CLINICAL STUDY

The usefulness of ^{99m}Tc -SestaMIBI scan in the diagnostic evaluation of thyroid nodules with oncocytic cytology

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Abstract

Objective: To assess the relevance of ^{99m}Tc -SestaMIBI (MIBI) scan in the diagnostic evaluation of thyroid nodules with oncocytic cytology.

Subjects and methods: Twenty-four patients with a single (or prevalent) 'cold' solid nodule with Hürthle cells (HC) at fine needle aspiration cytology (FNAC) were studied. Cytological diagnosis of oncocytic metaplasia (OM) or HC tumor (HCT) was made when HC on the smear were comprised 10–75%, or > 75%. Nodules concentrating MIBI at early and late (2 h after washout) stages were considered MIBI-positive. In all cases histological findings were obtained after total thyroidectomy.

Results: FNAC was malignant or suspect for malignancy in 16 cases (six HCT and 10 OM) and not suspect in eight (two HCT and six OM). Histological examination revealed 14 malignant tumors (11 HCT and three OM), and 10 benign thyroid lesions (three HCT and seven OM). Sensitivity of FNAC for malignancy was 92.8% and specificity was 70.0%; HCT were identified by FNAC in only 35.7% and OM in 70.0% of cases. No significant difference in MIBI positivity was found between malignant and benign thyroid nodules. The highest percentage of MIBI positivity was found in HCT (78.5%), but MIBI-positive nodules were also observed in thyroid lesions with HC metaplasia (40.0%).

Conclusions: MIBI scintiscan has no value in differentiating malignant from benign HC thyroid neoplasias. Most HCT are MIBI-positive, but this scan is not sufficiently specific to differentiate true HC neoplasias from other thyroid lesions showing HC at FNAC, although an MIBI-negative scan strongly supports the absence of true HCT.

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Introduction

Hürthle cells (HC) or oncocytes are polygonal thyroid follicular cells with abundant granular eosinophilic cytoplasm, containing numerous mitochondria (1, 2). The term 'oncocytic tumors' or HC tumors (HCT) is reserved for thyroid neoplasms composed exclusively or predominantly (over 75%) of follicular cells exhibiting oncocytic features (3–5). The term oncocytic metaplasia (OM) indicates the presence of a variable (< 75%) number of HC, often mixed with follicular monomorphic and intermediate cells, in other benign or malignant thyroid lesions. OM is a non-neoplastic hyperplasia of HC and appears to be particularly frequent in Hashimoto's thyroiditis and nontoxic goiter (3–6). Classically, HCT are considered a variant of follicular neoplasms and may be classified as carcinomas or adenomas, based primarily on the architectural features of capsular or vascular invasion (2–4, 7). More recently, an HC variant of papillary thyroid carcinoma (HC-PTC) has also been recognized (8, 9).

Fine-needle aspiration cytology (FNAC) is considered the best procedure in the diagnostic evaluation of thyroid nodules (10), since in most cases it allows one to define the precise histotype in a simple and non-invasive fashion (10, 11). With particular regard to oncocytic nodules, FNAC does not appear to be a very reliable technique to distinguish HC adenomas from carcinomas (1, 4, 5). As observed with other histotypes, thyroid ultrasound (12) may help to identify thyroid nodules with a high risk of malignancy, while conventional ^{99m}Tc -pertechnetate ($^{99m}\text{TcO}_4$) thyroid scintiscan has presently only an ancillary role in distinguishing malignant from benign lesions (13). During the last decade, ^{99m}Tc -SestaMIBI (MIBI), a lipophilic cationic molecule, was introduced as a myocardial perfusion and viability imaging agent (14–17). MIBI has been reported to accumulate in benign and malignant lesions, such as lung, brain, parathyroid tumors and bone lesions (18–21). Recently, a positive MIBI scan has been reported in different thyroid tumors (22–27), but, when applied to unselected

thyroid nodules, this procedure is not able to differentiate benign from malignant lesions (24, 27). Interestingly, however, MIBI scan has been found to be more frequently positive in HCT when compared with other thyroid neoplasias (27); however the relevance of this observation in the diagnostic evaluation of thyroid nodules is unclear, due to the very limited number of cases reported.

The aim of the present study was to evaluate the role of combined MIBI scintiscan and FNAC in the diagnostic evaluation of thyroid nodules with oxyphilic cytology, with particular regard to the differentiation of HCT from OM and the correct identification of malignant nodules.

Materials, methods and patients

Patients

A total of 24 euthyroid patients (20 women, age range 23–70 years, and four men, age range 42–72 years) with a single (or prevalent) thyroid nodule with HC at FNAC were included in this study. All patients were submitted to total thyroidectomy on the basis of clinical, echographic and/or cytological criteria independent from MIBI scan (see below). A summary of the main features of these patients, together with the final histology is reported in Table 1.

Conventional and color flow Doppler sonography

Thyroid ultrasonography (US) and color flow Doppler sonography (CFDS) using an Acuson 128 XP 10 color doppler system (Acuson Co., Mountain View, CA, USA) with a 7.5 MHz linear electronic transducer, were performed. The examination included first a conventional gray scale US, followed by CFDS; all thyroid nodules were identified, localized, counted and their diameters measured. The images were obtained by transverse and longitudinal planes scanning. All nodules were solid iso-hypoechoic, often heterogeneous due to the presence of calcifications and fluid areas, with a maximum diameter ranging from 10 to 60 mm. The CFDS patterns were classified (pattern 0–III) as previously reported (28). As shown in Table 1, most of the patients presented intense intranodular vascularity, while the remaining nodules showed only peripheral blood flow.

Thyroid function assays

All hormonal and antibody assays were carried out by commercial kits. Serum free thyroxine (FT4) and free tri-iodothyronine (FT3) were assayed by RIA (Technogenetics, Milan, Italy); thyrotropin (TSH) by an ultrasensitive chemiluminescent assay (Ortho Clinical Diagnostic SpA, Milan, Italy); and anti-thyroperoxidase

antibody (TPOAb) by RIA (Biocode, Liège, Belgium). Normal values were as follows: FT4, 8.4–20.4 pmol/l; FT3, 4.3–8.6 pmol/l; TSH, 0.2–3.0 mU/l; anti-TPOAb, <20 U/ml. All patients had normal thyroid function; as detailed in Table 1, 6/24 showed increased titers of TPOAb.

Thyroid ^{99m}Tc -pertechnetate scintiscan

Thyroid scintigraphy was performed by means of a computerized gamma-camera equipped with a pinhole collimator (Elsint, SP4; Haifa, Israel) 30 min after i.v. injection of 110 MBq of $^{99m}\text{TcO}_4$. Scans were performed in anterior, left-anterior oblique and right-anterior oblique projections. All patients showed a scintigraphic pattern characterized by a reduced uptake corresponding to a US position of prevalent thyroid nodules that often appeared typically 'cold'.

Thyroid ^{99m}Tc -SestaMIBI scintiscan

This was performed by means of the same gamma-camera used for ^{99m}Tc thyroid scan after i.v. injection of 740–1000 MBq of MIBI without any specific preparation. Two images were acquired: an early image with an acquisition time of 5–10 min at 15 min and a late image with an acquisition time of 10–15 min, 2–3 h after tracer administration. Visual inspection of the images was performed following the MIBI deposition in nodular and extranodular thyroidal tissue in both images. The nodules were described as 'hot' or MIBI-positive when the scintigraphic pattern showed increased localized uptake in both early and late images, and the extranodular tissue did not concentrate MIBI at a late stage.

Fine needle aspiration cytology (FNAC) and histology

US-guided FNAC was performed using 22–25-gauge needles and a 10 ml syringe. The smears (4–12 for each nodule) were immediately fixed with Cytfix Bio-Optica, Milan, Italy and stained with hematoxylin-eosin (HE). In all cases a variable number (10–100%) of follicular cells showed typical oncocyctic changes. The criteria used for cytological evaluation were as follows: (a) For the evaluation of malignancy, monomorphic thyroid follicular cells with abundant colloid and without nuclear changes were considered non suspect. The presence of atypias such as nuclear enlargement, nuclear pleomorphism, binucleation and prominent nucleoli or cellular nests loosely cohesive with marked overlap, were considered suspect. A cytological diagnosis of PTC was made on the basis of classical features (papillae and/or characteristic nuclear changes such as grooves and pseudoinclusions). (b) With regard to differentiation between true HCT and OM, the cytology specimens were considered as suggestive of HCT when

Table 1 Main clinical features of the study group.

Patient no.	Age (years)	Sex	TPOAb	Nodule (mm) US	CFDS* pattern	FNAC	Suspect for malignancy	MIBI scans	Histology
1	37	F	Pos	(37) hypo	III	OM	No	Pos	Foll A with OM in HT
2	61	F	Neg	(10) hypo	II	PTC with OM	Yes	Neg	PTC with OM in MNG
3	55	M	Neg	(60) iso	III	OM	Yes	Pos	MNG with OM
4	56	F	Neg	(22) iso	II	OM	No	Neg	HC-A
5	50	M	Neg	(16) iso	III	OM	No	Neg	Foll A with OM
6	44	F	Pos	(30) hypo	II	OM	Yes	Pos	Warthin's-like PTC in HT
7	23	F	Pos	(27) hypo	III	PTC with OM	Yes	Pos	Warthin's-like PTC in GD
8	45	F	Neg	(31) hypo	III	HC-N	Yes	Pos	HC-A
9	29	F	Neg	(25) iso	III	OM	No	Neg	Foll A with OM and occult PTC
10	69	F	Neg	(15) hypo	III	OM	Yes	Pos	Foll HC-C in HT
11	42	F	Pos	(18) hypo	II	HC-PTC	Yes	Neg	Warthin's-like PTC in HT
12	42	M	Neg	(15) hypo	II	HC-N	Yes	Pos	Foll HC-C
13	47	F	Neg	(17) hypo	III	OM	Yes	Pos	Foll HC-C in focal HT
14	65	F	Pos	(15) hypo	II	HC-N	Yes	Pos	PTC with OM in HT
15	53	F	Neg	(25) hypo	III	OM	Yes	Pos	Foll HC-C in HT
16	50	F	Neg	(20) hypo	III	HC-N	No	Pos	HC-A
17	72	M	Neg	(11) iso	II	OM	No	Neg	Nodular HT and occult PTC
18	51	F	Neg	(27) iso	III	OM	Yes	Pos	Foll HC-C
19	52	F	Neg	(30) iso	II	HC-N	No	Neg	OM in MNG
20	70	F	Neg	(25) hypo	III	OM	No	Pos	Foll HC-C
21	57	F	Pos	(12) iso	II	PTC with OM	Yes	Neg	PTC with OM in HT
22	60	F	Neg	(26) hypo	III	OM	Yes	Pos	Foll HC-C
23	53	F	Neg	(14) hypo	II	HC-PTC	Yes	Neg	HC-PTC
24	64	F	Neg	(19) hypo	III	HC-N	Yes	Pos	OM in MNG

M = male; F = female; hypo = hypoechoic; iso = isoechoic; N = neoplasia; C = carcinoma; A = adenoma; Foll = follicular; PTC = papillary thyroid carcinoma; HC = Hürthle cells; OM = oncocytic metaplasia; GD = Graves' disease; HT = Hashimoto's thyroiditis; MNG = multinodular goiter.

* CFDS pattern was classified 0–III as reported in (28).

HC represented >75% of the total follicular cells present on the smear. HCT were classified as follicular unless typical nuclear features of PTC were detected within the oxyphilic cells - in this case a cytological diagnosis of papillary variant of HCT (or Warthin's-like PTC) was performed. A lower number of HC was considered as evidence of OM (focal: 10–20% HC; moderate: 21–50% HC; marked 51–75% HC), which was associated with various patterns of other benign, suspect or malignant cytological features (see Table 1).

Surgical specimens were fixed with 10% tamponated formalin. Each nodule was totally or subtotally sampled (with at least 10 sections including the capsule) and included in paraffin. Serial slides stained with HE were observed. The presence of benign or malignant neoplasias, as well as non-neoplastic lesions was identified by common criteria. With regard to the oxyphilic cells, the final histotype was classified as HCT when HC were >75% and as OM (associated with various different benign or malignant thyroid lesions) when 10–75% of HC were detected.

Statistical analysis

The sensitivity and specificity for the correct identification of malignant nodules were calculated for the diagnostic procedures (single or in combination) by the Galen & Gambino formula (29).

Results

Cytological and histological findings

As shown in Table 1, 16 (66.7%) nodules were considered malignant or suspect for malignancy by FNAC criteria, while the remaining eight (33.3%) were not suspect. Histological examination showed 14 malignant and 10 benign lesions; in two of the latter cases a small occult PTC was also detected (Table 1), but this result was not considered when the sensitivity and specificity of FNAC was calculated (see below). As shown in Table 2, the sensitivity of FNAC for malignancy was 92.8% and the specificity was 70.0%.

With regard to the oncocytic changes, histological examination revealed the following: (a) 14 cases of HCT: 11 malignant (seven follicular carcinomas, three Warthin's-like PTC and one HC-PTC) and three benign HC adenomas; (b) 10 cases displayed OM

associated with three PTC and seven benign lesions (three follicular adenomas, three nontoxic multinodular goiters and one nodular Hashimoto's thyroiditis). Two cases of occult PTC were detected in benign thyroid lesions (one follicular adenoma and one nodular Hashimoto's thyroiditis).

The ability of FNAC to differentiate true HCT from OM is reported in Table 3. True HCT were correctly identified by FNAC in only 5/14 nodules, providing a sensitivity of 35.7%; on the other hand, FNAC correctly identified OM in 7/10 cases, corresponding to a specificity of 70%.

Results of MIBI scan

As reported in Table 4, 15/24 (62.5%) nodules displayed early and late MIBI uptake. No significant difference in MIBI positivity was found between malignant (10/15 = 66.7%) and benign (5/9 = 55.5%) nodules. The ability of MIBI to distinguish true HCT from OM is also reported in Table 4: most (11/14 = 78.5%) of the true HCT were MIBI-positive, while a few (4/10 = 40%) thyroid lesions with OM displayed significant MIBI uptake. This corresponded to a sensitivity of 78.5% and a specificity of 60% in correctly identifying true HCT.

Combination of FNAC and MIBI scan in the diagnostic evaluation of HC nodules

Finally, we evaluated the potential value of a combined approach by MIBI scan and FNAC to thyroid nodules with HC cytology. As reported in Table 5, the sensitivity

Table 2 Comparison between cytological and histological findings.

FNAC	Malignant	Benign
Suspect	13	3
Not suspect	1	7
Sensitivity	92.8%	
Specificity	70.0%	

Table 3 Oncocytic features: comparison between cytological and histological findings.

FNAC	Histology			
	HCT		Oncocytic metaplasia	
	Malignant	Benign	Malignant	Benign
HCT (8)	3	2	1	2
Oncocytic metaplasia (16)	8	1	2	5

Table 4 Comparison between MIBI results and malignant and benign thyroid tumors, and histological types.

MIBI	Malignant		Benign	
Positive (15)	10		5	
Negative (9)	5		4	
	HCT		Oncocytic metaplasia	
Positive (15)	11		4	
Negative (9)	3		6	
Sensitivity	78.5%			
Specificity	60.0%			

Table 5 Comparison between cytological and histological findings in MIBI-positive and -negative nodules.

MIBI	FNAC	Malignant	Benign
Positive (15)	Suspect	9	3
	Non-suspect	1	2
Negative (9)	Suspect	4	0
	Non-suspect	0	5

and specificity of FNAC for malignancies in the 15 MIBI-positive nodules was 90% and 40% respectively, while in the small subgroup of nine MIBI-negative nodules both sensitivity and specificity were 100%.

Discussion

The results of the present study confirm that FNAC has a lower diagnostic accuracy in thyroid nodules when cells with oxyphilic changes are present in the smear (1, 4, 5), mostly represented by a reduction in the specificity. The recent observation that MIBI scan is often positive in HC thyroid neoplasias (27) prompted us to ascertain whether and to what extent the addition of MIBI scan to FNAC could improve the diagnostic evaluation of 'cold' thyroid nodules with HC cytology. The results obtained did not provide any evidence that in this particular subgroup of thyroid nodules MIBI scan could improve the sensitivity and specificity in the pre-surgical detection of malignant tumors. Our data are in keeping with previous studies (23, 27) including a limited series of thyroid HC tumors (27).

Independently from the benign or malignant histotype, in our study the large majority (78.5%) of true HCT displayed an MIBI-positive scan, while only a minority (40%) of thyroid lesions with OM were MIBI-positive. This finding suggests a direct relationship between MIBI uptake and number/mass of oncocytes, which present high affinity and uptake for MIBI (23, 27). This phenomenon is believed to be due to crowded mitochondria (corresponding to the eosinophilic cytoplasmatic granules) independently from malignancy. It is interesting to note that in the present study, MIBI scan provided a higher sensitivity for the correct identification of true HC tumors when compared with FNAC. On the other hand, the specificity of MIBI in the identification of true HCT was slightly lower than that of FNAC. No further increase in the diagnostic accuracy for thyroid cancer was observed when MIBI scan and FNAC were combined.

In conclusion, the present study shows that most HC tumors are MIBI-positive, but this scan is not sufficiently specific to differentiate true HC neoplasias from other thyroid lesions showing HC at FNAC, although an MIBI-negative scan strongly supports the absence of true HC tumors. MIBI scintiscan has no value in differentiating malignant from benign HC neoplasias: due to the high proportion of malignancy

observed in HC tumors, a surgical approach is generally advised.

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