jnm/CASE REPORT

METASTATIC CALCIFICATION DETECTED THROUGH SCANNING WITH ^{99m}Tc-POLYPHOSPHATE

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A patient with hypercalcemia, calcinosis of the kidneys, renal failure, and a poorly differentiated malignancy of the bone marrow has been found to have striking uptake of ^{99m}Tc-polyphosphate throughout the lungs and stomach. This finding, which has persisted over 9 months, appears to have been due to metastatic calcification of these organs.

Metastatic calcification of soft tissues due to hypercalcemia is a well-recognized complication of various malignant diseases and renal failure. It usually can be recognized only through the microscopic study of tissues obtained through biopsy or autopsy. This report describes a patient with hypercalcemia due to renal failure and a malignant tumor of the bone marrow in whom striking uptake of ^{99m}Tc-polyphosphate occurred throughout the lungs and stomach in the course of a routine bone scan. This phenomenon appears to have been due to metastatic calcification of the lungs and stomach.

CASE REPORT

A 48-year-old man was transferred to the Royal Jubilee Hospital from another hospital where he had been admitted a week earlier because of headache, chest pain, shortness of breath, weakness, and fever. He had been well until 6 months before admission when he developed severe night sweats. On the day of admission to the first hospital he had developed retrosternal pain and shortness of breath. An x-ray film of the chest showed abnormalities consistent with pulmonary edema. An electrocardiogram was normal except for sinus tachycardia. The SGOT was said to be normal but the blood–urea nitrogen was found to be 75 mg/100 ml.

A brother had died at the age of 36 of coronary artery thrombosis and a sister had died at 35 of a cerebral hemorrhage. Two sisters were said to have high blood pressure.

On transfer to the Royal Jubilee Hospital he was a confused, ill-looking man. The respirations were rapid (36/min) and shallow. The neck veins were engorged and rales were audible at the base of the lungs on both sides. Gallop rhythm was noted. The pulse rate was 150/min. An electrocardiogram showed sinus tachycardia and minor S-T segment abnormalities. The liver came down 2 in. on inspiration. An x-ray film of the chest showed abnormalities consistent with pulmonary edema. After he was treated with digitalis and diuretics, the dyspnea and tachycardia subsided and the physical findings returned to normal. Ten days later an x-ray film of the chest showed no abnormality (Fig. 1) and subsequent films were normal.

The hemoglobin was 15 gm/100 ml. The white

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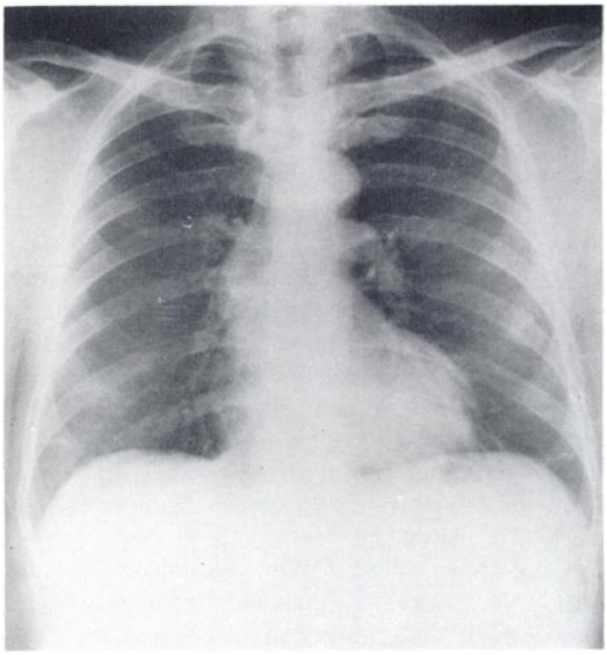

FIG. 1. X-ray film of chest taken 10 days after admission. There is no radiologic evidence of calcification of lungs.

FIG. 2. Anterior view of bone scan. Note normal uptake throughout skeleton and dense uptake throughout lungs and stomach.

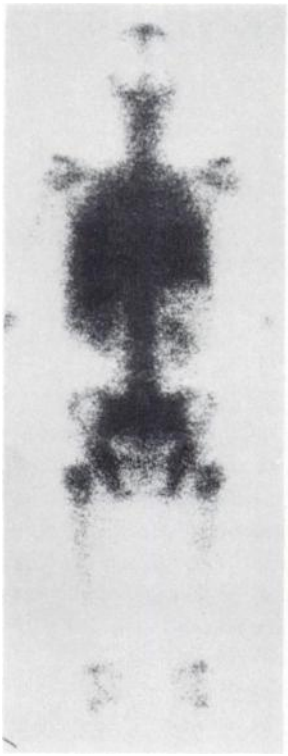

FIG. 3. Posterior view of bone scan. Dense uptake is present in lungs and stomach. Very little uptake is noted in right kidney. Left kidney is obscured by uptake in stomach.

count was 16,900 with a marked shift to the left. The urine contained a trace of albumin. The blood–urea nitrogen was 83 mg/100 ml and the creatinine was 2.3 mg/100 ml. The serum calcium was 16.8 mg/100 ml and the serum phosphorus 5.3 mg/100 ml. The serum uric acid was 17 mg/100 ml. The serum proteins and electrophoretic pattern were normal. The alkaline phosphatase was 28 I.U. (normal 4–17).

The serum calcium and phosphorus levels returned to normal after treatment with prednisone was commenced but the blood–urea nitrogen and creatinine remained elevated. A percutaneous renal biopsy showed nonspecific abnormalities and nephrocalcinosis, the depositions of calcium being most striking in the epithelial cells of the tubules and the lumen of the tubules. A bone marrow biopsy from the iliac crest showed infiltration of the marrow by a cellular tumor that appeared to be a malignant lymphoma or possibly a plasma cell myeloma. Definite classification of the tumor from its histologic features was not considered possible.

A bone scan with ^{99m}Tc-polyphosphate was carried out 3 weeks after admission. Scanning with an Ohio-Nuclear dual-probe scanner showed even uptake of nuclide throughout the skeleton and a striking diffuse uptake throughout the lungs and stomach. Uptake in the kidneys, although present, was less marked than usual with this nuclide. The scan was repeated 1 week later and identical findings were noted (Figs. 2–4).

Treatment with cyclophosphamide was then started. The patient returned for further studies 6 months after the initial admission. Once again the blood–urea nitrogen was elevated (81 mg/100 ml) and the creatinine was 12 mg/100 ml. The hemoglobin had fallen to 8 gm/100 ml. Scanning of the liver and spleen after the intravenous injection of

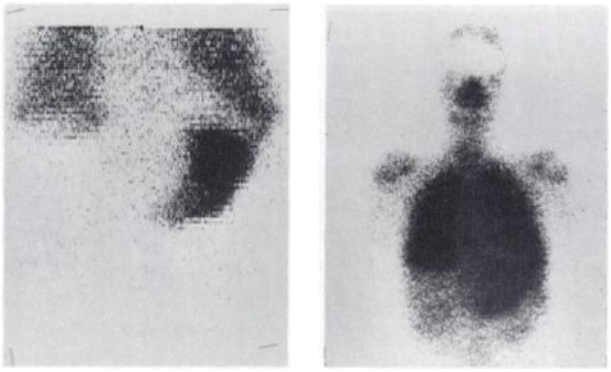

FIG. 4. (Left) 1:1 polyphosphate scan of stomach and lower portion of lungs. (Right) 2:1 scan of upper half of body showing dense uptake of polyphosphate throughout lungs and stomach.

^{99m}Tc-sulfur colloid showed even uptake of nuclide throughout the liver and spleen. The spleen was enlarged (calculated mass 400 gm). A repeat bone scan again showed diffuse uptake throughout the lungs and stomach identical to that noted earlier. Pulmonary function studies showed a forced vital capacity of 80% and a moderate reduction of the FEV 1 and the MMFR. These findings were considered consistent with a slight diffuse airway obstruction. Diffusion studies at rest were considered to be normal. The arterial pO_2 was 65 mmHg.

Permission to obtain a gastric biopsy was not obtained until 9 months after the original scan was performed. The clinical findings and a repeat bone scan were exactly as recorded at 6 months. Satisfactory material could not be obtained through the use of a biopsy capsule and it was necessary to carry out gastroscopy and perform the biopsy under direct vision with a fiber-optic gastroscope. The mucosa appeared grossly normal. Mucosa only was obtained in several biopsy specimens. These appeared to be normal on microscopic examination when stained with hematoxylin and eosin but clearly defined deposits of calcium were visible in the lamina propria of the gastric glands after staining with von Kossa's stain. These were considered consistent with metastatic calcification.

DISCUSSION

The chief causes of metastatic calcification are malignant disease of bone, chronic renal failure, hyperparathyroidism, and hypervitaminosis D. The patient described in this report has been found to have an undifferentiated tumor of the bone marrow and chronic renal failure. It is not possible to say with certainty whether chronic renal failure led to secondary hyperparathyroidism and then to metastatic calcification or whether the primary malignant disease of the bone marrow led to hypercalcemia, calcinosis of the kidneys, and finally, renal failure. Whichever mechanism prevailed, the end result appears to have been metastatic calcification of the kidneys and stomach (proven histologically) and of the lungs (inferred from the scan result).

Although it is generally held that metastatic calcification develops only after prolonged renal failure, it has been reported to develop in a few weeks after the onset of renal failure (*1*). The organs most commonly affected are the lungs, stomach, kidney, and heart (*2*). Our patient had one episode of left ventricular failure and pulmonary edema but this presumably was due to hypervolemia due to renal failure. There was no other conclusive evidence of heart disease and no increase in uptake of polyphosphate in the heart during scanning as might have occurred if there were calcinosis of the myocardium.

Hypercalcemia occurring in the course of malignant disease is most likely to occur when widespread destruction of bone has occurred. This may come about as a result of the production by the tumor of a parathormone-like polypeptide or as a result of increased resorption of bone that overwhelms the ability of the kidneys to excrete calcium and phosphorus. The resulting increase in the ion-product of calcium and phosphorus apparently leads to precipitation of these substances in the soft tissues. In the case of multiple myeloma, which our patient may have had, hypercalcemia may be expected when illness leads to physical inactivity. Hypercalcemia may then contribute to renal failure. At autopsy the kidneys may show Bence-Jones casts and amyloid infiltrates as well as calcium deposits in the interstitial renal tissue. Glucocorticoids commonly ameliorate the hypercalcemia in such patients (*3*).

Calcium deposits in the lungs are generally found in the walls of the alveoli and the walls of the arteries and veins. The bronchi and bronchioles are less commonly affected. Calcium deposits in the stomach have been found in the interglandular stroma and basement membrane of the glands (*4*). Although abnormalities of various types have been noted in x-ray films of the chest in patients with metastatic calcification, usually these are not related to the calcification itself and do not lead to a diagnosis of calcinosis by the radiologist (*5*).

Scanning after the intravenous injection of ^{99m}Tc-polyphosphate has become the accepted way of detecting both benign and malignant lesions of bone. Presumably the polyphosphate radical is metabolized in the same manner as phosphate, the technetium tag providing a convenient source of gamma rays to permit scanning. Areas of bone destruction and repair accumulate larger amounts of phosphate than normal bone and will show up as areas of increased uptake on the scan.

One case has been reported in which increased uptake of ^{99m}Tc-polyphosphate occurred in the pulmonary metastases of an osteogenic sarcoma, presumably because these were the sites of osteoid tissue formation (*6*). Chaudhuri, et al (*7,8*) have shown uptake of radiostrontium in the lungs of a patient with multiple myeloma and hypercalcemia who had no radiologic evidence of calcification of the lungs. They suggested that this might be due to the formation in vivo of macroaggregates of strontium–calcium–phosphate. This mechanism, if it exists, does not seem a likely explanation for the findings in our patient; it would not explain the uptake of polyphosphate in the stomach or the escape of polyphosphate through the pulmonary capillary system and hence into the skeleton.

The mechanism of uptake of polyphosphate in the lungs and stomach of our patient is not clear and we do not yet have histologic proof of calcification of the lung. However, we have histologic proof of calcification of the kidneys and stomach and, in view of the severe hypercalcemia and hyperphosphatemia on admission, the overwhelming likelihood is that metastatic calcification of other tissues has occurred. The stable clinical condition and chest x-ray film findings over a period of 9 months as well as the diffuse nature of the uptake in the lungs and stomach largely exclude the possibility that neoplastic deposits in these organs could have been taking up the nuclide. Lung biopsy by the open technique did not appear to be justified. Failure of the kidneys to take up polyphosphate in more than usual amounts appears to have been due to the advanced degree of renal failure.

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