

CASE STUDY

Constrictive bronchiolitis obliterans following gold therapy for psoriatic arthritis

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Constrictive bronchiolitis obliterans following gold therapy for psoriatic arthritis. K.J. Schwartzman, D.M. Bowie, C. Yeadon, R. Fraser, E.D. Sutton, R.D. Levy. ©ERS Journals Ltd.

ABSTRACT: A 41 year old male with psoriatic arthritis developed progressive dyspnoea and airflow obstruction following 4 months of intramuscular gold therapy. Open lung biopsy revealed bronchiolitis obliterans of the constrictive type.

This case suggests a possible aetiological role for gold in the pathogenesis of constrictive bronchiolitis obliterans, or alternatively an association between psoriatic arthritis and this inflammatory airway condition.

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Constrictive bronchiolitis obliterans is an inflammatory disease of the small airways characterized pathologically by fibrosis of the bronchiolar lumina and physiologically by progressive airflow obstruction. Recognized causes include viral respiratory infection, toxic fume inhalation, certain connective tissue diseases, and bone marrow and lung transplantation [1]. Several drugs, including penicillamine [2] and gold [3–5], have also been associated with the disorder. However, reports implicating these agents have often been confounded by the presence of rheumatoid arthritis, which has itself been linked with bronchiolitis obliterans [6]. We report a case of bronchiolitis obliterans of the constrictive type following gold therapy for psoriatic arthritis, a disease which has not previously been associated with this pulmonary condition.

Case report

A 41 year old male presented in July 1992 with a 2 month history of exertional dyspnoea. This was accompanied by a dry cough, without fever, chills, sweats or chest pain. There was no history of antecedent respiratory tract infection, and no one else in the household had been ill.

The patient had developed cutaneous psoriasis in 1982, complicated in 1990 by seronegative oligoarthritis involving the right wrist, elbow, and third proximal interphalangeal joint. By January 1992, there was no improvement despite therapy with nonsteroidal antiinflammatory agents. After test doses of 10 and 25 mg, he began a course of intramuscular gold injections (50 mg weekly). The

gold was discontinued in April because of severe oral mucositis after a cumulative dose of 595 mg. The only medications taken concurrently were sulphasalazine (for a duration of 1 month) and piroxicam, both of which were discontinued in July 1992.

The patient had a 2 pack-year smoking history, having stopped in 1980. He had no allergies. Family history was not contributory. He had worked briefly in a wood furniture factory in 1968. Since then, he had serviced aircraft engines until he became incapacitated by arthritis in 1991. There was no recognized history of exposure to fumes or mineral dusts. He had never travelled outside of North America.

At the time of evaluation in July 1992, respiratory rate was 20 breaths·min⁻¹ and clubbing was absent. Breath sounds were diminished, with diffuse expiratory rhonchi. The third proximal interphalangeal joint of the right hand was swollen, and the right elbow and wrist joints were tender. There was nail-pitting, as well as psoriatic plaques on the legs, arms, shoulders and chest.

Radiograph and computed tomographic (CT) scan of the chest were unremarkable, without hyperinflation or evidence of bullous disease. On July 27, the forced expiratory volume in one second (FEV₁) was 1.46 L (38% of predicted), and the forced vital capacity (FVC) was 3.43 L (73% pred). Residual volume (RV) was 2.85 L (167% pred), functional residual capacity (FRC) 3.52 L (112% pred), and single-breath transfer factor for carbon monoxide (T_{L,CO}) 115% predicted. Rheumatoid factor and antinuclear antibodies were negative. Eosinophil count, immunoglobulin E (IgE) level and alpha₁-antitrypsin level were normal. The patient was human leucocyte antigen (HLA) B27 negative. Joint radiographs

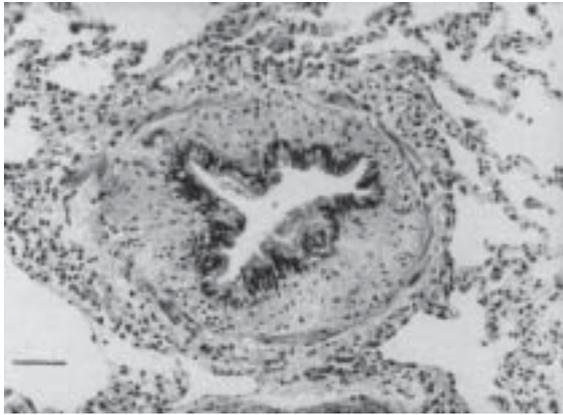


Fig. 1. – Small membranous bronchiole showing mild chronic inflammation and concentric fibrosis of the lamina propria. Haematoxylin and eosin; original magnification $\times 150$, internal bar = 100 μm .

showed only mild loss of the proximal interphalangeal joint spaces in both hands.

The patient was prescribed an inhaled beta-agonist agent as well as prednisone 40 mg daily. After 3 weeks, there was no subjective or objective improvement, and the prednisone was discontinued because of gastrointestinal side-effects. In the ensuing months, he developed progressive dyspnoea, to the point where he could no longer dress without pausing to catch his breath.

By October 1992, FEV₁ had fallen to 0.95 L. Room air arterial blood gas values were pH 7.40, arterial carbon dioxide tension ($P_{\text{a,CO}_2}$) 6.0 kPa, and arterial oxygen tension ($P_{\text{a,O}_2}$) 10.9 kPa. The patient underwent an open lung biopsy. A specimen from the lingula revealed partial obliteration of the bronchiolar lumina by loose fibroblastic connective tissue between the epithelium and the muscularis mucosa (fig. 1). A mild lymphocytic infiltrate was present in the peribronchiolar interstitial tissue and, to a lesser extent, in the airway mucosa. Neither mucosal ulceration nor intraluminal exudate was present. These findings were judged to be consistent with the constrictive type of bronchiolitis obliterans. Very mild nonspecific interstitial pneumonitis was also evident.

In January 1993, the FEV₁ was 0.59 L (15% pred). The patient was prescribed prednisone 60 mg *p.o.* daily and cyclophosphamide 125 mg *p.o.* daily. One month later, the patient's dyspnoea had stabilized, and his FEV₁ was 0.72 L (20% pred). On incremental bicycle exercise testing, he reached 45% of his predicted maximum oxygen consumption, with minute ventilation attaining 89% of the predicted maximum. The prednisone was gradually discontinued, and cyclophosphamide 125 mg *p.o.* daily was continued for the next 6 months. The patient experienced a gradual deterioration and he was placed on a waiting list for lung transplantation in February 1995, when his FEV₁ had fallen to 0.38 L (10% pred).

Discussion

Three previous reports of bronchiolitis obliierans following gold therapy described middle-aged women

with active, strongly seropositive rheumatoid arthritis [3–5]. In these women, progressive dyspnoea and cough began 2–6 months after initiation of gold therapy. Biopsy specimens revealed mucosal ulceration and plugging of small airways by inflammatory exudates.

As in these cases, our patient had no known prior respiratory disease, and symptoms developed after a similar cumulative gold dose. However, our patient differed from those in previously reported cases in several respects. Firstly, unlike other patients, ours had discontinued the gold 1 month before the onset of respiratory symptoms. Secondly, the arthritis in our patient was most likely psoriatic rather than rheumatoid, as it was seronegative, asymmetrical and pauciarticular, and it developed in the presence of cutaneous psoriasis. Finally, the pathological abnormality that we observed was characterized by concentric fibrosis of the lamina propria (constrictive bronchiolitis) [7], a form of bronchiolitis obliterans that differs histologically from that described in the earlier reports, in which there is mucosal ulceration and airway plugging with inflammatory exudate ("ulcerative" bronchiolitis obliterans).

Our patient had also received several other medications which could have been causative. Sulphasalazine has on rare occasions been associated with pulmonary toxicity, primarily fibrosing alveolitis and hypersensitivity pneumonitis [8]. One patient receiving ulphasalazine for ulcerative colitis developed lung disease characterized by bronchiolitis obliterans with features of organizing pneumonia and granulomas, associated with a restrictive ventilatory abnormality [9]. However, bronchiolitis obliterans of the constrictive type with airflow limitation has not previously been associated with sulphasalazine. Similarly, piroxicam has not been associated with bronchiolitis-obliterans despite its widespread use. Therefore, if a drug was responsible for the development of this patient's bronchiolitis obliterans, gold would be the most likely candidate. Although not performed in this patient, studies of lymphocyte transformation to gold with peripheral lymphocytes or those obtained from bronchoalveolar lavage might be helpful in future investigations of the gold/bronchiolitis obliterans association to help establish causality.

This case implicates gold as an inciting factor for bronchiolitis obliterans in the absence of rheumatoid arthritis. However, it remains possible that the patient's underlying psoriatic arthritis was responsible. Both parenchymal and airways diseases have been associated with rheumatoid arthritis as well as several of the seronegative arthropathies [1], although no previous report has associated airway disease with psoriatic arthritis. In one report of a patient with rheumatoid arthritis, successful treatment of bronchiolitis obliterans (and concomitant interstitial fibrosis) with cyclophosphamide and methylprednisolone was also associated with remission of the arthritis [5]. Our patient's arthritis became quiescent with immunosuppressive therapy. His lung disease, however, did not, which suggests that the two processes may not have been directly related in pathogenesis.

Unfortunately, this case provides little insight as to how gold therapy might lead to small airways disease. It

has been suggested that interstitial fibrosis following gold administration represents a type of hypersensitivity pneumonitis, associated in some instances with relative lymphocytosis and inversion of the helper:suppressor lymphocyte ratio in bronchoalveolar lavage fluid [10]. Bronchoalveolar lavage was not performed in our patient, however the peripheral eosinophilia frequently seen in cases of hypersensitivity pneumonitis was absent.

It could be speculated that the oral mucositis which prompted discontinuation of gold was a marker of mucosal damage in the lower respiratory tract. However, the lung biopsy specimen did not reveal mucosal ulceration, suggesting a different pattern of injury. Direct lung toxicity cannot be excluded, although earlier reports regarding the pulmonary effects of gold and penicillamine tend to imply an immune mechanism [2–5].

Unlike gold-induced interstitial pneumonitis, bronchiolitis obliterans of the constrictive type is generally irreversible. Although unproven, the combination of cyclophosphamide and prednisone may serve to stabilize the process [2, 5]. In view of its potentially devastating pulmonary complications, clinicians should carefully pursue respiratory complaints in patients receiving gold therapy.

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