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MARKED PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL PNEUMONITIS INDUCED BY GOLD THERAPY

(gold therapy/interstitial pneumonitis/pulmonary hypertension)

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We describe a case of pulmonary injury and pulmonary hypertension induced by gold therapy. To our knowledge, this is the first report of pulmonary hypertension due to gold therapy. In this case, type 4 allergic reaction to gold sodium thiomalate is evidenced, pulmonary hypertension decreased gradually with oxygen therapy, and pulmonary injury was improved with corticosteroids. In patients with gold therapy, great attention must be paid to gold-related pulmonary injury and pulmonary hypertension.

Reports of diffuse pulmonary injury, interstitial pneumonitis, associated with gold therapy are not so rare, but there has been no report of pulmonary hypertension in interstitial pneumonitis due to gold therapy.

We report a patient in whom interstitial pneumonitis and marked pulmonary hypertension developed during gold therapy, and marked improvement was seen with corticosteroids.

A 67-year old woman was admitted to the hospital because of severe dyspnea and edema.

Rheumatoid arthritis had been diagnosed a few years ago. The condition had been non-symptomatic until April 1982, when the routine chest X-ray film was normal. She developed arthralgia at her wrists bilaterally in May 1982, and gold (sodium thiomalate) was started. Three weeks later, when she had received 150mg of gold, she had a dry cough and breathlessness on exertion. Gold was administered to an amount of 240mg in total doses, but was stopped because she developed severe progressive cough, dyspnea

and edema, she was then admitted to this hospital.

The body temperature was 37.8°C, respiration rate 24/min, pulse rate 88/min and regular, and blood pressure 134/80 mmHg. Marked edema was noted on her whole body, but cyanosis was not noted. No deformity of joints was found. Chest examination detected bilateral basal impaired resonance and scattered coarse moist rales. In cardiac examination, pulmonary component of the second heart sound was accentuated and a Grade 2 systolic murmur was audible at the left sternal border. Examination of the abdomen disclosed a tender liver edge 3 fbs below the right costal margin, with a vertical span of 15 cm. The spleen was not palpable.

The urine was normal. The hemoglobin was 7.2 g/dl, hematocrit 32.8 %, the white cell count 11,000/mm^3, with 3 % bands, 75 % neutrophils, 15 % lymphocytes, 5 % monocytes and 6 % eosinophils. The platelet count was 167,000/mm^3, and the erythrocyte sedimentation rate was 120 mm/hour. The urea nitrogen was 30 mg/dl, and the serum protein was 6.5 g/dl (the albumin 3.0 g/dl and the globulin 3.5 g/dl). The serum glutamic oxalacetic transaminase (SGOT) was 934 IU/dl, the serum glutamic pyruvic transaminase (SGPT) 547 IU/dl, and the lactic dehydrogenase (LDH) 7,400 IU/dl. A specimen of arterial blood, drawn from the patient under room air breathing, disclosed that the partial pressure of oxygen (PaO_2) was 32 mmHg, the partial pressure of carbon dioxide ($PaCO_2$) 28 mmHg and PH 7.52. An electrocardiogram demonstrated a normal rhythm at a rate of 86 and a mean QRS axis of -60°; P waves were prominent in Leads II, III, aVF and V_1; the ST segments were depressed in Leads V_4 through V_6; T waves were inverted in Leads V_2 through V_6. X-ray film of the chest (Fig 1.(A)) showed bilateral diffuse interstitial shadow and cardiomegaly (CTR 68 %). An echocardiogram revealed considerable enlargement of the right ventricle; the pulmonic valve showed a flat diastolic slope, with a very steep opening, a midsystolic notching of the leaflet and a poor A wave; the E-F slope of the mitral valve was diminished; the aortic valve and the aortic root appeared normal; the left ventricle was normal (LVD(D) 41mm : LVD(S) 26mm) and had an ejection fraction of 74 %; the septal movement did not appear paradoxical; pericardial effusion was not present. Pulmonary function test indicated a combined disturbance, the forced vital capacity was 0.47 l/min (21 % predicted) and the

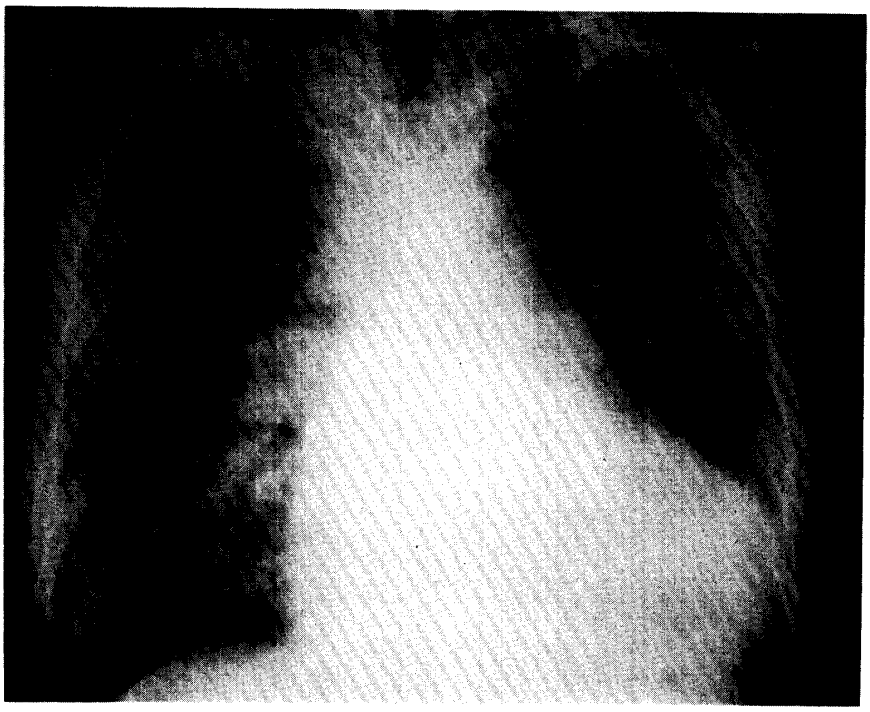

Fig.1.(A) X-ray Film of the chest on admission, showing diffuse interstitial infiltrate with no evidence of pleural disease.

Table I. A SPECIMEN OF ARTERIAL BLOOD AND PULMONARY ARTERIAL PRESSURE AFTER ADMISSION

	1 day*		2 day*	3 day*	4 day*
PH	7.52	7.46	7.44	7.53	7.47
$PaCO_2$ (mmHg)	28	33	33	29	33
PaO_2 (mmHg)	32	78	100	50	74
Inhalation** Oxygen(L/min)	room air	4	8	5	4
PA mean (mmHg)	50	48	45	35	23

* : hospital day
** : by nasal prong

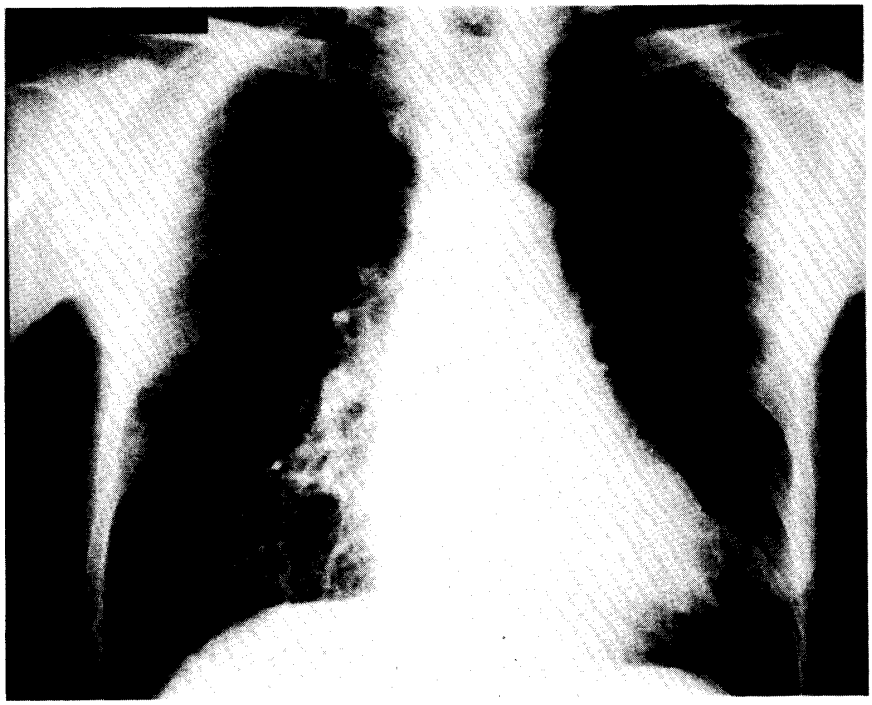

Fig.1.(B) X-ray Film of the chest after steroid therapy.

forced expiratory volume 1 second was 0.28 l. Right cardiac catheterization showed that the pulmonary capillary wedge mean pressure was 6 mmHg, the pulmonary arterial pressure 68/31 mmHg, with the mean pressure of 50 mmHg, the right ventricular pressure 68/8-15 mmHg and the right atrial mean pressure 15 mmHg. Perfusion scan of the lung fields with ^{99m}Tc macroaggregated albumin showed normal perfusion.

Furosemide of 40 mg oral dosage daily and oxygen were started. On the fourth hospital day the pulmonary arterial pressure decreased, the pulmonary arterial pressure was 32/8 mmHg and the pulmonary capillary wedge mean pressure 6 mmHg (Table I). Edema decreased, but dyspnea and cough continued and hypoxemia also remained (PaO_2 51 mmHg under room air breathing). On the eighth hospital day prednisolone was added (60 mg daily), and then symptomatically gradual improvement was noticed. On the eleventh hospital day a specimen of arterial blood disclosed that PaO_2 was 56 mmHg, PaCO2 38 mmHg, the PH 7.48 under room air breathing. On the twentieth hospital day the patient was

asymptomatic, X-ray film of the chest was almost normal except for mild cardiomegaly (CTR 53 %) (Fig 1.(B)) and a specimen of arterial blood gas was normal, PaO_2 84 mmHg, $PaCO_2$ 42 mmHg and the PH 7.45 under room air breathing. Prednisolone therapy was successfully discontinued after twenty weeks. Pulmonary function became normal. After six months, cardiac catheterization showed that the pulmonary capillary wedge mean pressure was 4 mmHg, the pulmonary arterial pressure 18/4 mmHg, with the mean pressure of 11 mmHg, the right ventricular pressure 18/2 mmHg, the right atrial mean pressure 2 mmHg and the cardiac index 2.9 l/min/m^2. The patient remained well during two years of observation.

DISCUSSION

Pulmonary injury associated with gold therapy was firstly reported by Savilahti in 1948 (1), from when there have been 43 reports up to 1985. However there has been no report of pulmonary hypertension associated with gold therapy. We believe that this was the first case in which pulmonary injury with pulmonary hypertension and acute right ventricular heart failure was caused as a result of gold therapy. There are, however, two problems that should be discussed.

Firstly, we must differentiate pulmonary injury due to gold from that due to rheumatoid arthritis itself, because interstitial pulmonary injury with pulmonary hypertension have been reported in association with rheumatoid arthritis (2-4). Judging from following evidence, 1) the occurrence was in a patient without an active rheumatoid arthritis condition, 2) the clinical course improved on withdrawal of gold and with corticosteroids, 3) a normal X-ray film of the chest and pulmonary function, and 4) LMIT (Leucocyte Migration Inhibition Test) using gold sodium thiomalate as an antigen showed significant inhibition (migration index 0.424) (Fig. 2. (A), (B)), we concluded that pulmonary injury in this patient was due to gold. The pathogenesis has been controversial until now, but the positive LMIT suggests that a type 4 allergic reaction might play some role on the mechanism of pulmonary injury associated with gold.

Secondly we must negate left-sided heart failure as a cause of the pulmonary hypertension. The right-sided cardiac catheterization study at admission disclosed elevation of the pulmonary arterial pressure and evidence of right ventricular

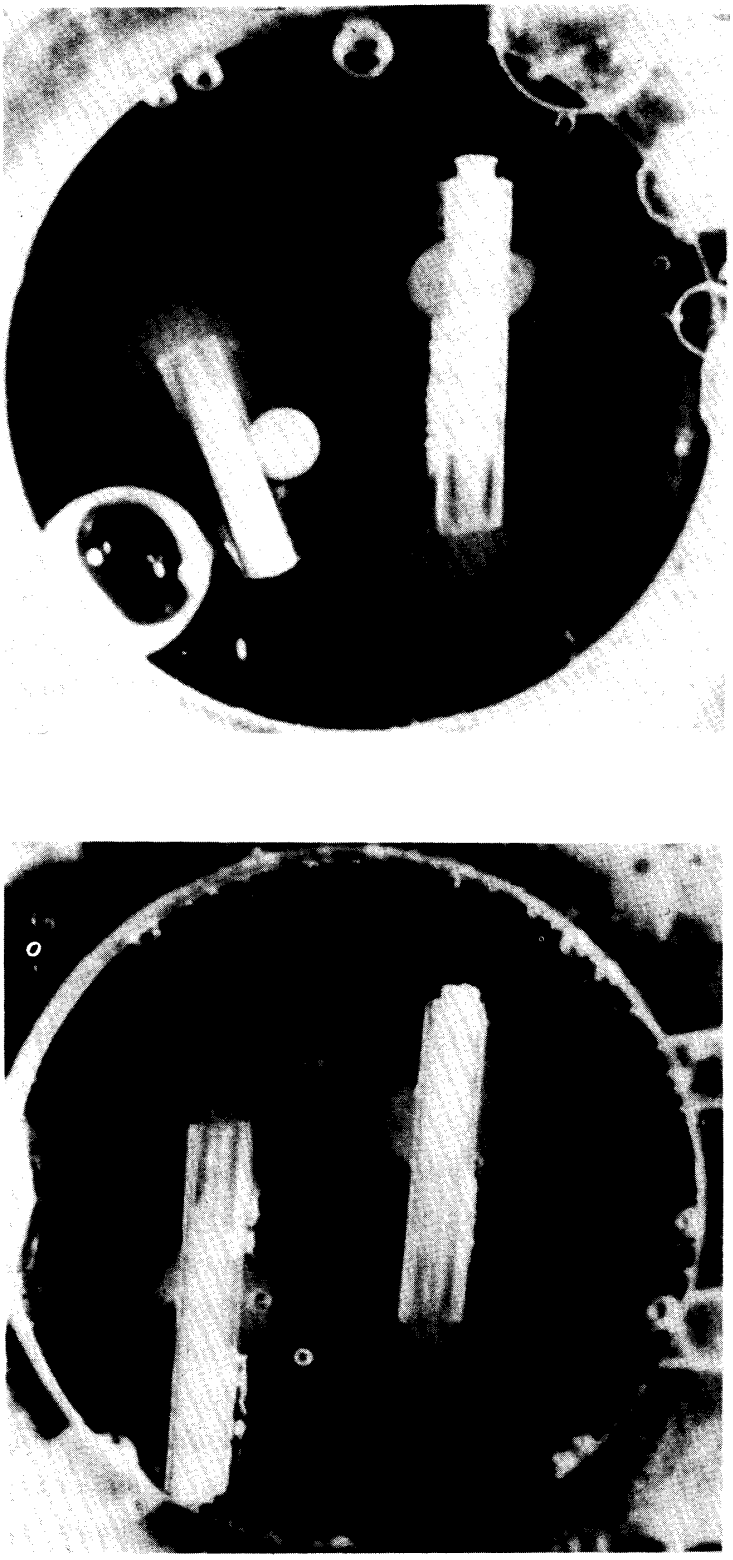

Fig.2. A leucocyte migration inhibition test with capillary method was performed using goldsodim thiomalate (10 to 100 μg/ml) as antigen. The mean migration was 53 mm^2 (8 x 8 and 7 x 6) with 10 μg/ml of gold sodium thiomalate (2-B), while it was 125 mm^2 (13 x 10 and 12 x 10) in the control without antigen (2-A). The migration index was 0.424, which revealed significant migration inhibition as a delayed type hypersensitivity.

failure. The pulmonary capillary wedge mean pressure, reflecting left-sided heart failure, was normal. The echocardiogram revealed considerable enlargement of the right ventricle and elevation of the pulmonary arterial pressure. The left ventricle was not enlarged in hyperkinetic state. The hyperkinetic movement could be thought to be due to hypoxia and anemia. These findings are indicative of pulmonary hypertension due to pulmonary disease itself, in contrast to pulmonary hypertension secondary to left-sided heart failure.

The mechanism of the elevation of pulmonary arterial pressure in interstitial pulmonary injury has been, hitherto, unknown. In this case, the pulmonary arterial pressure gradually decreased after oxygen inhalation, therefore we thought that the pulmonary vasoconstriction induced by hypoxemia could play an important role in the elevation of pulmonary artery pressure (5-7). Pulmonary embolism could be excluded from the normal perfusion radiography.

In summary, we urge that great attention must be paid to patients on gold therapy in relation to gold-related pulmonary injury and pulmonary hypertension, and therefore right-sided catheterization should be recommended.

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