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Pulmonary non-caseating granuloma in Waldenström macroglobulinemia

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Lung involvement is rare in Waldenström macroglobulinemia (WM). We encountered a male patient with WM who complained of breathlessness. Chest X-ray revealed diffuse infiltrative shadow throughout the both lungs. Transbronchial biopsy showed infiltration of atypical plasmacytoid lymphocytes and non-caseating granuloma. We treated the patients with fludarabine phosphate, and both his symptom and X-ray findings were then improved. To our knowledge, this is the first case showing non-caseating granuloma with lung involvement of WM. We discuss a mechanism of non-caseating granuloma formation in this case.

Key words: Waldenström macroglobulinemia, non-caseating granuloma, lung involvement

INTRODUCTION

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma associated with serum monoclonal immunogloblin (Ig) M. This disease, most common in the elderly, usually follows an insidious onset and pursues a chronic clinical course. Most patients with WM present with generalized malaise, anemia, and central nervous system depression, or mucous membrane bleeding due to plasma hyperviscosity caused by very high levels of IgM [1, 2]. The neoplastic cells tend to infiltrate into lymph nodes, liver, spleen and bone marrow. However, lung involvement is rare [3]. We encountered a patient with lung involvement of WM. The pathologic studies using lung tissues revealed infiltration of neoplastic cells with non-caseating granulomas.

CASE REPORT

A 58-year-old man was referred to a general outpatient clinic which was near his home because of cough and breathlessness on June 25, 2003. A chest X-ray showed infiltrative shadow in the right lower lung field, and blood tests revealed a high level of IgM. On July 1, he was admitted to a neighboring hospital for further examination. Immunofixation electrophoresis of serum showed monoclonal IgM of λ type, and he was suggested to have WM. Because the pulmonary infiltration spread to the both lungs during hospitalization, he was transferred to Tokai University Hospital for further respiratory care and examination on July 15.

At the time of admission, physical examination revealed no lymph node swelling nor significant hepatosplenomegaly. Fine crackles were audible in both lung fields on auscultation. Venous engorgement was observed in the eyeground. Peripheral blood examination revealed the following; WBC 6.3 $\times$ 10^9/L (neutrophils 54.3%, lymphocytes 36.0%, monocytes 4.6%, eosinophils 4.1%, basophils 1.0%, atypical lymphocytes 0.0%),

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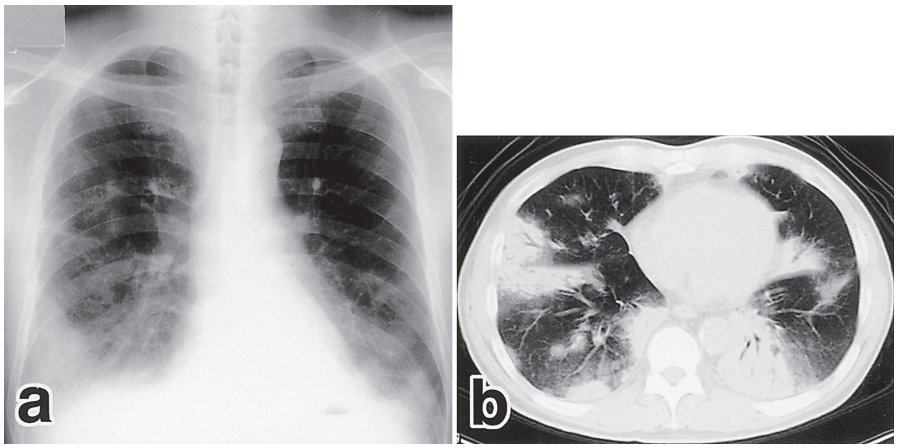

Fig. 1 X-ray findings of the lung.
a: Chest X-ray revealed bilateral consolidation at the time of admission.
b: X-ray computed tomography of the chest showed extensive bilateral peripheral parenchymal consolidation with air bronchogram.

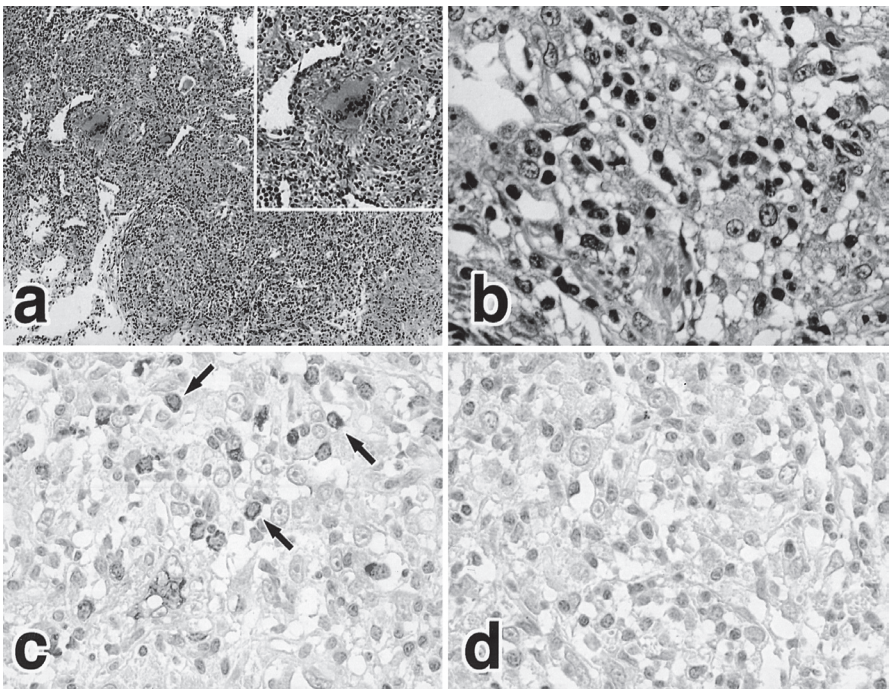

Fig. 2 Pathology of the pulmonary lesions.
a: The lung biopsy showed non-caseating granulomas in the bronchial mucosa and parenchyma forming nodular lesions. (Original magnification × 25)
b: The non-caseating granuloma was accompanied by inflammatory cell infiltration with lymphoid cells and lymphoplasmacytoid lymphocyte. (Original magnification × 200)
c, d: Immunostaining with the biotin-avidin-method revealed that the neoplastic cells are positive for monotypic immunoglobulin lambda chain (c) and negative for immunoglobulin kappa chain (d) in the cytoplasm. Arrows indicate lambda chain-positive cells. (Original magnification × 200)

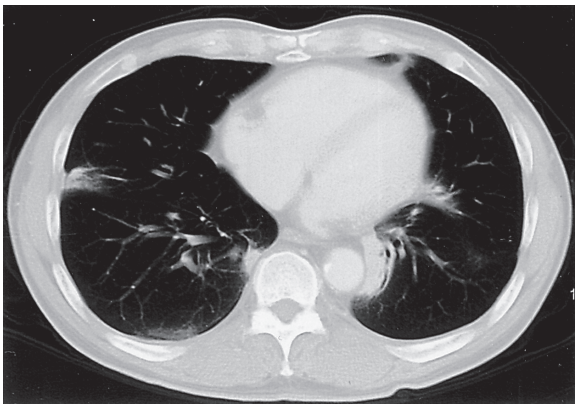

Fig. 3 X-ray computed tomography of the chest showed disappearance of consolidation after fludarabine phosphate therapy.

RBC 4.8 × 10^{12}/L, Hb 14.3 g/dL, hematocrit 42.6%, platelets 159 × 10^{9}/L, LDH 277U/L, β2-microglobulin 4.39 mg/L, total protein 9.9 g/dL, albumin 3.8 g/dL, IgM 4106 mg/dL, IgG 909 mg/dl, and IgA 399 mg/dl. Serum electrophoresis showed monoclonal IgM of λ type, and serum viscosity was increased by the monoclonal gammopathy. Urine electrophoresis showed λ Bence Jones protein. Bone marrow aspiration study revealed infiltration of atypical plasmacytoid lymphocytes. Chest X-ray and CT showed bilateral consolidation in both lungs (Fig. 1a and 1b). The cell number and CD4/CD8 ratio in bronchoalveolar lavage fluid were 853/μL (lymphocytes 34%, neutrophils 2%, histiocytes 61%, eosinophils 3%) and 1.35, respectively. Pathologic studies of transbronchial biopsy specimen revealed infiltration of plasmacytoid lymphocytes and non-caseating granulomas (Fig. 2a and 2b). Those infiltrating cells were positive for IgM and λ light chain, and negative for κ light chain (Fig. 2c and 2d). There were no cells that were stained with Grocott and methylene blue, Ziehl-Neelsen or Bacillus Calmette-Guerin in the lung specimens (data not shown), indicating that the non-caseating granulomas did not associate with bacteria, tuberculosis, fungi, protozoa communicable disease. The serum levels of angiotensin-converting enzyme (ACE) and calcium, sarcoidosis-associated markers, were within normal ranges (17.8 IU/L and 10.0 mg/dL, respectively).

We diagnosed him with WM manifested as lung involvement. Then, we administered Fludarabine Phosphate (20 mg/m^2 on day1-5). After 4 cycles of the treatment, the serum level of IgM was markedly decreased (812 mg/dL), and both his respiratory symptom and abnormal X-ray findings were disappeared (Fig. 3).

DISCUSSION

WM is a rare disorder; the incident rates are estimated to be 6.1 per million in men and 2.5 per million in women [4, 5]. To our knowledge, 78 cases of WM have been reported to develop lung involvement so far [3, 6, 7]. Based on these reports, the incidence of lung involvement was estimated to be 3-5% in WM. The age-range was 33-84 (62.12 ± 12.73). The male to female ratio was approximately 2:1 which was almost identical to that of usual cases [4]. Chest radiographic findings were inconstant; parenchymal infiltrates (21 patients), effusions (5 patients), confluent masses (7 patients), infiltrates and effusions (11 patients), masses and effusions (6 patients), masses and infiltrates (11 patients), masses and effusions and infiltrates (6 patients). On the pathologic examinations, pulmonary infiltration of plasmacytoid lymphocytes was observed in those cases, as was observed in our case. However, there was no report that described non-caseating granuloma with involvement of the lung.

Non-caseating granuloma is found in various pathological conditions. Sarcoidosis is a representative disorder forming non-caseating granulomas, and three cases of

sarcoidosis complicated with WM have been reported [8, 9]. In our patient, the CD4/CD8 ratio in bronchoalveolar lavage fluid was normal and serum levels of ACE and calcium were within normal ranges. Furthermore, there were no granuloma lesions in the eyes or bone marrow. Therefore, the possibility that our patients developed sarcoidosis was considered to be extremely low.

On the other hand, non-caseating granuloma is recognized in various malignancies including hematologic malignancies [10]. Especially, non-caseating granuloma is reported to be found in 20-50% of MALT lymphoma cases, and it is suggested that the granuloma is resulted in an anomalous immune reaction associated with MALT lymphoma [10]. Since monoclonal IgM produced in WM acts as antibodies and causes various complications such as peripheral neuropathy, hemolytic anemia, and crioglobulinemia, we speculated that abnormal IgM produced in our patients might associate with the non-caseating granuloma formation.

In conclusion, we reported WM showing lung involvement with non-caseating granuloma. When pulmonary non-caseating granuloma is present, WM should be considered in the differential diagnosis.

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