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CASE REPORT

Atypical mycobacteriosis as a complication of talc pneumoconiosis

C. De Coster*, J.M. Verstraeten**, P. Dumortier*, P. De Vuyst*

Atypical mycobacteriosis as a complication of talc pneumoconiosis C. De Coster, J.M. Verstraeten, P. Dumortier, P. De Vuyst ©ERS Journals Ltd 1996

ABSTRACT: A 57 year old man, receiving compensation for talc pneumoconiosis since 1977, was admitted to hospital for the first time in 1987, with symptoms of weight loss, fever, dyspnoea and productive cough. A chest roentgenogram showed bilateral cavitation. Two years later, *Mycobacterium xenopi* was found in sputum cultures. Despite specific oral antibiotherapy, the patient's health deteriorated and he died in 1990.

To the best of our knowledge, this is the first reported case of an association of talcosis with a *M. xenopi* pneumonia. The relative timing of the two diseases suggests that talc pneumoconiosis predisposed to the infection by *M. xenopi*.

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* Chest Dept, Erasme University Hospital, Université Libre de Bruxelles, Brussels
** Akadernisch Ziekenhuis Sint Vincentius Ghent, Belgium

Correspondence: P. De Vuyst, Chest Service, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium

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Case report

The patient, born in 1932, worked as a talc miller from 1969 until 1980 in a Belgian factory. The raw material was imported mainly from Montana, US (Yellowstone). Talc was crushed without addition of other materials and served as a high grade talc for pharmaceutical purposes. The patient had never previously been exposed to other minerals (e.g. silica, asbestos) and had a smoking history of 35 pack-years. In 1977, the diagnosis of talc pneumoconiosis was made, essentially on the basis of a chest radiograph. In 1983, chest radiographs showed a progression of the small opacities (graded q/q 2/2 according to

the International Labour Office (ILO) classification) and the appearance of a large opacity in the right upper lobe (graded A) (fig. 1a). The results of pulmonary function tests at that time were as follows: forced vital capacity (FVC) 2.7 L (65% of predicted), forced expiratory volume (FEV₁) 2.3 L (73% pred); total lung capacity (TLC) 5.2 L (91% pred); and transfer factor of the lung for carbon monoxide (Tl,CO) 61% pred. A bronchoalveolar lavage (BAL) performed in 1983 showed abundant talc particles, talc bodies and traces of tremolite [1]. Quartz was not detected in the BAL fluid, but due to the considerable amount of talc particles, traces of quartz could have remained undetected by this method.

a)



b)

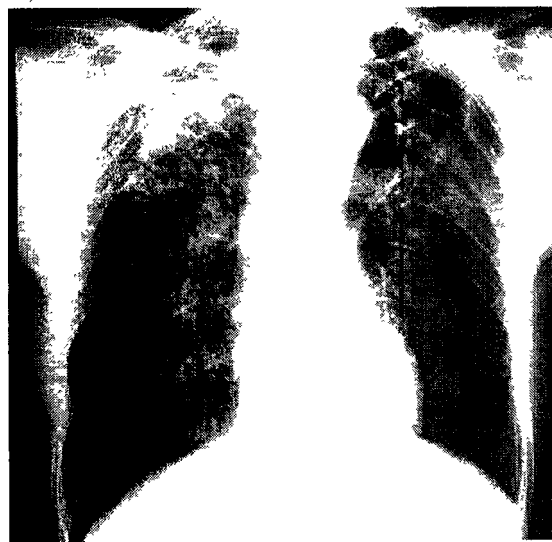


Fig. 1 -- a) Chest radiograph in 1983 showing bilateral rounded opacities and a large opacity in the right upper lobe. b) Chest radiograph in 1987, showing progression of the lesions with cavitations of both upper lobes.

In 1987, at the age of 55 yrs, the patient was admitted to the hospital with symptoms of fever, dyspnoea and purulent sputum. There was also a significant weight loss (38 kg body weight for 1.65 m). Chest radiographs showed a progression of the large opacity in the right upper lobe and cavitations of both upper lobes, predominating in the left upper lobe (fig. 1b). Pulmonary function tests showed a deterioration of the spirometric values: FVC 1.4 L (35% pred); FEV 0.6 L (21% pred); residual volume (RV) 4.0 L (190% pred); and $\dot{V}_{L,CO}$ 11% pred. The sedimentation rate reached $107 \text{ mm}\cdot\text{h}^{-1}$ and the white blood cell count $7 \times 10^9 \text{ cells}\cdot\text{L}^{-1}$. Arterial blood gas examination disclosed severe hypoxaemia (arterial oxygen tension (P_{a,O_2}) 4.9 kPa (37 mmHg)). Sputum smears for bacteria and acid-fast bacilli were negative. Clavulanic acid + amoxycillin had no effect on the fever but the patient recovered after antibiotic treatment of 10 days duration with co-trimoxazole.

In 1988, the patient was once more admitted because of fever and chest pain. A chest radiograph showed a "hydroaeric level" in the right upper lobe. Blood cultures were negative and there were no pathogens detected in the sputum. Oral antibiotherapy with co-trimoxazole was administered for 3 days, followed by cefuroxime. One year later, he was again admitted to the hospital with the same symptoms, chest radiographs showing a progression of the cavitary lesions.

At that time, the sputum culture yielded 20 colonies of *Mycobacterium xenopi* but was negative for *Mycobacterium tuberculosis*. Oral rifampicin, 600 mg·day⁻¹, and isoniazid (INH), 300 mg·day⁻¹, were initiated. However, because *M. xenopi* was resistant to INH, it was replaced by ofloxacin (400 mg day⁻¹).

Four months later, the patient was admitted for the last time because his condition had deteriorated. He developed severe renal failure, anaemia, leucocytosis and shock. Despite intensive care, the patient died a few days later.

Discussion

The first period (1977–1987) of this patient's disease is dominated by the diagnosis and the compensation for talc pneumoconiosis ("occupational" period). The second is dominated by mycobacterial infection leading to death (1987–1990) ("infectious" period). Knowing the diagnosis of *M. xenopi* infection, it is difficult to define its exact onset. On the radiograph from 1983, it is possible that the right upper lobe opacity already corresponds to an infectious process. Nevertheless, the discussion will consider two phases in the patient's evolution: the talc pneumoconiosis and the *M. xenopi* infection, and the possible relationship between them.

Talc pneumoconiosis is an uncommon pneumoconiosis, which classically requires a long duration of exposure to a high concentration of dust [2, 3]. Cigarette smoke appears to increase the risk of developing this disease. In the present case, the prolonged exposure to high levels of respirable talc particles, together with the presence of diffuse, bilateral, small, rounded opacities on chest radiographs is compatible with the diagnosis of talcosis [2, 3]. BAL confirmed the retention of a very high concentration of talc particles. The clinical and radiological

data were compatible with previous descriptions of pneumoconiosis in talc-exposed workers, so that no lung biopsies were taken. The Belgian Occupational Disease Fund agreed to recognize and compensate this disease.

Large opacities are also described in talcosis, and the abnormalities in the right upper lobe on the chest radiograph from 1983 were also considered as a part of the pneumoconiosis. However, the fact that this lesion was unilateral should have been considered as atypical. This underscores the problem of differential diagnosis of lung opacities appearing in pneumoconiotic subjects, usually considered as coniotic masses without any complementary investigations. Furthermore, there was a clear progression of the bilateral small opacities. No prior exposure to other mineral dust had been detected, and even if a few tremolite asbestos fibres were found in BAL, there were no evident signs of asbestosis (no pleural plaques or thickening, no evidence of interstitial fibrosis). The fact that the asbestos type was tremolite suggests a possible geological contamination of talc [1].

It is actually admitted that *M. xenopi* can be pathogenic for humans and lead to severe disease, but lung diseases due to this mycobacterial species are rare. Underlying pre-existing pulmonary diseases, such as pulmonary tuberculosis, chronic bronchitis, emphysema, bronchiectasis, interstitial pulmonary fibrosis, lung carcinoma and sarcoidosis, are predisposing factors for *M. xenopi* infection [4–6]. Diagnostic criteria exist for identifying pulmonary disease where *M. xenopi* is considered to be a pathogen, including repeated positive cultures, an abnormal chest roentgenogram consistent with mycobacterial infection, and absence of other pathogens in the sputum [4, 6]. Various radiographic manifestations of *M. xenopi* infection are described from multiple nodular shadows to cavitary lesions [7]. The clinical and radiological evolution of our patient since 1987 is consistent with a chronic lung infection by mycobacteria. *M. xenopi* was found twice in sputum cultures, whereas *M. tuberculosis* was never detected and could be excluded. Therefore, according to mycobacteriological and roentgenographic criteria, it is obvious that the patient died from destructive lung infection by *M. xenopi*. There are only a few cases described in the literature in which lung disease caused by *M. xenopi* led to death [4, 5, 7].

As far as we know, this is the first case report of the association of talc pneumoconiosis and lung infection by *M. xenopi*. Even if the succession of these two uncommon diseases in an individual case could be purely coincidental, this seems unlikely, and several clues suggest that the presence of talcosis predisposed to the secondary infection by *M. xenopi*. A parallel situation occurs in silicosis, another pneumoconiosis which is a well-known predisposing condition for tuberculosis or even non-tuberculous mycobacterial disease [8, 9]. The increased susceptibility to these other diseases could be explained by impaired function of macrophages due to silica [10, 11]. Alveolar macrophages are important in the defence against mycobacteria, not only through their phagocytic and bactericidal activities, but also through the amplification of the host defence by the release of cytokines (interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α)) [12]. In the case of talc pneumoconiosis, in which macrophages are overloaded by talc particles, it is conceivable that these activities can be impaired.

In conclusion, this case study suggests that lung infection by mycobacteria, at least *M. xenopi*, can complicate talc pneumoconiosis. In such a situation, it should be considered as a part of the occupational disease and compensated as well.

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36

Weekly Clinicopathological Exercises

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PRESENTATION OF CASE

A 69-year-old man was admitted to the hospital because of the radiologic finding of pulmonary nodules. The patient had been well until several weeks earlier, when a cough, fever, and dyspnea developed. A thoracic radiograph obtained at another hospital 11 days before admission (Fig. 1) showed an irregular nodule, 2 by 1.5 cm, in the right upper lobe and ad-



Figure 1. Posteroanterior Radiograph of the Chest Showing an Irregular Nodule in the Periphery of the Right Upper Lobe.

ditional bilateral nodules. There was no hilar or mediastinal lymphadenopathy. A thoracic computed tomographic (CT) scan (Fig. 2) revealed a spiculated mass in the periphery of the right upper lobe and multiple smaller nodules, 2 to 5 mm in diameter, in the lower lung zones. Microscopic examination of a specimen from a needle-aspiration biopsy of the mass in the right upper lobe was reported to show adenocarcinoma. The patient's cough improved, but slight exertional dyspnea persisted. He came to this hospital.

The patient was retired from a job in a rubber plant,



Figure 2. A CT Scan through the Right Upper Lobe (Panel A) Showing an Irregular Nodule, and a CT Scan through the Lower Lung Zones (Panel B) Showing Multiple Nodules, 2 to 5 mm in Diameter.

TABLE 1. HEMATOLOGIC AND BLOOD CHEMICAL VALUES

VARIABLE	VALUE
Hematocrit (%)	37.9
Mean corpuscular volume (μm^3)	92
White cell count (per mm^3)	6,900
Platelet count (per mm^3)	245,000
Sodium (mmol/liter)	142
Potassium (mmol/liter)	5.3
Chloride (mmol/liter)	102
Carbon dioxide (mmol/liter)	30.1
Urea nitrogen	Normal
Creatinine	Normal
Glucose	Normal

TABLE 2. RESULTS OF PULMONARY-FUNCTION TESTS

VARIABLE*	RESULT
	value (% of predicted)
FEV ₁ (liters)	1.49, 1.64† (49)
Vital capacity (liters)	2.51, 2.75† (64)
FEV ₁ /vital capacity	0.59 (76)‡
Flow rate at 50% of vital capacity (liters/sec)	1.04 (23)
Maximal breathing capacity (liters/min)	52 (49)
Total lung capacity (liters)	9.8 (176)
Residual volume (liters)	7.29 (324)
Residual volume/total lung capacity	0.74 (180)
Airway resistance (cm of water/liter/sec)	1.28§
Specific conductance (liters/sec/cm of water)	0.097¶
Single-breath carbon monoxide diffusing capacity (ml/min/mm Hg)	16.0 (67)
Carbon monoxide diffusing constant (ml/min/mm Hg)	4.4 (96)
Oxygen saturation (%)	99 , 97**

*FEV₁ denotes forced expiratory volume in one second.

†This value was obtained after the patient had inhaled a bronchodilator medication.

‡The value was based on the first measurements of FEV₁ and vital capacity.

§The predicted range is 0.8 to 2.4 cm of water per liter per second.

¶The predicted value is more than 0.12 liter per second per centimeter of water.

||This value was obtained while the patient was breathing ambient air at rest.

**This value was obtained after the patient had walked for three minutes.

where he had been exposed to talc for 28 years. There was no history of exposure to asbestos. He had smoked two cigarettes daily for six years. He resided in Arizona and was physically active. His medications were metoprolol, quinapril, and terazosin. There was no history of sputum production, wheezing, hemoptysis, chest pain, tuberculosis or exposure to it, coccidioidomycosis, weight loss, or a malignant tumor.

The temperature was 36.8°C, the pulse was 67, and the respirations were 20. The blood pressure was 120/85 mm Hg.

On examination, the patient was a slim man who appeared well. The lungs were clear except for a few rhonchi on the right side.

Laboratory tests were performed (Table 1). An electrocardiogram revealed a sinus bradycardia at a rate of 50, with nonspecific ST-segment and T-wave abnormalities. The results of pulmonary-function studies performed at the other hospital are shown in Table 2.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. SIMON D. SPIVACK*: This patient had an ill-defined respiratory illness characterized by fever, cough, and dyspnea. Since his cough improved without any known treatment, one can rule out the common acute, bilateral, bacterial pneumonias, such as those due to *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, particularly in the absence of known exposure to these organisms. If the patient was immunocompromised, however, a lung biopsy would be needed to rule out these infections. Systemic immunocompromise, such as that caused by the T-cell deficiency associated with lymphoma, infection with the human immunodeficiency virus (HIV), and use of corticosteroids or cyclosporine; the B-cell deficiency associated with multiple myeloma; neutrophil deficiency; or the combined deficiencies that may follow an allogeneic bone marrow transplantation, predisposes a host to infections with particular sets of organisms, depending on the critical elements of the host's defense that are lacking. Since this patient had no apparent risk factors for disseminated tuberculosis or pneumocystis pneumonia, these diagnoses are unlikely.

May we review the radiographic findings?

DR. JO-ANNE O. SHEPARD: The chest film (Fig. 1) obtained before admission shows an irregular nodule, 2 by 1.5 cm, in the right upper lobe, as well as smaller bilateral nodules. The CT scan (Fig. 2) shows the irregular nodule in the posterior segment of the

*Attending physician, Pulmonary and Critical Care Medicine, Albany Medical Center, associate professor, Albany Medical College, research physician, New York State Department of Health, Division of Human Toxicology and Molecular Epidemiology — all in Albany.

right upper lobe and numerous bilateral nodules, 2 to 5 mm in diameter, in the lower lung zones. No lymphadenopathy or pleural plaques were visible.

DR. SPIVACK: Since the patient had radiographically stable disease without treatment over a period of at least 11 days, we can rule out acute bacterial processes, such as those attributable to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and oral anaerobes. In the absence of a history of exposure and without a report of positive results of skin tests with purified protein derivative, localized *Mycobacterium tuberculosis* infection is unlikely. There is no clinical evidence that the patient had preexisting pulmonary abnormalities that might have made him susceptible to bacterial overgrowth, such as cavitary disease, which may lead to the formation of an aspergilloma. Nor is there ciliary dyskinesia syndromes or cystic fibrosis in this case.

The radiologic finding of bilateral small, nodular opacities suggests the presence of an underlying subacute or chronic lung process. The differential diagnosis of small nodules in this context includes exogenous as well as idiopathic and malignant disorders. Subacute infections such as coccidioidomycosis, blastomycosis, histoplasmosis, and miliary tuberculosis may account for the small nodules. There was no apparent evidence of exposure to *M. tuberculosis* or a predisposition to miliary tuberculosis, however, and there is no information about skin testing. Nodules and airflow abnormalities are typical of pneumoconioses, such as talcosis and silicosis, as well as hypersensitivity pneumonitis due to exposure to an organic antigen or beryllium, but the history in this case does not suggest either type of exposure. Moreover, the patient's pulmonary dysfunction is not characteristic of asbestosis, mixed-dust disease, or exposure to heavy metals.

Idiopathic disorders, including sarcoidosis, eosinophilic granuloma, and bronchocentric granulomatosis, may be accompanied by fever early in the course of the disease and may be associated with obstructive or mixed obstructive and restrictive pulmonary dysfunction. Lymphocytic interstitial pneumonitis is an unlikely diagnosis in the absence of progressive dyspnea, cough, and underlying disease. Similarly, Churg-Strauss vasculitis is unlikely in the absence of preexisting atopy or reactive airway disease. This patient may have had a bronchiole-based disorder, such as bronchiolitis obliterans or bronchiolitis obliterans with organizing pneumonia, particularly in view of the profound air trapping, with the preservation of large airway conductance and resistance.

Patients with malignant tumors present infrequently with bilateral small nodules. Non-Hodgkin's lymphoma is an unlikely diagnosis in the absence of peripheral or hilar lymphadenopathy. Patients with bronchioloalveolar-cell carcinoma may present with nodular or alveolus-filling lesions. Lymphangitic spread of car-

cinoma or leukemia may also be characterized by the presence of such lesions. I shall return to the possibility of a malignant tumor.

Coccidioidomycosis deserves serious consideration in this case because the patient lived in Arizona. *Coccidioides immitis* is present in soil and is endemic in the southwestern United States. Clusters of cases in other areas have been attributed to dust storms that carried the pathogen to distant sites.¹ The fungus is dimorphic, existing as a saprobe or a parasite. Mycelial forms grow in soil and disarticulate, releasing arthroconidia into the air, which are inhaled by the host. Person-to-person transmission and indirect transmission through secretion-to-wound contact are very rare.^{1,3} Respiratory isolation is therefore not required. Inhalation of arthroconidia from soil is virtually the only route of entry into the human host, placing those who have frequent contact with contaminated soil, such as archaeologists and excavators, at highest risk. The immune response is partly T-cell-dependent, and the infection has increased among HIV-infected persons who live in the Southwest. The parasitic portion of the life cycle entails the release of a substance with elastase activity that promotes the degradation of molecules in the connective-tissue matrix of the host, resulting in the spread of infection and the formation of the microcysts or macrocysts seen on microscopical examination.^{1,3}

Clinical evidence of disease is barely apparent in approximately 60 percent of patients with acute primary infections. In these patients, symptoms are absent or, if present, consist of a mild cough and low-grade fever, making them difficult to distinguish from the symptoms of an upper respiratory tract infection. The remaining 40 percent of patients have an illness one to three weeks after exposure that often mimics a lower respiratory tract infection, with fever, diaphoresis, dyspnea, chest pain, sputum production, anorexia, arthralgias, and weakness. Radiologic examination may show an infiltrate, an effusion, hilar lymphadenopathy, or a combination of these findings. Skin manifestations include erythroderma, erythema nodosum, and erythema multiforme. Without specific therapy, the primary infection resolves spontaneously within several weeks in most cases. Radiographic residua in the form of nodules or thin-walled cavities are present in 5 percent of such cases. Spontaneous clinical resolution and radiographic residua were features of this patient's illness at the time of admission.

Extrapulmonary disease, which develops in less than 1 percent of patients with *C. immitis* infections, includes meningitis, osteomyelitis, septic arthritis, genitourinary infection, and skin involvement. The meningitis may be subtle in terms of both clinical findings and cerebrospinal fluid characteristics, warranting diagnostic vigilance. In regions where the infection is endemic, rapid and widespread dissemination in im-

munocompromised patients has closely paralleled the epidemic of the acquired immunodeficiency syndrome. Patients receiving corticosteroids or other T-cell suppressants, infants, and nonwhites (particularly Filipinos, for unclear reasons) are also susceptible to coccidioidomycosis.^{1,3}

The diagnosis can be confirmed by examination of smears of aspirated fluid from pulmonary or other sites. False positive results may be caused by the presence of contaminating pollens from mulberry, cottonwood, and elm trees.⁴ False negative results may be due to sampling error or a failure to alert the cytopathologist to the possibility of *C. immitis* infection. As in this case, reactive atypia of pneumocytes is often seen in cytologic aspirates, and if spherules are undetected, the reactive atypia may be mistaken for carcinoma.^{5,7} Tissue-biopsy specimens are superior to cytologic aspirates for direct visualization of the organism; the large endosporeulating spherules are readily visible with routine staining. Culture of the organism is possible but poses a major biohazard. Growth is generally visible within three to four days, although the yield is reduced in patients with HIV infection. Skin testing shows a delayed type of hypersensitivity to intradermally injected antigen in 93 percent of patients 14 days after the onset of symptoms, and in 99 percent at 21 days.⁸ An area of induration, at least 5 mm in diameter, that develops 24 to 72 hours after injection is considered a positive result, and determining the result within this period reduces the false positive rate.⁹ Waning of the reaction is slow, and a positive skin test therefore does not indicate the date of onset of the infection. Conversely, anergy, which may result from overwhelming infection, impairs the sensitivity of the test.

Serologic testing is very useful for diagnosing *C. immitis* infection. Primary infection elicits IgM antibodies in 90 percent of symptomatic patients within one to three weeks after the onset of symptoms, as detected by tube-precipitin, immunodiffusion, or latex-agglutination tests. Tests for complement-fixing IgG antibody become positive weeks after the onset of symptoms — after the IgM response — and the titer may parallel the disease activity and dissemination. False positive results can be caused by cross-reactivity of the organism with *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Serologic results may be negative if infection is confined to the meninges. Methods that circumvent these problems are being developed, such as direct detection of circulating antigen and detection of circulating genomic material by the polymerase-chain-reaction assay.^{1,3}

Inhalation of talc may explain the bilateral micronodular disease in this patient. Industrial-grade talc is commonly used to dust rubber products; it is lubricating, flaky, fibrous, and chemically inert. Talc is a hydrous magnesium silicate that also contains iron and trace amounts of aluminum. Industrial talc of-

ten contains mixtures of silicate, tremolite, amphibole and serpentine asbestos, anthophyllite, and other talcose rocks. The content depends on the mining source, and contamination by silica and asbestos has caused considerable confusion about the fibrogenicity and carcinogenicity of talc.^{10,11} Obtaining a precise history of exposure to talc, including the respiratory protection used and data on confounding exposure, such as exposure to other dusts or to tobacco smoke, is often a problem.

Inhalation is the most frequent form of exposure to talc. Although most talc-related illnesses are caused by exposure during the milling and processing of talc, industrial use of the end product, and even the use of talc in high doses for personal care have caused respiratory illness.^{10,12} Among the respiratory diseases associated with the inhalation of talc that does not contain silica or asbestos is talcosis, a bilateral, diffuse, micronodular, granulomatous disease affecting the pulmonary interstitium, with acute or chronic bronchitis. Emphysema with the formation of bullae may be present. The microscopical findings include diffuse interstitial fibrosis, occasionally with bronchial or bronchiolar distortion, ill-defined nodules with birefringent talc particles but with little of the whorled collagen that is characteristic of silicosis, and foreign-body granulomas with or without interstitial and pleural fibrosis.^{13,14} Pleural plaques may be present, especially after exposure to asbestos-containing talc. Reactions to pure talc usually result in less fibrosis than those to talc that contains silica, asbestos, or both.

Although there is a general dose-response relation in talcosis, progressive disease can occur in the absence of continued exposure, leading to progressive dyspnea, weight loss from labored breathing and hypoxia, and cor pulmonale with eventual right-sided heart failure. This patient had mild dyspnea and was slim, but no signs of profound hypoxia or cor pulmonale were apparent on physical examination or on the electrocardiogram. In patients with talcosis, chest radiographs typically show interstitial infiltration or granulomas in the midzones and bases of the lungs, with sparing of the apexes, in contrast to the distribution of lesions in patients with silicosis. Since talc is frequently mixed with silica and asbestos, the clinical and radiographic findings associated with these three dusts may merge. Both restrictive and obstructive disease can occur and even coexist in talcosis, as in other granulomatous diseases such as silicosis and sarcoidosis. Both airflow obstruction and small-airway disease have been observed in talc workers in the rubber industry.^{12,15} Symptoms are often mild, despite abnormalities on radiographs and pulmonary-function testing, again as with silicosis and sarcoidosis.

Rubber workers who have never been exposed to talc may have "industrial bronchitis" that persists in-

definitely after their exposure to rubber has ceased and they have retired. Multivariate analyses stratified for the confounding influences of cigarette smoking and preexisting lung disease suggest that, in addition to talc, fumes from curing and other particulates involved in rubber manufacturing are important airway irritants.^{12,16-18}

The biopsy report of adenocarcinoma of the lung in this case bears close scrutiny. Cellular atypia, particularly in the presence of an acute inflammatory condition, can be difficult to distinguish from carcinoma cytologically. A positive test for p53 protein may prove helpful in confirming the diagnosis of carcinoma in the future.¹⁹ The possibility of a false positive cytologic report must be considered in this man, who had symptoms of an acute illness compatible with tracheobronchitis. Atypia as a result of coccidioidomycosis has been reported.^{5,7} In this case, the radiographic stability of the lesion over the course of the illness, although nonspecific, is more compatible with the diagnosis of a subacute or chronic inflammation than with the diagnosis of carcinoma.

If the patient had adenocarcinoma of the lung, it may have been metastatic. The cancer may have originated in the gastrointestinal tract, kidney, or prostate gland. Gastric carcinoma has been linked to substances used in the chemical and rubber industries, including benzidine, α - and β -naphthylamine, crystalline silica, and asbestos, and also to drinking water containing nitrates.²⁰⁻²² However, there is no evidence that this man, who appeared well, had an extrapulmonary primary tumor.

The carcinogenicity of inhaled talc is controversial.^{10,23-25} Stille and Tabershaw²⁵ did not find an increased number of cases of lung cancer in employees of a talc-processing plant in New York State over a period of 31 years. Similar findings have been reported by other investigators.²⁴ Exposure to a combination of silica and talc, however, results in a higher rate of death from lung cancer than exposure to silica alone.²³ The carcinogenicity of silica has been proposed but has not been definitively demonstrated in humans²⁶⁻²⁸; the carcinogenicity of asbestos is well documented.²⁹ Industrial exposure to a mixture of talc and silica or talc and asbestos may explain the development of lung cancer in this patient, who did not have a history of heavy smoking, but it is an unlikely explanation. A considerable number of nontalc substances used in the rubber industry are also known or suspected lung carcinogens, such as nitrosamines. Although bronchogenic carcinoma, especially adenocarcinoma, can occur in the absence of known exposure to carcinogens, such cases account for less than 5 percent of cases of lung cancers in the general population. The risk of lung cancer depends partly on host factors, including the presence or absence of preexisting lung disease, diet, family history, and genetic factors.³⁰ Polymorphisms of genes associated

with carcinogenesis have been reported to confer a risk of lung cancer.³¹

The need to identify a carcinogen or a host risk factor would be obviated by ruling out carcinoma in the lesion in question. Radiographic evidence of multiple lesions usually indicates the presence of either metastatic cancer or a noncancerous process. Bronchioloalveolar-cell carcinoma is a notable exception, with lesions that are often multifocal. A careful review of the cytopathological smears would therefore be an important diagnostic approach.

It is not clear whether this patient could tolerate resection of an adenocarcinoma. A curative lobectomy might remove enough functioning lung tissue to impair his subsequent tolerance of physical exertion. Until recently, the criterion for resectability of the lung was an estimated postoperative forced expiratory volume in one second (FEV₁) of 0.80 liter, a requirement this man might meet if he needed a right upper lobectomy, but not if he required a pneumonectomy. The refined criteria for operability include a measure of integrated cardiopulmonary and muscular function, a test readily available in most pulmonary-function laboratories.³²⁻³⁴ Some surgeons consider this test excessive and instead have patients walk upstairs to test their tolerance of exertion. The ability to climb three flights of stairs may be correlated with maximal oxygen uptake rate.³⁵

This patient's ratio of FEV₁ to vital capacity is low, clearly indicating an obstructive component of his pulmonary dysfunction that was unresponsive to the inhalation of a β_2 -agonist. The usual sites of airflow obstruction that are evident on spirometry are the small bronchi and bronchioles, as in patients with asthma, emphysema, or chronic bronchitis. This patient's low forced expiratory volume may be due to air trapping behind obstructed airways or to an independent restrictive process, such as interstitial fibrosis. These two possibilities are best distinguished by body-box plethysmography. The high values for residual volume and total lung capacity are compatible with severe air trapping as the predominant dysfunctional process. Major or minor airway obstruction, bullous lung disease, or both can cause this pattern, but bullae were absent on CT scanning. The low carbon monoxide diffusing capacity (which can be falsely decreased by anemia and heavy cigarette smoking, neither of which applies to this patient) must be attributed to parenchymal damage, probably similar to that causing the air trapping.

Possible explanations for this patient's lung dysfunction include one or more of the following: small-airway disease due to coccidioidomycosis, chronic obstructive small-airway disease caused by exposure to talc or rubber fumes, previously undetected chronic airflow obstruction of unknown origin, or a confounding repair process such as bronchiolitis obliterans with or without organizing pneumonia. A patho-

logic repair process often occurs after a variety of pulmonary insults such as viral infections in infants and young children, *M. pneumoniae* or *L. pneumophila* infection in adults, inhalation of nitrogen oxide, connective-tissue disease, drug reactions, and bone marrow and lung transplantation.^{36,37} Tests of airway resistance and conductance measure airflow across the smallest total cross-sectional area of the airways — paradoxically, the large airways; thus bronchiole-based lesions have relatively little effect on such measurements.³⁸ In cases of bronchiolitis, measurements of lung volume may reveal hyperinflation, reflected by high values for functional residual volume and total lung capacity. One usually expects a greater abnormality in gas transfer than that demonstrated by ambulatory oximetry in this patient, although the technique used even for this simple maneuver can be questioned. Finally, this patient's initial chest CT scan was not of high resolution and therefore would not have revealed the bronchiolar-wall thickening, bronchiolar dilatation, and mosaic perfusion that have been reported on high-resolution CT scanning in patients with this disorder.^{39,40} Expiratory-phase, high-resolution CT scanning, which might have been helpful in detecting air trapping, was not performed.

In conclusion, I believe that this patient had acute coccidioidomycosis, possibly complicated by obliterative bronchiolitis, with underlying talcosis and silicosis. I doubt that he had bronchogenic carcinoma.

The most important diagnostic procedure would have been a reexamination of the cytologic smear to detect coccidioidomycosis spherules or to confirm the presence of a malignant tumor. The decision to perform an excisional biopsy would have depended on the results of this reexamination.

CLINICAL DIAGNOSES

Talcosis.
Carcinoma of the lung.

DR. SIMON D. SPIVACK'S DIAGNOSES

Talcosis and silicosis due to occupational inhalation of talc.
Acute primary coccidioidomycosis, possibly with obliterative bronchiolitis.

PATHOLOGICAL DISCUSSION

DR. EUGENE J. MARK: The diagnostic procedure was an exploratory thoracotomy. The surgeon felt a mass in the right upper lobe and performed a lobectomy. He also removed two smaller nodules from the right lower lobe.

The right upper lobe contained numerous firm, gray nodules, 1 to 7 mm in diameter. On microscopic examination, they were circular or resembled a caput medusae (Fig. 3). They were composed of histiocytes, including multinucleated forms of a for-



Figure 3. Cellular Nodule with a Caput Medusae Configuration (Hematoxylin and Eosin, $\times 35$).

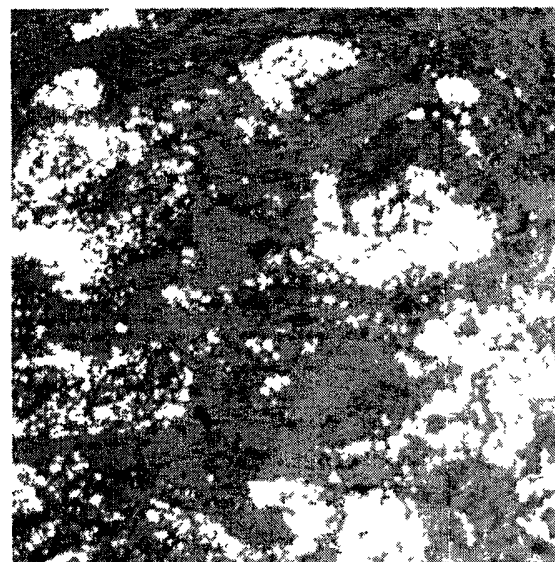


Figure 4. Clusters of Birefringent Talc Crystals within Fibrotic Tissue, Viewed under Partially Polarized Light ($\times 75$).



Figure 5. Large Nodule with Hyalinized Fibrous Tissue in the Center (Hematoxylin and Eosin, $\times 20$).



Figure 6. Multiple Ferruginous Bodies and Histiocytes in an Alveolus (Hematoxylin and Eosin, $\times 330$)

cign-body type. Pale-yellow birefringent crystals were packed into clumps and sheaves within the histiocytes or in fibrotic tissue (Fig. 4). The centers of the larger nodules were replaced by hyalinized fibrous tissue (Fig. 5). Long crystals of talc encrusted with iron formed ferruginous bodies in some areas (Fig. 6). These crystals account for one type of pseudo-asbestos body. True asbestos bodies were present as well, but the interstitial fibrosis characteristic of asbestosis was absent. The appearance of the lesions and the presence of the crystals are characteristic of talcosis.^{15,41}

The largest mass, which was 3 cm in diameter, had a central cavity that contained a watery mixture of talc (Fig. 7). The only case with similar pathological features described in the literature consisted of multiple loculated cavities filled with talc; the talc in that case, however, had probably entered the lung through a bronchopleural fistula after the instillation of talc in the pleural cavity to treat recurrent pleural effusions.⁴²

Inhalation of finely dispersed talc probably caused the diffuse disease in this case, and a plug of talc probably led to the formation of the cavity. Also, histiocytes and talc crystals had eroded into pulmonary arteries in the vicinity of the cavity and caused an obliterative endarteritis (Fig. 8), which may have had a role in causing cavitation. Talc and other silicates tend to cause intense vascular inflammation and sclerosis, which contributes to the pulmonary scarring.^{15,43-45} There were no compact granulomas, the presence of which would have suggested infection, nor were any organisms detected with special stains. Pneumocytes in areas of scarring were reactive and atypical, probably accounting for the cytologic diagnosis of adenocarcinoma. Unfortunately, the cytologic smears were not available for review at this hospital.

Talc usually produces small nodular scars or linear interstitial fibrosis, which can lead to bronchiectasis, honeycomb fibrosis, or both, as well as progressive massive fibrosis.^{41,43} Areas of massive fibrosis can appear radiographically as central or peripheral masses, and in some cases, they have been resected surgically.⁴¹

Impacted talc was found to have plugged and destroyed bronchioles in a child who died after aspirating talcum powder.⁴⁶ Tumor-like masses on chest radiographs of workers in two talc factories in Greece were thought to be due to concretions of talc that had obstructed bronchioles and then caused atelectasis and fibrosis.⁴⁷

Historically, workers in talc mines and mills were at greatest risk for talcosis.^{15,41,47} Rubber workers are now probably the most commonly exposed persons.^{41,43,48,49}

DR. DAVID J. KANAREK: This patient worked in eastern Massachusetts for 28 years, making bands eight hours a day, and every time he made a rubber band, he sprayed it with talc. Then he moved to Arizona. His exercise tolerance was very good, despite the results of the pulmonary-function tests.

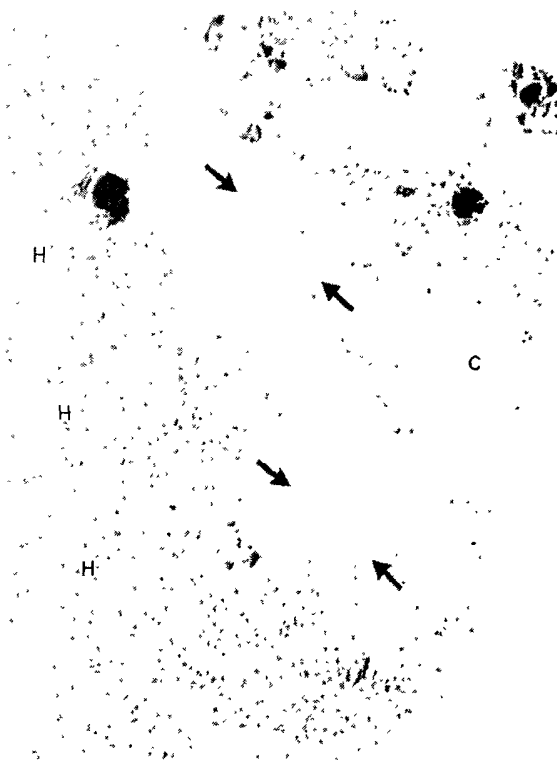


Figure 7. Edge of a Cavity (C), Containing Groups of Pale Talc Crystals (between Arrows) and Talc-Laden Histiocytes (H) (Hematoxylin and Eosin, $\times 20$).

Calcified concretions (dark staining) are present (top).

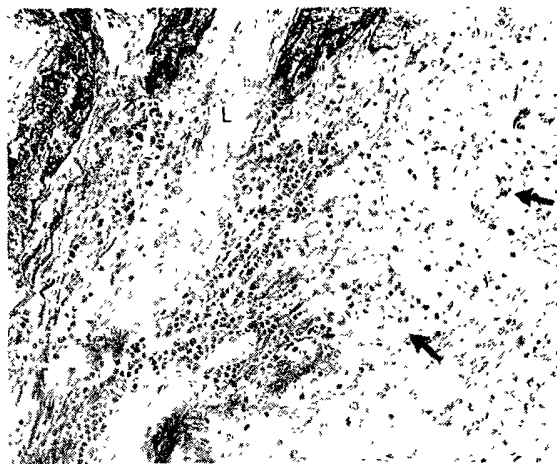


Figure 8. Thrombosed Artery Adjacent to the Cavity (Verhoeff-van Gieson Stain, $\times 150$).

Histiocytes (arrows) with talc crystals have eroded the arterial wall, causing reduplication of elastic fibers (black) and fibrosis and narrowing of the lumen (L)

DR. SPIVACK: What was the acute illness, and why did the pulmonary-function studies show such marked abnormalities?

DR. KANAREK: The patient probably had a respiratory tract infection, which prompted his physician to obtain the radiograph of the chest; the talcosis was an incidental finding. The pulmonary-function studies showed much more hyperinflation than one would expect from viewing the radiologic images. The hyperinflation was probably related to the obliteration of the airways seen on microscopical examination.

DR. MARK: In addition to bronchiolar scarring due to the inhalation of talc, there was also marked centriacinar emphysema, probably related to smoking.

ANATOMICAL DIAGNOSIS

Pulmonary talcosis, with liquified mineral in a cavitated tumor-like mass, granulomatous inflammation, and sclerosis.

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