A Patient with Exacerbation of Idiopathic Pulmonary Fibrosis Which was Resolved Probably due to the Coexisting Hyperbilirubinemia?

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OHRUI, T., HIGUCHI, M., KANDA, A., MATSUI, T., SATO, E. and SASAKI, H. A Patient with Exacerbation of Idiopathic Pulmonary Fibrosis Which was Resolved Probably due to the Coexisting Hyperbilirubinemia? Tohoku J. Exp. Med., 2001, 193(3), 245-249 —— This report presents the case of a patient with corticosteroid and cyclophosphamide resistant exacerbation of idiopathic pulmonary fibrosis (IPF), which was definitely resolved in accordance with increased levels of serum conjugated bilirubin due to biliary tract obstruction. Histological examination of the lung showed an accumulation of bile pigments in the alveolar mural tissues, especially in the cytoplasm of the alveolar macrophages, which play crucial roles in the development of IPF. This case suggests that bile pigments have some important roles in tissue protection against inflammatory damage in IPF, and may illustrate an important key for treatment of this fatal disorder. —— alveolitis; reactive oxygen species; conjugated bilirubin; antioxidant activity

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Idiopathic pulmonary fibrosis (IPF) is a devastating illness for which current therapy is minimally effective. IPF is characterized by varying degrees of chronic alveolar epithelial injury and interstitial fibrosis (Crystal et al. 1984). There is evidence for a role of oxidative stress in the pathogenesis of IPF (Strausz et al. 1990; Jack et al. 1996). Reactive oxygen species (ROS) are unstable compounds with unpaired electrons, capable of initiating oxidation. In IPF, ROS are produced by activated immune and inflammatory cells, and play a central part in the progression of the disease (Barnes 1990; Jack et al. 1996). Biliverdin and various physiologically relevant forms of bilirubin are highly potent scavengers of peroxyl

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radicals and it is proposed that bile pigments function as natural antioxidants (Stocke et al. 1987; Nakagami et al. 1993). In the present report, we describe a patient with exacerbation of IPF, which was definitely resolved in accordance with a reduction in serum free radical activity, probably due to hyperbilirubinemia. This case suggests that bile pigments may have some protective roles against inflammatory damage in IPF, and may provide a new strategy for treatment of this fatal disorder.

CASE REPORT

A 78-year-old man was admitted to hospital with a 3-year history of progressive dyspnea and dry cough. His work was sedentary, and there were neither any risk factors of environmental exposure to toxic materials nor any history of hypersensitivity pneumonitis or collagen diseases. On admission, he was cyanotic and afebril with a respiratory rate of 26 per minutes. Bilateral mid-zone crackles and marked clubbing were present. Analysis of arterial blood gas revealed hypoxemia (PaO₂ 52 mmHg), hypocapnea (PaCO₂ 29 mmHg), HCO₃⁻ 21.2 mmol/liter and pH 7.45 under air breathing. Lung function tests showed a reduction in vital capacity of 58% predicted and a normal forced expiratory volume in 1 second of 86% predicted. A chest radiograph (Fig. 1A) and a computed-tomography (CT) scan of the chest (Fig. 2A) showed fine reticulo-nodular shadows in the bilateral middle to lower lung fields. His laboratory tests showed an increase, of the erythrocyte sedimentation rate (75 mm/hour) and a lactate dehydrogenase of 638 IU/liter (normal value <474 IU/liter). A serum desferrioxamine-chelatable iron level, an indicator of free radical activity, was increased to 6.8 nmol·ml⁻¹ (normal range: 0 to 3.8 nmol·ml⁻¹) and a serum level of KL-6, a circulating MUC1 mucin, was increased to 1850 U·ml⁻¹ (normal range: less than 458 U·ml⁻¹). Serum desferrioxamine-chelatable iron levels were assayed as described previously (Jack et al. 1996) in our laboratory and the concentrations of KL-6 in serum were determined by a specific ELISA as described previously (Yokoyama et al. 1998). Microscopic observation of the lung obtained by video-assisted thoracoscopic procedures revealed histologic variation from one low-magnification field to another, with alternating zones of interstitial fibrosis, honeycomb change, and normal lung, which is consistent with usual interstitial pneumonia (Crystal et al. 1984). There were not significant findings compatible with nonspecific interstitial pneumonia/fibrosis.

He received oxygen inhalation and was intensively treated. Despite the increasing concentration of inhaled oxygen, respiratory failure gradually progressed. Thus, we determined to use corticosteroid and immunosuppressive therapy. One mg·kg⁻¹·day⁻¹ of pred-

![Fig. 1. Chest radiographs before (A) and after (B) obstructive jaundice.](image)
nisolone and \(2 \, \text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}\) of cyclophosphamide were orally administered for 6 weeks. However, his condition further deteriorated. Any other disorders contributing to progressive hypoxemia such as heart failure, fluid overload or nosocomial pneumonia were not present. Treatment with prednisolone and cyclophosphamide was continued until 9 weeks after the admission. About 8 weeks after the admission, he began to suffer from jaundice. His laboratory test showed increased serum levels of total bilirubin 4.8 mg/100 ml (normal range, 0.2–1.2 mg/100 ml), alkaline phosphatase (ALP) 1808 U/liter (normal range, 112–330 U/liter), glutamic oxaloacetic transaminase (GOT) 118 U/liter (normal range, 12–30 U/liter), and glutamic pyruvic transaminase (GPT) 165 U/liter (normal range, 8–35 U/liter). An abdominal CT scan showed a tumor of the pancreas head, but the patient did not opt for further examinations or treatment for the abdominal lesion. Nine weeks after the admission, when the serum total bilirubin level reached 6 mg/100 ml of which 96% was conjugated, his respiratory condition rapidly improved (Fig. 3) and the prednisolone tapering was started. Despite

Fig. 2. Computed tomography (CT) scans of the chest before (A) and after (B) obstructive jaundice. R indicates the right side.

Fig. 3. Time course of serum total bilirubin and \(\text{PaO}_2\) after admission. Open circles indicate concentrations of serum total bilirubin and closed circles indicate \(\text{PaO}_2\) values measured under air breathing.
the reduction of inhaled oxygen, prednisolone was tapered to 10 mg daily and with the cessation of the administration of cyclophosphamide, an improvement in blood gas analysis was obtained (pH 7.406, PaO₂ 87 mmHg, PaCO₂ 37.4 mmHg, and HCO₃⁻ 23.0 mmol/liter under air breathing). Diffuse bilateral reticulonodular infiltrates were obviously resolved on the chest radiograph (Fig. 1B) and CT scan (Fig. 2B). The serum total bilirubin levels fluctuated between 8 and 10 mg/100 ml and his improved respiratory condition was maintained thereafter. Serum levels of desferrioxamine-chelatable iron and KL-6 decreased to 3.6 nmol·ml⁻¹ and 412 U·ml⁻¹, respectively.

Six months after the admission, he died of hepatic failure. Postmortem examination showed the existence of carcinoma of the pancreas head along with bile stasis of the liver, and marked dilation of the choledochus and gallbladder. Microscopic observation of the lung revealed the accumulation of the bile pigments in the intraalveolar and alveolar mural tissues, especially in the cytoplasm of the alveolar macrophages (Fig. 4). Findings of active alveolitis and mural inflammation were minimal.

**DISCUSSION**

The prognosis of acute exacerbation of IPF is considered to be grave, especially in cases not responding to corticosteroid and immunosuppressive therapy (Hiwatari et al. 1994; Chang-Yeung and Müller-Quernheim 1997). The present case appears to be the first report to resolve the exacerbation of IPF during obstructive jaundice, although corticosteroid and immunosuppressive therapy was ineffective. The precise mechanism for this effect is unclear, but one possible mechanism is through hyperbilirubinemia and its antioxidant activity. In IPF, the inflammatory cells are mainly composed of alveolar macrophages and neutrophils, and they have been reported to be capable of releasing oxygen metabolites (Barnes 1990; Strausz et al. 1990; Jack et al. 1996). Thus, it is likely that the oxidant burden at the alveolar epithelial surface is increased.

Bile pigments may have potent antioxidant (Stocker et al. 1987) and anticomplement activity (Nakagami et al. 1993), and may represent an endogenous protective mechanism against the tissue damage that occurs during inflammation. In this patient, the exacerbation...
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...tion of IPF was resolved and a serum level of desferrioxamine-chelatable iron, which is related to clinical disease activity (Jack et al. 1996), was decreased to normal range in association with an elevation of serum conjugated bilirubin. Furthermore, bile pigments were mainly deposited in the alveolar mural wall and were phagocytized by alveolar macrophages, around which findings of active inflammation were minimal. According to the present case, the beneficial effect of serum bilirubin might be achieved at a concentration higher than 6 mg/100 ml, which is comparable to the bilirubin concentrations showing antioxidant effect in vitro experimental data (Stocker et al. 1987; Nakagami et al. 1993).

Recently, there have been several reports describing the effects of various types of antioxidant agents or free radical scavengers on the progression of pulmonary fibrosis. A previous report showed that dimethyl sulfoxide (DMSO), a putative anti-inflammatory agent and free radical scavenger, had no effect on bleomycin or butylated hydroxytoluene-induced pulmonary toxicity in the rat and mouse (Haschek et al. 1989). Another study demonstrated the inhibitory effects of a lecithinized superoxide dismutase on bleomycin-induced pulmonary fibrosis in mice (Tamagawa et al. 2000). Our case suggests that serum bilirubin and its metabolites have some important roles in tissue protection against inflammatory damage in IPF, and that agents that possess antioxidant properties might be useful for the treatment of exacerbation of IPF.

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References


