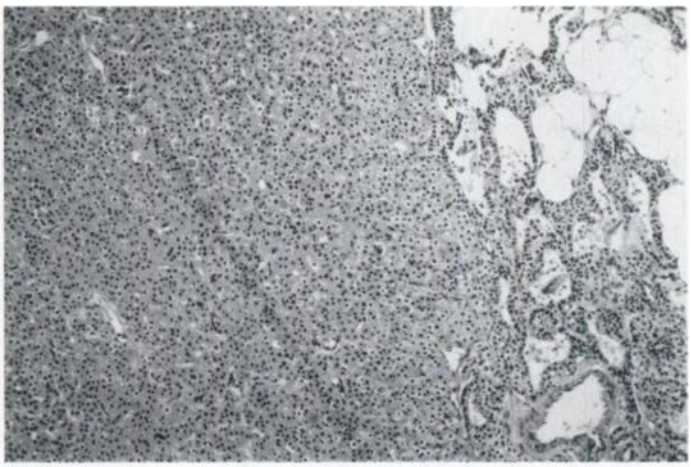

FIGURE 6. Microscopic appearance of the parathyroid adenoma of Patient 3.

CONCLUSION

Technetium-99m-MIBI scintigraphy provides a simple, reliable, accurate and noninvasive method for the detection of ectopic parathyroid adenomas. Our results suggest that ^{99m}Tc-MIBI scintigraphy could be considered as the first elective imaging technique and part of the routine in the management and localization of parathyroid adenomas.

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Disseminated Bone Marrow Metastases of Insular Thyroid Carcinoma Detected by Radioiodine Whole-Body Scintigraphy

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We present ^{131}I scintigraphic findings in a patient with insular carcinoma of the thyroid showing diffuse abnormal uptake throughout the skeleton. The scintigraph closely resembled the pattern of [^{131}I]MIBG distribution in children with bone marrow metastases of neuroblastoma. The extent of involvement was underestimated by bone scintigraphy and radiography. Insular carcinoma of the thyroid in the bone marrow was subsequently demonstrated by biopsy. The patient was treated with 242 mCi ^{131}I given in two courses, which led to severe myelosuppression and died as a result of progressive disease and severe pancytopenia 10 mo after initial therapy.

Key Words: insular thyroid carcinoma; bone marrow metastases; iodine-131

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Whole-body ^{131}I scintigraphy is the method of choice for postoperative evaluation of differentiated thyroid carcinoma for the detection of metastatic lesions, the positive rate of ^{131}I whole-body scan for metastases in differentiated thyroid carcinoma being approximately 75% (*1–6*).

Uptake of ^{131}I has also been demonstrated in recurrent and metastatic insular carcinoma of the thyroid, a recently recognized histologic entity believed to be of follicular cell origin and having a characteristic histopathologic appearance, consisting of nests or "insulae" of medium sized tumor cells (*7,8*). This tumor demonstrates an aggressive clinical course with distant metastases developing in many cases (*9*).

We present a case with unusual scintigraphic finding of intense, diffuse ^{131}I accumulation throughout the skeleton in a patient with insular carcinoma of the thyroid. The images resembled the scintigraphic pattern of MIBG distribution in patients with diffuse bone marrow infiltration by neuroblastoma (*10*). Bone marrow involvement by insular carcinoma of the thyroid was subsequently confirmed by iliac crest biopsy.

CASE REPORT

A 61-yr-old woman presented in April 1993 with a fixed nodule in the right thyroid lobe. For several years she suffered from diffuse bone pain, which had been interpreted as being due to osteoporosis and which had been treated with calcium and calcitonin. A ^{131}I

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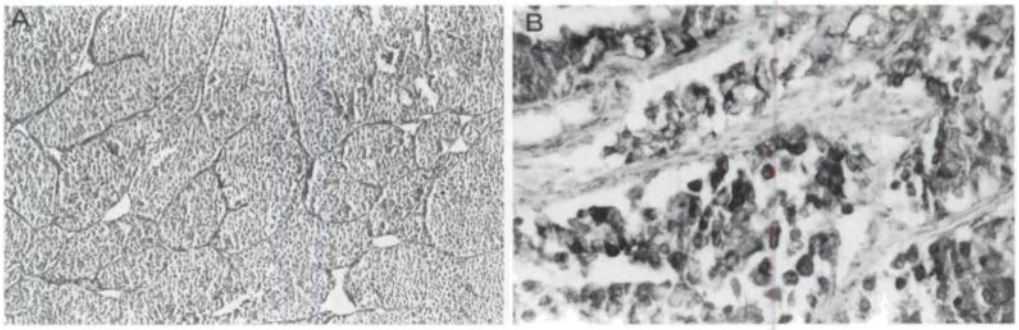

FIGURE 1. (A) Histopathology of the primary tumor shows a solid pattern with undifferentiated cells characteristic of insular carcinoma (hematoxilin and eosin, 100×). (B) Immunohistochemical study showing positive cytoplasmic staining for thyroglobulin (ABC, 400×).

thyroid scan showed a cold lesion in the right lobe. Fine needle aspiration biopsy suggested medullary thyroid carcinoma. In October 1993, total thyroidectomy revealed a 4-cm nodule in the inferior pole of the right lobe, without cervical lymphadenopathy. Histology showed a rather homogeneous, solid, poorly-differentiated tumor having the characteristics of an insular carcinoma, with capsular invasion (Fig. 1A). Immunohistochemistry demonstrated thyroglobulin (Fig. 1B) and was negative for calcitonin.

Six weeks postoperatively, the patient underwent whole-body imaging 48 and 72 hr after oral administration of 5 mCi (185 Mbq) ^{131}I. Serum TSH was 41 μUI/ml and thyroglobulin was >1000 ng/ml. The ^{131}I whole-body scan showed thyroid bed remnants and intense, diffuse uptake throughout the skeleton with additional foci in the skull, one left lower rib and one mid-dorsal vertebra (Fig. 2). A bone scan performed with ^{99m}Tc-MDP (20 mCi, 740 MBq) showed focal areas of activity in the skull, 7th dorsal vertebra, distal right humerus and diffuse uptake in the proximal femora and humeri (Fig. 3A, C).

Radiographic skeletal survey showed spondyloarthrosis of the spine, a fracture in the 8th left rib and osteopenia of both proximal humeral metaphyses, more severe on the left.

Whole-body bone marrow scintigraphy performed two weeks after the bone scan with ^{99m}Tc-sulfur colloid (20 mCi, 740 MBq) revealed a focal defect in marrow distribution corresponding to the 7th dorsal vertebral lesion, patchy extension of active marrow into the distal humeri and femora and the proximal ulnae and a focal area of increased uptake in the skull (Fig. 3B, D). Many areas of intense skeletal ^{131}I uptake also showed the presence of functioning bone marrow, indicating an intimate admixture of metastatic tumor with hematopoietic bone marrow.

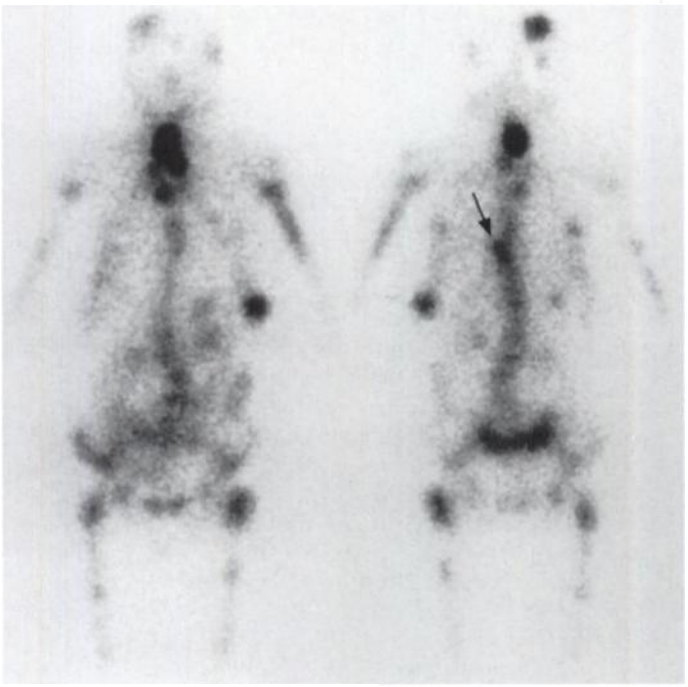

FIGURE 2. Iodine-131 whole-body images: anterior (left) and posterior (right) views show diffuse ^{131}I uptake throughout the skeleton with foci of activity in the skull, a left lower rib and a mid-dorsal vertebra (arrow).

Blood survey revealed: hemoglobin 8.9 g/dl, red blood cells 3.3×10^{10}/liter, hematocrit 27.2%, platelets 530×10^7/liter and white blood cells 9.0×10^7/liter (neutrophils 63.2%, lymphocytes 26.2%, monocytes 6.4%, eosinophils 2.3%, basophils 0.7%, large lymphocytes 1.2%).

Because the ^{131}I whole-body scan suggested diffuse bone marrow infiltration by insular thyroid cancer, a bone marrow biopsy was performed. Immunohistochemistry for thyroglobulin and calcitonin was positive for the former. Histology revealed small nests of tumor tissue having the same appearance as the primary tumor and mixed with the hematopoietic marrow.

The patient was treated with 242 mCi (8.9 Gbq) ^{131}I given in two courses (November 1993 and April 1994). Severe myelosuppression requiring multiple transfusions occurred. The nadir was 11 days after the second ^{131}I dose (92 mCi, 3.4 GBq): hemoglobin 6.4 g/dl, red blood cells 2.34×10^{10}/liter, hematocrit 23.5%, platelets 96×10^7/liter and white blood cells 3.5×10^7/liter (neutrophils 78.8%, lymphocytes 12%, monocytes 5.5%, eosinophils 1.5%, basophils 0.3%, large lymphocytes 1.9%). After the second dose of ^{131}I, a pathological fracture of the left humerus occurred which was treated by surgical stabilization and subsequent external beam radiation therapy (3250 rads). Despite all therapy, the disease progressed rapidly, with extension of bone involvement and development of metastases in the lungs, liver and brain. The patient died in September 1994 with severe, persistent pancytopenia: hemoglobin 7.7 g/dl, red blood cells 2.38×10^{10}/liter, hematocrit 22.5%, platelets 22×10^7/liter and white blood cells 3.37×10^7/liter (neutrophils 91%, lymphocytes 4.8%, monocytes 3.7%, eosinophils 0.1%, basophils 0.4%).

DISCUSSION

Extensive bone marrow infiltration by thyroid cancer is rare. Anner and Dewrinko evaluated bone marrow aspirates from 2877 patients with solid tumors for the presence of clinically unsuspected metastases and found involvement in only 1 of 33 patients (3%) with known thyroid cancer (*11*). Another review by Meinshausen et al. of 581 patients reports a somewhat higher incidence of bone marrow metastases in thyroid cancer (19%) (*12*), but this study was in a select population with clinical evidence of bone involvement. Recently, Vassilopoulou-Sellin et al. (*13*) reported a case of metastatic follicular thyroid

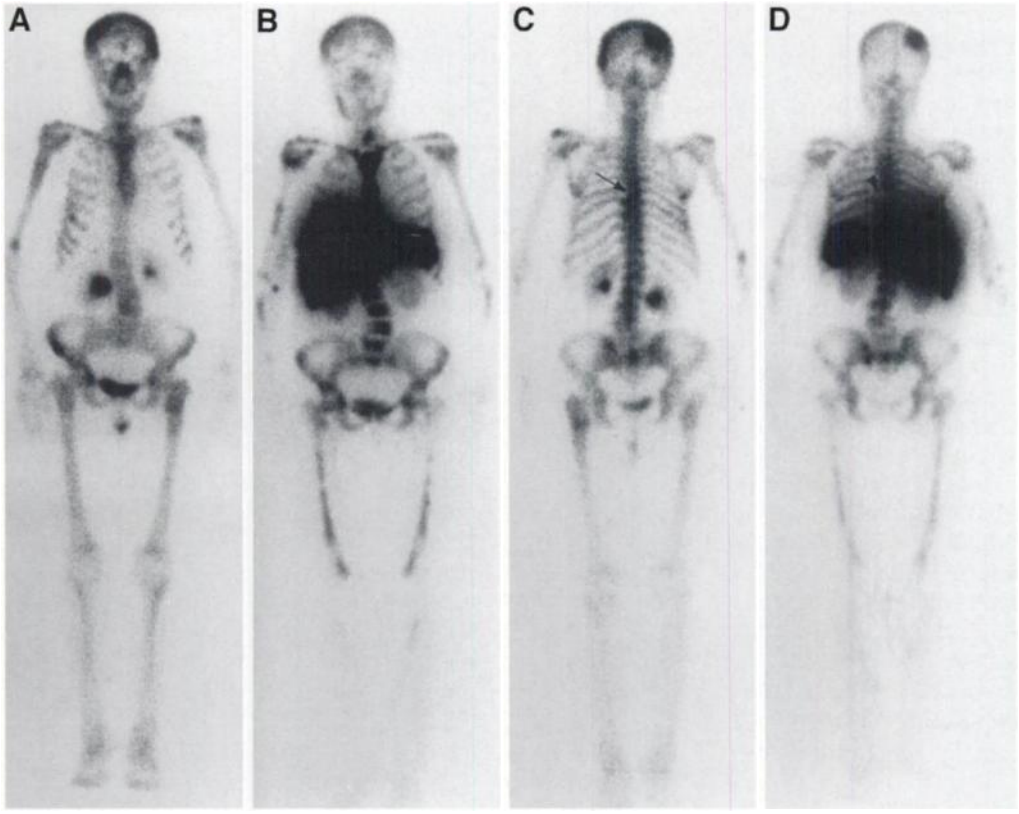

FIGURE 3. Technetium-99m-MDP bone images, anterior (A) and posterior (C), show foci of activity in the skull, 7th dorsal vertebra (arrow) and distal right humerus; diffuse uptake in the proximal femurs and humeri is also evident. ^{99m}Tc-sulfur colloid bone marrow images, anterior (B) and posterior (D), show a focal defect in the 7th dorsal vertebra (arrowhead) and patchy distribution of active marrow in the long bones and a focus of uptake in the skull.

carcinoma diagnosed by bone marrow biopsy performed during the staging of lymphoma.

In our patient, the diagnosis of thyroid cancer metastatic to bone marrow was suggested by the scintigraphic pattern on ^{131}I whole-body scan. The diffuse, intense uptake of radioiodine throughout the skeleton closely resembled the pattern observed with MIBG in patients with diffuse bone marrow infiltration by neuroblastoma (*10*). The extent of involvement was markedly underestimated by the bone scan which demonstrated only focal lesions in the skull, one vertebra and the right humerus. Furthermore, radiography of the spine was misinterpreted as spondyloarthrosis and osteoporosis.

The detection of bone marrow metastases is of great importance for staging and prognosis and can markedly influence therapeutic planning. Thus, decreased hematopoietic function due to bone marrow infiltration usually necessitates scaling down of the dosage of myelosuppressive drugs and/or radiation therapy (*11*).

Metastatic differentiated thyroid carcinoma, which concentrates ^{131}I, is best treated with large activities of ^{131}I (*5*). With skeletal metastases, even if ^{131}I is rarely curative, it nevertheless has a palliative role, often resulting in the relief of pain (especially if combined with external radiation) (*6*). In the patient described in this report, whose thyroid cancer had an aggressive clinical course, diffuse bone marrow involvement posed serious problems in the choice of therapeutic strategy, particularly where ^{131}I therapy was concerned.

The most important potential complication of ^{131}I therapy is radiation myelosuppression, which is dose dependent (*5,14,15*). Hematological changes occur most frequently in patients with distant metastases who receive the largest doses (*14*).

The estimation of bone marrow radiation dosimetry in ^{131}I therapy is extremely difficult because direct measurements are not practical and the microanatomy and microdosimetry of the red bone marrow is complex. For this reason, many clinicians have sought to use an approximate index for true bone marrow radiation dose. These approaches include: the use of whole-body radiation doses (based on an assumption of uniform distribution within the body of the activity retained, as measured by external counting) and/or the self irradiation dose to the blood (based on measurements of radioactivity in serial blood samples) (*15–17*). Normally the blood is intimately mixed with the red bone marrow which it continually perfuses; ^{131}I in the blood may be in the form of [^{131}I] iodide (which is rapidly cleared by renal excretion) or ^{131}I thyroid hormones, due to biosynthesis by residual normal thyroid tissue and/or metastatic thyroid cancer which retains the capacity for hormonogenesis (and which circulates with a much longer half-life than ^{131}I). In addition to this absorbed radiation dose, primarily derived from beta irradiation, extensive residual normal thyroid tissue in the neck and/or focal metastatic tumor deposits at various sites can be considered as point sources of gamma irradiation to the bone marrow, although the gamma radiation dose would be less than that from beta irradiation from the ^{131}I in the blood in contact with the marrow (*18*). The normal bone marrow does not appear to show significant *specific* uptake of either ^{131}I or ^{131}I-labeled thyroid hormones; therefore, either the same radiation dose as blood was assumed or a lesser value (based on very limited data) used (*18–20*). McEwan et al. (*18*) calculated a dose ratio of red marrow to blood of 0.73. This value depends mainly upon the choice of marrow-to-blood concentration ratio, the greatest potential source of error in estimating the absorbed dose to the red marrow.

Benua et al. (*15*) estimated the total-body radiation dose for 85 ^{131}I treatments performed in 59 patients with metastatic thyroid cancer. The estimated radiation dose ranged from 0.31 to 3.21 rads/mCi, with a mean of 1.15 rads/mCi (45 to 740 rads with a mean of 267 rads). Severe myelosuppression requiring multiple transfusions occurred in 8 patients with average cumulative doses of 624 mCi (range 210–1030 mCi). This serious complication was related to either a blood radiation dose

exceeding 200 rads, the administration of more than 300 mCi or the retention of more than 150 mCi at 48 hr.

With intense ^{131}I uptake throughout the marrow due to diffuse metastatic infiltration, the usual dosimetric assumptions clearly do not apply in our patient. As can be seen from the ^{131}I whole-body scan, the bone marrow scan and the histology of the marrow biopsy, there is ^{131}I-avid thyroid cancer intimately mixed with the red hematopoietic marrow throughout the entire normal marrow space. Thus, the red marrow radiation exposure would include that from beta irradiation from ^{131}I in perfusing the blood and in contact with the marrow, gamma irradiation from focal distant metastatic tumor deposits (e.g., skull, vertebra, humerus) and, most importantly, tumor present in and in direct contact with the marrow. The exact radiation dose to the bone marrow in these circumstances cannot be calculated but is clearly far greater than that normally encountered.

The patient received modest doses of ^{131}I for distant metastatic thyroid cancer (150 and 92 mCi) but developed significant myelosuppression which would not normally be anticipated even if ^{131}I labeled thyroid hormones were synthesized in substantial quantities. The myelosuppression resulted, at least in part, from the intense, specific uptake of ^{131}I by thyroid cancer intimately admixed with the bone marrow. The tumorous infiltration of the bone marrow may have also caused part of the myelosuppression, as is suggested by the abnormal hemogram prior to ^{131}I therapy.

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Pleuroperitoneal Migration of Intraperitoneal Phosphorus-32-Chromic Phosphate Therapy for Stage I Ovarian Carcinoma

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A patient with postoperative Stage I ovarian carcinoma received 15 mCi of ^{32}P-chromic phosphate suspension in normal saline intraperitoneally as part of her therapy. The following day, a portion of the infused radiopharmaceutical and normal saline had passed transdiaphragmatically into the patient's right pleural cavity. Thoracentesis removed as much fluid as possible and this fluid contained radioactive material. In the ensuing 4 yr, the patient has not manifested any detectable pleural or pulmonary abnormalities attributable to the radioactivity. Retrospective review of 100 consecutive patients receiving ^{32}P-chromic phosphate intraperitoneal therapy resulted in 43 patients in whom the hemithoraces could be evaluated scintigraphically. Three of the 43 patients (7%) had right pleural fluid radioactivity. This is similar to the percentages reported in patients with cirrhosis with ascites in whom hepatic hydrothorax is identified.

Key Words: ovarian carcinoma; phosphorus-32-phosphate pleural radioactivity; radiopharmaceutical therapy

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The unexpected finding of ^{32}P-chromic phosphate suspension within the right pleural cavity 24 hr after therapeutic intraperitoneal instillation of the radiopharmaceutical is reported. This led to close observation of this patient and the subsequent review of our similarly treated patient population about the frequency of this phenomenon.

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