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## Demonstration of Pulmonary Calcinosis by $^{99m}\text{Tc}$ Diphosphonate Bone Scanning

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### $^{99m}\text{Tc}$ 骨スキャンで検出し得た肺石灰症の一例

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高カルシウム血症を伴つた胃癌患者に施行した  $^{99m}\text{Tc}$  ジホスホネートによる骨スキャンで、両側肺に著明な RI 集積を認めた。スキャン施行 9 日後に剖検して得た肺の組織標本で、肺胞壁の強い石灰化が認められた。高カルシウム血症患者における骨スキャン用 RI の肺への集積メカニズムに関しては議論のある所であるが、我々の症例の肺

の組織所見は、肺胞壁に沈着するカルシウムに取込まれるという説を示唆するものである。

高カルシウム血症に肺石灰症は、しばしば伴うが、X線写真で診断するのはきわめて困難であるので、本症の診断に骨スキャンは有効であると思われる。

Radionuclide bone scanning is a sensitive indicator of skeletal diseases and its clinical usefulness is widely accepted. In addition to skeletal diseases, various soft tissue lesions caused by deposition of calcium are also demonstrated<sup>1,2)</sup>. The following case report describes the intense uptake of  $^{99m}\text{Tc}$  diphosphonate found in a patient with histologically proved pulmonary calcinosis.

#### Case Report

A 38 year old man was referred to this hospital for evaluation of epigastralgia and dysphagia. Upper gastrointestinal series and endoscopic examination disclosed a large mass in the cardia of the stomach. Biopsy

during the endoscopy established the diagnosis of adenocarcinoma.

Physical examination revealed swollen left supraclavicular lymph nodes and multiple firm nodules in the abdominal wall. Liver and spleen were not enlarged. He was treated with combination of radiation by  $^{60}\text{Co}$  and arterial infusion of 5-fluorouracil. His condition, however, did not improve and he began to have back pain. Bone scan was ordered to rule out bone metastasis. Multiple images of the bone were obtained 3 hours after injection of 15 mCi of  $^{99\text{m}}\text{Tc}$  diphosphonate. Multiple areas of increased activity indicating bone metastases were seen in the thoracic and lumbar vertebrae (Fig. 1a) and dense uptake of radionuclide was also seen in the whole lungs (Fig. 1b). A chest X-ray obtained on the next day of the bone scanning did show increased interstitial markings in both lower lung fields and pulmonary edema and/or lymphangitis carcinomatosa were suspected (Fig. 2). At that time his urea nitrogen was 104 mg/dl, creatinine 5.6 mg/dl, calcium 18.5 mg/dl, lactic dehydrogenase 1285 U/l, and alkaline phosphatase 162 U/l. He deteriorated gradually and died 9 days after bone scanning.

At autopsy, metastatic foci were found in the lumbar vertebrae and ribs. There were bilateral pleural effusions of about 500 ml each and both lungs were edematous. The left and right lungs weighed 1800 g and 1200 g, respectively. Histologically metastatic calcification was found in the lungs and kidneys. The sections from both lungs showed extensive calcification in the alveolar septa (Fig. 3).

#### Discussion

A number of different processes associated with abnormalities in calcium and phosphorous metabolism have been reported to cause metastatic calcification. However, the most common causes of metastatic calcification are malignant bone tumor, chronic renal failure, hyperparathyroidism and hypervitaminosis D<sup>3</sup>. In this patient it is not possible to say with certainty which cause led to metastatic calcification of the lungs and kidneys, but multiple bone metastases from gastric cancer might be responsible for hypercalcemia which in turn predisposed to the precipitation of calcium salts in these organs. The possibility of the secondary hyperparathyroidism due to renal failure, however, can not be ruled out. Pathologically, the most common sites of

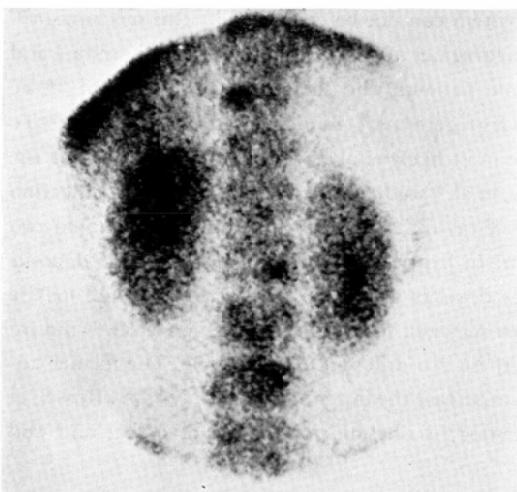


Fig. 1a. Posterior image of the vertebrae shows multiple areas of increased activity in the thoracic and lumbar vertebrae.



Fig. 1b. Anterior image of the chest does show increased activity in the both lungs.

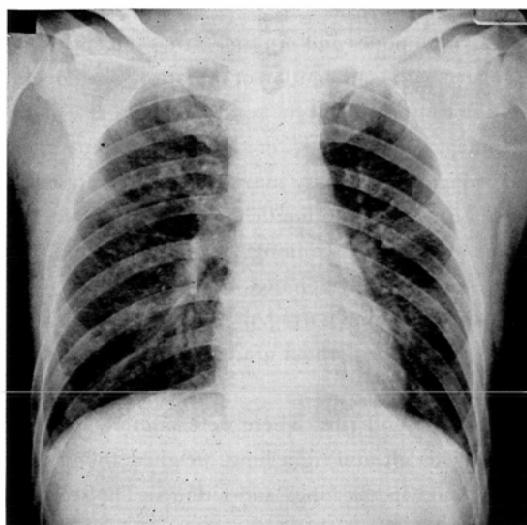


Fig. 2. PA chest X-ray reveals increased interstitial markings in both lung fields.

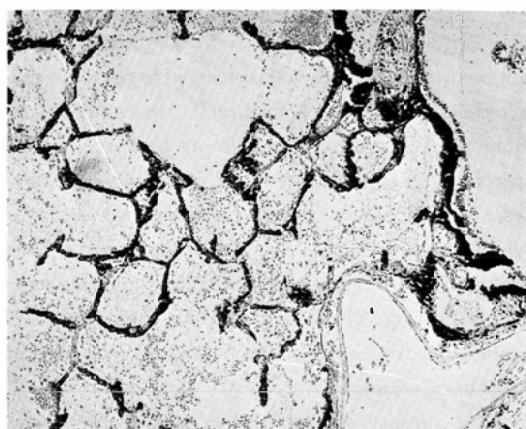


Fig. 3. Extensive calcification of the alveolar septa (von Kossa stain).

calcium deposition are the kidneys, lungs and gastric mucosa. The patient described in this report also had calcium deposition in the lungs and kidneys.

Several papers describing accumulation of bone scanning agents in the lung have been published<sup>4)5)6)7)8)</sup>, but only few cases are histologically verified<sup>5)6)8)</sup>. The exact mechanism of localization of  $^{99m}\text{Tc}$  diphosphonate in the lung with calcinosis is not clear. The possibility of preformed diphosphonate macroaggregates was ruled out because  $^{99m}\text{Tc}$  diphosphonate from the same vial were not taken up by the lungs of the other patients who had bone scanning on the same day. Chaudhuri, et al.<sup>4)</sup> proposed that pulmonary accumulation of activity might be due to the in-vivo formation of macroaggregates, but the uptake of diphosphonate in the bone or escape of diphosphonate through the pulmonary capillary system can not be explained by this mechanism<sup>7)</sup>. Schlangen, et al.<sup>8)</sup> did in-vitro studies of formation of macroaggregates of  $^{99m}\text{Tc}$  diphosphonate, phosphate and calcium within the serum obtained from the hypercalcemic patients who showed accumulation of  $^{99m}\text{Tc}$  diphosphonate in the lung, but no formation of macroaggregates was found. Chemisorption of  $^{99m}\text{Tc}$  diphosphonate by calcium complexes in the lung seems to be most likely explanation in our case, because the alveolar septa were extensively calcified histologically. Alfrey, et al.<sup>9)</sup> studied the nature of visceral calcification in hypercalcemic patients and uremic patients by means of X-ray diffraction method and demonstrated two distinct forms of calcium phosphate in visceral calcification. In hypercalcemic patients the visceral deposits were hydroxyapatite, but uremic visceral calciumphosphate deposits were mainly magnesium white lockite ( $\text{CaMg}_3(\text{PO}_4)_2$ ). In our patient both serum calcium and urea nitrogen were elevated. Conger, et al.<sup>10)</sup> did in-vitro studies of relative uptakes of  $^{99m}\text{Tc}$  diphosphonate by these two different calcifications. The former adsorbed nearly 98% of the radionuclide from the bath media, whereas the latter adsorbed only 24%. Russel, et al.<sup>11)</sup> have reported that pyrophosphate, diphosphonate analog, is physiological regulator of calcium and phosphate kinetics of bone.

Roentgenologically, metastatic calcification of the lung is rarely recognized prior to death<sup>12)13)14)</sup>. The difficulty in recognition may also be due to confusing shadows produced by associated cardio-renal conditions. Felson<sup>15)</sup> noted that differentiation of the calcification, which is primarily interstitial, from alveolar disease of

water density may be difficult. The chest roentgenogram in our case resembled the interstitial edema pattern in uremia or congestive heart failure. Conger, et al.<sup>12)</sup> reported the results of the pulmonary function studies showed a close relation between change in vital capacity, carbon dioxide diffusion capacity and blood oxygen levels, and the presence of interstitial lung calcification. These results, however, are not specific for the deposition of calcium in the lung and pulmonary function studies may show normal values until late stage of the disease. Bone scanning, therefore, might be useful for early detection of pulmonary calcinosis in the hypercalcemic patients with unexplained respiratory symptoms.

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