Pulmonary granulomatous reaction: talc pneumoconiosis or chronic sarcoidosis?

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ABSTRACT A chronic pulmonary granulomatous reaction was associated with an almost identical clinical picture in two patients exposed to talc. In both patients lung biopsy showed the deposition of talc particles and a heavy granulomatous reaction. At the time of diagnosis the Kveim test result was negative in both patients, urinary calcium excretion was normal, and there were no extrapulmonary manifestations and no response to steroid treatment. These findings point against sarcoidosis. The serum angiotensin-converting enzyme level, however, was raised in both patients. It was concluded that the patient who was exposed to talc in the rubber industry had a true talc pneumoconiosis. The other patient, who was exposed to cosmetic talcum powder, suffered from chronic sarcoidosis with talc deposition in the lungs, since an enlarged axillar lymph node containing granulomatous inflammation was discovered after two years' follow up. These cases show that it may be extremely difficult to differentiate between chronic sarcoidosis and talc pneumoconiosis even after careful clinical and histological analysis.

True talc is a hydrous magnesium silicate. Depending on where it is mined, commercially available talc also contains varying amounts of asbestos minerals which form chains or fibres and may therefore have an asbestos like effect on the lungs. Owing to the widespread industrial and private use of talc and talcum powder much interest has been directed to the biological effects of this mineral, which have been reported to cause pneumoconiosis in people employed in talc mills and talc mines, and in workers using talc in production processes—for example, in the rubber industry.¹

Although widely used as a dusting powder, talc is not generally considered a health hazard when exposure is limited to cosmetic application at home. A search has found four reports of chronic granulomatous pulmonary disease referable to excessive use of cosmetic talc in adults.²⁻⁵ In all these cases the question arises whether it was a true talc pneumoconiosis or talc deposition and coincidental sarcoidosis.

We report a case of chronic pulmonary granulomatous reaction in a patient who had used cosmetic talcum powder for several years. As a

comparison we describe a patient who was exposed to talc in the rubber industry and who showed a chronic granulomatous lung reaction which we believe represents true talc pneumoconiosis.

Case 1

A 58 year old woman had a history of myomectomy in 1952, cholecystectomy in 1968, and hysterectomy in 1977. She had been a smoker for 20 years. In April 1977 she was operated on because of a traumatic leg fracture. As a complication she had thrombosis in the left femoral vein and pulmonary embolism. The symptoms and signs of embolism disappeared during treatment with anticoagulants. Chest radiography was normal at that time. The patient was in good condition until summer 1980 when she began to suffer from dry cough, dyspnoea, tachycardia, and low grade fever. In November 1980 crepitant rales were heard at the bases of the lungs. Chest radiography showed fine diffuse opacities. Spirometry showed normal lung volumes. Diffusing capacity was lowered (DL_{CO} 64% of predicted). The sedimentation rate was 38 mm/h. The following variables were within normal limits: haemoglobin, white cell count, differential and thrombocyte counts, creatinine, transaminases,

Received 5 November 1982
Accepted 10 January 1983

alkaline phosphatase, serum calcium, urinary calcium excretion, and urine analysis. Serum lysozyme was slightly raised (27 mg/l (normal 20 mg/l)) and serum angiotensin converting enzyme (ACE) was normal (38 U/l). Mantoux 10 TU was negative.

The concentration of serum immunoglobulins, C3 and C4, and the titres of cryoprecipitins, direct Coombs-test, Latex-fixation test, Waaler-Rose, and antinuclear antibodies were normal. The Kveim test result was negative.

Three months later, in February 1981, laboratory results were the same as before, except that the serum ACE was raised (70 U/l). For diagnostic purposes an anterolateral thoracotomy was performed. The lung showed a diffuse nodular consistency. A biopsy specimen was taken from the lingula. Cultures for tuberculosis, bacteria, and fungi were negative. Histological examination showed a heavy intra-alveolar and interstitial granulomatous inflammation (fig 1) consisting of epithelioid and giant cells forming granules, macrophages, lymphocytes, plasma cells, some eosinophils, and fibrosis. Numerous birefringent particles were discovered inside the giant cells (fig 1). For elemental electron probe microanalysis 5 μ m thick tissue sections of the lung were deparaffinised in xylene, mounted on carbon coated nylon grids by conductive carbon cement, and examined by scanning electron microscopy (SEM) in a graphite holder (JEM-100 CX electron microscope fitted with a Princeton Gamma-Tech PGT System III energy dispersive x ray microanalyser). The foreign body material inside the granulomas contained magnesium and silicon in combination with chlorine, calcium, iron, and zinc (fig 2), characteristic of talc.

Because the examinations pointed to the possibility of talcosis a careful inquiry was undertaken into the dust exposure of the patient. She had applied non-powdering talc on her face for 20 years and

after that, talcum powder two to three times a day during a 10 year period, usually in an unventilated room. The total amount of powder used was two boxes a year. In the patient's own opinion the amount of powder used was not excessive enough to cause any disease. Elemental analysis of two different commercially available talcum powder preparations was also carried out. Electron probe microanalysis of these preparations showed magnesium, aluminium, silicon, potassium, iron, and zinc (fig 3).

In March 1981, treatment with prednisolone was started with an initial dose of 40 mg. The dose was gradually lowered to 10 mg a day over a period of four months. When the treatment was discontinued after nine months no improvement of pulmonary function or radiographs was observed. The serum angiotensin values fell to normal during the steroid treatment (26 U/l) but rose again after treatment ceased (77 U/l).

After two years' follow up an enlarged axillar lymph node was noticed. A biopsy specimen showed granulomatous inflammation.

Case 2

A 55 year old woman had smoked 10 cigarettes a day for 30 years. From 1958 to 1968 she had packed rubber balls and was exposed to the talc used as a dusting agent to prevent adhesion of the balls. During the first five years after exposure she began to suffer insidiously from dyspnoea. In April 1973 a chest radiograph showed diffuse nodular opacities; lung auscultation was normal. All the following variables were within normal limits: sedimentation rate, haemoglobin, white cell count, differential and thrombocyte counts, creatinine, transaminases, alkaline phosphatase, serum calcium, daily urinary calcium excretion, urine analysis, titres of latex

Fig 1 Open lung biopsy specimen of case 1 showing heavy granulomatous inflammation (a) with strongly birefringent crystal inside a giant cell (b) van Gieson, $\times 230$ (a), $\times 1200$ (b).

Fig 2 Electron probe microanalysis from a pulmonary birefringent crystal showing magnesium (Mg), silicon (Si), chlorine (Cl), calcium (Ca), iron (Fe), and zinc (Zn) characteristic of talc. Copper (Cu) is derived from supporting material.

fixation test, Waaler-Rose, cryoprecipitins, and antinuclear antibodies. Mantoux 10 tuberculin unit (TU) was positive. Spirometry showed normal lung volumes (FVC 107% of predicted), but diffusing capacity was lowered (DL_{CO} 60% of predicted). The Kveim test result was negative.

A lung biopsy was performed with a transthoracic TruCut needle in the right lower lobe. The biopsy specimen showed numerous small interstitial granulomas (fig 4a). Within these granulomas numerous particles were found, most of them double-refractile and resembling talc particles (fig 4b). Some ferruginous bodies were also seen. The alveolar spaces were patent.

In July 1973 treatment with prednisolone was started with an initial dose of 40 mg. The dose was gradually lowered and the treatment was terminated after two months because no objective improvement

Fig 3 Electron probe microanalysis from a commercially available talcum powder preparation showing magnesium (Mg), aluminium (Al), silicon (Si), potassium (K), iron (Fe), and zinc (Zn). Copper (Cu) is derived from supporting material.

Fig 4 TruCut needle biopsy specimen of case 2. (a) A perivascular granulomatous inflammation. Haematoxylin & eosin, original magnification $\times 150$. (b) Numerous birefringent particles in polarised light in areas of inflammation.

was observed in the chest radiograph or in pulmonary function.

In April 1980 spirometry showed normal lung volumes (FVC 84% of predicted) and diffusing capacity was lowered (DL_{CO} 51% of predicted). At that time serum ACE was slightly raised at $49 \mu\text{mol/l}$ (normal $40 \mu\text{mol/l}$).

Discussion

Talc used in the manufacture of cosmetic talcum powder is normally of high purity. Nevertheless, x ray diffraction analysis of 21 powders obtained through retail channels in the United States showed that few of them consisted of pure talc. Quartz, ranging from 2% to 5% was found in eight, while one sample contained 35%. Detectable amounts of fibrous tremolite and anthophyllite were reported to be present in 10, and chrysotile in two.⁶ Epidemiological studies indicate that prolonged exposure to cosmetic grade talc is not associated with the development of pneumoconiosis, though exposure to industrial grade talc may result in this condition.^{7,8}

Exposure to talc causes three distinct types of

lesion depending on the composition of the "talc."¹ Ill defined nodular lesions are associated with a relatively high quartz content in the lungs. Diffuse interstitial fibrosis is associated with exposure to talc containing significant amounts of tremolite, anthophyllite, or other fibrous minerals. Foreign body granulomas are obviously caused by pure talc.

An extensive use of talcum powder was reported in association with pure talc pneumoconiosis.²⁻⁵ The histological changes were identical in all these cases—foreign body granulomas and varying amounts of interstitial fibrosis.

Although one of our patients (case 1) had used talcum powder for 10 years, usually in a small unventilated room, the amount of talc was obviously not as excessive as in the patient previously reported. Therefore, the question arises whether our case is an example of talc pneumoconiosis or of talc deposition in the lungs with coincidental sarcoidosis.

Neither of our patients showed extrapulmonary manifestations compatible with sarcoidosis. The Kveim test result was negative and urinary calcium excretion was normal. No improvement was observed during treatment with steroids even though the histological alterations were mainly inflammatory. On the other hand, both patients had raised values for serum ACE, which is known to be raised in about 75% of patients with active sarcoidosis.⁹ Other diseases with raised ACE levels are Gauher's disease, leprosy, berylliosis, Lennert's lymphoma, lymphangioleiomyomatosis, *Mycobacterium intracellulare* infection, osteoarthritis, plasmocytoma with lung involvement, and Q fever. Farber *et al* reported raised levels of ACE in a case of talc pneumoconiosis in a pentazocine abuser (drug containing talc as filler).¹⁰ Thus the possibility of talc pneumoconiosis cannot be excluded on the bases of raised ACE alone. Epithelioid cells are known to excrete ACE,⁹ thus this might be an unspecific phenomenon independent of the aetiology of the granulomatous reaction. In the present cases granulomas seemed to be able to produce ACE.

In both our patients histological examination showed excessive amounts of birefringent dust particles in the lung tissue and foreign body granulomas and talc particles in the cytoplasm of giant cells. Except, perhaps, for the talc containing giant cells,¹

these findings do not establish any causal relationship between talc and the disease.

In our patients the quantity of dust exposure seemed to be important in the differential diagnosis of sarcoidosis and talc pneumoconiosis before the detection of granulomatous inflammation of an axillary node in case 1. The patient who handled talc powdered rubber balls had an exposure that may be classified as typical, and therefore we believe the patient had a true talc pneumoconiosis. The patient who used talcum powder at home had an exposure that was not unusual. Therefore the quantity of dust exposure seems to be insufficient, even though the quantity of dust in the lung tissue was excessive. We believe that this patient represents a case of chronic sarcoidosis and coincidental talc deposition in the lungs.

Our report shows that even after careful clinical and laboratory examination together with analysis of lung biopsy specimens it may be extremely difficult to differentiate between chronic sarcoidosis and talc pneumoconiosis.

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