the mediastinal lymph node (Figure 2A, B) and many hyperplastic lymphoid follicles with reactive germinal centers, located around the bronchioles in the lung tissue (Figure 2C). No remarkable lymphocytic and plasma cell infiltration were observed in the interstitium of alveolar walls.

She was diagnosed as having multicentric CD with a pulmonary involvement. She received a high dose prednisolone therapy (1 mg/kg/day), which was tapered over 6 months. At 6 months, a repeat CT scan demonstrated a slight reduction in size of mediastinal lymph nodes, but no significant improvement was observed in lung parenchymal lesions. Then, she underwent azathioprine combined with prednisolone, but did not experience any significant improvement on chest CT scan.

Discussion

To our knowledge, this case is the first report regarding the pulmonary involvement of multicentric CD in South Korea. Furthermore, this report demonstrated that follicular bronchiolitis, a benign lymphoprolferative disorder, might be a pathologic form of pulmonary involvement in multicentric CD, as well as LIP. Lastly, the patient did not respond to high dose corticosteroid and azathioprine combined with prednisolone.

The most characteristic clinical feature of multicentric CD is a frequent association with systemic manifestations, including general weakness, fever, night sweat, weight loss, splenomegaly, hepatomegaly, skin rash, and neurologic findings[5,6]. These systemic symptoms are speculated to be caused by an elevated level of in-

terleukin-6 (IL-6) or IL-6 producing B cells, excessive antibody production, and disseminated human herpes virus-8 infection[5]. The patient had weight loss, anemia, polyclonal gammopathy, and an elevated blood ESR and CRP levels.

Noteworthy, she had an abnormal finding of the lung involvement, which was pathologically diagnosed with follicular bronchiolitis. The frequency of multicentric CD associated with a lung lesion is reported relatively frequently in a Japanese study (18/28, 64%)[4,7]. Johkoh et al.[4] assessed the CT findings of intrathoracic involvement for 12 patients with multicentric CD. Common CT findings of these patients included poorly defined centrilobular nodules (n=12), thin-walled cysts (n=10), thickening of the bronchovascular bundles (n=10), and interlobular septal thickening (n=9). In 6 patients, who underwent lung biopsy (open lung biopsy, n=3; transbronchial lung biopsy, n=4), the findings consistent with LIP were identified. In this case, the pathologic diagnosis was follicular bronchiolitis. LIP is characterized by an extensive infiltration of the lymphocytes and plasma cells in peribronchovascular interstitium and alveolar walls, while follicular bronchiolitis, a focal form of lymphoid hyperplasia, is characterized by the presence of lymphoid follicles with a well formed germinal center, surrounding the bronchiolar wall[4]. Follicular bronchiolitis and LIP are considered to be on the same spectrum of the diseases and the distinction is based on the extent and distribution of the lymphocytic infiltration[4]. Thus, follicular bronchiolitis is thought to be a feasible pathologic diagnosis. However, the possibility of a sampling error for LIP caused by a wedge lung biopsy could not be excluded because the CT findings were very similar to those cases of Johkoh et al.[4], except for thin-walled cysts, which was absent in this case.

In contrast of unicentric CD, which is usually cured by surgical resection, the clinical course of multicentric CD is variable[5,6]. One-third to a half patients with multicentric CD have episodic remissions and exacerbations, and others have lesser severity but persistent clinical manifestations[8,9]. A few patients may have very aggressive clinical course with relentless progression, and ultimately reach death[6]. The treatment for multicentric CD remains to be established. A variety of therapeutic strategies, including corticosteroids, immunosuppressants, chemotherapy, radiotherapy, and anti-IL-6 antibody, have been tried with a various degree of success[5,7,10,11]. The patient received high dose corticosteroids and then, azathioprine combined with prednisolone but no significant improvement was noted with regards to the size of lymph nodes and pulmonary parenchymal lesions on a repeat CT scan.

In conclusion, we report a first South Korean case of multicentric CD with lung involvement, which was diagnosed with follicular bronchiolitis.

References

1. Ko SF, Hsieh MJ, Ng SH, Lin JW, Wan YL, Lee TY, et al. Imaging spectrum of Castleman's disease. AJR Am J Roentgenol 2004;182:769-75.
2. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972;29:670-83.
3. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956;9:822-30.
4. Johkoh T, Muller NL, Ichikado K, Nishimoto N, Yoshizaki K, Honda O, et al. Intrathoracic multicentric Castleman disease: CT findings in 12 patients. Radiology 1998;209:477-81.
5. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol 2005;129:3-17.
6. Peterson BA, Frizzera G. Multicentric Castleman's disease. Semin Oncol 1993;20:636-47.
7. Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, Nakano S, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106:2627-32.
8. Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H. Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. Hum Pathol 1985;16:162-72.
9. Frizzera G, Peterson BA, Bayrd ED, Goldman A. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: clinical findings and clinicopathologic correlations in 15 patients. J Clin

Oncol 1985;3:1202-16.
10. Iyonaga K, Ichikado K, Muranaka H, Fujii K, Yamaguchi T, Suga M. Multicentric Castleman's disease manifesting in the lung: clinical, radiographic, and pathologic findings and successful treatment with corticosteroid and cyclophosphamide. Intern Med 2003;42:182-6.
11. Higuchi T, Nakanishi T, Takada K, Matsumoto M, Okada M, Horikoshi H, et al. A case of multicentric Castleman's disease having lung lesion successfully treated with humanized anti-interleukin-6 receptor antibody, tocilizumab. J Korean Med Sci 2010;25:1364-7.