



Hypercalcemia Due to Talc Granulomatosis*

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Pulmonary disease due to talc, a group of hydrous magnesium silicates, is almost exclusively encountered after occupational exposure. One form of this rare disorder is talc granulomatosis. In varying degrees, hypercalcemia is typical of granulomatous disease but has not yet been reported in talcosis. We report the case of a former mold maker who presented with hypercalcemia. Laboratory findings indicated extra-renal 1- α -hydroxylation of 25-hydroxyvitamin D. Pulmonary infiltrates prompted a lung biopsy that disclosed talc granulomatosis. We suggest that talc granulomatosis should be added to the list of granulomatous disorders capable of causing hypercalcemia due to increased extra-renal 1- α -hydroxylation of 25-hydroxyvitamin D.

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Talc, a heterogeneous group of hydrous magnesium silicates, is widely used as a glidant and lubricant for a broad variety of industrial purposes. Manufacturing of ceramic, plastic, rubber and cosmetics accounts for the majority of talc consumption worldwide, but even the paint and confectionery industries use talc. Talc granulomatosis is one form of pulmonary disease due to inhalation of pure talc. We report the first case of hypercalcemia, a salient feature of many granulomatous disorders, in a 68-year-old former mold maker with talc granulomatosis.

CASE REPORT

A 68-year-old man was found to have a serum calcium concentration of 3.36 mmol/L and an increased serum creatinine of 281 μ mol/L at a routine follow-up examination for aortic and mitral valve replacement that had been performed in 1997. At that time, both calcium and creatinine concentrations had been within the normal range. However, a chest roentgenogram had shown reticulonodular infiltrations of both lung fields that had

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been interpreted as sequelae to congestive heart failure. The patient had occasionally observed a dry cough, without shortness of breath or fatigue for years. He was a nonsmoker and had already presented with hypercalcemia 6 months earlier when he had eventually undergone neck exploration elsewhere for suspected hyperparathyroidism based on elevated parathyroid hormone values. To the consternation of his physicians, all four parathyroid glands had been normal. Thereafter, his serum calcium concentrations had decreased to within the normal range. The patient was a retired gardener but had worked at various professions. He denied weight loss, immobilization, excessive intake of milk, thiazide diuretics, vitamins or over-the-counter medications. On admission, he appeared chronically ill. His cardiac examination revealed no evidence of aortic or mitral prosthesis malfunction. He had harsh, end-inspiratory crackles over both lung fields. There was no evidence of congestive heart failure. Pulmonary function tests revealed almost normal lung volumes with a mild decrease in diffusing capacity. A chest roentgenogram showed extensive nodular infiltrations of both lung fields (Fig 1). A CT scan confirmed multiple ill-defined coalescing nodular structures. Lymph nodes of up to 1 cm in diameter were observed in the mediastinum. The alkaline phosphatase concentration was 11 U/L (normal), parathyroid hormone concentration < 10 ng/L (low), 25-hydroxyvitamin D 60 nmol/L (normal), and 1,25-dihydroxyvitamin D 201 pmol/L (elevated). Angiotensin-converting enzyme levels were normal. An open lung biopsy was performed, revealing fibrous reactions with granuloma formation. The granulomas were atypical for sarcoidosis. Microscopy with polarized light demonstrated the presence of talc (Fig 2). Inquiries into the occupational history revealed that he had manufactured molds for porcelain insulators during the 1960s. Talc was used to permit the separation of the insulators from the molds. A diagnosis of talc pneumoconiosis



FIGURE 1. Chest roentgenogram on admission; note the extensive reticulonodular and patchy infiltrations in both lung fields.

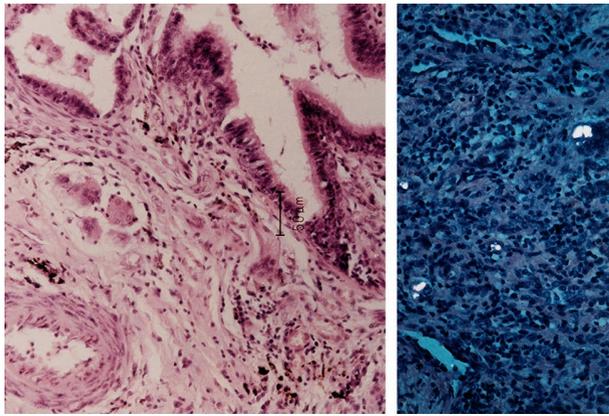


FIGURE 2. Specimen obtained during open lung biopsy. *Left:* foreign body giant cells with inclusions and mild fibrosis (hematoxylin/eosin stain, original $\times 250$). *Right:* microscopy with polarized light reveals strongly birefringent particles typical of talc deposition.

was made, and the patient responded well to steroids; serum calcium and serum creatinine reverted to normal.

COMMENT

Talc¹ is defined as hydrous magnesium silicate with the approximate formula $Mg_3(Si_2O_5)_2(OH)_2$. A crystalline structure of magnesium ions sandwiched in between sheets of silica accounts for the smoothness commonly associated with talcum powder. Five to six million tons of talc are mined yearly throughout the world. Consumer applications of talc include pharmaceutical tablet production, confectionery manufacturing, and cosmetic applications such as antiperspirant sticks or body powder. In contrast, impure talc, used as a gliding, lubricating, or dusting agent for industrial purposes, contains free silica, sulfides, asbestos, and iron. Since Thorel's original description in 1896, talc pneumoconiosis² has been attributed to various contaminants such as silica, rather than talc itself, and the term mixed pneumoconiosis has been coined. Mixed pneumoconiosis in mold makers, our patient's earlier profession, has been reported previously.³

Our patient presented with severe hypercalcemia, and laboratory findings indicated increased 1,25-dihydroxyvitamin D production. We felt that sarcoidosis, a disorder not infrequently complicated or even heralded by hypercalcemia, was the most likely diagnosis and concluded that the elevated parathyroid hormone value leading to neck surgery was probably erroneous. However, hypercalcemia from granulomatous disease can occasionally be associated with elevated instead of low parathyroid hormone values. Young et al⁴ recently described a patient with sarcoidosis who had a parathyroid hormone concentration above normal. In that patient, parathyroidectomy was also performed, revealing normal glands. The combination of sarcoidosis and hyperparathyroidism is quite uncommon, but has been reported.⁵ Interestingly, sarcoid granulomas may also produce parathyroid hormone-related peptide.⁶ Extra-renal 1- α -hydroxylation of 25-hydroxyvitamin D by

activated macrophages in granulomatous lesions is believed to be primarily responsible for hypercalcemia.^{4,7} Considerable overlap has been reported between talc pneumoconiosis and sarcoidosis, both in terms of clinical presentation and laboratory findings.⁸

The list of granulomatous disorders that are capable of endogenous 1,25-dihydroxyvitamin D production is a lengthy one and includes diverse conditions such as tuberculosis, leprosy, and Crohn's disease. Recently, cat-scratch disease was added.⁹ Reporting the first case of hypercalcemia in this disorder, we believe that talc pneumoconiosis should be added to the list. We conclude that granulomatous disorders in general are capable of causing hypercalcemia by increased 1- α -hydroxylation of 25-hydroxyvitamin D in activated macrophages.^{4,7}

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Bilateral Diaphragm Paralysis Secondary to Central von Recklinghausen's Disease*

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Bilateral paralysis of the diaphragm is either idiopathic or associated with several medical conditions, including trauma or thoracic surgery, viral infections, and neurologic congenital or degenerative disorders. We describe the case of a 36-year-old man with a history of neurofibromatosis who developed severe bilateral diaphragmatic paralysis from involvement of the phrenic nerve roots with neurofibromas. The patient manifested progressive exer-