cell-mediated immunity to thyroid tissue are present and jury. Graves' disease has also been suggested as a subacute (giant cell) thyroiditis. Viral titers have been a history of a preceding upper respiratory tract infection and Hashimoto's and Graves' disease they probably reflect PULMONARY CALCIFICATION IN MULTIPLE MYELOMA

The right lung weighed 1000 grams, the left 450. The upper lobe of the right lung showed a tumor measuring 8×7 cm. It was gray, soft and extended into the trachea through the upper lobe bronchus. Microscopically, the tumor was composed of poorly differentiated cells showing frequent mitotic figures. Neither keratinization nor mucin production was identified. Hilar nodes showed metastatic anaplastic carcinoma.

**Discussion**

Viruses probably represent the etiologic agents in subacute (giant cell) thyroiditis. Viral titers have been observed to increase during the course of the disease and a history of a preceding upper respiratory tract infection is common. Viruses probably represent the etiologic agents in subacute (giant cell) thyroiditis. Viral titers have been observed to increase during the course of the disease and a history of a preceding upper respiratory tract infection is common.

The etiology of giant cell myocarditis is not known. The giant cells seen in this entity, although in some instances reminiscent of both the Langhans' and foreign body types, most probably represent myocytes undergoing regeneration. Although the coexistence of the above diseases may be coincidental, their coassociation suggests a common etiology, viral infection. Immune mechanisms have been implicated in the pathogenesis of both thyroid and myocardial disease. The former is best exemplified by Hashimoto's struma in which both cell-mediated immunity and antibodies directed against thyroid antigens have been demonstrated. The latter appears to be significant etiologically while the former appears to represent a response to tissue injury.

**References**


**Pulmonary Calcification in a Patient with Multiple Myeloma**

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A patient with multiple myeloma and hypercalcemia was treated with intravenous sodium sulfate and prolonged oral sodium phosphate. She subsequently developed extensive metastatic calcification in the lungs, alveolar-
capillary block and severe respiratory distress. The probable mechanism of phosphate and sulfate induced soft tissue calcification in hypercalcemia is reviewed and caution is urged in the administration of phosphate as a hypocalcemic agent.

Elevation of serum calcium levels in patients with neoplastic disease, with or without skeletal metastasis is well known. The ability of phosphates to lower serum calcium levels in myeloma and hypercalcemia. Since then inorganic phosphates, administered either orally or intravenously, have attracted attention as an effective means of treatment for hypercalcemia of various origins. This treatment is not without complications as evidenced by reports of metastatic calcification,4,5 hypotension,6 acute renal failure and hypocalcemia.7 Recently we studied a patient with multiple myeloma, in whom widespread metastatic calcification occurred following intravenous sodium sulfate and prolonged oral sodium phosphate therapy for hypercalcemia.

Case Report

A 63-year-old white woman was admitted to The Mount Sinai Hospital because of fatigue, weakness and weight loss. Significant physical findings included palpable liver and spleen, two and three fingerbreadths below the right and left costal margins respectively. Laboratory data showed hemoglobin 5.2 g per 100 ml, white blood cell count (WBC), 17,000 per mm², platelets 120,000 per mm², erythrocyte sedimentation rate 105 mm in the first hour, calcium 12.6 mg per 100 ml, phosphorus 4.4 mg per 100 ml. Urine contained 4+ protein and 3+ calcium. Serum electrolytes, blood urea nitrogen, bilirubin and cholesterol were normal. Radiographs of the chest were unremarkable. Radiographs of the skull revealed multiple lytic lesions. A bone marrow aspirate showed sheets of plasma cells. A 24-hour urine specimen contained 12 gm of Bence Jones protein per liter. Plasma electrophoresis showed an extra spike, quantitated at 0.9 gm per 100 ml, located between beta and gamma spikes, and the immunoelectrophoresis showed the spike to consist of type II (lambda) Bence Jones protein. A diagnosis of multiple myeloma was made and the patient was discharged on melphalan (Alkeran), allopurinol and prednisone treatment. She was subsequently treated with intermittent blood transfusions for anemia, and with ferrous sulfate and sodium fluoride.

She was readmitted to the hospital because of severe back pain. The spleen was palpable one fingerbreadth below the right costal margin and moderate pitting edema was noted. Radiographs of the spine showed osteoporosis and partial collapse of several lumbar vertebrae; the myelogram revealed bilateral extradural involvement from L1 to L4, without complete block. Serum calcium levels reached up to 13.8 mg per 100 ml. The patient was treated with radiotherapy to the back, blood transfusions and sodium fluoride after which she showed symptomatic improvement. Two weeks later she was admitted for the third time because of nausea and vomiting. The lungs were clear to percussion and auscultation. Both spleen and liver were palpable. Stool contained occult blood, and clotted blood was aspirated from the stomach. Initial laboratory data showed hemoglobin 3 gm per 100 ml, platelets 230,000 per mm², WBC 44,000 per mm², calcium 14.5 mg per 100 ml, glucose 135 mg per 100 ml, potassium 5.8 mEq per liter. The urine contained large amounts of Bence Jones protein. Bilirubin was 12.0 mg per 100 ml (direct 9.0), cholesterol 184 mg per 100 ml, SGOT 1000 units, LDH 160 units, SGPT 800 units, alkaline phosphatase 350 international units. Upper gastrointestinal series showed a large pyloric peptic ulcer.

The patient was treated with sodium fluoride, sodium sulfate and phosphate, gelusil and allopurinol. The major clinical problem was jaundice, maintenance of normal serum calcium and respiratory symptoms that began about eight weeks before death. Chest radiographs, which were initially clear, showed increasing generalized thickening of interstitial markings (Fig 1). However the lungs remained clear to auscultation until a few days prior to the patient's death, when she developed multiple bilateral rales. She complained of nonproductive cough, pleuritic pain, and in her last few days severe dyspnea. Arterial gas studies showed pH 7.8, Pco₂ 41 mm Hg, and Po₂ 51 mm Hg. Serum electrolytes and urea remained normal. Tests of liver function, though still abnormal were much improved; calcium levels remained relatively normal except when the patient refused oral phosphate therapy or the medication was withheld (Fig 2). Anemia was moderate. She became disoriented, developed progressive respiratory failure and died 13 weeks after admission.

Postmortem Examination

The heart showed left ventricular hypertrophy. The right and left lungs, which weighed 850 gm and 750

Figure 1. Chest radiograph few days prior to patient's death showing extensive interstitial markings throughout both lung fields.

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respectively, were very firm, and their external surfaces showed miliary yellowish nodules ranging from 1 mm to 5 mm in size. The cut surface was gritty and yellowish. One of the upper calyces of the right kidney contained a calculus measuring 1x0.5x0.5 cm. The arteries in most organs showed severe calcification of their walls.

Microscopic examination of the lungs disclosed widespread calcification involving mainly the alveolar septa. There was severe proliferative alveolitis characterized by intra-alveolar fibroblastic proliferation, occasional obliterated alveolar spaces and a few giant cells (Fig 3). All lobes of the lung were uniformly involved. Extensive calcific deposits were seen in the blood vessels of all organs. These were predominantly in the media of large- and medium-sized arteries. The intima showed mild cellular proliferation and severe edematous swelling. Focal calcific deposits were scattered throughout the myocardium (Fig 4), both kidneys, particularly within the interstitium, tubular epithelium and occasional Bowman’s space. The architecture of the spleen and lymph node was destroyed by sheets of mature and immature plasma cells. The liver revealed subsiding hepatitis and deposits of myeloma cells.

**DISCUSSION**

Metastatic calcification resulting from hypercalcemia is well recognized, although the frequency with which it occurs is difficult to assess. Virchow documented the first case of metastatic calcification in a woman with disseminated carcinoma. Mulligan found a total of 88 cases reported in the world literature. Less well known, however, is metastatic calcification following phosphate therapy in hypercalcemia of neoplastic origin. In 1930, Bulger and colleagues reported the first case in a patient with multiple myeloma and hypercalcemia who had received oral supplements of phosphate. At autopsy, extensive calcification was found in the lungs, gastric mucosa and the kidneys. In a review of the literature we found 24 cases manifesting this complication of phosphate therapy in hypercalcemia of neoplastic origin.

There was equal sex ratio and the ages of the patients ranged from 19 to 68 years. The period over which phosphate was administered lasted few hours to three months. About half of the cases showed extremely high levels of serum calcium, precipitous fall in calcium levels following phosphate treatment and were moribund at the start of the treatment. They also showed less soft tissue calcification than those cases that received

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**Figure 2.** Serum calcium levels during final hospitalization. Note hypercalcemic episodes correspond to interruption of sodium phosphate administration.

**Figure 3.** Photomicrograph of the lung showing severe alveolar calcification and partial occlusion of alveolar spaces by proliferative alveolitis (hematoxylin-eosin × 100).
prolonged oral or intermittent intravenous therapy. The lungs and kidneys were involved in all cases and fewer than a quarter showed involvement of other organs notably myocardium and stomach.

The parameters pertinent to metastatic calcification include blood pH, serum calcium and phosphorus levels and their ionic product and tissue phosphatase activity. Thus, clinical situations characterized by elevated serum phosphorus (hypoparathyroidism) or elevated serum calcium (hyperparathyroidism, vitamin D intoxication), show metastatic calcification. The patient reported here was treated with intravenous sodium sulfate, oral sodium phosphate and prednisone. Steroids are known to decrease the absorption of calcium from the gastrointestinal tract and to increase the urinary output of calcium. The effect of prednisone on calcium metabolism in patients with multiple myeloma and hypercalcemia was investigated by Bentzel and co-workers. They observed a lowering of serum calcium levels due to a reduction in the miscible calcium pool, bone formation rate and bone resorption rate as determined by 47Ca kinetics studies.

In studies reported by Kahil and colleagues and by Chakamakjian and Bethune, administration of sulfate produced a striking increase in urinary calcium excretion. Sulfate enhances renal excretion of calcium by increasing delivery of sodium to the distal tubule and also by the formation of a nonreabsorbable calcium-sodium-sulfate complex. The mechanism by which phosphate lowers serum phosphate was investigated by Herbert and co-workers, who found that the fall in serum calcium was directly proportional to the magnitude by which calcium biphosphate (CaHPO₄) solubility was exceeded during phosphate infusion. Their data was consistent with the view that phosphate lowers serum calcium by simple physico-chemical precipitation of CaHPO₄. These findings were confirmed by Stamp, who also found that the decline in plasma calcium is directly proportional to both plasma phosphorus increment and to the initial height of plasma calcium. In addition he showed that metabolic factors (preexisting bone resorption or osteoblastic activity) may be important determinants in the fall of plasma calcium.

Controversy exists as to whether the metastatic calcification seen in hypercalcemic patients treated with phosphates is due to hypercalcemia per se or is it enhanced by the administered phosphate. Many authors favor the view that extraskeletal calcification is not necessarily a complication of phosphate therapy while others stress the real dangers that exist in the use of this form of therapy. In the present case metastatic calcification could be explained on the basis of prolonged hypercalcemia per se, treatment with steroids, sulfate and phosphate, operating singly or in combination. However, considering the precipitous fall in serum calcium following phosphate administration, it is conceivable that the latter constitutes an important contributory factor to soft tissue calcification.

The present case is similar in many ways to previously reported cases but differs from them in the extent of pulmonary involvement. Symptomatology resulting from metastatic calcification has not been emphasized by previous reports, except for renal failure. The prominent respiratory symptoms probably stemmed from the development of alveolar capillary block caused by extensive deposits of calcium in the alveolar septa and severe diffuse proliferative alveolitis.

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Calcific Rheumatoid Constrictive Pericarditis with Cardiac Failure Treated by Pericardiectomy*

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A 74-year-old man with classic rheumatoid arthritis developed constrictive pericarditis accompanied by gross pericardial calcification. Pericardiectomy was followed by marked clinical improvement, substantiated by hemodynamic data. Immunofluorescent staining of the resected pericardium demonstrated precipitates of IgG, IgM, and complement C3. Similar precipitates were not encountered in normal pericardium or pericarditis due to other etiology.

Rheumatoid pericarditis is generally a benign and self-limiting process, and it rarely leads to constrictive pericarditis requiring pericardiectomy. A review of the literature has yielded studies on 28 patients who underwent surgery for the treatment of rheumatoid constrictive pericarditis; their ages ranged from 19 to 70 years. Radiographic evidence of calcification was not seen in any of these patients, but microscopic calcification was encountered in one case. Hemodynamic data substantiating symptomatic improvement are sparse. Immunofluorescent staining of the resected pericardium has not been described in the reported cases. This report deals with a 74-year-old patient with rheumatoid calcific constrictive pericarditis, in whom hemodynamic and immunofluorescent studies were obtained.

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