Diffuse Bony Uptake of Thallium-201-Chloride in the Granulocyte Colony-Stimulating Factor-Producing Lung Carcinoma

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Diffuse uptake of ^{201}Tl in the axial bone is reported in a patient with large cell carcinoma of the lung who showed leukocytosis and an increased concentration of granulocyte colony-stimulating factor (G-CSF) in plasma. The abnormal bony uptake of ^{201}Tl disappeared in association with normalization of the elevated plasma G-CSF level after complete tumor resection. The production of G-CSF was confirmed by immunoperoxidase staining of the tumor tissue.

Key Words: granulocyte colony-stimulating factor; lung cancer; bony uptake; thallium-201-chloride; gallium-67-citrate

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Thallium-201 scintigraphy is increasingly used for the detection of viable tumor lesions as well as the conventional imaging of myocardial perfusion. Thallium-201-chloride does not usually accumulate in the bone. In this report, a case of lung cancer, in which G-CSF production is considered to have caused diffusely increased uptake of ^{201}Tl-chloride and ^{67}Ga-citrate in bones, is described.

CASE REPORT

A 60-yr-old man presented with left thoracic pain and fever in October 1995. He had been found to have leukocytosis and left chest wall thickening since July 1995. He had an erythrocyte sedimentation rate (ESR) of 132 mm/hr and a total white blood cell count of 18,100/μl with 86% neutrophils, 8% lymphocytes and 6% monocytes. His plasma granulocyte colony-stimulating factor (G-CSF) concentration was 49 pg/ml (normal range: <30 pg/ml) measured by enzyme immunoassay (EIA) (*1*). Chest radiographs and CT showed large, irregularly marginated mass lesions (6.5 × 3.0 cm) with destruction of ribs. A CT-guided needle biopsy was performed, and the histology revealed homogeneously proliferated large-sized tumor cells and sparsely scattered giant cells, suggesting large cell lung carcinoma.

The lung cancer was visualized by ^{201}Tl scan, which also revealed unexpected diffuse uptake in the axial bone (Fig. 1). Within 10 days after the ^{201}Tl study, ^{99m}Tc-hydroxymethylene diphosphonate bone and ^{67}Ga scans were performed. Gallium-67 scintigraphy showed increased osseous but decreased hepatic uptake (Fig. 2A). On the other hand, the image on ^{99m}Tc-HMDP bone scanning appeared normal (Fig. 2B).

The patient was treated with complete tumor resection on November 28, 1995 preceded by the mass volume reduction by use of radiotherapy (42 Gy) to the main tumor and combined chemotherapy. The immunohistochemical study of the resected specimen using anti G-CSF monoclonal antibody (*2*) demonstrated positive cytoplasmic staining of the tumor cells.

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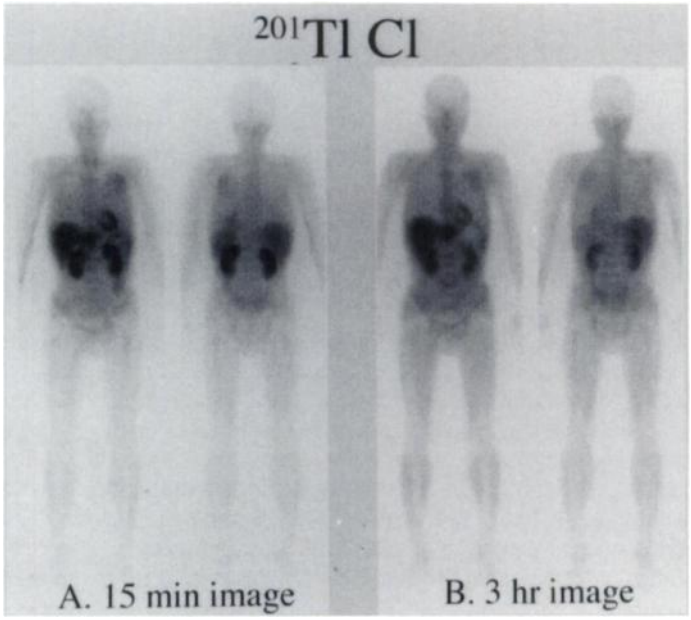

FIGURE 1. Thallium-201 scanning was performed after intravenous administration of 111 MBq ^{201}Tl. Anterior and posterior views of the whole body were acquired 15 min (A) and 180 min (B) after the injection. Both 15 min and 3 hr images on ^{201}Tl scintigraphy show diffuse bony uptake.

On January 30, 1996, he had an ESR of 10 mm/hr and a total white blood cell count of 4800/μl with 64% neutrophils, 26% lymphocytes, 9% monocytes and 1% eosinophils. The postoperative ^{201}Tl and ^{67}Ga scans showed physiological normal distribution of each radionuclide (Fig. 3) in accordance with the normalization of his plasma G-CSF concentration (22 pg/ml).

DISCUSSION

The proliferation and differentiation of hematopoietic cells is under the control of specific growth stimuli known as colony-stimulating factors (CSF) (*3*). G-CSF, a member of the CSF family, stimulates the colony formation of granulocytes from precursor cells in semisolid agar culture (*3*), and the production and functional activation of neutrophilic granulocytes of hamster (*4*), in vitro and in vivo, respectively. G-CSF, which was first detected in serum and urine of patients with granulocytosis and neoplasia, was also identified in plasma of tumor-transplanted nude mice and in the tumor extract itself originally from human lung cancer (*5*) by the in vitro colony formation assay (*6*). Currently, recombinant human G-CSF (rhG-CSF) produced in Chinese hamster ovary cells by recombinant DNA technique (*7*) is widely used for the prevention of chemotherapy-associated infectious complications.

Since the first discovery of G-CSF-producing lung cancer (*5*), G-CSF has been regarded as the principal substance to

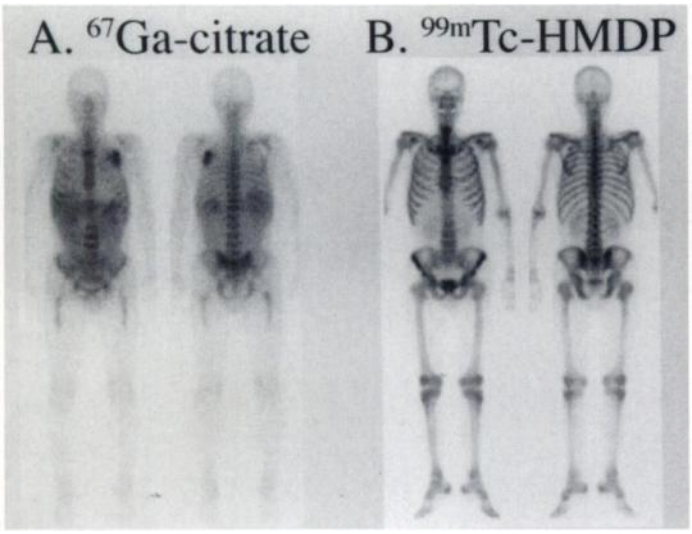

FIGURE 2. The anterior and posterior whole-body views were acquired 72 hr and 3 hr after intravenous injection of 111 MBq ^{67}Ga and 740 MBq ^{99m}Tc-HMDP, respectively. Gallium-67 scintigraphy (A) shows increased osseous uptake, however, ^{99m}Tc-HMDP bone scan (B) appears normal.

cause leukocytosis observed in some patients with malignant tumors. The recent development of EIA for measuring G-CSF (*1*) has enabled the increase in the number of case reports of G-CSF-producing malignancy and further clarification of the role of G-CSF in the cause of leukocytosis. According to Iwasa et al. (*8*), a total of 68 patients with nonhematological G-CSF-producing malignancies have been reported in Japanese literature. Although various primary tumor sites (thyroid gland, urinary bladder, gallbladder, stomach, pancreas, ovary, ureter, submandible and mesothelium) have been documented, half of them were lung carcinoma with the predominant histology of large cell carcinoma or squamous cell carcinoma (*9*). In spite of the stimulatory effect of G-CSF on the hematopoietic progenitor cells, there has been no report in which the pattern of radionuclide distribution especially in the bone is described in patients with G-CSF-producing malignancy.

Our patient with large cell carcinoma of the lung and leukocytosis showed a high plasma level of G-CSF and an increased uptake of ^{201}Tl and ^{67}Ga in the bone. The diffuse bony uptake of ^{201}Tl disappeared in concurrence with normalization of the serum G-CSF levels and the peripheral white blood cell count after complete removal of the primary tumor. Furthermore, G-CSF localization in the tumor was confirmed by immunoperoxidase staining using the monoclonal antibody against human G-CSF. Therefore, bone marrow stimulation by G-CSF was considered responsible for diffuse bony uptake of ^{201}Tl as well as leukocytosis in this patient. Diffusely increased uptake of ^{201}Tl in the bone was also observed in an AIDS patient under treatment with rhG-CSF by Abdel-Dayem et al. (*10*).

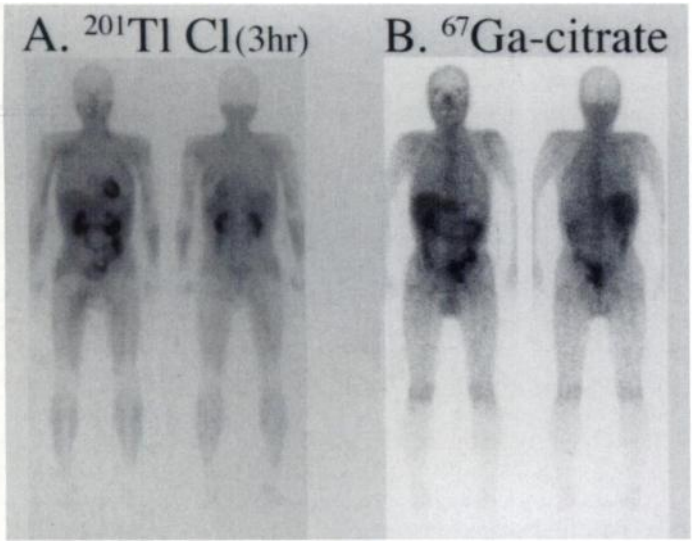

FIGURE 3. Postoperative ^{201}Tl (A) and ^{67}Ga (B) scintigraphies show normal radionuclide distribution.

As for the bony uptake of ^{67}Ga, Kondoh et al. (*11*) reported two cases of malignant lymphoma in which G-CSF administration had caused increased uptake of ^{67}Ga in the extramedullary neutropoietic areas such as liver and spleen as well as red bone marrow. Our patient showed rather decreased liver uptake. Although premedication of antineoplastic agents (*12*) and saturation of iron-binding sites due to iron overload (*13,14*) have been known to lead to reduced hepatic but increased bony uptake, similarly to the presented case, the chemotherapy had not been done before the preoperative ^{67}Ga scanning and the blood transfusion was not performed in the course of this case. Considering physiological normal distribution of ^{67}Ga in the bone revealed by the postoperative scan, the preoperative finding may also reflect bone marrow hyperplasia induced by G-CSF.

The preoperative ^{99m}Tc-HMDP bone scan appeared normal in disagreement with a marked increase in the uptake observed in a case of breast cancer undergoing rhG-CSF treatment (*15*). The discrepancy is inexplicable, but the difference in the serum G-CSF concentration might be attributable.

CONCLUSION

The mechanism of stimulated uptake of ^{201}Tl-chloride as well as ^{67}Ga-citrate in the axial bone in response to G-CSF remains to be clarified. However, the present case report indicates that we should be careful in the interpretation of ^{201}Tl and ^{67}Ga images in those who are supposed to have elevated G-CSF levels in serum and are under treatment with G-CSF.

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Somatostatin Receptor Expression in Hürthle Cell Cancer of the Thyroid

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Somatostatin receptor expression, which was not a previously described marker for Hürthle cell cancer of the thyroid, was demonstrated by in vivo imaging with ^{111}In-pentetreotide in three patients. This phenomenon not only adds another imaging technique to the nuclear medicine armamentarium for detecting recurrent and metastatic cancer in patients with Hürthle cell cancer but also opens up an alternative therapeutic avenue with somatostatin analogs or their radiolabeled compounds.

Key Words: Hürthle cell cancer; somatostatin receptors; indium-111-pentetreotide; thyroid cancer

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Hürthle cell tumors of the thyroid are neoplasms composed exclusively or predominantly (over 75%) of oncocytic follicular cells. Hürthle cells originate from follicular cells as evidenced by an intact thyroid stimulating hormone (TSH) receptor-adenylate cyclase system, which remains functional in the neoplastic state. Hürthle cell tumors are identified by the presence of cells with an abundant granular cytoplasm attributable to a large number of mitochondria ultrastructurally.

Carcangiu et al. (*1*) classify these neoplasms as malignant, intermediate or benign based on the presence and degree of capsular and vascular invasion, pattern of growth (follicular, trabecular or solid), nuclear atypia and necrosis. Malignant Hürthle cell tumors comprise 18% of Hürthle cell neoplasms of the thyroid and account for 2%–3% of all patients with thyroid cancer.

As in all other types of thyroid cancer, all aspects of patient management including extent of initial surgery, the role of radioactive iodine treatment and appropriate metastatic workup are controversial in Hürthle cell cancer (*2–4*). The oncocyte phenotypic differentiation in Hürthle cell cancer has not only morphologic significance, but also connotes metabolic and biologic behavior differences which justify categorizing of these tumors as a different clinical entity. The number of patients who die of Hürthle cell cancer is approximately 10 times that of patients dying from papillary or follicular cancers (*5*). Radioactive iodine uptake of Hürthle cell cancers is minimal and probably due to the uptake in the follicular component (*6*). As a consequence, the clinical role of radioactive iodine treatment is largely limited to postsurgical ablation. The rationale for ablation is the fact that the Hürthle cell phenotype usually preserves the thyroglobulin production capacity and, thus, thyroglobulin can be used as a tumor marker for metastatic/recurrent disease after radioactive iodine ablation.

A prominent subcellular marker of Hürthle cells is the large number of mitochondria, which is the reason why ^{99m}Tc-sestamibi localization is particularly useful for these tumors. Nonspecific tumor localization also can be achieved using ^{201}Tl-chloride and ^{99m}Tc-pentavalent DMSA (*7,8*).

Hürthle cell tumors have neither the morphologic features nor the classical histochemical markers which characterize neuroendocrine differentiation. Hürthle cell carcinomas in the three patients discussed in this article were shown to express varying degrees of somatostatin receptor expression on in vivo ^{111}In-pentetreotide (octreoscan) imaging.

CASE REPORT

Patients

Patient 1 is a 65-yr-old man with a history of a 1-cm left thyroid lobe nodule presented in 1976, the pathology of which was initially reported as benign. The diagnosis of Hürthle cell cancer was made after two subsequent thyroidal recurrences which led to left and right subtotal thyroidectomies in 1983 and 1985, respectively. In 1989, he presented with right cervical nodal disease and had a total thyroidectomy with right radical neck dissection. The patient received radiation therapy to the neck for nodal recurrence in 1990. He developed lung metastases in 1993. He was given three radioactive iodine treatments (2220 MBq (60 mCi) in June 1993, 2960 MBq (80 mCi) in December 1993 and 3700 MBq (100 mCi) in April 1994) with no clinical response.

The patient was referred to the University of Miami in August 1996 for further evaluation and treatment. He complained of pain, pressure and occasional spasms in the neck as well as some difficulty in swallowing. He did not have any respiratory symptoms or signs. The CT scan showed bilateral macronodular lung disease and mediastinal nodal disease. A ^{99m}Tc-sestamibi scan showed positive localization in all thoracic lesions. The patient had whole-body ^{123}I imaging with 10 mCi with a TSH level of 77 uIU/ml and plasma iodine level of 2.1 mcg/dl. There was no radioactive iodine uptake in any of the lesions.

Indium-111-pentetreotide imaging was performed to assess the somatostatin receptor status of the tumor. Intense tracer uptake was noted in all the lesions with a tumor-to-background ratio of 19:1 at 24 hr postinjection (Fig. 1).

Patient 2 is a 61-yr-old man with a history of left thyroid lobectomy who presented in 1975. The pathology was initially reported as benign. The patient incidentally was found to have

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