Multicentric Castleman’s Disease Manifesting in the Lung: Clinical, Radiographic, and Pathologic Findings and Successful Treatment with Corticosteroid and Cyclophosphamide

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Abstract

Multicentric Castleman’s disease (MCD) is an uncommon and often incurable lymphoproliferative disorder. There has been some recent evidence that rare cases of MCD manifest diffuse lung involvement, but the features in these cases are not well characterized. We report just such a biopsy-proven case of MCD with typical laboratory abnormalities including serum interleukin-6 elevation and characteristic high-resolution CT findings. Immunopathologically, the features of the lung tissue resembled those of lymphocytic interstitial pneumonia with predominant infiltration of B cells and plasma cells. In addition, the abnormal appearance of B cells in bronchoalveolar lavage fluid was of diagnostic value. Although MCD is often refractory to treatment including corticosteroid, chemo- and immuno-therapy, we show successful treatment with corticosteroid and cyclophosphamide and 4 years of complete remission.

Key words: Multicentric Castleman’s disease (MCD), lymphocytic interstitial pneumonia (LIP), bronchoalveolar lavage (BAL), corticosteroid and cyclophosphamide

Introduction

Castleman’s disease (CD) is an uncommon lymphoproliferative disorder characterized by mass lesions that occur most often in the mediastinum (1). There are two major histologic variants (2, 3): hyaline-vascular CD, which presents as an asymptomatic mediastinal or hilar mass, and plasma cell CD, which presents with systemic symptoms that result from the production of interleukin-6 (IL-6) by hyperplastic lymph nodes (4, 5). Although most cases of plasma cell CD involve mainly the thorax, a generalized form is recognized as multicentric Castleman’s disease (MCD) (4, 6). This form is relatively rare and is characterized by systemic lymphadenopathy, multiple organ involvement, polyclonal hyper globulinemia, elevated erythrocyte sedimentation, increased IL-6, and other nonspecific clinical manifestations such as fever and anemia. In contrast to the localized disease, MCD does not benefit from surgical management, and it is often refractory to treatment even with corticosteroid or chemotherapy and immunotherapies with anti-IL-6 or anti-IL-6 receptor monoclonal antibodies (4, 6, 7). It has been understood recently that MCD occasionally involves the pulmonary parenchyma, and to our knowledge, a limited number of such cases have been reported as cases of lymphoid interstitial pneumonia (8–10). Here, we report a case of MCD with diffuse interstitial infiltrates, pathologically proved by video-thoracoscopic lung and mediastinal lymph node biopsy. We describe the characteristic clinical, laboratory, radiographic, and pathologic findings of the disease, as well as successful treatment with corticosteroid and cyclophosphamide leading to 4 years of remission.

Case Report

A 53-year-old HIV-negative Japanese woman had been in excellent health until 4 months prior to hospitalization for fatigue, dry cough, and continuous low grade fever. Physical examination on admission showed no abnormality except for slightly swollen cervical and axillary lymph nodes and mild splenomegaly. Laboratory tests disclosed increased serum
total protein (9.7 g/dl) with hypoalbuminemia (2.9 g/dl) and a normochromic anemia with a HB of 11.2 g/dl and a RBC count of 450×10⁴, although WBC count was 7,600 with a normal differential count. Serum immunoelectrophoresis showed high levels of serum polyclonal immunoglobulins (Ig) G (6,030 mg/dl). Although the erythrocyte sedimentation rate (ESR) (128 mm/h) and C-reactive protein level (6.08 mg/dl) were elevated, the lactate dehydrogenase (LDH) level was low (194 IU/ml: normal 236–427 IU/ml). Blood gas analysis showed a slight decrease in partial pressure of oxygen at rest (81.2 mmHg) with a normal acid-base balance. Lung function including vital capacity, residual volume, and diffusing capacity, was within the normal range. Chest radiographs on admission showed diffuse bilateral reticulo-nodular opacities predominantly in the lower lobes. Chest high-resolution computed tomography (HRCT) showed thickening of the peribronchovascular interstitium, interlobular septa, and poorly defined centrilobular ground glass opacities that were perilymphatic in distribution (Fig. 1A). HRCT images enhanced with iodinated contrast material demonstrated multiple enlarged mediastinal and hilar lymph nodes.

For a pathological diagnosis, video thoracoscopic lung and mediastinal lymph node biopsy were carried out under the patient’s informed consent. Microscopic examination of the lymph node showed typical features of plasma cell-type CD. Further immunohistochemical examination with anti-human IgG, A, M, and D, and anti-human Ig light chain, kappa and lambda revealed predominant expression of IgG by B cells and plasma cells. Lung specimens revealed marked infiltration of B cells and plasma cells in the interstitium. This was more predominant in the peribronchovascular and
Lung changes were predominant in the peribronchovascular and interlobular interstitium rather than in the alveolar septa (HE stain, A: x20, B: x100).

Bronchoalveolar lavage showed an increase in the total number of cells (4.81x10^5/ml). Although the differential cell count appeared normal (96% alveolar macrophages and 4% lymphocytes), flowcytometric analysis disclosed a reduced CD4^+CD8^+ cell ratio (0.58) among T cells defined by CD3 staining and an abnormal appearance of CD19^+ B cell count (4.8% of total lymphocytes). 67Ga citrate radioisotope scanning showed no abnormal uptake. Bone marrow was normoplastic, but clusters of plasma cells were found. Serum levels of IL-6 (26.3 pg/ml) and soluble IL-2 receptor (IL-2R) (1,540 U/ml) were elevated. On the basis of these observations, we diagnosed this as a case of MCD with lymphocytic interstitial pneumonia (LIP) of the lung. Human herpesvirus type 8 (HHV-8) DNA in the peripheral blood cells or lung tissue of this patient was not detected by polymerase chain reaction analysis.

Oral prednisolone was administered at 60 mg/day tapering to 25 mg/day by 4 months; thereafter it was maintained at 25 mg/day. Three months after the start of prednisolone therapy, the patient’s symptoms disappeared and her serum IgG (2,570 mg/dl), C-reactive protein (1.64 mg/dl), ESR (53 mm/h), IL-6 (4.6 pg/ml), IL-2R (900 U/ml), and LDH (307 IU/ml) levels showed improvement. According to HRCT, the mediastinal and hilar lymphadenopathy had completely remitted, but a slight thickening of the peribronchovascular interstitium and interlobular septa remained. Five months after the start of steroid therapy, the disease relapsed; serum markers were abnormal (IgG, 4,020 mg/dl; C-reactive protein, 3.22 mg/dl; ESR, 83 mm/h; IL-6, 124.0 pg/ml; IL-2R, 1,150 U/ml; and LDH, 203 IU/ml). Chest HRCT revealed increased interstitial opacities and enlargement of mediastinal and hilar lymph nodes. Methyl-prednisolone pulse therapy (1 g/day for 3 days) was conducted and followed by oral prednisolone at 25 mg/day and cyclophosphamide (CPA) at 100 mg/day. Three months after adding oral CPA, IgG (1,730 mg/dl), C-reactive protein (0.33 mg/dl), ESR (4 mm/h), IL-6 (2.3 pg/ml), IL-2R (677 U/ml), LDH (383 IU/ml) and HB (13.2 g/dl) had normalized. The mediastinal and hilar lymphadenopathy had resolved completely, and the lung abnormalities were absent except for some linear opacity at the interstitium (Fig. 1B). During the follow-up period of 48 months, MCD activity was well controlled, however, the patient had two episodes of skin eruption due to Herpes-Zoster virus, severe back pain caused by steroid-induced compression fracture of the thoracic vertebrae and osteoporosis, and steroid-induced deep venous thrombosis of the right iliac vein. To decrease the adverse effects of the long-term and relatively high-dose corticosteroid therapy, the oral prednisolone was gradually reduced to 7.5 mg/day. The oral CPA was gradually reduced to 25 mg/day and maintained at that level. The treatment course is summarized in Fig. 3.

Discussion

MCD has become to be known to occasionally manifest primarily as a pulmonary parenchymal disease. However, only a limited number of cases have been reported, and the clinical, laboratory, and pathological details including those of bronchoalveolar lavage study have not been well clarified (8-10). Recently, Barrie et al (8) reported a case of MCD with lung involvement, and noted that peribronchovascular interstitial thickening and centrilobular nodules on HRCT correlated well with the histologic findings of open lung biopsy. Johkoh et al (10) reported HRCT evidence of lung involvement in cases of MCD that resembled LIP. In the present case, no nodular lesion or cyst was observed in the lung parenchyma; however, fundamental distribution of the lesions in the lungs was in accordance with that previously reported (10). Involvement was perilymphatic and characterized by dense lymphocytic infiltration at the peribronchovascular interstitium and interlobular septa. It should be emphasized that alveolar septa appeared to be less involved. The distribution of lesions in our case was different from the original description of LIP in the narrow sense, in which the alveolar interstitium is the main lesion of lymphocyte...
Multicentric Castleman’s Disease in the Lung

Figure 3. Course of successful treatment with corticosteroid and cyclophosphamide. Complete remission was maintained by low doses of these drugs in combination. PSL: prednisolone, CPA: cyclophosphamide, Met-PSL: methyl-prednisolone pulse therapy (1 g/day for 3 days), IgG: immunoglobulin G, CRP: C-reactive protein, IL-2R: soluble IL-2 receptor.

infiltration and there is no marked hilar or mediastinum lymphadenopathy (11). Histological evaluation of the lung specimen in our case showed the infiltrating cells to mainly comprise B lymphocytes that were accompanied by plasma cells and histiocytes. Furthermore, the abnormal appearance of CD19+ B lymphocytes in the bronchoalveolar lavage fluid was thought to be clinically important, because the recovered lymphocytes in lavage fluid were believed to be T cells under a variety of disease conditions and in normal healthy individuals.

Dysregulated overproduction of IL-6 from the germinal center of hyperplastic lymph nodes of patients with plasma cell-type CD including MCD is thought to be responsible for the systemic manifestation of the disease (4, 5). The present patient showed the typical laboratory abnormalities. Serum levels of IgG, C-reactive protein, ESR, IL-6, IL-2R, and LDH have been useful markers of disease activity in cases of MCD. Interestingly, serum LDH was abnormally decreased in our case when the disease activity was high. The reason for this is unclear, however, it may be related to an increase in IL-6, which can lead to orderly cell cycle arrest, differentiation, and apoptosis of an increased number of an B cells and plasma cells (12).

Patients with MCD often develop secondary tumors, such as Kaposi’s sarcoma, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, and immunoblastic or plasmacytic B-cell lymphoma. Recently, several reports described that HHV-8 sequences, which play a major role in the pathogenesis of Kaposi’s sarcoma, have been identified in the tissues of some cases of MCD, although the prevalence of HHV-8 in the different type of CD and its relationship to the development of related lymphoma remain unclear (13). Recently, Dupin et al (14) reported that HHV-8 is associated with a plasmablastic variant of CD, a variant of plasma cell type
CD, in which HHV-8-positive plasmablasts present in the mantle zone of the tissues, although these plasmablasts are not present in the tissues of HHV-8-negative CD. The present case was HHV-8-negative, and defined as not such a variant case but a common case of plasma cell type of CD, in which plasmablasts defined as IgM-positive immunoblasts were absent.

The optimal therapeutic approach to MCD is still unclear. A variety of therapies including corticosteroid therapy, chemotherapy, radiotherapy, immunotherapy with anti-IL-6 or anti-IL-6 receptor monoclonal antibody, interferon-alpha, and retinoic acid therapy have been employed with various degrees of success (4, 6, 7, 15–17). Most patients have been treated with corticosteroid or single- or multiple-drug chemotherapy, but the disease is refractory and the prognosis is uncertain. Recently, Chronowski et al (16) reported a fairly good response to regimens including corticosteroid and cyclophosphamide in the regimen in 9 MCD cases. Four of their patients achieved complete remission. Donaghy et al (18) reported 2 patients who achieved complete remission for more than 12 months; these 2 patients were treated with prednisolone and cyclophosphamide. In the present case, corticosteroid therapy including pulse therapy was partially effective with some success to reduce disease activity, however, it failed to achieve complete remission. MCD remitted after cyclophosphamide was added to corticosteroids, and remission was maintained with low doses of these drugs over a 48-month period. Adding cyclophosphamide to prednisolone was of value to lead to disease remission and reduce the dosage of prednisolone. Particularly with respect to the reduced side effects, the combination of cyclophosphamide and low-dose steroids may be an attractive regimen for the treatment of MCD.

References