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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.

Keywords 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 intraarticular 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...
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 x 10^6/µl, 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 1s (FEV1) of 0.50 l (FEV1/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 bronchial 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 FEV1 of 1.67 l (FEV1/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. reported six patients with obliterative bronchiolitis and suggested an association between RA and airway disease. Airway disease including bronchiolitis, bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP), follicular bronchiolitis (FB), and diffuse panbronchiolitis (DPB) have recently been associated with RA. Some of these cases have occurred in conjunction with penicillamine or gold compound therapy.

Gold-induced lung disease is difficult to diagnose. Tomioka and King 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