^{67}Ga-CITRATE AND THE NONFUNCTIONING THYROID NODULE

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Nineteen patients identified by ^{125}I, ^{131}I, or ^{99m}Tc-pertechnetate imaging as harboring a solitary "cold nodule" of the thyroid gland were evaluated further by ^{67}Ga-citrate thyroid scans. Histologic examination of the thyroid tumors was performed in all cases.

Of the seven thyroid tumors shown to be malignant, only three selectively concentrated ^{67}Ga-citrate. Two of these were anaplastic carcinoma; the third was a mixed papillary-follicular carcinoma containing multiple foci of poorly differentiated cells. None of the 12 benign nodules in this investigation concentrated ^{67}Ga-citrate. These included follicular adenomas and colloid nodules. No cases of subacute or chronic lymphocytic thyroiditis were encountered.

Our results indicate that although ^{67}Ga-citrate may be of value in identifying anaplastic thyroid tumors, it has limited application in the diagnosis of solitary cold nodules.

Identification of a solitary, nonfunctioning thyroid nodule by radioiodine or pertechnetate imaging is of significant clinical importance to the patient; the usual course includes thyroid suppression, frequent clinical evaluations, reimaging, and needle or excisional biopsy. Because 20–30% of these nodules may be malignant (*1–3*) a widely applicable technique is needed to differentiate thyroid cancer from benign tumors.

Gallium-67 as the citrate has been proposed as a potential indicator of malignant foci; the concentration of this radionuclide has been investigated in a variety of neoplastic lesions (*4–14*). Localization within thyroid carcinoma has been demonstrable, usually in poorly differentiated carcinoma, but these reports are few in number, limited in description, and frequently lack histopathologic classification (Table 1).

A collaborative prospective study was undertaken to investigate the propensity of various thyroid nodules to sequester ^{67}Ga-citrate and to assess the practicality of employing this radionuclide in the clinical differentiation of the "cold" thyroid nodule.

METHODS

Between May 1971 and November 1972, 19 patients from the nuclear medicine laboratories of the Peter Bent Brigham Hospital, Boston, Massachusetts, Mount Auburn Hospital, Cambridge, Massachusetts, and the Milwaukee County General Hospital, Milwaukee, Wisconsin were selected for evaluation.

Received Aug. 27, 1973; revision accepted Dec. 31, 1973.

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TABLE 1. HISTOLOGIC DIAGNOSIS AND ^{67}Ga-CITRATE THYROID SCAN RESULTS OF HYPOFUNCTIONING NODULES FROM A REVIEW OF THE LITERATURE

Histology	No of cases	Scan results	Reference
Benign			
Cyst	3	—	7, 11
Adenoma	14	—	12, 13
Malignant			
Poorly differentiated	1	+	4
Adenocarcinoma	1	+	7
Anaplastic carcinoma	5	+	7, 13
Undifferentiated carcinoma	1	+	10
No report of histology	3	+	11
Papillary adenocarcinoma	4	—	10, 12
Medullary carcinoma	2	—	9
Anaplastic carcinoma	2	—	13
Postirradiation	2	—	5
No report of histology	1	—	11

TABLE 2. PATIENT DATA RELATING TO ^{67}Ga-CITRATE THYROID SCANS

Case	Age/Sex	Days between scans 1 and 2*	% ^{131}I RAIU 24 hr	Thyroid hormone†	Tissue diagnosis	^{67}Ga scan
Malignant						
1	57/F	47	9	—	Anaplastic carcinoma	+
2	77/F	5	30	—	Anaplastic carcinoma	+
3	12/F	15	3	—	Mixed pap-foll adenocarcinoma	+
4	28/F	2	26	—	Papillary adenocarcinoma	—
5	34/F	28	37	—	Papillary adenocarcinoma	—
6	49/F	180	26	+	Follicular adenocarcinoma	—
7	47/F	72	12	—	Medullary carcinoma	—
Benign						
8	27/F	9	8	+	Follicular adenoma	—
9	31/M	10	17	—	Follicular adenoma	—
10	19/F	8	23	—	Follicular adenoma	—
11	48/F	13	21	—	Follicular adenoma	—
12	25/M	7	12	—	Follicular adenoma	—
13	29/F	41	24	—	Follicular adenoma	—
14	42/M	19	36	+	Colloid nodule	—
15	28/F	17	20	—	Colloid nodule	—
16	26/F	19	29	—	Colloid nodule	—
17	36/F	10	29	+	Colloid nodule	—
18	42/F	4	22	—	Colloid nodule	—
19	17/F	8	18	+	Colloid nodule	—

* Scan 1 = ^{125}I, ^{131}I, or $^{99m}TcO_4^-$; scan 2 = ^{67}Ga-citrate.
† Exogenous thyroid hormone administered before ^{67}Ga-citrate scanning.

Inclusion in the study was determined by the following criteria:

1. a single "cold" nodule was identified by scintigraphic examination 24 hr after the oral ingestion of ^{131}I or ^{125}I or imaging twenty min after intravenous administration of $^{99m}TcO_4^-$;
2. histologic identification of the tissue was available.

Gallium-67 was administered intravenously at a dose of 35–50 μCi/kg (*5,7,15*) and scanning was performed 72 hr after injection (*5,7,10,15,16*) using a rectilinear scanner equipped with a 5-in. NaI crystal. A window setting of 170–310 keV was used to encompass two of the four ^{67}Ga photopeaks (46% of the total gamma emissions). The patients were scanned anteriorly in the supine position with the neck hyperextended. Normal anatomical landmarks, such as the sternal notch as well as the boundaries of the nodule in question, were accurately delineated and recorded. With three exceptions, an interval of at least 1 week elapsed between the initial iodine or pertechnetate imaging and the ^{67}Ga-citrate scanning procedure. Table 2 outlines the tissue types which were examined. During the 18-month study, no patients with clinical, subacute, or chronic thyroiditis were encountered.

RESULTS

Of the 19 patients scanned, only 3 evidenced concentration of ^{67}Ga-citrate within their previously identified cold nodules (Cases 1, 2, and 3). In Cases 1 and 2, the lesions were diagnosed histologically as anaplastic carcinoma; Case 3 was that of a mixed papillary-follicular adenocarcinoma containing multiple foci of poorly differentiated carcinoma.

The lateral aspect of the tumor in Case 1, a region subsequently shown to be involved with hemorrhage and necrosis, evidenced decreased ^{67}Ga-citrate concentration by scan when compared with the more medial portion of the lesion (Fig. 1). Case 2 represented a lesion that was severely involved with degenerative change and showed only minimal to moderate concentration of ^{67}Ga in a diffuse pattern of distribution.

Case 3 showed localized concentration of ^{67}Ga in only a single small focus of the thyroid gland. Functioning thyroid carcinoma in cervical lymph nodes and in metastatic pulmonary nodules demonstrated by ^{131}I scan did not accumulate ^{67}Ga.

In our series, ^{67}Ga-citrate activity was not observed in malignant nodules involved with medullary carcinoma, adenocarcinomas of the pure papillary or follicular type, or in the 12 histologically benign nodules (Table 2).

DISCUSSION

Attempts at scintigraphic differentiation of the malignant from the benign "cold" nodule have followed a number of investigative courses. Complimentary scanning with ^{75}Se-selenomethionine and radioiodine

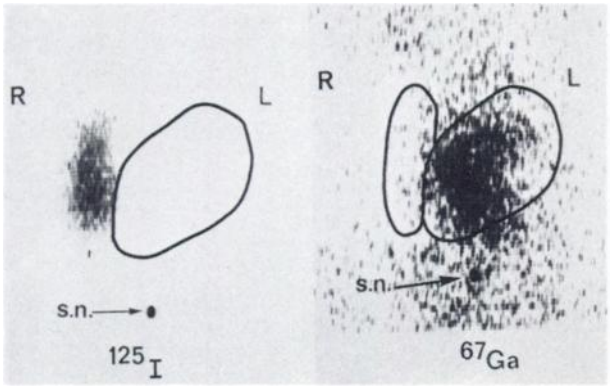

FIG. 1. ^{125}I thyroid scan (left) with area of enlarged "cold" left lobe indicated. ^{67}Ga-citrate thyroid scan (right) showing significant concentration of isotope within medial aspect of left lobe mass. (s.n. = sternal notch)

has alternately shown no false-negative results (*17*) and a 24% incidence false-negative scans (*18*). In addition, false-positive ^{75}Se-selenomethionine scans have been associated with thyroiditis and follicular adenomas (*17*).

Technetium-99m-pertechnetate flow studies performed in patients with "cold" thyroid nodules (*19*) have indicated increased vascularity associated with carcinoma. However, adenomas and nodular hyperplastic lesions also produced positive flow studies. In addition, a 1.5-cm carcinoma, partially obscured by adjacent functioning vascularized tissue, escaped detection.

The successful experience with ^{67}Ga-citrate for detecting and staging various malignancies and the initially encouraging results in patients with anaplastic and undifferentiated carcinoma (Table 1) prompted our investigation.

In this study, the ^{67}Ga-citrate thyroid scan was positive in only three instances, two of which were highly anaplastic tumors. The third, a rapidly growing tumor with widespread pulmonary and lymph node metastases, showed a mixed histologic picture including well-differentiated papillary and follicular components as well as multiple foci of poorly differentiated follicular carcinoma. Pure papillary and follicular adenocarcinomas, tumors which in large series represent up to 75% of thyroid malignancies, (*20*) did not concentrate ^{67}Ga-citrate above background levels.

The localization of ^{67}Ga-citrate within tumors is known to follow some general patterns of distribution; viable tumors show the greatest concentrations of activity with lesser amounts of the radionuclide seen in necrotic lesions (*6*). Our findings are consistent with this observation.

The sites of ^{67}Ga-citrate deposition have been shown to include macrophages (*21*), lymphocyte membranes (*22*), and intracellular localization within lysosomes (*10,23*). The propensity of anaplastic thyroid carcinoma to undergo degenerative change with an associated subsequent increase in the level of lysosomal activity (*24,25*) may explain ^{67}Ga-citrate deposition in these lesions.

The great variation in growth pattern and biological behavior of well-differentiated thyroid carcinoma (*26*) is exemplified by Case 3. The aggressive clinical course of this tumor may be explained by the presence of multiple foci of poorly differentiated cells throughout the regional lymph nodes and the thyroid gland itself. Why this lesion sequestered ^{67}Ga-citrate in only a single location cannot be explained satisfactorily.

The recent report of positive ^{67}Ga-citrate scans in subacute thyroiditis (*12*) is significant in the interpretation of our findings. Thyroiditis, subacute and more commonly the chronic lymphoid variety, is known to produce hypofunctioning areas on the thyroid scan (*27–32*). These may be indistinguishable from similar findings seen in malignancy. Further clinical confusion with a thyroid neoplasm can occur when a patient with a focal area of thyroiditis presents with no local or systemic complaints (*28, 33,34*) as well as when a carcinoma of the thyroid clinically simulates subacute thyroiditis (*35*) or occurs concomitantly with a thyroiditis (*36–39*).

Our results indicate that a definite diagnosis of thyroid carcinoma cannot be conclusively substantiated by a positive ^{67}Ga-citrate scan. Evaluation of the hypofunctioning nodule by ^{67}Ga-citrate is severely hampered by an inability to identify the more frequently occurring papillary and follicular carcinomas and by sequestration of the isotope in both anaplastic carcinoma of the thyroid and subacute thyroiditis. Further experience with this isotope in thyroid scanning, particularly in chronic thyroiditis, may help to clarify its clinical value in the diagnosis of thyroid malignancy.

ACKNOWLEDGMENTS

The authors thank William A. Meissner for his review of the pathologic specimens from Case 3 and Sergio Cervi-Skinner for his help in studying the patient represented by Case 7. This work was supported in part by USPHS Grant GM 02201.

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