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Case report

Waldenström's macroglobulinemia

Report of an autopsy case presenting with a pulmonary manifestation

Motomu Tsuji[1], Yasuyoshi Yoshii[1], Toshihiko Taka[2], Kyong-yob Min[2], and Hiroshi Mori[1]

[1] Department of Pathology and [2] Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka 569, Japan

Summary. An autopsy case of Waldenström's macroglobulinemia is reported, in whom an abnormal pulmonary shadow had already existed 2 years before the diagnosis of the disease and was proved to be pulmonary involvement. Immunoelectrophoresis demonstrated a monoclonal increase in immunoglobulin M with kappa light chain. A chest X-ray film showed a reticulo-nodular shadow in the right lower lobe of the lung. A bronchial biopsy specimen revealed a diffuse and dense lymphocytic infiltration. Bone marrow aspirate revealed no remarkable change except for a slight increase in plasma cells (1.7%) and an appearance of atypical lymphocytes (0.5%). At autopsy, more than half of the right lower lobe of the lung was occupied by a pale whitish, viscid and glossy tumour mass. Heptosplenomegaly and lymph node enlargement were not observed. Histological findings of the tumour tissue were similar to those of the biopsy specimen. Lymphocytic infiltration was observed also in the liver, kidneys, spleen, bone marrow and lymph nodes, but was of minor degree. Other reported cases of Waldenström's macroglobulinemia accompanied by pulmonary involvement are reviewed.

Key words: Waldenström's macroglobulinemia – Pulmonary involvement – Transbronchial lung biopsy

Introduction

Waldenström's macroglobulinemia (WMG), originally reported in 1944 (Waldenström 1944) is a rare, lymphoproliferative disorder characterized by anaemia, an elevated erythrocyte sedimentation rate and a monoclonal IgM-gammopathy. This disease usually occurs in elderly individuals with an insidious onset and pursues a chronic clinical course. Histologically, IgM-secreting lymphocytic proliferation was observed mainly in lymph nodes, spleen and bone marrow (Cohen et al. 1966; Mc Callister et al. 1967; MacKenzie and Fudenberg 1972; Yamaguchi 1973). The lungs may also be involved in limited extent during the course of the disease. A few cases have been reported in whom pulmonary manifestations related to the involvement of WMG appeared even before the diagnosis of the disease (Winterbauer et al. 1974; Rausch et al. 1980). Chest X-ray findings in those patients consisted of hilar enlargement, infiltrate, nodular mass and pleural effusion. In this paper we report an autopsy case with WMG presenting a reticulonodular shadow in a chest X-ray film 2 years before the diagnosis of the disease, which was demonstrated to be pulmonary involvement by autopsy.

Offprint requests to: H. Mori, Department of Pathology, Osaka Medical College, 2–7 Daigaku-machi, Takatsuki, Osaka 569, Japan

Case report

The patient, an 83-year-old man, was referred to Osaka Medical College Hospital in February 1987 for continuous cough of a few months' duration. Two years before the admission when he had had an operation for cataracts, his chest X-ray had revealed a fibrous and reticular shadow in the lower lobe and a nodular shadow in the upper lobe of the lung. In spite of ophthalmologist's advice, he had never consulted a physician until the present hospitalization because of being asymptomatic. Physical examination revealed ankle oedema and moist rales over the right lower lung field. The liver tip was palpable 2 cm below the costal margin, but the spleen was not enlarged. Enlargement of systemic lymph nodes was not present. Laboratory data included the following values: erythrocyte sedimentation rate, 136 mm/hr; haemoglobin, 11.0 g/dl; hematocrit, 32.2%; reticulocyte, 20‰; WBC count 4,480/mm^3 with a small number of atypical lymphocytes (<0.5%); serum total protein, 5.9 g/dl; serum albumin, 2.4 g/dl; gamma globulin, 2.1 g/dl

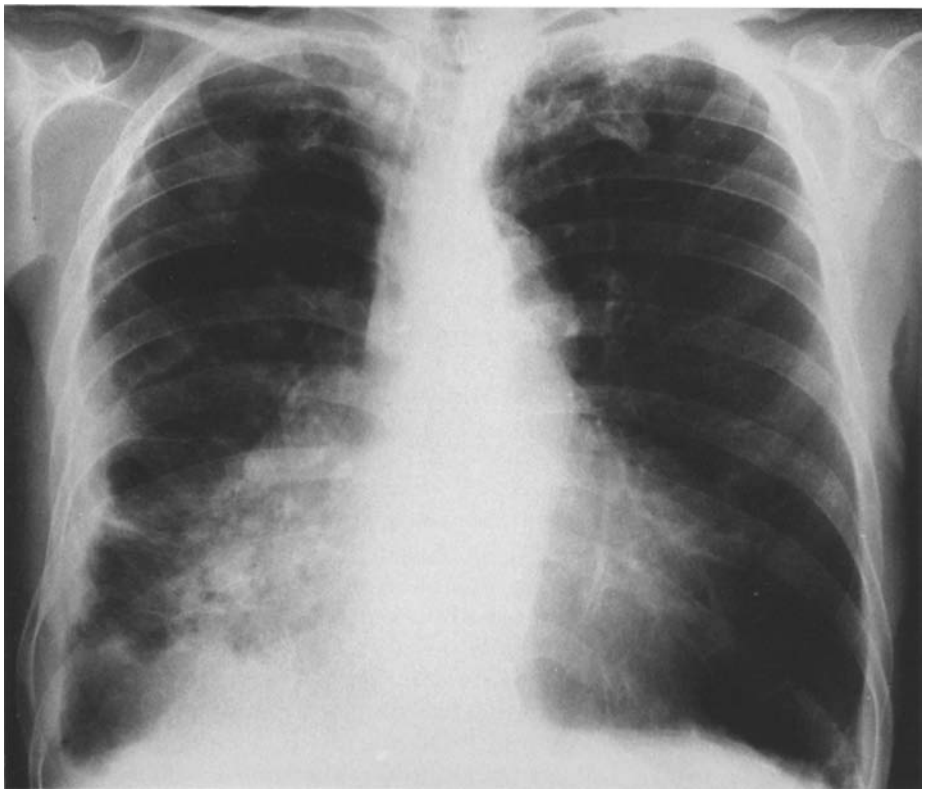

Fig. 1. Chest X-ray on admission. Note a reticulo-nodular shadow in the lower lobe and a nodular shadow in the upper lobe, and pleural thickening of the right lung

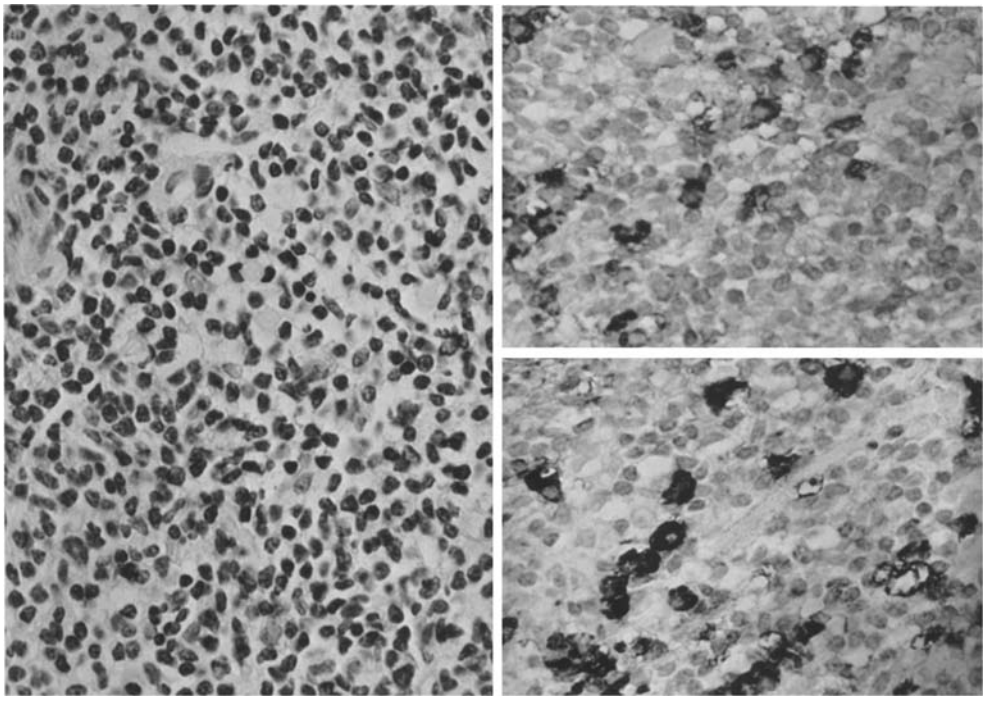

Fig. 2. Photomicrographs of a bronchial biopsy specimen. Note the small-lymphocytic and plasmacytoid cell infiltration beneath the bronchial membrane (*left*, H.E.). A number of lymphocytes and plasmacytoid cells were positive for IgM (*right upper*), and kappa chain (*right lower*) on immunoperoxidase stain. × 660, respectively

(normal 0.7–1.7); BUN 18 mg/dl, serum creatinine 1.0 mg/dl. Urinary protein excretion was 0.5 g/24 hrs. Bone marrow aspiration revealed no hypercellularity and no remarkable change except for a slight increase in number of plasma cells (1.7%) and an appearance of atypical lymphocytes (0.5%). Rheumatoid factor was not detected. Anti-nuclear antibody was positive at a dilution of 1:5,120 in a speckled pattern. No anti-DNA antibody was detected. Cold haemagglutinin was positive at a dilution of 1:256. Serum IgG was 1,957 mg/dl, IgM 2,252 mg/dl and IgA 417 mg/dl. Serum electrophoresis revealed a M-component in the gamma region, which was classified as an IgM M-component bearing kappa light chain by immunoelectrophoresis.

A chest X-ray on admission (Fig. 1) demonstrated an enlargement of the reticulo-nodular shadow in the right lower lobe with pleural thickening, compared to the film of two years before. The nodular shadow in the right upper lobe remained almost unchanged. Bronchoscopy revealed that lower lobe bronchi of the right lung were narrow, accompanied by mucosal swelling, and the bifurcation of the middle and lower lobe bronchi of the right lung was obtuse in angle with oedematous mucosa. A bronchial biopsy specimen revealed a diffuse, dense infiltration of small cleaved and non-cleaved lymphocytes with mild atypism and scattered plasmacytoid cells (Fig. 2). Cells positive for IgM and kappa light chain on immunoperoxidase stain predominated in these cells.

After admission, the patient was at first given antiphlogistic and antibiotic agents with a trivial amelioration of cough and dyspnoea. He was then started on chemotherapy with vincristine, endoxan, adriamycin and prednisolone. However, the chemotherapy was stopped after one course because of the occurrence of leukopaenia and thrombocytopaenia. He began to suffer from progressive proteinuria and general oedema so that albumin (10–20 g/day) was given intravenously. For three weeks prior to his death, prednisolone (30 mg daily) was given with a remarkable improvement in proteinuria. Chest X-ray showed no notable change; there was perhaps a diminution of the shadow in the upper lobe but a high-voltage film was used. He died of pneumonia 11 months after the admission.

Results

The right lung weighed 820 g and more than half of the lower lobe was occupied by a firm tumour mass. The thickened pleura adhered to the chest. On cut surface, the tumour consisted of pale whitish, viscid and glossy mass mixed with anthracotic areas and scattered inflammatory foci with abscess formation (Fig. 3). The lower bronchus was extremely narrow and peripheral bronchi were obliterated by tumour. The upper lobe contained a nodular, firm mass beneath the pleura in the posterior aspect. The mass consisted of scar-like fibrous tissue with anthracosis, and was not viscid or glossy. The hilar lymph nodes were soft and anthracotic, but not enlarged. The liver and spleen weighed 800 g and 80 g, respectively, and showed no remarkable change. Superficial lymph nodes as well as mediastinal, abdominal and retroperitoneal ones were not enlarged.

On microscopic examination, the thickened pleura was free of infiltrates. The tumour tissue in the right lower lobe consisted of mixed areas of the diffuse and dense lymphocytic infiltration as observed in the biopsy specimen, and fibrosis with anthracosis. The nodule in the upper lobe consisted of abundant fibrous tissue with dust- and/or haemosiderin-bearing macrophages. Patches of lymphocytic infiltration occurred around bronchioles and vessels. Multiple abscesses were formed in and around the tumour tissue in the right lower lobe. Areas in which alveolar space was filled with exudates organized in varying degree were seen in both lungs. The bone marrow was slightly hypercellular and there was an increase in the number of atypical lymphocytes, but it also contained a considerable number of the three series of haematopoietic cells. Lymph nodes were well preserved in the architecture and included a small number of atypical lymphocytes and plasmacytoid cells in the sinuses. Infiltration of these cells was also observed in the white pulp of the spleen, Glisson's sheath of the liver, submucosal tissue of renal pelvis and the gastrointestinal mucosa, but was in a minor degree.

Discussion

The immunological properties of the abnormal plasma protein and the histological appearance of the bronchial biopsy specimen identified the present case as Waldenström's macroglobulinemia with pulmonary involvement. Immunoelectrophoresis disclosed the abnormal protein to be a monoclonal IgM bearing kappa light chain. The biopsy specimen revealed a diffuse and dense infiltration of lymphocytic and plasmacytoid cells and the predominance of IgM- and kappa chain-positive cells in the infiltrates on immunoperoxidase stain. Autopsy revealed an intense infiltration of lymphoid cells with mild atypia in the lower lobe of the right lung, and in several other organs in a lesser degree.

In WMG, IgM-producing cells proliferate mainly in the lymph nodes, spleen and the bone marrow, but rarely in the lung. Imhof et al. (1959), Cohen et al. (1966) and MacKenzie and Fudenberg (1972) examined 114, 10 and 40 cases of WMG, respectively, but nothing was documented about signs of pleuropulmonary involvement. McCallister et al. (1967) found 2 WMG cases with pleural effusion and 1 with pneumonia out of 31 patients, and considered only 1 case with pleural effusion to have pleural involvement. In the review of Kappeler et al. (1958), five of 126 cases were reported to be accompanied by pulmonary involvement. Examining autopsy cases of WMG in Japan, Yamaguchi (1973) found that 15 of

Fig. 3. Vertical-section of the right lung. More than half of the lower lobe was occupied by tumour tissue. Lower lobe bronchus (*arrow*) was extremely narrow because of the submucosal infiltrates

32 cases showed infiltration of lymphoid cells around bronchi and vessels, and interlobular connective tissue of the lung. The extent of the pulmonary infiltration was not documented, nor was there any comment on whether the infiltrates were noted as abnormal shadows on antemortem chest X-ray films. In the series of Winterbauer et al. (1974), 5 out of 20 cases were revealed to have abnormal chest X-ray findings, which were identified to be pleuropulmonary involvement by autopsy or biopsy in 4 cases.

However, cases of WMG which seemingly originate in the lung are extremely rare. In 3 cases (Essig et al. 1974; Chonabayashi et al. 1982; Filuk and Warren 1986), pulmonary involvement with preceding clinical manifestations was demonstrated at the time of diagnosis of WMG by biopsy or cytology. We found 7 cases in the literature, in which the abnormal chest X-ray picture preceded the appearance of M-component by more than 2 years (Strunge 1969; Ward et al. 1971; Rabiner et al. 1972; Major et al. 1973; Winterbauer et al. 1974; Hakozaki et al. 1980; Nii et al. 1988). The pulmonary lesions in those cases were later confirmed to be involvement by WMG, by biopsy and/or autopsy. In the case of Rabiner et al., hilar enlargement had been pointed out 10 years before, and perihilar infiltrates in the lower lobe of the left lung was observed 3 years before the diagnosis of WMG. In Strunge's case, chest X-ray film

showed a hilar enlargement together with an infiltrate in the right upper lobe 9 years before the identification of WMG. In these cases, therefore, the disease appeared to originate in the hilar lymph nodes but not in the lung itself. In our case, a chest X-ray of 2 years before the present admission had already shown a fibrous and reticular shadow with infiltrates in the lower lobe and a nodular shadow in the upper lobe of the right lung, believed to be lung cancer by a radiologist. Neither enlargement of systemic lymph nodes nor hepatosplenomegaly had been observed. At autopsy the main tumour mass was found in the lower lobe of the right lung. The right upper lobe and several other organs including hilar lymph nodes were only infiltrated with a small number of cells, identical to those in the tumour mass. Therefore, it appears that the primary lesion of the present case occurred in the lung, although a possibility remains that the bone marrow was in fact the primary focus.

Rausch and Herion (1980) collected 44 cases with pleuropulmonary involvement in the literature, including their own case. All of these were confirmed by autopsy and/or biopsy. Symptoms at the onset of pulmonary involvement included dyspnoea (54%), nonproductive cough (33%) and chest pain (7%); 15% were asymptomatic. The chest X-ray findings, evident in most patients when first seen, consisted of masses (22 cases), infiltrates (31) and pleural effusions (19). More than half of the patients had two or more of these manifestations. The pulmonary lesions contained small lymphocytic and plasmacytoid cells with few mitotic figures typical of WMG. These cells were restricted to interalveolar and interlobular septa in some cases, while in others they formed cohesive masses which obliterated the normal pulmonary architecture. Similar cells were also observed to infiltrate the mucosa and submucosa of the bronchi. It is noteworthy that the tumour mass showed a viscid and glossy appearance with uniform texture as described in the present and Strunge's cases. This seems to reflect the hyperviscosity of macroglobulin secreted from the tumour cells.

Pulmonary involvement in WMG is clearly not rare. When symptoms of respiratory illness appear in patients with WMG, pulmonary involvement should be suspected in addition to infections. Prompt recognition and appropriate treatment may prevent the increasing morbidity from pulmonary dysfunction.

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