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CASE REPORT

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Bronchiolar disease associated with gold compounds administration in a patient with rheumatoid arthritis

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Abstract We report the case of a female patient with rheumatoid arthritis (RA) treated with gold sodium thiomalate and auranofin who developed bronchopulmonary involvement. Chest X-ray films showed diffuse mottled infiltrates and bronchial wall thickness in both lungs. Computed tomography revealed opacities along the thickening of the bronchovascular bundles. The pathologic findings were indistinguishable from those of diffuse panbronchiolitis. After discontinuation of gold compounds and initiation of steroid administration, her subjective symptoms immediately subsided. We conclude that our patient, who had suffered from chronic sinusitis and had a predisposition to bronchiolar disease, had bronchiolar disease induced by gold compounds.

Key words Bronchiolar disease · Diffuse panbronchiolitis · Disease-modifying antirheumatic drugs (DMARDs) · DMARDs-induced pulmonary injury · Gold compounds · Rheumatoid arthritis (RA)

Introduction

Reports of respiratory involvement in patients with rheumatoid arthritis (RA) include pleural disease, interstitial fibrosis, small airway disease, nodular lung disease, arteritis, and chest infections. Respiratory involvement is often induced by disease-modifying antirheumatic drugs (DMARDs). Gold compounds are often used as DMARDs, and intramuscularly injected gold sodium thiomalate (GST) and oral formulations of auranofin, in particular, are commonly administered in Japan. Adverse effects associated with gold compounds include rashes, renal dysfunction, cytopenia, and interstitial pneumonia. When respiratory injury appears in RA patients receiving gold compounds, it is often debated whether it is caused by the disease or drugs, although some diagnostic criteria for gold-induced interstitial lung disease are proposed. We report herein a case of bronchiolar disease in an RA patient induced by gold compounds.

Case report

A 60-year-old woman presented to the Department of Orthopedics, Kawasaki Kyodo Hospital in July 1998 with bilateral swelling and pain in her wrist joints. She had also experienced bilateral arthralgia in her knees and received intrajoint injection of drugs by an orthopedist at her neighborhood clinic approximately 1 year earlier. She had morning stiffness as well as bilateral joint space narrowing and erosion of her wrist joints visible on X-ray films. Laboratory blood tests revealed an erythrocyte sedimentation rate of 80 mm/h, C-reactive protein 1.3 mg/dl, and rheumatoid factor titer <40. She was diagnosed with RA and began intramuscular GST. Two months later, when the total amount of GST injected reached 195 mg, rashes appeared on her skin. Auranofin administration was initiated to replace GST. Over 2 months later, she developed cough and dyspnea on exertion, and her chest X-ray revealed diffuse, mottled infiltrates and bronchial wall thickness in both lungs (Fig. 1). She was admitted to the Department of Internal Medicine, Kawasaki Kyodo Hospital on November 27, 1998. Her medical history included chronic sinusitis, for which she underwent surgical treatment when she was 20 years old. She had no history of smoking.

Physical examination revealed the following: body temperature 36.9°C, blood pressure 130/90, and pulse rate 94/min. Auscultation of the lungs revealed coarse crackles

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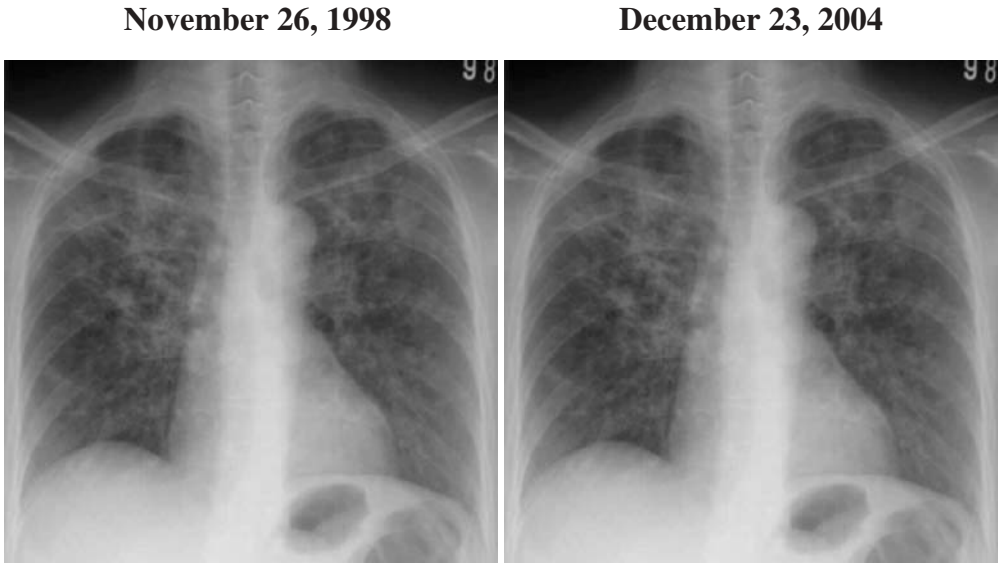

Fig. 1. Posteroanterior chest X-ray at admission (November 26, 1998) shows diffuse mottled infiltrates and bronchial wall thickness in both lungs. These findings were to improve within 1 month

in the right upper field of her back, and bilateral mild swelling of the hands and knee joints was observed.

Laboratory test results were as follows: white blood cell count 5200/μl (75.7% neutrophils, 18.1% lymphocytes, 3.8% monocytes, 1.2% eosinophils, 1.2% basophils), red blood cell count 449 × 10^4μl, hemoglobin value 12.7 g/dl, platelet count 315000/μl, erythrocyte sedimentation rate 65 mm/h, and normal transaminase and lactate dehydrogenase. Additional laboratory values included C-reactive protein 0.6 mg/dl, IgG 2144 mg/dl, IgA 367 mg/dl, IgM 89 mg/dl, IgE 277 U/ml (normal range <250 U/ml), rheumatoid factor <40, antinuclear antibody titer 1:160 with a speckled pattern, cold agglutination 1:32 (within normal range), and anti-human T lymphotropic virus type I antibody negative. Sputum cultures were negative for bacteria and fungi. Oxygen saturation was 98% in room air. Pulmonary function tests revealed a forced vital capacity (FVC) of 1.73 l (% predicted 60.8) and a forced expiratory volume in 1 s (FEV_1) of 0.50 l (FEV_1/FVC 28.9%), which was indicative of a restrictive and severe obstructive ventilatory defect.

Chest computed tomography (CT) revealed opacities along the thickening of the bronchovascular bundles and centrilobular, rounded areas of attenuation. Their distribution was diffuse but occurred predominantly in the upper lung field and sparing subpleura (Fig. 2).

The lung specimens for histological examination were obtained by thoracoscopic lung biopsy of the right S6 and S10, fixed in 10% formaldehyde using inflation apparatus, and stained with hematoxylin–eosin (H&E) and elastica van Gieson (EVG) stains. The primary lesion was located in the low magnification area shown in Fig. 3a. The bronchiolar walls were thickened by infiltration of mononuclear cells and fibrosis. Accumulation of foamy cells was observed in the alveoli around the thickening bronchiole at higher magnification (Fig. 3b).

We discontinued gold therapy and administered prednisone 30 mg daily. Subsequently, the patient's symptoms of cough, dyspnea, and polyarthralgia improved. Improvement of radiographic abnormality of her lungs was gradual (Fig. 2). Pulmonary function tests 5 years later revealed a normalized FVC of 2.68 l and an improved FEV_1 of 1.67 l (FEV_1/FVC 62.3%). The prednisone dosage was gradually reduced to the maintenance dosage of 7.5 mg daily. She did not receive erythromycin treatment.

Discussion

Little attention had been paid to the airways in RA until Geddes et al.[1] reported six patients with obliterative bronchiolitis and suggested an association between RA and airway disease. Airway disease including bronchiolitis,[2–4] bronchiolitis obliterans (BO),[1,5,6] bronchiolitis obliterans organizing pneumonia (BOOP),[7] follicular bronchiolitis (FB),[5,8] and diffuse panbronchiolitis (DPB)[9,10] have recently been associated with RA. Some of these cases have occurred in conjunction with penicillamine or gold compound therapy.[1,2,4]

Gold-induced lung disease is difficult to diagnose. Tomioka and King[11] analyzed the literature to define the clinical features and prognosis of gold-induced pulmonary disease and to identify those features that distinguish gold-induced pulmonary disease from RA-induced pulmonary disease. They found that gold-induced pulmonary disease most often followed gold therapy-induced improvement in RA. Features that distinguish gold-induced pulmonary disease from rheumatoid lung disease include female predominance, acute onset, presence of fever or skin rash, absence of subcutaneous nodules or finger clubbing, low titers of rheumatoid factor at onset of lung disease, lymphocytosis in bronchoalveolar lavage fluid (BALF), and alveolar opacities along the bronchovascular bundles on chest CT scan. These authors also found that bronchiolitis accompanied

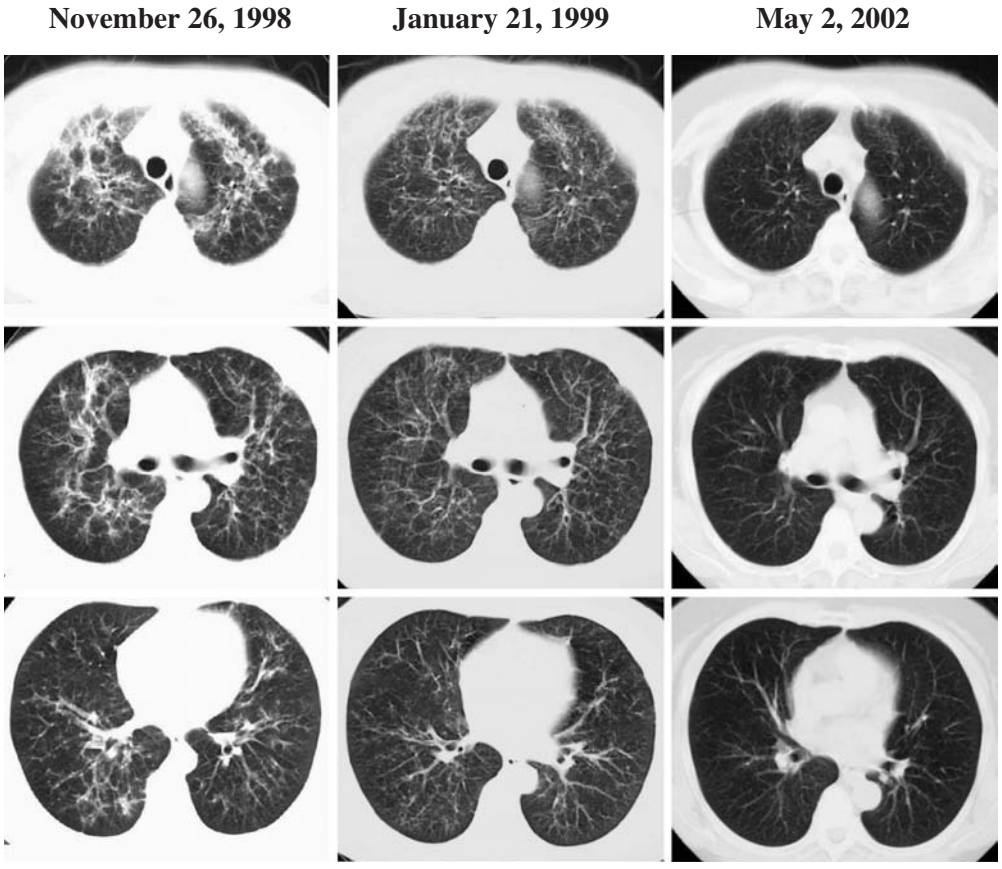

Fig. 2. Time-dependent changes in chest computed tomography (CT). Chest CT at admission (November 26, 1998) shows opacities along the thickening of the bronchovascular bundles. Their distribution was diffuse but occurred predominantly in the upper lung field and sparing subpleura. Gradual improvement of radiographic abnormalities was observed

Table 1. Suggested diagnostic criteria for gold-induced interstitial lung disease

Clinical	
1	Acute onset of dyspnea
2	Recent onset of dry cough
3	Fever (>38°C)
4	Skin rash
5	Absence of finger clubbing
6	Crackles on chest examination
Laboratory	
7	Peripheral blood eosinophilia
8	Positive lymphocyte stimulation testing to gold salts
9	Bronchoalveolar lavage lymphocytosis (≥25%) with a low CD4/CD8 ratio (<1)
Pulmonary function tests	
10	Restrictive pattern or decreased diffusion
Radiological	
11	Interstitial or alveolar opacities on chest X-ray
12	Alveolar opacities along bronchovascular bundles on chest CT
Histopathology	
13	Nonspecific, but useful for exclusion of other pulmonary disease

Probable: ≥9 out of 13 criteria. Possible: 7 to 8 out of 13 criteria. From Tomioka and King[11]

the predominant parenchymal alterations in some cases of gold-induced interstitial lung disease. On the basis of these findings, these researchers proposed criteria for gold-induced interstitial lung disease (Table 1).

Inokuma et al.[12] reported that bucillamine-induced lung injury has characteristic features graphically and in laboratory findings. Pulmonary infiltration occurred primarily in the center of the lung, including the upper and middle fields, on bronchovascular bundles. The mottled dense cotton flower appearance was distinct from the diffuse subpleural infiltration observed in the lower back of RA-induced interstitial pneumonitis. Finally, DMARD-induced injury occurred in DMARD responders.

In our patient, bronchopulmonary involvement was considered to have resulted from gold compounds rather than RA because of the following clinical features: female gen-

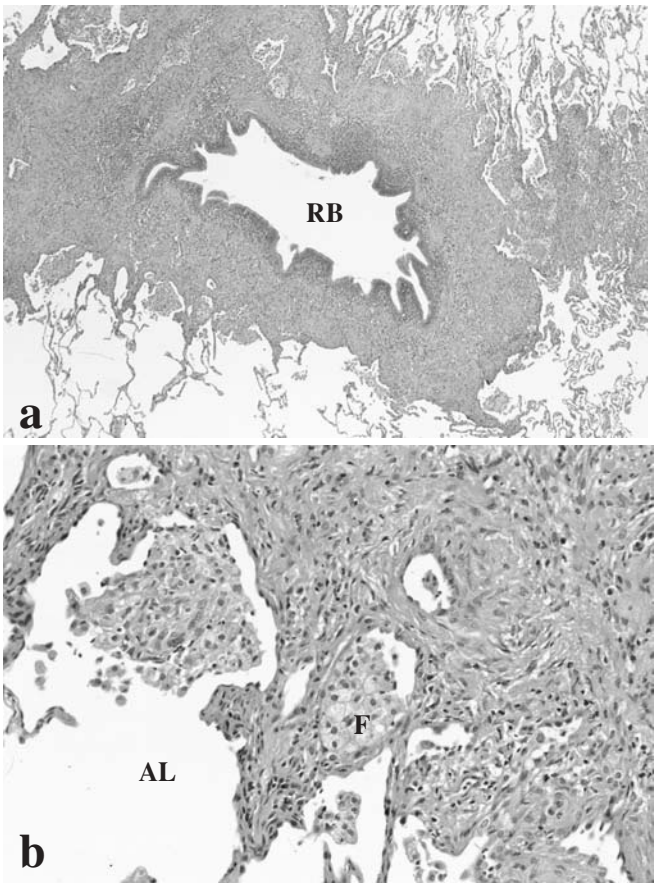

Fig. 3. **a** The walls of the respiratory bronchiole (*RB*) were thickened by infiltration of many lymphocytes, plasma cells, and a few eosinophils, as well as by fibrosis; alveolar spaces are slightly overinflated (H&E, ×4). **b** Focal accumulation of foamy cells can be observed in the alveoli surrounding the thickening bronchiole. *F*, foamy cells; *AL*, alveoli (H&E, ×20)

der, acute onset, presence of skin rash, graphical findings, responder to gold compounds, and low titer of rheumatoid factor. In addition, the patient's subjective symptoms immediately subsided upon prednisone treatment.

Although a prospective study revealed that drug-induced lung disease occurred in 0.003% patients,[13] studies on the prevalence of drug-induced lung disease are scant and an accurate prevalence has not been determined due to the difficulty associated with diagnosing this disease. However, the frequency of identified cases of drug-induced lung disease is increasing, and over 100 drugs are now known to cause lung injury. Pathological patterns of drug-induced lung disease include diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), and BOOP, as well as eosinophilic pneumonia, alveolar hemorrhage, and pulmonary edema, although classification of these patterns remains controversial.[14,15] To our knowledge, no reports of drug-induced lung disease presenting in a DPB pattern have been published to date. The prevalence of gold-induced lung disease in patients receiving such treatment is <1%. Diffuse alveolar damage and NSIP are the most common patterns of gold-induced lung disease, with BOOP being less common.[16]

Diffuse panbronchiolitis is a clinicopathologic entity found primarily in Japan[17,18] and is characterized by chronic recurrent sinopulmonary infection and inflammation. Radiographically, DPB is characterized by diffuse small nodular shadows involving the lungs and mild to moderate hyperinflation.[18] High-resolution CT findings of DPB include centrilobularly distributed, small, rounded areas of attenuation; branched linear areas of attenuation, contiguous with the small rounded areas; dilated airways with thick walls, which are also common outside secondary pulmonary lobes; and decreased lung attenuation in peripheral areas due to air trapping caused by bronchiolar narrowing in the subpleural zones.[19]

Many of the pathologic findings from our patient were similar to those from DPB patients: the walls of the respiratory bronchiole and terminal bronchiole were thickened by infiltration of mononuclear cells, the alveolar spaces were slightly overinflated, and accumulation of foamy cells could be observed in the alveoli surrounding the thickening bronchiole. However, several clinical features also differed from those associated with DPB: lack of sputum, scant centrilobular nodulation and hyperinflation/decreased lung attenuation on chest CT (although no high-resolution CT images were obtained), and improved symptoms following discontinuation of gold therapy and administration of prednisone.

Diffuse panbronchiolitis has been considered to be one of the bronchopulmonary involvements associated with RA, because DPB has been reported to develop after the onset of RA and there have been no reports of DPB associated with connective tissue diseases other than RA.[20] The bronchopulmonary involvement in three RA patients reported by Yamanishi et al.[20] were rather mild compared with those associated with typical DPB: fine nodular shadows were not clear in the upper lung fields and hyperinflation appeared mild on chest X-ray films; the sputum volume was not higher than 50–100 ml/day, which is usually observed in a typical DPB patient; and the extent of FEV_1 reduction was mild and the residual volumes did not exceed 150% of the predicted values.

Hayakawa et al.[21] assessed that DPB- and RA-associated bronchiolar disease were distinct entities because long-term treatment with erythromycin had less effect in RA-associated bronchiolar disease than DPB, and the frequency of human leukocyte antigen (HLA) B54 tended to be higher in DPB than RA-associated bronchiolar disease. Small airway disease is reported to be associated with Sjögren's syndrome; small airway involvement in Sjögren's syndrome is thought to be due to peribronchiolar mononuclear cell infiltrates. In our patient, Sjögren's syndrome was thought to be unlikely due to the lack of complaints of dry eyes and dry mouth, and because of the absence of anti SSA/Ro and anti SSB/La. In conclusion, we feel that our patient, who had suffered from chronic sinusitis and had a predisposition to bronchiolar disease, had RA-associated bronchiolar disease induced by gold compounds.

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