Diagnostic Evaluation of Thyroid Involvement by Histiocytosis X

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We report the successful diagnosis of thyroid involvement by histiocytosis X due to accurate evaluation of nuclear medicine results. **Methods:** A total thyroidectomy specimen from our patient was initially suggestive of medullary thyroid carcinoma. However, histologic reevaluation was performed on the basis of nuclear medicine findings which were incompatible with the original histologic diagnosis. **Results:** Immunohistochemical and light microscopy studies were performed to obtain the correct diagnosis. Diffuse thyroid involvement by histiocytosis X was demonstrated. **Conclusion:** Thyroid scintigraphy was helpful in successfully diagnosing thyroid involvement by histiocytosis X. Because tracer uptake is related to increased cellularity and metabolism, none of these tracers reported here is specific for defining histiocytosis X.

Key Words: histiocytosis X; thyroid; tumor-seeking agents

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Histiocytosis X is a systemic granulomatosis of unknown etiology usually associated with diabetes insipidus, obesity and growth hormone deficiency (*1*). Thyroid involvement by histiocytosis X, either nodular or diffuse, rarely occurs and only a few cases have been described (*1–3*). The diagnosis of thyroid histiocytosis X is usually made by evidence of Birbeck granules using electron microscopy, however, histologic features of thyroid histiocytosis X are often misleading (*2,3*). We present a case of diffuse thyroid histiocytosis X associated with diabetes insipidus and obesity in which the initial diagnosis was medullary thyroid carcinoma (MTC).

CASE REPORT

A 61-yr-old female was diagnosed with diabetes insipidus, obesity and hypothyroidism one year prior to presentation in June 1992 for the evaluation of a palpable nodule (about 4 cm) located anterolaterally in the right region of the neck. No abnormal lymph nodes were detected in the neck and no palpable lesions were documented elsewhere in the body. The patient was symptomatic showing asthenia, sensitivity to cold, pallor of the skin, edema of face, slow speech and cardiovascular abnormalities such as bradycardia, hypotension (100/70 mmHg) and diffuse left ventricular hypokinesia by echocardiography. Although the patient had received an oral dose (100 μg) of L-thyroxine daily for one year, she still had slightly increased thyroid-stimulating hormone (5.9 μU/liter, normal value = 0.5–4.0), low free triiodothyronine (1.3 pg/ml, normal value = 2.8–6.2) and free L-thyroxine (4.1 pg/ml, normal value = 6.6–18) plasma levels. Serum thyroglobulin was 250 ng/ml (normal value less than 50), while baseline calcitonin, carcinoembryonic antigen (CEA) and alpha-fetoprotein levels were normal. Anti-thyroid autoantibodies were absent. Baseline plasma and urine osmolality were 287 mOsm/liter and 77 mOsm/liter, respectively. Response of plasma and urine osmolality to water deprivation and vasopressin injection was suggestive of severe central diabetes insipidus (289 mOsm/liter and 95 mOsm/liter, respectively).

Thyroid ultrasonography (US) demonstrated a large, solid nodule entirely occupying the right lobe of the gland (Fig. 1). The left lobe had reduced dimensions and irregular borders with a US signal consistent with a fibrotic structure mixed to calcification foci. A CT scan of the neck and of the mediastinum confirmed the presence of an inhomogeneous solid mass in the right lobe of the thyroid (Fig. 1). Thallium-201 chloride scintigraphy (2 mCi i.v., spot and whole-body images were obtained 30 min p.i.) showed intense tracer uptake in the nodule occupying the entire right lobe of the thyroid (Fig. 2), while no abnormal uptake was observed either in the left thyroid lobe or elsewhere in the body. Targeted fine needle aspiration cytology of the lesion was suggestive of MTC. Pentavalent ^{99m}Tc-dimercaptosuccinic acid (V-DMSA) and ^{131}I-metaiodobenzylguanidine (MIBG), two radiopharmaceuticals able to image MTC (*4,5*), were used to corroborate the cytological diagnosis. The ^{99m}Tc-V-DMSA scan (10 mCi i.v., images were obtained at 2 hr p.i.) showed a scintigraphic pattern similar to the thallium scan with associated faint tracer uptake in the left lobe of the gland (Fig. 2). Conversely, whole-body scans at 24, 48 and 72 hr after injection of 0.5 mCi of MIBG demonstrated no abnormal uptake either in the thyroid region (Fig. 2) or elsewhere in the body. Thyroid scintigraphy using ^{99m}Tc methoxy isobutyl isonitrile (MIBI) (20 mCi i.v., images were obtained at 30 min p.i.) was also performed once the patient gave informed consent. Technetium-99m-MIBI was highly concentrated in the nodule within the right lobe (Fig. 2) without significant uptake in the left lobe.

The patient underwent a near-total thyroidectomy. Fine needle aspiration cytology diagnosis of MTC was confirmed by pathologists using light microscopy (Fig. 3A). However, increased serum thyroglobulin, normal serum calcitonin and CEA levels as well as a negative MIBG scan raised the suspicion that the histopathological

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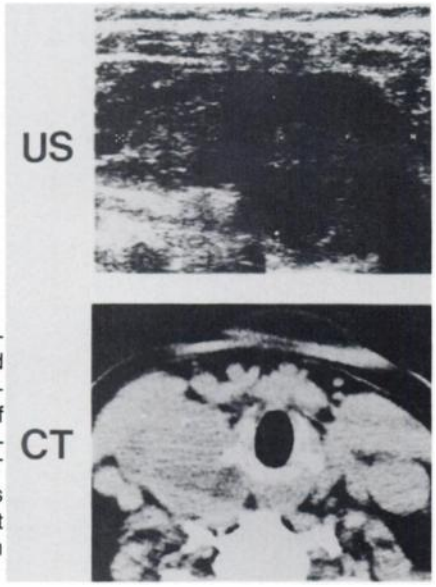

FIGURE 1.
Thyroid ultrasound reveals a large, solid nodule entirely occupying the right lobe of the gland on the transverse scan. Neck CT shows a round mass detected in the right lobe of the thyroid on the axial scan.

diagnosis of MTC was incorrect, which resulted in reevaluation of the pathologic material. Cell morphology was highly suggestive for histiocytosis X by light microscopy (Fig. 3B–C). Immunostaining studies for calcitonin and thyroglobulin were negative (Fig. 3D–E, respectively); conversely, it was positive for S-100, a specific protein for histiocytosis X (Fig. 3F).

DISCUSSION

Thyroid involvement by histiocytosis X is uncommon (*1*). In particular, Coode et al. (*2*) describe a patient in whom a partial thyroidectomy specimen was initially diagnosed as showing poorly differentiated follicular thyroid carcinoma. Subsequent electron microscopy showed the presence of Birbeck granules found in histiocytosis X. These histologic findings can be more confusing when both histiocytosis X and papillary thyroid carcinoma are concomitant (*3*). These data show that even histopathologic thyroid findings may be imprecise and that the incidence of thyroid abnormalities in histiocytosis X may have been underestimated in the past.

In this report, we describe our experience regarding the correct diagnosis of thyroid involvement by histiocytosis X in a patient who was initially misdiagnosed as having MTC. In particular, laboratory and radionuclide imaging results lead to doubts about the histopathology findings. The normal serum calcitonin and CEA, and the abnormal level of serum thyroglobulin were not suggestive of MTC (*6,7*). Although some MTC tumors do not concentrate MIBG, this radiopharmaceutical is commonly used to image MTC (*8*). In this patient, a normal MIBG scan did not support the initial diagnosis of MTC. Subsequently, immunohistochemistry for calcitonin was negative, although it was positive for S-100 and thus ruled out the diagnosis of MTC. The increased serum level of thyroglobulin was thought to be due to inflammation and thyroid cell lysis. Radionuclide imaging studies have demonstrated that the thyroid nodule was clearly detected using other radiopharmaceuticals used to evaluate thyroid tumors. In particular, ^{201}Tl, ^{99m}Tc-V-DMSA and ^{99m}Tc-MIBI were highly concentrated in the thyroid lesion.

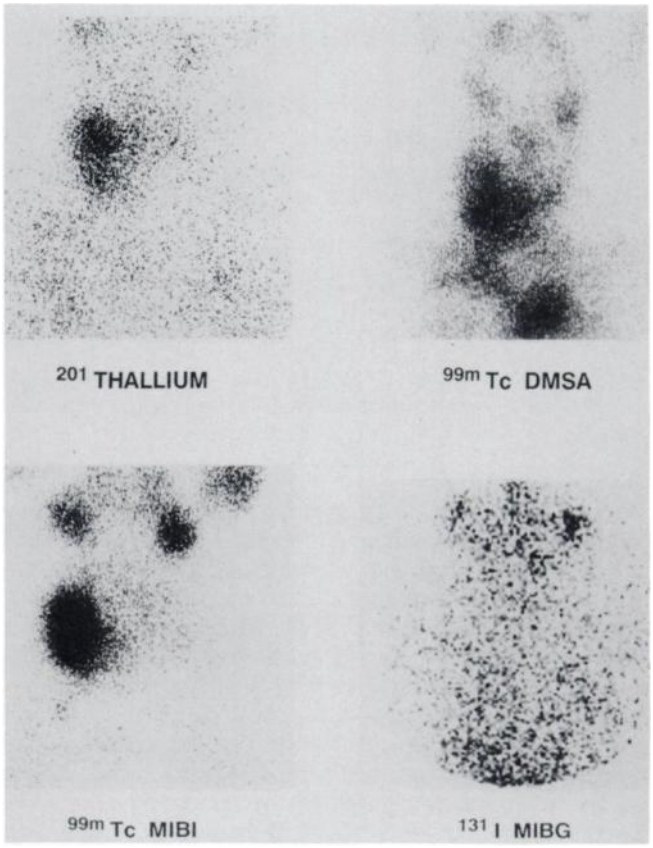

FIGURE 2. Thallium-201 thyroid scintigraphy. Abnormal uptake is present in the right lobe, whereas no uptake is detected on the left side. Pentavalent ^{99m}Tc-DMSA thyroid scintigraphy shows abnormal uptake clearly visible in the right lobe of the thyroid, whereas faint uptake is present on the left side. Technetium-99m-MIBI thyroid scintigraphy shows abnormal intense uptake clearly present in the right lobe, whereas no uptake on the left side is detected. Iodine-131-MIBG thyroid scintigraphy; anterior view at 48 hr shows normal uptake in the salivary glands. No thyroid uptake is detected.

Thallium-201 is a potassium analogue commonly used for myocardial imaging (*9*). Its cellular uptake depends on two different mechanisms: the Na/K ATPase pump and passive intracytoplasmic diffusion along concentration gradients. Tumor thyroid imaging using thallium has been reported. Its uptake, however, is nonspecific since it is concentrated in both benign and malignant nodules (*10*).

Technetium-99m-V-DMSA has been shown to be useful in evaluating patients with MTC (*4*). This radiopharmaceutical contains a TcO_4^3 core, which has a structural analogy and exhibits similar features to the orthophosphate ion PO_4^3, which has been demonstrated to be accumulated in neoplastic tissues probably as a consequence of intratumoral calcification deposits (*11*). Technetium-99m-V-DMSA uptake in a thyroid nodule is commonly considered diagnostic for MTC (*8*). However, our group has recently demonstrated that ^{99m}Tc-V-DMSA is also concentrated in primary and metastatic sites of differentiated thyroid carcinomas (*12*). Furthermore, the present study shows that ^{99m}Tc-V-DMSA accumulated in the thyroid when the gland is involved by histiocytosis X. Therefore, the conclusion that ^{99m}Tc-V-DMSA is a specific agent for MTC should definitely be revised.

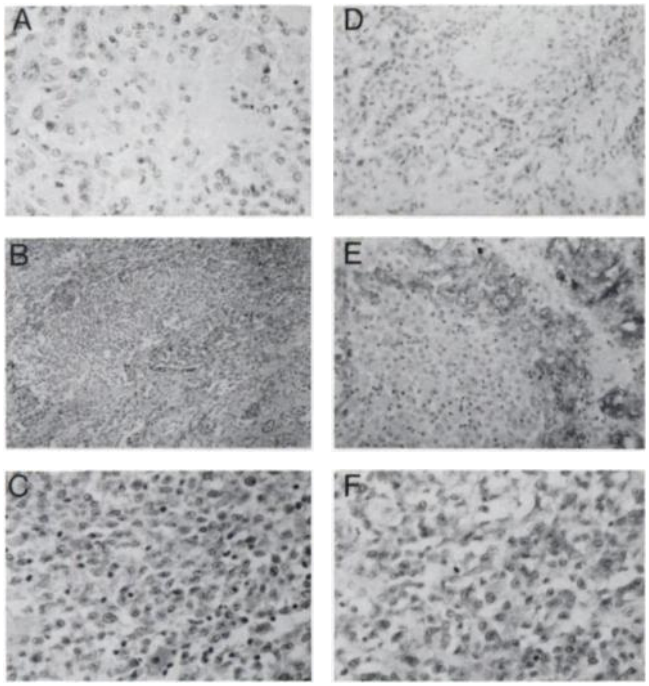

FIGURE 3. (A) Initial histologic section simulates a medullary thyroid carcinoma in a field of the surgical specimen. The cellular component is more solid with abundant amiloid-like sclerotic stroma (HE ×100). (B) This histologic section shows a diffuse infiltrate of histiocytes admixed with inflammatory cells effacing the normal thyroid follicles (HE ×100). (C) High magnification of histiocyte infiltration. These cells contain scantly cytoplasm and vescicular nuclei. Some cells show "coffee bean" grooved oval nuclei. Lymphocytes and eosinophils are also present (HE ×400). (D) Negative immunostaining for calcitonin. (E) Positive immunostaining of the reactive follicular thyroid cells for thyroglobulin. Note the negative immunostaining of the Langerhans' cells for thyroglobulin. (E) Positive immunostaining of Langerhans' cells for S-100 protein.

Technetium-99m-MIBI, a radiopharmaceutical of lipophilic nature, was introduced for cardiac imaging (*13*), however, its biological features have recently found application in oncology (*14–16*). Intracellular uptake of ^{99m}Tc-MIBI is dependent on negative transmembrane potentials and there is evidence that malignant tumor cells have higher negative mitochondrial and transmembrane potentials than normal and/or benign tissue cells. These observations could explain the uptake of ^{99m}Tc-MIBI in the thyroid nodule of this case. The slightly different pattern of tumor uptake between ^{99m}Tc-MIBI and ^{99m}Tc-V-DMSA imaging deserves comment. Technetium-99m-MIBI uptake has been described in both normal and suppressed thyroid tissue (*14,17*). In our patient, however, ^{99m}Tc-MIBI was not taken up by the left lobe of the thyroid since this was entirely fibrotic with mixed calcifications, as shown by means of US study. Conversely, ^{99m}Tc-V-DMSA trapping in this lobe could be due to the presence of calcium deposits.

MIBG, a useful agent to image neuroendocrine tumors (*5,18–20*), was used to confirm the initial suspicion of MTC. It is likely that the lack of MIBG uptake in the thyroid nodule was determined by the absence of neuroendocrine cells in histiocytosis X.

CONCLUSION

Since thyroid involvement by histiocytosis X can be easily confused with other thyroid disorders, accurate diagnostic assessment is recommended. The radiopharmaceuticals used in this study, although helpful in defining histiocytosis X, are not specific. For diagnostic purposes, their uptake mechanisms are related to increased cellularity and metabolism rather than "specific" cell binding.

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