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CASE STUDY

Interstitial lung disease more than 40 years after a 5 year occupational exposure to talc

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Interstitial lung disease more than 40 years after a 5 year occupational exposure to talc. C. Gysbrechts, E. Michiels, E. Verbeken, J. Verschakelen, D. Dinsdale, B. Nemery, M. Demedts. ©ERS Journals Ltd 1998.

ABSTRACT: A 62 yr old woman was initially diagnosed with sarcoidosis until a thoracoscopic biopsy revealed the presence of numerous birefringent particles in fibrotic areas of the centrilobular lung zones. These particles were examined by electron microscopy and X-ray spectrometry and characterized as impure talc. Further inquiry into her occupational history revealed that she had worked from the age of 14–18 yrs in a factory making rubber hoses, where she had had an intense exposure to talc. There was no evidence of silicosis or asbestosis, and other significant causes of interstitial lung disease were excluded.

This case emphasizes the importance of a thorough occupational history, which may reveal a remote and forgotten exposure to a significant cause of interstitial lung disease. Although this presentation of talcosis is unusual, this case suggests that even a relatively short, but presumably intense exposure to talc more than 40 yrs previously may be a cause of progressive lung fibrosis.

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Talcosis or talc pneumoconiosis is one of the rarer forms of silicate-induced lung disease. It has been described in workers exposed during its production or its industrial use [1], and occasionally in users of cosmetic talc and in intravenous drug addicts [2]. Talcosis is generally considered to be relatively benign.

We present here a case of interstitial lung disease in a woman who had experienced an intense, relatively short, remote and forgotten exposure to talc. This case emphasizes the importance of taking a thorough occupational history in all instances of suspected sarcoidosis, as well as the value of a mineral analysis of tissue to obtain an aetiological diagnosis of some forms of interstitial lung disease.

Case report

A 62 yr old, nonsmoking woman first presented in 1991 with complaints of chronic cough. Her medical history was unremarkable. The initial report of her occupational history indicated that she had been a housewife from 18–34 yrs of age, after which she had worked as a cleaning lady in pubs until the present. Auscultation revealed crackles at the lung bases and a chest radiograph showed mild cardiomegaly, and she was treated with digitalis and lisinopril, an angiotensin-converting enzyme (ACE) inhibitor. The dry cough persisted despite stopping the lisinopril.

In 1993 she was admitted for observation because of dyspnoea and chronic cough. Diffuse, mainly basal crepitations were heard on auscultation and a chest radiograph showed reticular opacities in both lungs, especially in the middle and lower parts (fig. 1). High-resolution computed tomography (HRCT) showed bronchial wall thickening with irregular bronchovascular interfaces, ground-glass opacities and discrete peripheral lung deformation suggestive for fibrosis, mainly in the lower and middle lobes (fig. 2). Mild lymph node enlargement was also evident, but no pleural plaques were seen. Spirometry showed a moderate restrictive impairment (vital capacity (VC) 1.56 L,

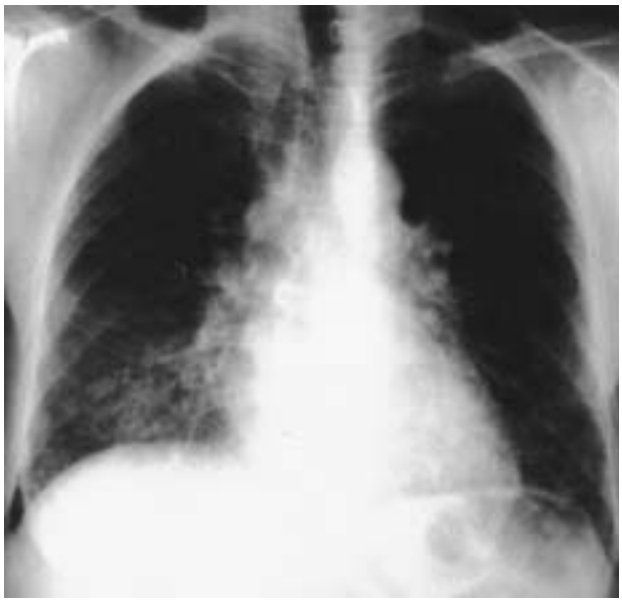
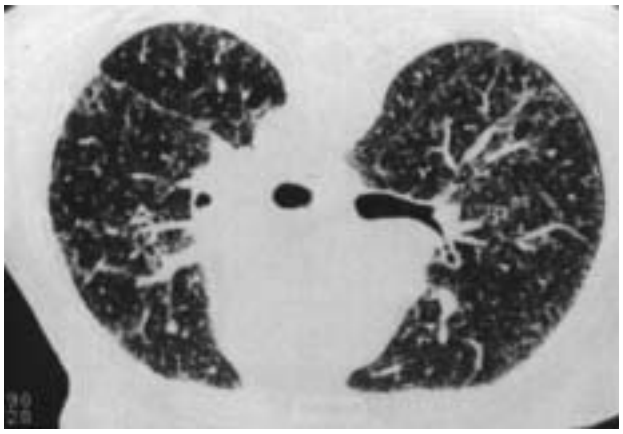


Fig. 1. – Posteroanterior chest film showing reticular opacities in both lungs, predominantly in the middle and low parts.

71% predicted, total lung capacity (TLC) 2.39 L, 60% pred) with a markedly reduced carbon monoxide diffusing capacity ($D_{L,CO}$ 6.41 mmol·min^{-1}·kPa^{-1}, 36% pred) (predicted values according to [3]). Static lung compliance was 71 mL·cmH_2O^{-1} (38% pred. [4]). An echocardiograph was normal. Bronchoscopy did not reveal any endobronchial abnormalities, with transbronchial biopsies showing signs of chronic bronchitis but no granulomas. Bronchoalveolar lavage (BAL) was negative for mycobacteria and other infectious agents, and no neoplastic cells were found. However, the inflammatory cell distribution was abnormal with an increased proportion of lymphocytes (54%; normal <20% [5]), an elevated CD4/CD8 ratio of 5.6 (normal <2.5), and no abnormal values for the total cell number (6.7×10^6), polymorphonuclear neutrophils (3%) and eosinophils (0%). The mineral content of the BAL fluid was not studied, but macrophages did not contain conspicuous particles and no asbestos bodies were found. Except for an increased erythrocyte sedimentation rate (ESR) (70 mm·h^{-1}), a slightly elevated lactate dehydrogenase (LDH) (598 U·L^{-1}), and a polyclonally increased paraprotein, no significant alterations in haematological, blood chemistry or other serological parameters (including autoantibodies) were found.

a)



b)

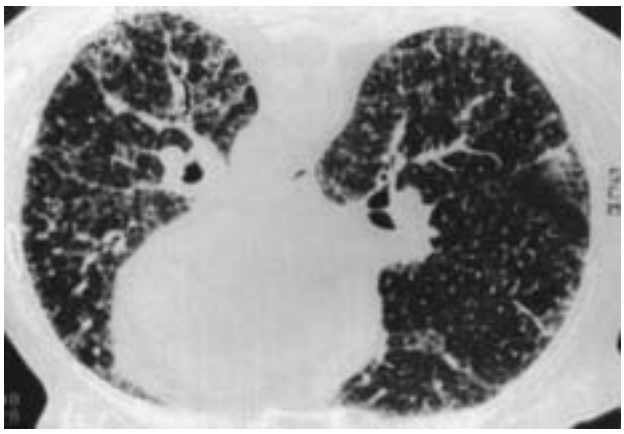


Fig. 2. – Prone high-resolution computed tomographic scan at the level of: a) the carina; b) the left atrium; showing thickening of the bronchial wall with an irregular interface between the bronchovascular structures and the lung. There is also nodular thickening of the fissure, and multiple subpleural nodules can be seen. Discrete lung deformation at the periphery suggests fibrosis.

Based on the radiology and BAL results, a presumptive diagnosis of sarcoidosis stage II was suggested, despite low values of serum ACE and low urinary calcium, and treatment with methylprednisolone was started, at an initial daily dose of 32 mg. This was followed by a symptomatic improvement, a decrease in the ESR and an improvement in pulmonary function (to VC 93% pred and $D_{L,CO}$ 52% pred), but this was not sustained and, after 6 months, when methylprednisolone had been progressively tapered to 4 mg·day^{-1}, the pulmonary function parameters were again markedly decreased, to levels below the initial values (VC 62% pred and $D_{L,CO}$ 26% pred). There was slight arterial hypoxaemia (P_{a,O_2} 8.5 kPa (64 mmHg)) and development of finger clubbing. The radiological picture worsened. Lev-els of serum ACE, immunoglobulins, complement factors, antinuclear antibodies and rheumatoid tests were normal or negative. There were no precipitating antibodies against bird or other common antigens.

Because the presumptive diagnosis of sarcoidosis was challenged, a mediastinoscopy was performed, followed by thoracoscopy to take pulmonary biopsies (in the apex of the left lower lobe) in February 1994. The lung biopsies showed interstitial fibrosis, with only the centriacinar areas being affected and with deposits of collagen along the respiratory bronchioles. Within this fibrous matrix, and only there, numerous birefringent structures, often acicular in appearance, were visible, along with anthracotic macrophages (fig. 3a). All lesions were in the same stage of evolution and the interstitial inflammatory infiltrate of mononuclear cells was very sparse. The distal acinar areas, as well as the pleura and interlobular septa, were normal and were free of crystalline particles and fibrosis. Vascular structures were not affected and bronchioles were not obliterated. No sarcoid granulomas were found and no asbestos (ferruginous) bodies were observed. The mediastinal lymph nodes were unremarkable and, as in the lung, they did not contain typical hyaline silicotic nodules. Because pathological criteria for infectious pulmonary disease or for idiopathic or other forms of interstitial pneumonia were not met and because there was a perfect spatial relation between the mineral deposits and the fibrosis, the presence of these particles was considered not to be incidental, but most probably to be causal for the fibrosis.

The histological findings of pneumoconiotic lung disease led us to suspect a significant inhalation of mineral particles, and this prompted the taking of a more thorough occupational and environmental history. The patient recalled that she had been exposed to a lot of dust, presumably talc, when she had worked, from the age of 14–18 yrs, in a factory making rubber hoses. She had operated a machine in which talc was injected into the hoses to prevent adhesion of the rubber. There were no dust controls and "the room was so dusty that the whole area and the workers were covered with white dust". The woman denied having had any other exposures to dust except for this period before her marriage. Her husband had first worked for 3 yrs in the same rubber plant, and then for 8 yrs in a coal mine, but he had not had a dusty job later.

To investigate the significance of this exposure, sections of the lung tissue were prepared for transmission electron microscopy and energy-dispersive X-ray spectrometry [6], with 100 particles being analysed. The majority of particles (>90%) were lamellar in form and profiles

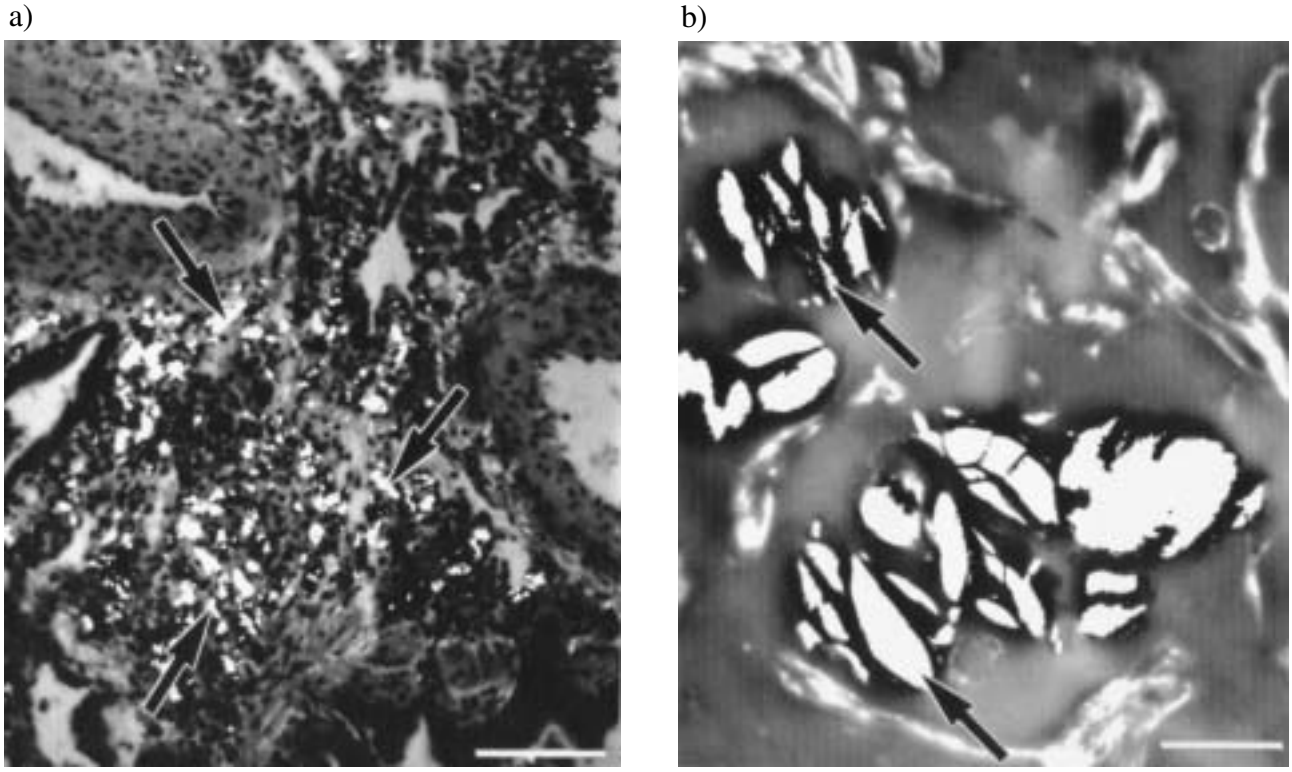


Fig. 3. – Serial sections from a pulmonary biopsy: a) wax section, stained with haematoxylin and eosin, showing a region of interstitial fibrosis containing numerous birefringent particles (internal scale bar = 100 μm); b) unstained resin section, from the region shown in a), showing the characteristic ultrastructure of the predominant type of particle (internal scale bar=5 μm).

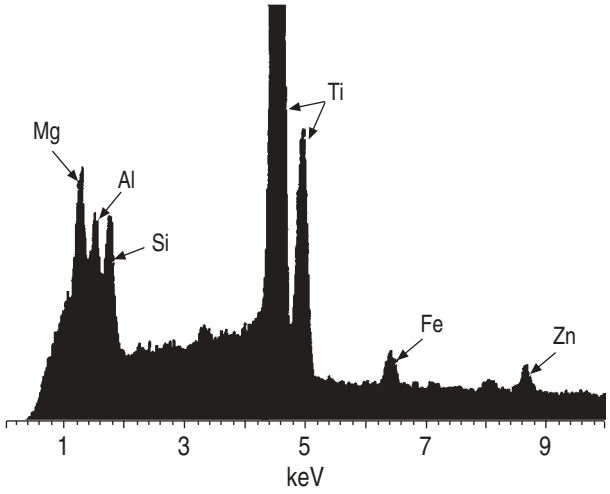


Fig. 4. – Energy-dispersive X-ray spectrum from a particle, adjacent to those shown in figure 3b, showing the characteristic peaks for magnesium (1.253 keV) and silicon (1.740 keV). Contamination by aluminium (1.486 keV), iron (6.403 keV) and zinc (8.638 keV) is also evident. The small copper peak (8.047 keV) originates from the instrument and that of titanium (4.510 keV) comes from the support grid/holder.

were 5–10 μm in their longest dimension. Transverse sections through these particles showed the presence of numerous layers, which tended to separate during sectioning and examination (fig. 3b). The structure of these particles, together with the presence of magnesium and silicon (fig. 4), is consistent with talc. Semiquantitative analysis, however, showed a reversal of the usual (approximately 1:2) proportion of these elements, indicating contamination of the talc with other minerals, *e.g.* chlorite. (The composition of the industrial talc to which the patient had been exposed could, understandably, no longer be traced after 40 yrs). The high concentration of aluminium is consistent with this interpretation, but some elemental substitution, with aluminium, iron and zinc, may also have occurred to the mineral itself.

On the basis of the occupational history, the compatible clinical, radiological, histological and mineralogical findings, and the exclusion of other plausible causes, a diagnosis of talc-induced interstitial lung disease was made.

The follow-up of the patient showed a progressive deterioration in ventilatory function and $D_{L,CO}$, with the development of arterial hypoxaemia. There were also radiographic signs of evolution towards fibrosis. Despite another course of steroid therapy, and treatment with cyclophosphamide, there was no clinical, functional or radiological improvement. She eventually died on April 1, 1997. Autopsy could not be performed.

Discussion

Pure talc is a phyllosilicate [$Mg_3Si_4O_{10}(OH)_2$] used for many purposes in industry and daily life. In practice, talc contains variable amounts of aluminium, iron and calcium. In addition, depending on its origin and its intended use, talc may contain varying amounts of asbestos and silica [1]. High-purity talc is used in cosmetic and pharmaceutical industries, and there is no conclusive evidence that cosmetic talc, when used as intended, presents a health hazard [7]. However, intravenous drug addicts may

exhibit pulmonary granulomatous disease as a result of the injection of crushed tablets or drugs cut with talc [2, 8]. Low-grade talcs contain as much as 50%, or more, of other compounds such as chlorite, amphibole (mainly tremolite) and serpentine asbestos fibres, as well as variable amounts of quartz. This industrial talc has a wide variety of uses in paints, lubricants, insecticides, roofing products, asphalt, ceramics, the rubber industry, metal foundries, and jewellery manufacture. Individuals in any of these oc-cupational settings may be exposed to the potentially harmful effects of talc dust [1].

The patterns of pulmonary disease observed in these occupationally exposed subjects include "talco-asbestosis", which is indistinguishable from pure asbestosis, and "talco-silicosis", which is equally indistinguishable from silicosis. In our patient there was no radiological or histological evidence of either asbestosis or silicosis, and this was supported by the mineralogical analysis of the lung biopsy. Pneumoconiosis has, however, also been described in persons exposed occupationally to talc without asbestos or silica [8–10]. Radiologically, talcosis is characterized by small nodules and reticulations, either diffuse or predominantly in the lower zones and hilar adenopathy may occur. Foreign body granulomas may be found on histology. Thus, the possibility of exposure to talc (as well as to beryllium and other dusts) must be investigated in any case of sarcoidosis [11]. In our patient no granulomas were found, but it is possible that, as in other instances of granulomatous lung disease, the granulomas disappear when the disease progresses towards fibrosis.

Exposure to talc may be revealed or confirmed by mineralogical analysis of BAL or pulmonary tissue, and although the finding of talc particles is in itself not diagnostic for talc pneumoconiosis, mineralogical analysis may be extremely helpful in making such a diagnosis in the presence of compatible clinical, radiological and histological data and after the exclusion of other possible causes of interstitial lung disease [10, 12, 13]. In the present case, the latter was achieved mainly on morphological grounds, whereby the pathological criteria for usual and other forms of interstitial pneumonia, as well as hypersensitivity pneumonitis, were absent. Moreover, the perfect spatial correlation between the mineral deposits and the areas of fibrosis strongly suggests that the presence of (impure) talc particles was not merely incidental, but most probably causal for the fibrosis.

The natural history of talcosis is said to be slowly progressive, even after exposure to the dust has ceased [1], and the present case certainly confirms this, even though her ultimate evolution was admittedly unusual. As with other pneumoconioses, no specific treatment exists and this too was observed in our patient, who showed little or no benefit from steroid and immunosuppressive treatment.

Although there was no absolute proof of a cause and effect relationship between the accumulation of talc dust and the development of progressive interstitial lung disease in this patient, we have shown that: 1) the initial diagnosis of sarcoidosis (which would have been made by many) was wrong, 2) 40 yrs previously the patient had had a brief, but substantial (and well-documented) occupational exposure to talc; 3) this mineral (which is known to cause pneumoconiosis) was conspicuously associated with fibrotic lesions in the lung; and 4) other causes of interstitial lung disease could be reasonably excluded. The main message of these observations is, therefore, that a detailed occupational history, including occult exposures in the distant past, is necessary in every case of interstitial lung disease, and that a relatively short but presumably high exposure to industrial talc may be a significant factor in the causation of interstitial lung disease.

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