Short reports

Lung fibrosis induced by Thorotrast

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Abstract

A 63 year old woman developed progressive shortness of breath, pulmonary hypertension, and respiratory failure and died from pulmonary fibrosis 45 years after thoracic fistulography with Thorotrast. Bouts of acute respiratory failure occurred with features of non-cardiogenic pulmonary oedema. Lung tissue obtained by biopsy and at necropsy showed abundant radioactive particles of thorium dioxide in the lungs. The particles were congregated in the walls of blood vessels and in perivascular fibrous zones, consistent with a causal role of Thorotrast in the development of lung fibrosis. It is suggested that the fibrosis was due to the combined effects of alpha radiation on the interstitial perivascular zones and of recurrent pulmonary oedema due to endothelial damage.

Thorotrast, which contains radioactive thorium dioxide and was used formerly as a contrast material, has been shown to cause malignant tumours and fibrotic lesions at the sites of injection and in the reticuloendothelial

system.¹⁻⁵ Except for isolated cases of lung cancer,^{2,6} the lungs have not been considered to be specifically injured by Thorotrast. We report a case of lung fibrosis causing death 45 years after thoracic fistulography with Thorotrast.

Case report

At the age of 18, in 1940 during the second world war, our patient sustained extensive shrapnel wounds to the back of her chest. She required drainage of bilateral haemothoraces and during her hospital stay an unknown amount of Thorotrast was injected to outline thoracic fistulas. She recovered fully and led a normal life in Canada from 1945 until 1977. She smoked about 20 cigarettes a day and worked as a bank employee. Since 1978, however, she had increasing dyspnoea and reduced effort tolerance and in 1983 was admitted to hospital in Vancouver with severe breathlessness and hypoxaemic respiratory failure. Chest radiographs showed transient alveolar infiltrates and Kerley B lines, consistent with pulmonary oedema.

On her return to Belgium in September 1983 physical examination showed bilateral posterior thoracic scars and inspiratory basal crackles. Chest radiographs showed radio-opaque tracks of blind fistulas in the mid zones and a diffuse reticular pattern predominant in the lower lung fields (fig 1). Lung function tests showed a restrictive ventilatory defect—forced vital capacity (FVC) 1.44 (predicted 2.73) litres, total lung capacity (TLC) 3.02 (predicted 4.36) l—and a low single breath carbon monoxide transfer factor of 2.8 (predicted 7.7) mmol min⁻¹ kPa⁻¹ l⁻¹. Arterial blood gas tensions in room air were: pH 7.37, carbon dioxide tension 5.3 kPa, oxygen tension 7.3 kPa. Right heart catheterisation showed an increased pulmonary artery pressure (45/20, mean 35 mm Hg) with a normal wedge pressure and cardiac output. Bronchoalveolar lavage yielded 38.7×10^6 cells with a normal differential count. There had been no chronic drug intake, no occupational dust exposure, and no domestic exposure to birds or moulds. Other investigations (including tests for autoantibodies) gave normal results apart from a haemoglobin concentration of 18.2 g/dl and a serum potassium concentration of 3.3 mmol/l. In autumn 1983 the patient had a sudden exacerbation with hypoxaemia and radiographic signs of pulmonary oedema. At open lung biopsy through a left thoracotomy almost complete pleural fusion was noted. Histological examination showed subpleural fibrosis, particularly in relation to blood vessels within the lung parenchyma (fig 2a). Transparent refractile irregular particles were easily detected in the fibrous zones (intermingled with anthracotic

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Figure 1 Chest radiograph showing a radio-opaque track in the right mid zone.

Figure 2 (a) Histological section of the lung biopsy specimen showing perivascular and interstitial fibrosis with particulate deposits (scale bar 100 μm). (b) Histoautoradiograph of the lung biopsy specimen showing short and straight tracks indicating alpha emission from particles of thorium dioxide.

pigment) and in the walls of small vessels in both giant cells and endothelial cells, suggesting that they had passed through the vessels. The pulmonary arteries had normal or mildly thickened media but no signs of veno-occlusive disease, our presumed diagnosis. Only supportive treatment was given.

The patient returned to Canada and died in October 1985. Necropsy confirmed severe pulmonary fibrosis, with acute bilateral pneumonia as the immediate cause of death; mild hepatic cirrhosis was also present. Mineralogical and autoradiographic studies were performed on a lung biopsy sample and on lung, liver and spleen necropsy samples. In the lung biopsy specimen histoautoradiography showed abundant short and straight tracks typical of alpha emission from the refractile particles (fig 2b). These were identified as thorium particles (0.1–20 μm in diameter) by analytical electron microscopic studies using an x ray dispersive spectrometer. Autoradiography of digested necropsy samples showed 131 370 emissions of radioactivity a day per gram of dry lung tissue, 135 822 from liver tissue, and 577 548 from spleen tissue. A cumulative radiation dosage was extrapolated from these data on the following basis:⁷ an energy value of 4 MeV for alpha emission by thorium, a quality factor of 15 for alpha emission, a conversion factor of 6242.10 for the transformation of MeV into rads, an exposure of 16 425 days (45 years), and a dry:wet weight ratio of 0.1. The calculated dose is about 210 rem (2.1 Sv), or 14 rad (0.14 Gy).

Discussion

Thorotrast has been associated with long term complications, particularly malignant tumours developing either near injection sites (thorotrastomas) or in the reticuloendothelial system. Thorium dioxide is retained in the reticuloendothelial system, from which it emits

alpha particles in great quantities over prolonged periods.^{13,14} Fibrosis has also been found frequently near the injection sites as a result of extravasation in subcutaneous tissue⁸ as well as in the reticuloendothelial system. Thus liver cirrhosis, fibrosis of the spleen, and myelofibrosis may occur.⁹

Our patient died from lung fibrosis 45 years after the injection of Thorotrast into her thoracic fistulas. Several features are consistent with a causal role of thorium in the induction of her lung fibrosis. The first is the presence of abundant thorium dioxide particles in the lung sections, particularly in the fibrous zones and in the vascular walls. Histologically, the perivascular fibrosis suggests that the offending agent may have entered the lungs via the bloodstream. It is conceivable that radioactive thorium particles within the endothelial cells of the pulmonary capillaries could lead to modification of their permeability, and thus explain the episodes of non-cardiogenic pulmonary oedema. Lung fibrosis may result from chronic or recurrent pulmonary oedema, as in mitral stenosis.¹⁰

In addition, radiation is a well known cause of lung fibrosis and Thorotrast has been implicated in the development of fibrosis in other organs. Determination of the radiation dose to a target tissue is difficult,^{5,11} and calculation of the total cumulative radiation dose to the lungs is impossible because the initial injected doses and the change in thorium dioxide concentration in the lung parenchyma over 45 years are not known. The doses to tissues adjacent to the surface of Thorotrast aggregates, however, are considered to be very high,¹² and this is supported by the appearances of the autoradiographs of the lung sections from our patient.

There were no occupational, environmental, or drug related causes for lung fibrosis and no apparent systemic disease. We infer therefore that Thorotrast was the cause of the lung fibrosis. We can find no previous reports of

lung fibrosis due to Thorotrast despite the many thousands of patients injected with it.^{2,3,9} The type of injection (thoracic fistulography), however, appears to have been rare. Among 168 patients described by Boyd *et al*³ who received Thorotrast, 141 had intra-arterial injections and 27 cerebral ventricular or sub-arachnoid injections.

Particles were found in the liver and spleen of our patient and microscopy of the lung tissue suggested transendothelial passage. Probably thorium particles were resorbed by lymphatics from the tissue around the fistulas and passed into the bloodstream. The presence of thorium particles in the blood vessel walls suggests that this "embolisation" process was continuing at the time of lung biopsy, which is consistent with the episodes of pulmonary oedema that characterised our patient's illness. It is also possible that thoracic lymphatic drainage was impaired by adhesions between the parietal and visceral pleura, and by obstruction due to thorium induced fibrosis¹³ in thoracic lymph nodes, thus reducing the clearance of lung particles and increasing their retention in the interstitium of the lung.

We conclude that lung fibrosis should be considered as a late complication of thoracic fistulography with Thorotrast.

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Adult respiratory distress syndrome after limited resection of adenocarcinoma of the lung

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Abstract

Two cases of the adult respiratory distress syndrome developed after limited resection for lung carcinoma. No other known precipitants were evident. The adult respiratory distress syndrome is a clinical expression of acute lung injury¹ that may arise from various insults and include air and blood borne factors.² Tumour related blood borne factors may have contributed to lung injury in these cases.

Case reports

CASE 1

A 71 year old woman with a history of obstructive airways disease underwent resec-

tion of a mass in the right lung. Preoperative pulmonary function tests showed a one second forced expiratory volume (FEV₁) of 0.96 litres (60% predicted) and a forced vital capacity (FVC) of 1.62 l (70% predicted). When she was breathing air her pH was 7.40, arterial carbon dioxide tension (Paco₂) 4.0 kPa, and arterial oxygen tension (Pao₂) 8.5 kPa. No evidence of mediastinal disease was seen on a chest computed tomogram or at mediastinoscopy. Right upper and middle lobectomies were performed. She was extubated without difficulty two days later. On the third post-operative day she developed mild dyspnoea. This rapidly progressed in severity and diffuse bilateral alveolar infiltrates were noted on her chest radiograph.

Her temperature was 38°C and white blood cell count $12.2 \times 10^9/l$ (90% segmented forms, 4% lymphocytes, 3% band forms, and 3% monocytes). Arterial blood gas analysis while she breathed oxygen (fractional inspired oxygen (Fio₂) 60%) showed: pH 7.40, Paco₂ 5.3 kPa, and Pao₂ 4.9 kPa. She was intubated; urine, blood, and sputum were cultured; and empirical treatment with gentamicin and mezlocillin was started. Pulmonary capillary wedge pressure was 8 mm Hg and cardiac output was 5.90 l/min. Bronchoscopy showed scanty mucus in the left lower lobe bronchus and an intact anastomotic site. She did not respond to treatment and died on the seventh postoperative day. At necropsy the lung showed changes consistent with the adult respiratory distress syndrome with no

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