

## DIFFUSE INTERSTITIAL PULMONARY CALCIFICATION IN UREMIA: REPORT OF A CASE

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Recent progress in the treatment of chronic renal failure such as hemodialysis and renal transplantation have made the longer survival and rehabilitation of the patients possible. On the other hand, various complications have become the matter of problem in which metabolic disorder is one of the important. Here reported is a case of diffuse interstitial pulmonary metastatic calcification.

### CASE

A 26-year-old man was first said to have proteinuria at his high school age and treated as chronic nephritis at his family doctor's office. In 1973 he visited a hospital because of poor vision of the right eye where he was found to have proteinuria, high blood urea nitrogen level (40 mg/dl) and high blood pressure (230/140 mmHg), normal electrolyte level and bilateral retinal bleeding. After one year's hospitalization, the vision improved but kidney function got progressively impaired resulting in anorexia, vomiting, high blood urea nitrogen over 100 mg/dl and creatinine 9.5 mg/dl. Despite of peritoneal lavage of one month period, hypertension and general condition did not improve. He was transferred to us for hemodialysis on June 20, 1973 when urine output was 200 ml per day, hematocrit 10%, blood urea nitrogen 150 mg/dl, creatinine 15.9 mg/dl, blood pressure 170/100 mmHg, cardio-thoracic ratio 60% and there were

facial edema and findings of uremic lung on chest x-ray.

The external shunt was created for hemodialysis, which was performed three times per week. The dialysate used was Kindaly® II (calcium 5 mg/dl, acetate 33 mEq/L and magnesium 1.5 mEq/L). The biochemical data became stabilized to such levels as blood urea nitrogen 80~40 mg/dl and creatinine 12.0~7.0 mg/dl along with improvement of general conditions. In July 1973, he started intractable cough without remarkable changes on chest x-ray (Fig. 1). Various anti-cough medications were not effective. In September 1973, he began to complain of pain of the second phalanx of the left small finger with gradually progressing swelling.

His cough continued with occasional bloody sputum but without changes in the chest x-ray. In February 1974, the whole body bone scintigraphy using <sup>99m</sup>Tc diphosphate showed high uptake over the pulmonary field (Fig. 2). At this time, a magnifying x-ray film of the chest demonstrated punctate calcification (Fig. 3) which was first interpreted as metastatic calcification due to secondary hyperparathyroidism. The serum calcium was normal (10.4~9.3 mg/dl) but inorganic phosphorus remained high (10.5~9.8 mg/dl). Oral administration of Almi-gel of 3.0 grams per day was then commenced. Serum phosphorus level was effectively lowered to 4.4~3.0 mg/dl without change of cal-

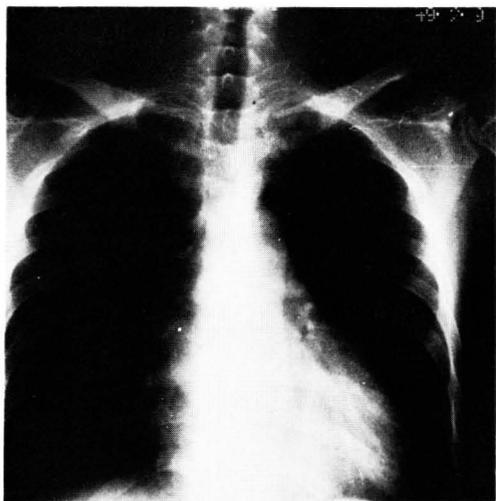


Fig. 1. Chest x-ray film shows unremarkable signs, but he complained of intractable cough.

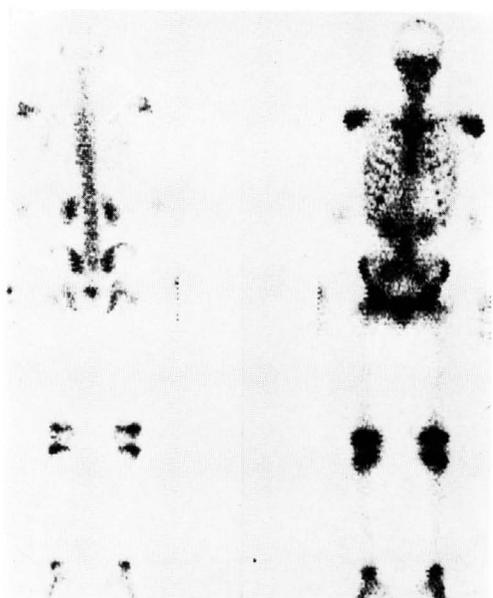


Fig. 2. Control patient of chronic hemodialysis shows moderate uptake of  $^{99m}\text{Tc}$ -diphosphate in whole body bone scintigraphy.

cium level and cough improved within one month and disappeared within two months of administration. At the same time, calcification of the left finger joint also disappeared. The repeated bone scintigraphy showed less uptake of the lung, the x-ray of which showing no distinct calcification any longer. The pulmonary function tests were within normal limits;

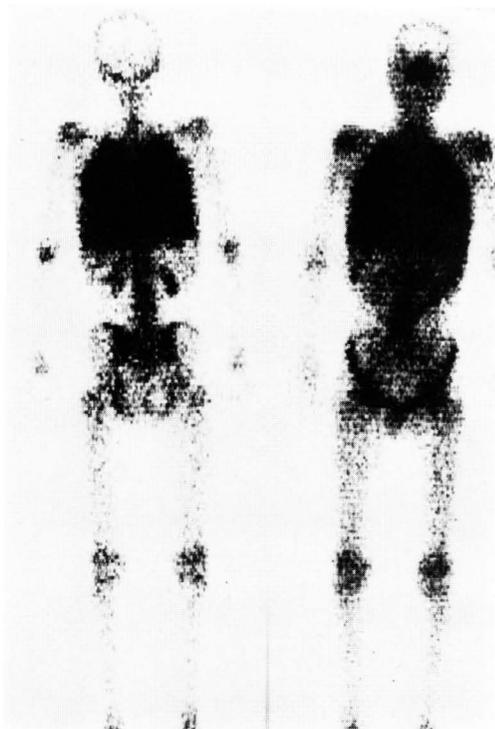


Fig. 3. High uptake over the pulmonary field in whole body bone scintigraphy using  $^{99m}\text{Tc}$ -diphosphate.



Fig. 4. Magnifying x-ray film of the chest demonstrated diffuse punctate calcification over bronchus, bronchiolus and alveolus.

vital capacity 3710 ml (91% of the normal expected value), lung capacity 134 L/min (104% of the normal expected value), one

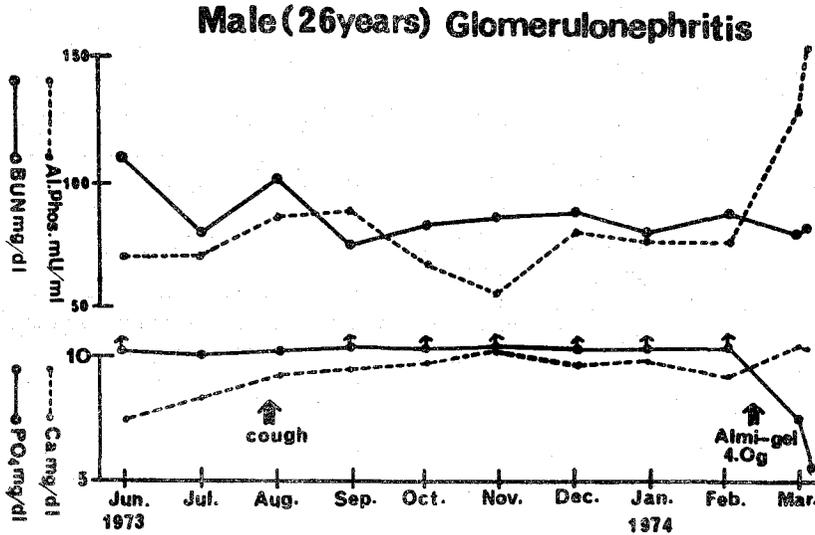


Fig. 5. Values of BUN, Al-P changed before and after oral administration of Alumi-gel®.

second expiratory volume 3180 ml (rate 86%). Changes of serum calcium, phosphorus and alkaline phosphatase were shown on Table 1. In August 1974, he was discharged from the hospital for the outpatient dialysis program. In September 1976, he became the father of a normal boy. Now (September 1978) his rehabilitation is full time, with the biochemical values such as blood urea nitrogen 60~80 mg/dl, creatinine 12.7~16.0 mg/dl, calcium 7.2~9.6 mg/dl, phosphorus 4.2~6.7 mg/dl, alkaline phosphatase 123~152 units, hematocrit 22%, cardio-thoracic ratio 48.3%.

#### DISCUSSION

Ectopic calcification was first reported by Virchow (1855)<sup>1)</sup> and 157 cases were collected in the Franke's report (1960), 79 of which being that of the lung. Ectopic calcification can be classified into four groups according to its causes, 1) bone disease, especially neoplasms such as myeloma, 2) chronic renal insufficiency, 3) parathyroid tumor and 4) hypervitaminosis D. In most of the reported cases of ectopic calcifications in chronic renal insufficiency, the usual locations reported are periarticular and vascular. On the

other hand, visceral metastatic calcification was few reported. Cardiac or pulmonary calcifications are, however, of great clinical importance because they can cause death or respiratory insufficiency. Wells (1911) stated that organs such as lung, kidney and stomach produce free hydrogen ion and the extracellular fluid becomes relatively alkaline particularly in the lung where the high oxygen and low carbon dioxide level in the alveolus leads to alkalization and calcium deposit. In the patients receiving hemodialysis, predialysis acidosis and postdialysis alkalosis might precipitate calcium.<sup>5)</sup> In 1941, Herbert<sup>6)</sup> attributed the cause of metastatic calcification in chronic renal insufficiency to the high  $\text{Ca} \times \text{P}$  product over 75. This is thought to be true even now, and hyperphosphatemia and high  $\text{Ca} \times \text{P}$  product are considered to be important. In hemodialysis patients, change of the serum pH due to hemodialysis, high calcium and acetate content of dialysate are also contributing factors.

In our case, administration of Alumi-gel® resulted in lowering the  $\text{Ca} \times \text{P}$  product and disappearance of symptoms.

Pulmonary calcification in chronic renal insufficiency was reported by Rubin<sup>7)</sup> and

Conger.<sup>8)</sup> In their reports, antemortem diagnosis was rare. Only one case was clinically diagnosed by chest x-ray out of 31 chronic renal insufficiency. Postmortem study, however, disclosed pulmonary calcification in 9 out of 15 autopsy cases including 8 extrapulmonary calcification. Therefore, metastatic calcification might be more prevalent but clinical detection of it is just difficult. In previous report, interstitial pulmonary calcification was usually massive with positive x-ray findings. Extremely fine calcification such as seen in our case began to appear in the reports as the result of progress of nuclear medicine particularly that of bone scintigraphy. In 1970, Holmes utilized 85-strontium and detected diffuse interstitial pulmonary calcification. At the present, we have more radionuclide methods using <sup>87m</sup>-strontium, 18-fluoride, and non-polar radiopharmaceutical including <sup>99m</sup>-Tc polyphosphate. Mechanism of <sup>99m</sup>-Tc labeled phosphate radiopharmaceuticals was first explained by "chemisorption" in which radioactive substance gets chemically bound with hydroxy-apatite crystals. It is, however, not probable because the calcium content in the organs is whitelockite compared with hydroxyapatite in the periarticular or vascular deposit as well as in the uptake in the non-osseous tissue. Binding with the tissue receptor such as alkaline phosphatase is suggested as a mechanism but it is still uncertain.

Patients with chronic renal insufficiency should be carefully evaluated by bone scintigraphy whenever respiratory symptoms, pulmonary edema or pneumonia persist. Reported cases of diffuse interstitial pulmonary calcification detected by use of isotope are mostly those seen in bone diseases or metastatic malignancies and rare in chronic renal insufficiency. The most important clinical aspect of diffuse interstitial pulmonary calcification is the deposit in the interalveolar wall leading to impairment of diffusion ability, finally to established alveolar capillary block syndrome. Early diagnosis might prevent such progress as in our case. As to treatment, it does not

diffuse from other type of metastatic calcification. Hyperphosphatemia can be controlled by administration of Almi-gel, vitamin D of active form, calcitonin and by lowering acetate content of the dialysate. Preventively, serum phosphorus should be kept below 6 mg/dl.

### CONCLUSION

A 26-year-old man with chronic renal failure due to chronic glomerulonephritis has been treated by hemodialysis and started to show intractable cough. Periarticular calcium deposit was also found. Six months after that, diffuse interstitial pulmonary calcification was detected by means of <sup>99m</sup>-Tc diphosphate. Excellent response was observed on administration of Almi-gel. Some discussion was made on the causes of metastatic calcification, and importance of <sup>99m</sup>Tc uptake in bone scintigraphy.

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## 和文抄録

## 肺に広範な Ca 沈着をきたした 1 症例

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長期血液透析療法の合併症の 1 つに Ca 代謝異常があり、腎性骨異栄養症とよばれる骨軟化症、線維性骨炎、骨多孔症と転移性石灰化がみられたりする。この転移性石灰化は骨や関節内および周囲組織にかぎらず、動脈、角膜、心、腎、肝、胃粘膜などの軟部組織にも起りうる。

今回頑固な咳嗽を主訴とした 26 歳の男子透析患者に、 $^{99m}\text{Tc}$ -polyphosphate をつかって全身のシンチグラフィを行なったところ、肺実質部で一様な高度の  $^{99m}\text{Tc}$ -diphosphate のとりこみがみられた。胸部 X 線像に注意すると気管支幹、末梢気管支、さらに肺胞部にも点状石灰化病変が広範にみられ、これが頑固な咳嗽の原因となったと考えられた。血清 Ca, P 濃度をふ

りかえて調べたところ血清 Ca 値は 10.4~9.3 mg % と正常値であったが、血清 P 値は 10.5~9.8 mg % と上昇していたことが判明した。直ちにアルミゲル 3.0 g, 3×分の経口投与を開始したところ Ca 値は 11.4~10.2 mg % と僅かに上昇したが、P 値は 4.4~3.0 mg % と著明に正常化し、投与開始後 2 カ月で咳嗽も消失し左手関節周囲の疼痛、腫脹も消失した。

その後経過をみてきたが、肺実質部の点状石灰化陰影も大幅に消失改善し、1975年9月には正常男子の出生をえて、1978年9月現在、週3回の血液透析で元気に社会復帰している 1 症例を報告し文献的検討を行なった。