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Poorly Differentiated and Undifferentiated Thyroid Carcinomas

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ABSTRACT

Thyroid cancer is the most common endocrine malignancy and its incidence goes on increasing worldwide. The majority of thyroid tumours comprise well-differentiated (papillary and follicular) thyroid carcinomas that usually carry an excellent prognosis, while a minority progress to poorly differentiated carcinoma (PDTC) and, ultimately, to the highly aggressive and lethal undifferentiated carcinoma (UTC). Recently, some major advances have been made on the histologic and imunohistochemical identification, as well as on the molecular characterization of PDTC and UTC. In this review we summarize the most recent immunohistochemical and molecular findings in PDTC and UTC, giving a particular emphasis to the diagnostic and prognostic meaning of the genetic alterations.

Key Words: Anaplastic thyroid carcinoma, Non-medullary thyroid carcinoma, Molecular medicine, Small cell carcinomas, Poorly differentiated thyroid carcinoma

INTRODUCTION

The most important difference between the classifications of thyroid tumours in the WHO books of 1988 and 2004 concerns the individualization in the latter of the group of poorly differentiated carcinomas (PDTC) (1, 2). It was also recognized that all sorts of benign and malignant thyroid tumours may be composed by the individualization of oncocytic (oxyphilic or Hürthle) cells, thus leading to oncocytic/Hürthle cell variants of adenoma and of follicular papillary and poorly differentiated thyroid carcinoma (1). It is usually advanced that the absence of an oncocytic/Hürthle cell variant of undifferentiated carcinoma (UTC) reflects the high mitotic ratio of such tumours (the cells of undifferentiated/anaplastic carcinoma divide too fast to allow the accumulation of mitochondria in their cytoplasm) (3).

The immunohistochemical and molecular characteristics of poorly differentiated and undifferentiated carcinomas were thoroughly addressed in the 2004 edition of the WHO book, as well as in a number of review papers by Garcia-Rostan et al., Nikiforov et al. (4-6) and Soares et al. (7) (Tables 1, 2).

Most of the problems found in the stratification of such immunohistochemical and/or molecular markers reflect differential diagnostic difficulties – it is not easy, for instance, to separate a poorly differentiated carcinoma from a widely invasive follicular carcinoma with a trabecular/solid growth pattern – and the intrinsic heterogeneity of both groups of carcinoma.

Another problem regards the existence of several clinico-pathological entities in thyroid oncology that may be considered as a sort of poorly differentiated carcinoma [e.g. (sclerosing) mucoepidermoid carcinoma and mucinous carcinoma)]. Such entities have been recently described and discussed in the 2014 - AFIP book on Thyroid and Parathyroid Tumours (8) and will not be addressed in the present review. The only exception concerns the group of Small cell carcinomas/Carcinoma of the thyroid with Ewing Family Tumour Elements (CEFTE) because it represents a particularly interesting end result of new developments in the immunohistochemical and molecular study of peculiar thyroid tumour that raise difficult differential diagnostic problems (9-12).

POORLY DIFFERENTIATED CARCINOMA

The histological description should follow the 2004 WHO book and the AFIP book of Rosai et al. (1, 8) (Figure 1A-E). The diagnostic guidelines and the histological pictures in the latter are excellent and review thoroughly the steps used in the diagnosis of PDTC following the algorithmic approach advanced by Volante et al. (13).

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Table I: Poorly differentiated carcinoma

	Antibodies usually expressed	Antibodies variably expressed	Antibodies usually not expressed
Immunohistochemical features	Cytokeratins TTF1 Thyroglobulin (focal) Ki-67 (labelling index is higher than in well differentiated carcinomas) Cyclin D1	Synaptophysin p53 E-cadherin	Calcitonin Chromogranin
Molecular features	**Molecular alterations**	**Prevalence (%)**	**References**
	RAS	20-50	(7); (4)
	TP53	15-40	(7); (4)
	BRAF	5-20	(7); (4); (31)
	CTNNB1	5-25	(31); (28)
	PIK3CA	5-14	(7); (4); (31)
	PTEN	20	(31)
	AKT1	5-10	(4)
	TERT	20-50	(7); (36)
	STRN/ALK	9	(42)

PDTC: Immunohistochemical and molecular features (poorly differentiated carcinomas).

Table II: Undifferentiated thyroid carcinoma

	Antibodies usually expressed	Antibodies variably expressed	Antibodies usually not expressed
Immunohistochemical features	Cytokeratins (usually focal) Ki-67 (labelling index is higher than in PDTC) p53 Vimentin Cyclin D1	TTF1 PAX8 E-cadherin EMA P63 CEA	Calcitonin Chromogranin Thyroglobulin Synaptophysin Bcl-2 CD31 CD34
Molecular features	**Molecular alterations**	**Prevalence (%)**	**References**
	TP53	50-80	(19); (4)
	TERT promoter mutation	30-50	(19);(56)
	RAS	4-60	(49)
	BRAF	10-50	(19);(4)
	CTNNB1	5-66	(29)
	PI3KCA	5-25	(19)
	PTEN	5-15	(19); (4)
	AKT1	5-10	(19); (4)
	ALK	0-10	(19)

UTC: Immunohistochemical and molecular features (undifferentiated carcinoma).

The most difficult diagnostic problems occur in the border between well differentiated (WDTC) and poorly differentiated carcinoma. The separation between papillary thyroid carcinoma (PTC) and PDTC is based upon the nuclear features of the neoplastic cells. In case the nuclei are of the PTC type the tumour is classified as a solid or trabecular variant of PTC regardless of the existence of necrotic foci and/or high mitotic number (6, 14, 15).

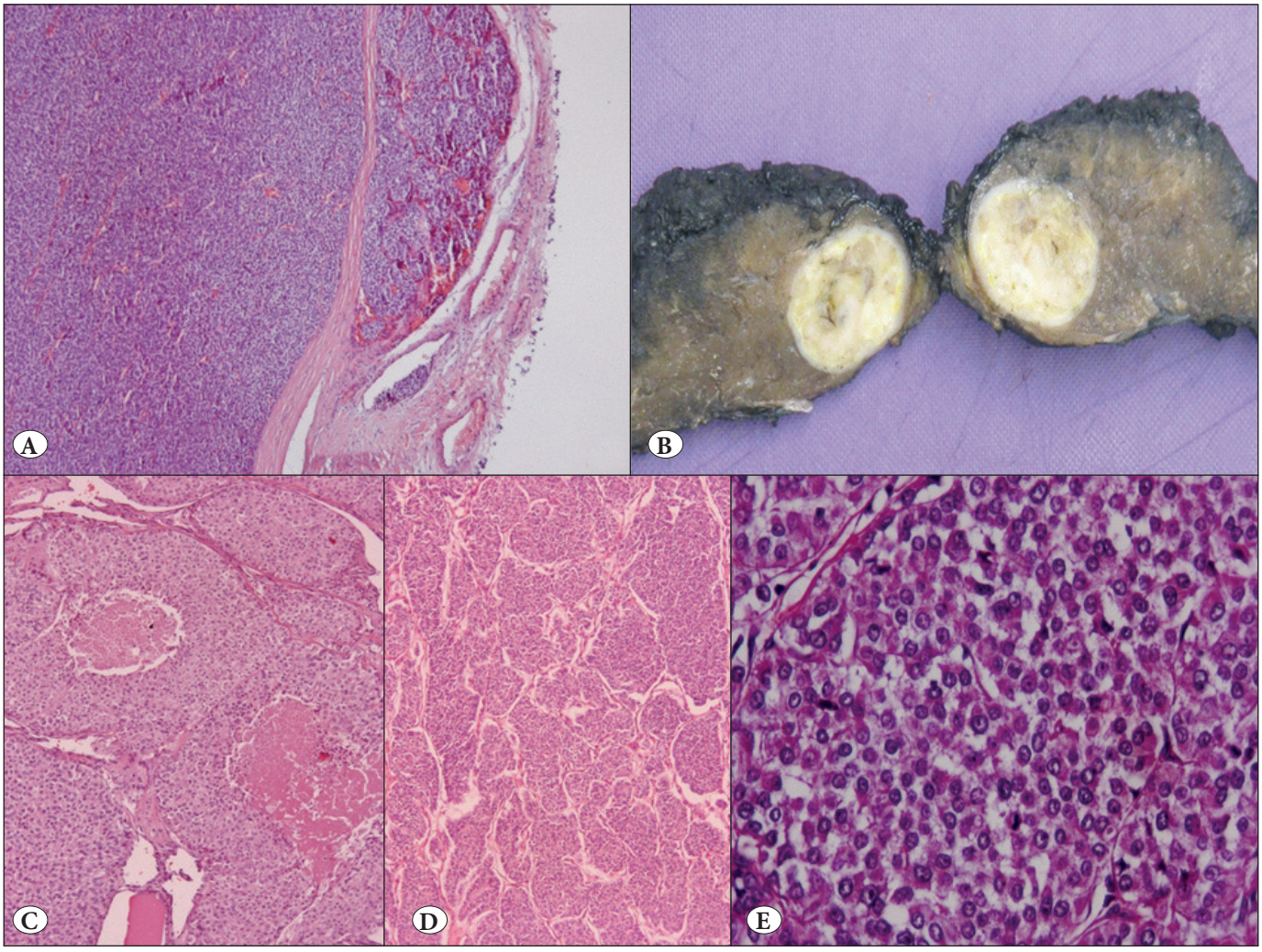

Figure 1: Poorly Differentiated Thyroid Carcinoma (PDTC): A) Tumour with expansive growth pattern, invasion of the capsule and images of vascular invasion, **B)** Macroscopic appearance of an apparently well circumscribed PDTC whose histological characteristics are documented below, **C, D)** Nested pattern area with foci of necrosis (H&E, 40x), **E)** Focus with numerous mitoses and without PTC type nuclei (H&E, 400x).

The separation between widely invasive follicular thyroid carcinomas (FTC) with foci of necrosis and/or high mitotic index and PDTC is almost impossible to establish in many situations (15). Molecular data did not provide so far any diagnostic clue and the pathology reports are written assuming the aforementioned limitations. This does not constitute a major drawback since the prognosis and treatments are similar in both situations (1, 8, 15).

In different fields of well differentiated thyroid carcinomas there are reports of tumours displaying poorly differentiated features [e.g. cribriform morular variant of PTC (16)]. These cases should not be lumped together with common PDTC.

The differential diagnosis between PDTC and UTC/ anaplastic carcinoma may be difficult in intermediate cases but is based upon a very precise immunohistochemical feature: PDTC exhibits diffuse nuclear positivity for TTF1 and focal positivity, frequently with a dot-like pattern, for thyroglobulin, and UTC by definition are thyroglobulin negative and almost always TTF1 negative.

The hottest topic in the world of PDTC regards the diagnosis of PDTC, which do not exhibit unequivocal signs of capsular and/or vascular invasion. The question is simple but the answer is difficult. Which are the criteria for diagnosing a PDTC in an apparently non-invasive thyroid tumour? There are anecdotic reports in the literature claiming that such cases exist and have given rise to metastases (17). Ghossein et al. (18) did not find evidence supporting this claim and we must confess we do not know how to solve the problem. In real life, and whenever the

tumour displays (very) aggressive histological features without showing concomitant signs of invasion, we sample the capsule completely and look at deeper sections of the tumour in an attempt to find such signs. The only molecular feature which might be used for making a diagnosis of noninvasive PDTC would be the demonstration of clonal TP53 mutations or diffuse nuclear immunoreactivity for p53, but even then the classification of noninvasive PDTC is questionable (we must confess we have never made such diagnosis).

In the future, there will hopefully exist drugs that can be efficiently used to treat patients with thyroid carcinomas not responding to radioactive iodine, in these settings the focus will rest on the identification of specific molecular targets rather than on the histological classification of the carcinomas.

The molecular features of PDTC are summarized in Table 1. Activating point mutations of the *RAS* gene typically affect codons 12, 13 and 61. At variance with differentiated thyroid cancer where *NRAS* codon 61 mutations are the most frequent, *HRAS* and *KRAS* codon 12 and 13 are also found mutated in PDTC (4, 7, 19). Volante et al. reported *RAS* mutations as the most common genetic alteration in PDTC (20). Moreover, the detection of *RAS* mutations appears to be clinically relevant in terms of prognosis, identifying a subset of more aggressive tumours (20). It was shown that PDTC cases with mutated *NRAS* are significantly associated with the appearance of haematogenous (particularly bone) metastases (19). Due to the association found between *RAS* mutations and guarded prognosis in PDTC and UTC, Wang et al. proposed that a particular attention should also be paid to WDTC, namely FTC, harbouring *RAS* mutations (7, 21).

TP53 gene, encoding a nuclear transcription factor that is typically involved in the negative regulation of the cell cycle and in promoting apoptosis, is a frequently impaired gene during thyroid tumour dedifferentiation (22-24). In thyroid, *TP53* shows a mutational pattern located in known hotspots (exons 5-9) in 15-40% of cases. Moreover, there is a relatively good correlation between mutations and p53 immunohistochemical reactivity: aberrant p53 immunoreactivity is detectable in 40-50% of PDTC (1, 7, 19). *TP53* mutation seems to be (one of) the dedifferentiation switches necessary for progression and dedifferentiation in thyroid tumours (7).

$BRAF^{V600E}$ mutation occurs in 5-20% of PDTC (25, 26). Many of these carcinomas also reveal areas of PTC, and $BRAF^{V600E}$ is present in both tumour components, thus suggesting that this mutation is an early event that do not impair tumour dedifferentiation (4). In accordance with a stepwise progression model, BRAF mutations are almost exclusively found in PDTC arising from PTC, being extremely rare in PDTC associated with FTC (7). Ricarte-Filho et al. (27) reported that 39% of PDTC, FDG-PET positive tumours refractory to radioactive iodine (RAI) treatment harbouring *BRAF* mutations, whereas non-RAI-refractory PDTCs display a significantly lower prevalence of *BRAF* mutations (12%) (27). These results indicate that *BRAF* mutated PDTC are more often refractory to RAI treatment than *BRAF* wild type PDTC.

Two of the most common rearrangements in WDTC are RET/PTC and *PAX8/PPARγ* (4); however, these specific rearrangements are only rarely detected in PDTC (19). This finding suggests that WDTC harbouring such rearrangements do not usually evolve toward less differentiated carcinomas, thus reinforcing the assumption that the majority of "rearranged" PTC and FTC cases do not tend to progress towards further advanced steps of neoplastic development (19).

Another gene reported as frequently mutated in PDTC and UTC is *CTNNB1*, which encodes βcatenin that is involved in cell adhesion and WNT signalling (4). The seminal paper of Garcia-Rostan et al. (28) showed a frequency of 25% of *CTNNB1* mutations in PDTC. The activating mutations cluster in exon 3 at the phosphorylation sites for ubiquitination and degradation of β-catenin and are associated with aberrant nuclear immunoreactivity, suggesting WNT pathway activation (28, 29). In contrast Rocha et al. (30) did not find mutations in *CTNNB1* nor in the *CDH1* gene (encoding E-cadherin) in a series of PDTC. Rocha et al. observed alterations of protein expression, concluding that loss of E-cadherin rather than *CTNNB1* mutation appears to be the crucial event in determining the degree of differentiation of thyroid carcinomas (19, 30). In accordance with these latter results, Pita et al. (31) found *CTNNB1* mutations in a minority (5%) of PDTCs.

Thyroid carcinoma dedifferentiation involves also the progressive accumulation of other mutations, particularly those in genes that encode effectors of the PI3K–AKT pathway, such as the *PIK3CA* (the gene that encodes PI3K), *AKT1* and *PTEN* (4). Among PDTC carcinomas, 5-14% harbour mutations in *PIK3CA*, 20% in *PTEN* and 5–10% in *AKT1* (4, 8, 31, 32).

Telomerase activation is known to be a hallmark of cancer being detected in up to 80% of malignant tumours (7). Normal thyroid tissue is thought to be telomerase

negative, thus raising the possibility that the reactivation of telomerase may be a useful marker of tumour development (33, 34). *TERT* promoter mutations were found in 20-50% of PDTC (8, 33, 35, 36). These findings concur with the evidences that *TERT* promoter mutations associates with a more aggressive behaviour of thyroid tumours (37, 38).

Some PDTC and every UTC constitute the majority of clinically aggressive tumours that cause the death of the patients. In an attempt to address this lethality, efforts have been made for identify other genetic alterations in less differentiated and undifferentiated thyroid carcinomas that could pinpoint new therapeutic targets. Analysis of miRNA expression in normal thyroid tissue and in major types of thyroid tumours revealed that the majority of known miRNAs were expressed in normal thyroid tissues, whereas in thyroid neoplasms 32% of miRNAs were found to be consistently upregulated, and 38% were downregulated with more than a 2-fold change as compared to normal tissue (39). The most highly upregulated miRNAs in PDTC were miR-187, -221, -129, -222, -146b, -339, -183 (39).

The rearrangement involving the anaplastic lymphoma kinase (*ALK*) gene (40) and the striatin (*STRN*) gene (STRN/ALK) leads to constitutive activation of ALK kinase via dimerization mediated by the coiled-coil domain of STRN and to a kinase-dependent, thyroid-stimulating hormone-independent proliferation of thyroid cells. Expression of *STRN/ALK* transforms cells *in vitro* and induces tumour formation in nude mice. Kelly et al. (41) reported this gene arrangement in 9% of PDTC and demonstrated that *STRN/ALK* gene fusion occurs in a subset of patients with aggressive types of thyroid cancer, providing initial evidence that ALK inhibitors may represent a therapeutic option in these cases (41).

Other molecular alterations include downregulation of genes responsible for specialized thyroid function and in cell adhesion, upregulation of genes involved in motility and cell–cell interaction, and different patterns of deregulation of the expression of genes that encode cytokines and other proteins involved in inflammation and immune response. Although the list of specific deregulated genes varies substantially between different studies, a number of genes have been consistently found to be deregulated at the mRNA level: *MET*, *TPO*, *TIMP1*, *DPP4, LGALS3* and *KRT19* (42-46).

UNDIFFERENTIATED (ANAPLASTIC) CARCINOMA

For a thorough and extremely competent review on the macroscopic and histologic aspects of these tumours please see the respective AFIP chapter (8). A typical case of UTC is illustrated in Figure 2A,B. The immunohistochemical and molecular data on the whole group are summarized in Table 2.

Undifferentiated thyroid carcinoma (UTC) corresponds to the most aggressive form of thyroid cancer, being the final step of the progression of thyroid epithelial neoplasms. The concept of stepwise progression from a pre-existing well-differentiated thyroid carcinoma to poorly differentiated and undifferentiated carcinoma is supported by clinical, epidemiologic, pathologic and molecular evidence (studies of loss of heterozygosity, comparative genomic hybridization, genetic and epigenetic alterations), although anaplastic carcinoma may apparently also arise *de novo* (7, 47, 48).

Thyroid tumours are part of the minority of those human cancer types that do not follow the classical Vogelstein model, in which mutational inactivation of *TP53* is a crucial step in the first steps of progression (from adenoma

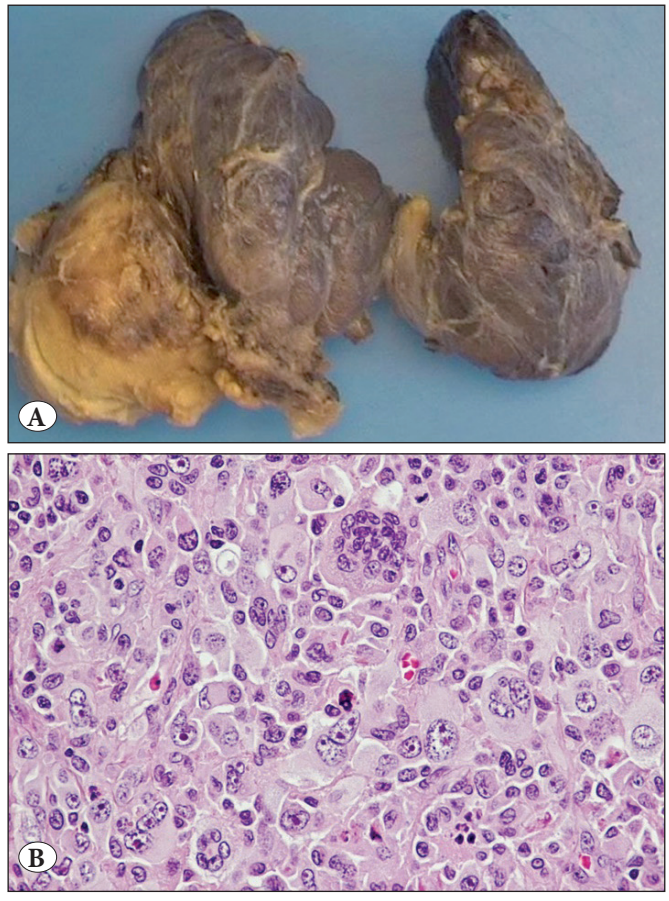

Figure 2: Undifferentiated Thyroid Carcinoma: A) Large tumour that grows beyond the thyroid limits, **B)** The neoplastic cells are mitotically active, atypical and pleomorphic displaying epithelioid to spindle cell morphology and co-existing with giant cells (H&E, 400x).

to carcinoma) (49). *TP53* gene inactivation seems to play a major role in the progression from differentiated to undifferentiated carcinoma, being a late event in the carcinogenic process and occurring together with a marked increase of cell proliferation (7). At variance with well-differentiated tumours in which TP53 gene mutations are rare, in UTC the loss of function mutations in different reports ranges from 50 to 80% (19, 27, 50-52). Many studies have shown that, when the same tumour contained well-differentiated and undifferentiated components, *TP53* mutation was restricted to the anaplastic foci (50, 53, 54). No clear prognostic significance has been attributed to the presence of *TP53* mutations in UTC.

The second most frequent genetic alteration in UTC is the recently described *TERT* promoter mutation. The -124 and -146 mutations in *TERT* promoter are detected in up to 50% of UTC; this percentage is higher to the percentage found in PDTC, and much higher than that reported in well-differentiated thyroid carcinomas (8, 55). The -124 mutation occurs more frequently, being the two mutations mutually exclusive. It was reported that -124 and -146 *TERT* promoter mutations coexist frequently with $BRAF^{V600E}$ mutation (33, 35, 36). In one report, Landa et al. (37) stated that *TERT* promoter mutations were collectively associated with *BRAF* and *RAS* mutations when UTC and PDTC were lumped together. Recently, Shi et al. (56) found that a-124 *TERT* promoter mutation in UTC is typically associated with older age of the patients and with distant metastasis, thus suggesting that this mutation plays an important role in the pathogenesis and aggressiveness of UTC.

The prevalence of *RAS* mutations in UTC ranges from 4 to 60% (13, 31, 57, 58). Activating point mutations typically affect codons 12, 13 and 61 of the *NRAS* gene. *In vitro RAS* activation leads to the rapid loss of differentiation markers, such as thyroglobulin, thyroid peroxidase, and thyrotropin receptor, and increased proliferation, but it is not sufficient to induce per se complete transformation of thyroid cells (59-61). Dedifferentiation is likely not driven by *RAS* mutations individually, but rather by the combined effect of multiple genetic alterations (62) including *TP53* and *TERT* promoter gene mutations

The $BRAF^{V600E}$ point mutation that constitutes about 98–99% of all BRAF mutations found in thyroid cancer, and it is present in up to 40% of UTC (25, 27, 63). Nikiforov et al. (47) reported that *BRAF* mutation was detected in areas of PTC and of PDTC or UTC coexisting in the same tumours, providing molecular evidence for stepwise progression from PTC to PDTC and UTC. The results on the record also suggest that constitutive activation of *BRAF* may predispose to such a progression, although it appears that this mutation represents an early event and additional genetic alterations (namely *TP53* mutation) are required to promote the process of dedifferentiation (47).

Molecular alterations are progressively accumulated in thyroid cancer during the dedifferentiation process, and this occurs particularly in those genes that encode effectors of the PI3K-AKT pathway. Among UTC, 5–25% of the tumours harbour mutations in *PIK3CA* (8), 5–15% *PTEN* mutations and 5–10% *AKT1* mutations (22, 27, 32, 64). Amplification of the *PIK3CA* genomic locus in 3q26.3 is found in about 40% of UTC suggesting that alteration of the PI3K-AKT pathway plays a pivotal role in the pathogenesis of UTC (55).

The *STRN/ALK* gene rearrangement has been identified in a subset of UTC that appears to develop from PTC. This gene rearrangement was also reported in one of 24 UTC coexisting with a follicular variant of PTC component (41). Murugan et al. (65) identified activating point mutations in *ALK* (encoding the tyrosine kinase domain of the protein) in two tumours from a series containing 18 UTC.

Recently, a critical role for miRNAs in carcinomas has emerged with increasing evidence showing that they may drive and potentiate tumourigenesis and neoplastic progression. Some miRNAs appear to be reduced in thyroid cancer, such as the let-7 family, but other miRNAs, such as the miR-200 and miR-30 families, are exclusively downregulated in UTC, indicating that its loss may play a role in the acquisition of more aggressive tumour characteristics (i.e., enhanced cell invasion and migration or dedifferentiation) (66, 67). On the other hand, miRNAs such as miR-146, miR-221, miR-222, and miR-17-92 are upregulated in UTC and in well-differentiated thyroid cancer, indicating that reinforced expression of these miRNAs appears to play a role in the maintenance of the oncogenic process (66).

The low-density lipoprotein receptor-related protein gene (LRP1B) originally isolated on the basis of homozygous deletions detected in human lung cancer cell lines (68) is among the top 10 most significantly deleted genes across 3312 human cancer specimens (69). LRP1B localizes at 2q21, a susceptibility locus for familial non-medullary thyroid cancer and encodes for a member of the endocytic low-density lipoprotein receptor superfamily (68). Our group reported that the LRP1B expression level in UTCs was significantly lower than in differentiated thyroid cancers, and that such reduced expression was due to frameshift mutation and genomic loss of *LRP1B* gene (68). Moreover,

UTC showed frequent methylation of the promoter region of the gene leading the loss of the expression of LRP1B in more than 80% of UTCs (68).

Among the proteins whose expression is altered in UTC, some appear as promising novel therapeutic targets namely Aurora kinases and transferrin receptor. In UTC, Aurora kinases are often found overexpressed (70). Aurora kinases are serine/threonine kinases that play an essential role in cell division. Their aberrant expression and/or function induce severe mitotic abnormalities resulting in either cell death or aneuploidy. Baldini et al. (71) reported the *in vitro* efficacy of Aurora kinase inhibitors (MLN8237 inhibitor for Aurora-A and AZD1152 inhibitor for Aurora-B) in restraining cell growth and survival of four human UTC cell lines (CAL-62, BHT-101, 8305C, 8505C). Baldini showed furthermore that Aurora A inhibition appears to be more effective than that of Aurora B in UTC cell lines (71). These data indicate that inhibitors for overexpressed proteins, such as Aurora kinases, alone or in combination with other drugs, including microtubule inhibitors, display an anticancer effect in preclinical models of UTCs suggesting that this approach may be used as an alternative therapeutic strategy for patients with UTC (72, 73).

The TfR1/CD71 is a cell membrane glycoprotein involved in iron homeostasis and cell growth. Parenti et al. (74) reported immunohistochemical data demonstrating the overexpression of TfR1/CD71 in UTC and discuss the possibility of targeting TfR1/CD71 by monoclonal or recombinant antibodies or transferrin-gallium-TfR1/CD71 molecular complexes or even small interfering RNAs (siRNAs) (74).

Finally, aberrant methylation of gene promoter regions and histone modifications can alter the function of tumour suppressor genes and thus contribute to activation of signalling pathways, such as PI3K–AKT and MAPK cascades. Changes in the epigenetic regulation of oncogenic steps might also lead to downregulation of thyroid-specific genes during tumour progression and dedifferentiation (75).

SMALL CELL THYROID CARCINOMAS

In thyroid, the small cell phenotype has been observed mainly in poorly differentiated carcinoma and lymphoma (76). Other primary tumours that may exhibit small cell features include medullary thyroid carcinoma, undifferentiated carcinoma, squamous cell carcinoma, CASTLE, primary extra-skeletal Ewing family tumours (PEEFTs) (76-79) as well as other rare flowers such as neuroblastoma (80) and basaloid neoplasm with solid cell nest features (81). Until now, the rare reports of primary neuroendocrine and non-neuroendocrine small cell carcinomas of the thyroid (82, 83) have not provided enough evidence to support the recognition of a primary small cell carcinoma of the thyroid as an entity.

In 2011, our group reported the first case of carcinoma of the thyroid with Ewing family tumour elements (CEFTE) (9). CEFTE is a unique small cell epithelial tumour that showed neither C cell nor follicular cell differentiation. It occurs in young patients and presents as large lobulated thyroid nodules. Histologically, CEFTE are unencapsulated, predominantly expansive neoplasms, displaying vascular invasion and growing in a nested pattern consisting of well-defined, variable sized insulae with central necrosis, as well as trabeculae and solid areas (Figure 3A,B). The cells are small, uniform, with regular and fairly round nuclei disclosing fine chromatin and variable nucleoli. The

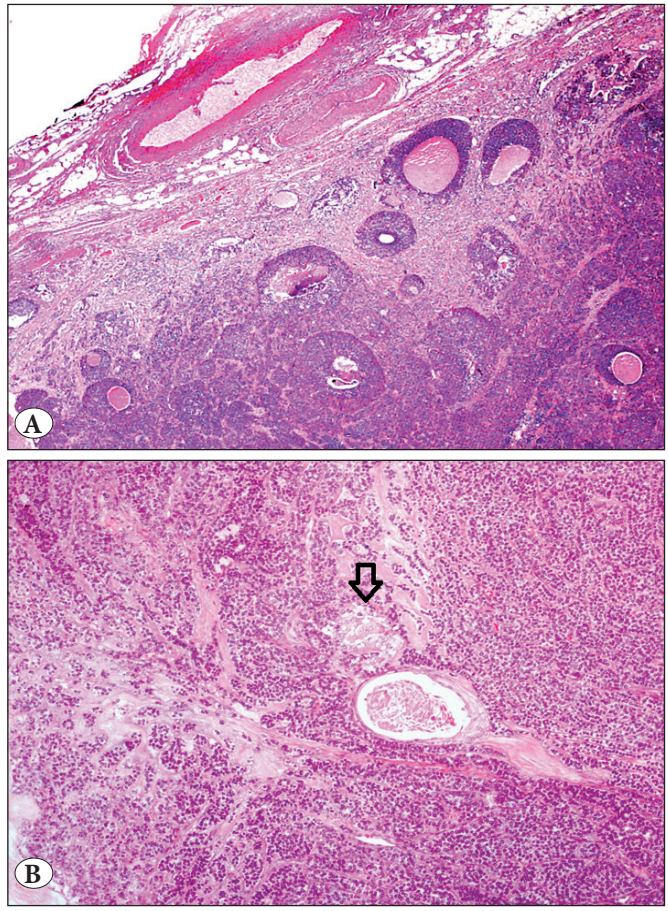

Figure 3: Histological aspect of carcinoma of the thyroid with Ewing family tumour elements (CEFTE): A) Nested pattern area with foci of necrosis (H&E, 20x), **B)** The majority of the neoplastic cells are small, there are foci of squamous differentiation and some follicles composed by cells with papillary thyroid carcinoma-type nuclei (arrow) (H&E, 100x).

cytoplasm is scant with ill-defined boundaries. Additionally, epidermoid-like areas and co-existing follicular foci with papillary-like nuclear features may be observed (9). Mitotic activity is variable.

The neoplastic cells of CEFTE diffusely express cytokeratins, p63, E-cadherin and CD99 in the absence of vimentin expression (9-11). In Table 3 we summarized the immunohistochemical features of CEFTE. CEFTE should be distinguished from basaloid tumor with solid cell nests features that is a PTC related tumor composed by small cells that express p63, cytokeratin 5 and galectin3 in the absence of CD5 and CD99 expression (81).

CEFTE discloses the EWSR1-FLI1 rearrangement typical of PEEFTs (9-11) (Figure 4A,B). We do not know if CEFTE should be considered as a type of PEEFT with extensive carcinomatous differentiation, or true small cell non-neuroendocrine carcinoma exhibiting the *EWSR1-FLI1* rearrangement. As in other locations, the diagnosis of thyroid PEEFT relies on the detection of the typical *EWSR1-FLI1* rearrangement (84). The *EWSR1* rearrangements with other partners have been reported in other non-PEEFT tumours (85,86).

It is worthwhile stressing the apparent good prognosis of these tumours, despite their poorly differentiated appearance, vascular invasiveness and necrotic foci.

The etiopathogenesis of such small cell carcinomas of the thyroid remains unknown: do they derive from "dedifferentiated" PTC cells that have acquired the *EWSR1-FLI1* rearrangement and entirely lost thyroid differentiation

Table III: Immunohistochemical features of carcinoma of the thyroid with Ewing family tumour elements (CEFTE)

Antibody	Expression
Pan-cytokeratins	Present
Cytokeratin 5	Absent
Cytokeratin19	Present
Vimentin	Absent
TTF1	Absent
Thyroglobulin	Absent
Calcitonin	Absent
p63	Present
Chromogranin	Variable
Synaptophysin	Variable
CD99	Present
Galectin3	Absent
Ki67 labeling index	Variable

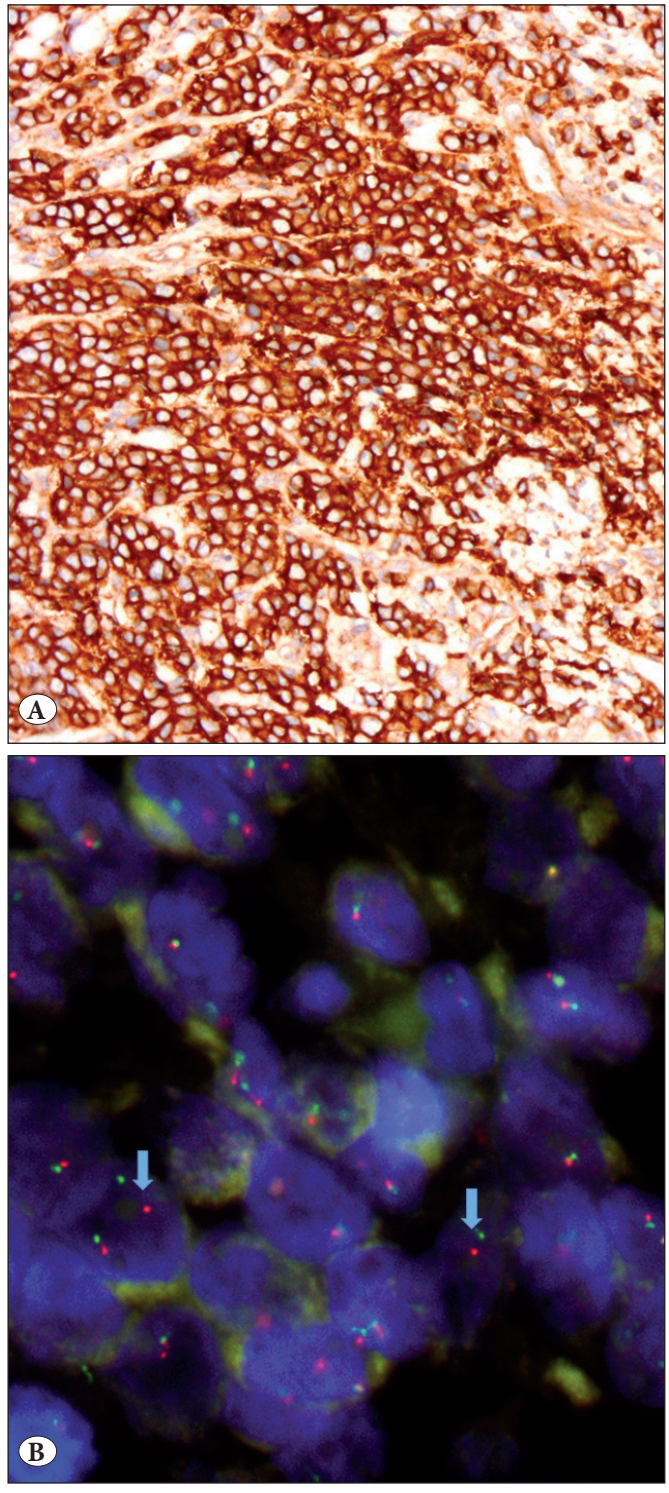

Figure 4: CD99 expression and EWSR1/FLI1 rearrangement in a case of carcinoma of the thyroid with Ewing family tumour elements (CEFTE): A) CD99 diffuse and membrane expression in the small cells (200x), **B)** EWSR1/FLI1 rearrangement detected by FISH dual color probe in the same case (break apart signs – arrow).

(negativity for TTF-1 and thyroglobulin), or do they originate from thymic/branchial pouch remnants such as the main cells of solid cell nests? (10).

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CONFLICT OF INTEREST

Authors declared that they have no conflict of interest.

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