Metastatic Calcification in the Thyroid Gland Demonstrated on Bone Scan in a Patient with Primary Hyperparathyroidism

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Bone scanning agents are known to accumulate in extraskeletal sites. We report the case of a patient with primary hyperparathyroidism whose bone scan performed with [^{99m}Tc]HMDP revealed not only the classic pattern described in hyperparathyroidism, but also a striking visceral uptake in the lungs, heart, stomach, and thyroid gland. Metastatic calcification was found on histologic examination of the thyroid.

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We observed a patient with hyperparathyroidism whose bone scan performed with technetium-99m hydroxy methylene diphosphonate ([^{99m}Tc]HMDP) showed the classic pattern encountered in this disease and multiple visceral uptakes, including a remarkable uptake in the thyroid gland. Metastatic calcification was proven histologically in this gland.

CASE REPORT

Primary hyperparathyroidism was diagnosed in a 74-year-old patient from the following factors: intense bone pain predominating in the pelvic bones, diffuse demineralization with subperiostal resorption and multiple lytic lesions as seen on the x-ray of the skull, hands and pelvis. The diagnosis was further supported by the following laboratory data: hypercalcemia 4.3 mmol/l, hyperphosphatemia 1.9 mmol/l, hypercalciuria 8.5 mmol/24 hr (normal laboratory values: 3.75 to 7.5), hypophosphaturia 8.6 mmol/24 hr (normal values: 13 to 26) and overall elevation of quantifiable sections of parathyroid hormone on radioimmunoassay; i.e., C-terminal 65-84 fragment 10.5 ng/ml (normal value <0.6) and middle 44-68 fragment 2.5 ng/ml (normal value <0.3). Severe renal failure with proteinuria, increase in blood creatinine 510 umol/l and BUN 44 mmol/l was noted.

A bone scan was performed using a whole-body imager 3 hr after i.v. injection of 15 mCi (555 MBq) of [^{99m}Tc]HMDP It revealed several abnormalities (Fig. 1): (a) a slightly increased uptake in the calvarium and in the leg bones; (b) a marked activity in the lower half of the left humerus; (c) intense extraosseous uptake in the thyroid gland, lungs, heart, stomach and, to a lesser extent, in the thigh adductors; and (d) no activity in the bladder area.

Thyroid tests showed a low serum level of the thyroid hormones: T3 0.36 ng/ml (normal values 5 to 10), FT4 2.5 pg/ml (normal values 8 to 17); the TSH level was found to be at an above normal rate for a 74-yr-old patient.

Ultrasonographic and CT scans of the neck were negative. An exploratory cervicotomy was therefore decided on; however, the patient developed a uremic coma which lead to death 24 hr later. A postmortem examination of the cervical area was carried out, removing the thyroid gland, two parathyroid glands and a part of the trachea, which was several centimeters long. The two parathyroid glands were enlarged, nodular, and measured, respectively, 3.5 × 1.5 × 1 cm and 2 × 1.5 × 1 cm. The examination of formalin-fixed, paraffin-embedded sections from parathyroid glands showed cords, sheets, and follicular arrangements of chief cells, surrounded by fibrous annular strands, without normal tissue around the nodules. There was neither nuclear variation nor mitosis. Microscopic examination of the thyroid revealed follicles dilated by abundant colloid lined by a purple border stained black by Von Kossa's calcic stain (Fig. 2). These deposits were also found in the vessel walls, especially in the interna elastica lamina of the arteries, and scattered in stroma.

DISCUSSION

Visceral uptake of the bone-seeking radionuclides is not exceptional. Since the introduction of the phos-

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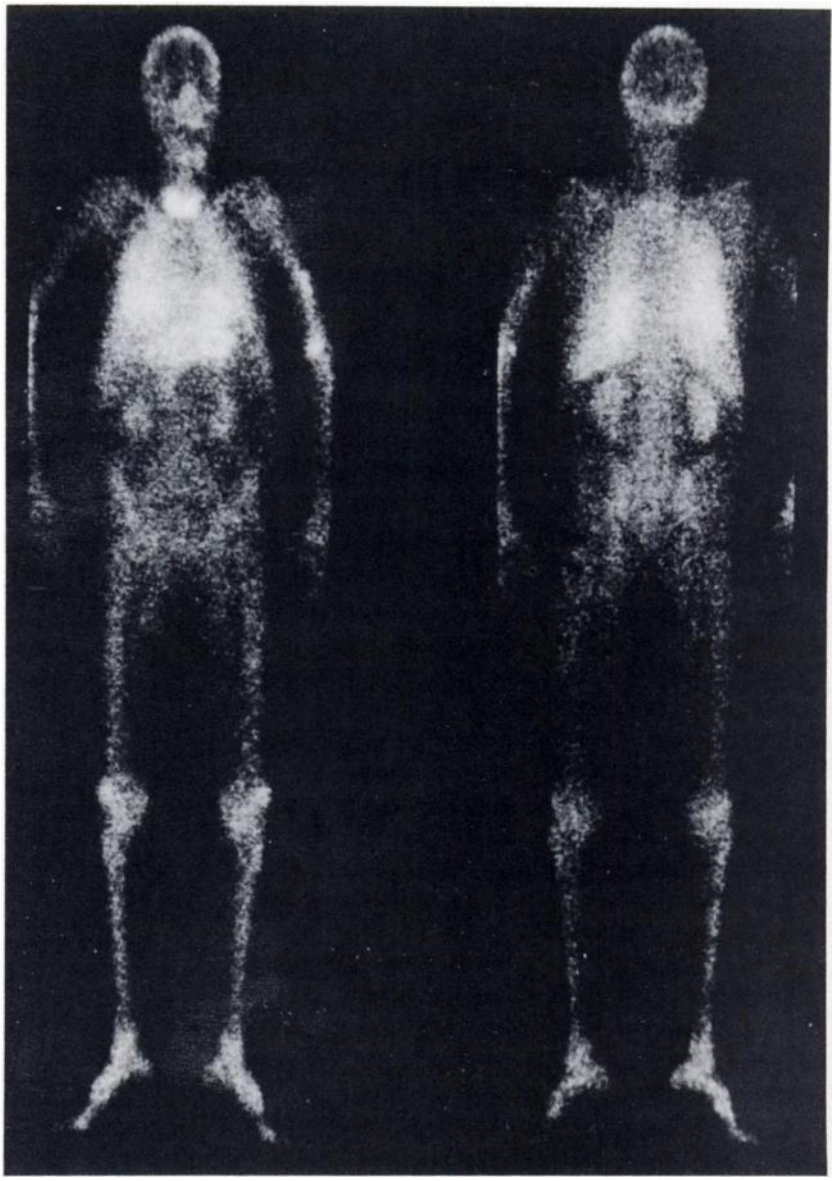

FIGURE 1
Bone scan (anterior and posterior views). Note classic pattern described in hyperparathyroidism and multiple visceral uptakes

phate compounds labeled with ^{99m}Tc, unusual extraosseous accumulations have been described by several authors. The affected tissues are either solely those of the lungs (*1–12*) or the lung tissues in association with gastric (*6,12–18*), renal (*12,14,19*), myocardic (*14,19*) and in exceptional cases with thyroid (*19*) or hepatic uptakes (*12*). There has even been a case of isolated gastric uptake. (*20*).

This phenomenon is histologically supported by the presence of calcifications deposited in the different viscerae: the lungs (*1,5,11,12,14–17*), stomach (*12,13,16*), kidneys (*12,14,15*), and heart (*12,14*). This heterotopic calcification occurs in two forms, the dystrophic and the metastatic varieties. The dystrophic calcification is formed in necrotic or degenerative tissues; generally it appears localized and is not associated with any alteration of the blood calcium and phosphorus levels. This form of calcification includes the nonosseous uptakes described in benign or malignant tumors (*21–27*).

The other variety, first described by Virchow and called metastatic calcification, is a consequence of the precipitation of calcium salts in normal tissues, following an increase in the serum calcium and phosphorus levels. Velentzas et al. (*17*) have outlined the importance of the product of the blood concentration of calcium and phosphorus (both in mg/ml). A rate above 60 seems necessary for the presence of this type of calcification. In our observation, this product Ca × P was >100; the hyperphosphatemia resulted from renal failure. Renal failure is described in most reports on visceral uptakes and also explains the lack of activity in the bladder area. The etiologies of metastatic calcification are predominantly primary or secondary osteolytic

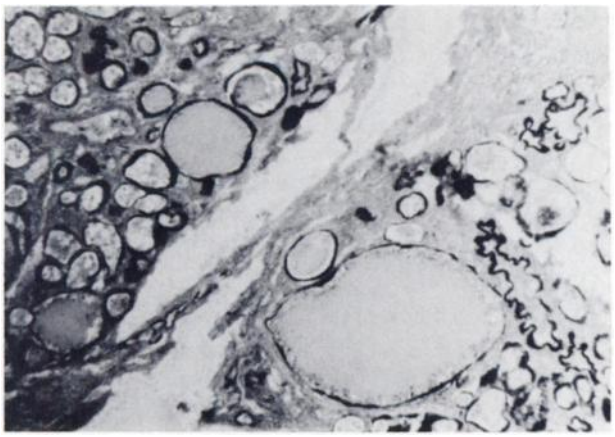

FIGURE 2
Microscopic section of thyroid gland. Note border of dilated follicles colored in black by Von Kossa's stain

bone tumors (*6,10–12,16,17,19*), hyperparathyroidism (*7,8,14,15*) and hypervitaminosis D (*14*). Another major cause is chronic renal failure (*1–5,28,29*). This visceral calcification is made up of hydroxyapatite crystals; however, the nature of calcification is different in uremic patients where it has been shown that visceral metastatic calcification is chiefly composed of an amorphous calcium or withlockite crystal (*2,30,31*). The calcifications are often undetectable on x-ray studies because they are microscopic, as we observed.

In our investigation, the visceral uptake of [^{99m}Tc]HMDP concerned the lungs, stomach, heart, thigh muscles, and thyroid gland. This last accumulation was not due to the presence of free pertechnetate since we were unable to visualize the salivary glands. Moreover, no other bone scan performed the same day with the same batch of radiopharmaceuticals showed such uptake. Histologic examination revealed a nodular hyperplasia of the two parathyroids, but overall showed the presence of vascular and vesicular diffuse metastatic calcification in the thyroid gland. The exact location of the calcification was better established by means of Von Kossa's stain (vascular, perifollicular or in the connective tissue). The dilated vesicles, with a large amount of colloid, probably explain the decline in the serum hormone level.

Although thyroid uptake had been reported by Arbona (*19*) in a patient with multiple myeloma, no histologic examination was undertaken. To our knowledge, this is the first time that the thyroid uptake of [^{99m}Tc]HMDP, which is exceptional, could be linked to the presence of histologically-proven metastatic calcification. The bone scan also showed increased uptake in the calvarium and leg bones. This is the classic pattern, described by several authors (*32–34*), encountered in patients with hyperparathyroidism.

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