MORPHOLOGICAL, IMMUNOHISTOCHEMISTRY AND MOLECULAR ANALYSIS OF DIFFERENTIATED HIGH-GRADE CARCINOMA

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High-grade non-anaplastic (HGFC-NA) thyroid tumors belong to a rare and aggressive category of neoplasms that occupy an intermediate position between differentiated and anaplastic carcinomas. There are high mortality rate and limited standard treatment options, which usually include surgical tumor removal with subsequent radioiodine treatment and levothyroxine suppression therapy. Targeted tyrosine kinase inhibitors are additionally considered in radioiodine-resistant forms, but the efficacy of those is limited. A clinical case of differentiated high-grade thyroid carcinoma (DHGTC) in a 62-year-old female patient post hemithyroidectomy is presented. Histological assessment, immunohistochemistry (TTF-1, PAX8, CK19, p53, Ki-67), and the key marker (*TERT*, *TP53*, *BRAF*) molecular testing methods were used. The tumor size was 3.4 × 2.8 × 2.5 cm; the tumor showed pronounced architectonic heterogeneity, focal necrosis, high mitotic activity — 8–10 mitoses per 10 fields of view at ×400 (corresponding to ≥ 5 per 2 mm^2), and the Ki-67 proliferation index reached 35%. IHC was used to detect the TTF-1 and PAX8 expression, mutational p53 pattern of expression, suggesting the TP53 mutation. Molecular testing revealed no alteration of the *TERT* and *BRAF* genes. These characteristics made it possible to verify the diagnosis of DHGTC. A conclusion was drawn about the need for comprehensive morphological and molecular diagnosis of HGFC-NA tumors, since the mitotic activity quantitative parameters, Ki-67, and TERT/TP53 status determine the prognosis and the personalized therapy selection.

Keywords: thyroid carcinoma, high-grade non-anaplastic tumors, DHGTC, PDTC, Ki-67, *TERT*, *TP53*

Author contribution: FMakhachev DR, Bulanov DV, Shovkhalov MM, Bekmurziev BZ, Geroev IA — data analysis and interpretation, manuscript writing, editing; Netsvetova AM, Zhusupova AR — manuscript writing, editing; Gubich DS, Manovski AM — clinical data acquisition, editing.

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Received: 02.09.2025 **Accepted:** 15.09.2025 **Published online:** 24.09.2025

DOI: 10.24075/brsmu.2025.042

МОРФОЛОГИЧЕСКИЙ, ИММУНОГИСТОХИМИЧЕСКИЙ И МОЛЕКУЛЯРНЫЙ АНАЛИЗ ДИФФЕРЕНЦИРОВАННОЙ ВЫСОКОЗЛОКАЧЕСТВЕННОЙ КАРЦИНОМЫ

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Высокозлокачественные неанапластические опухоли щитовидной железы (HGFC-NA) относятся к редкой и агрессивной категории новообразований, занимающих промежуточное положение между дифференцированными и анапластическими карциномами. Имеют место высокая смертность и ограниченные возможности стандартного лечения, которое обычно включает хирургическое удаление опухоли с последующей радиойодтерапией и супрессивной терапией левотироксином. При радиойодрезистентных формах дополнительно рассматривают таргетные тирозинкиназные ингибиторы, однако их эффективность ограничена. Представлен клинический случай дифференцированной высокозлокачественной карциномы (DHGTC) у пациентки 62 лет, перенесшей гемитиреоидэктомию. Использованы методы гистологического анализа, иммуногистохимии (TTF-1, PAX8, CK19, p53, Ki-67) и молекулярного тестирования ключевых маркеров (*TERT*, *TP53*, *BRAF*). Опухоль имела размеры 3,4 × 2,8 × 2,5 см, демонстрировала выраженную архитектоническую гетерогенность, очаговый некроз, высокую митотическую активность — 8–10 митозов на 10 полей зрения при ×400 (что соответствует ≥ 5 на 2 мм^2), а индекс пролиферации Ki-67 достигал 35%. С помощью ИГХ выявлена экспрессия TTF-1 и PAX8, p53 с мутационным типом экспрессии, что указывает на мутацию TP53. Молекулярное исследование не показало изменения в генах *TERT* и *BRAF*. Эти признаки позволили верифицировать диагноз DHGTC. Сделан вывод о необходимости комплексной морфо-молекулярной диагностики HGFC-NA, поскольку количественные параметры митотической активности, Ki-67 и статус TERT/TP53 определяют прогноз и выбор персонализированной терапии.

Ключевые слова: рак щитовидной железы, высокозлокачественные неанапластические опухоли, DHGTC, PDTC, Ki-67, *TERT*, *TP53*

Вклад авторов: Д. Р. Махачев, Д. В. Буланов, М. М. Шовхалов, Б. З. Бекмурзиев, И. А. Героев — анализ и интерпретация данных, написание текста статьи, редактирование; А. М. Нецветова, А. Р. Жусупова — написание текста статьи, редактирование; Д. С. Губич, А. М. Мановски — сбор клинических данных, редактирование.

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Статья получена: 02.09.2025 **Статья принята к печати:** 15.09.2025 **Опубликована онлайн:** 24.09.2025

DOI: 10.24075/vrgmu.2025.042

In recent years, the high-grade follicular cell-derived non-anaplastic (HGFC-NA) thyroid carcinomas attract attention of experts in endocrine disorders. According to the WHO classification (2022), this group is classified as a separate category combining aggressive neoplasms with the thyroid differentiation, high mitotic activity, necrotic foci, and poor prognosis. HGFC-NA tumors occupy an intermediate position between differentiated and anaplastic carcinomas [1].

Two subtypes are distinguished in the structure of HGFC-NA tumors: poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (DHGTC). The PDTC diagnostic criteria fixed in the Turin Proposal (2006)

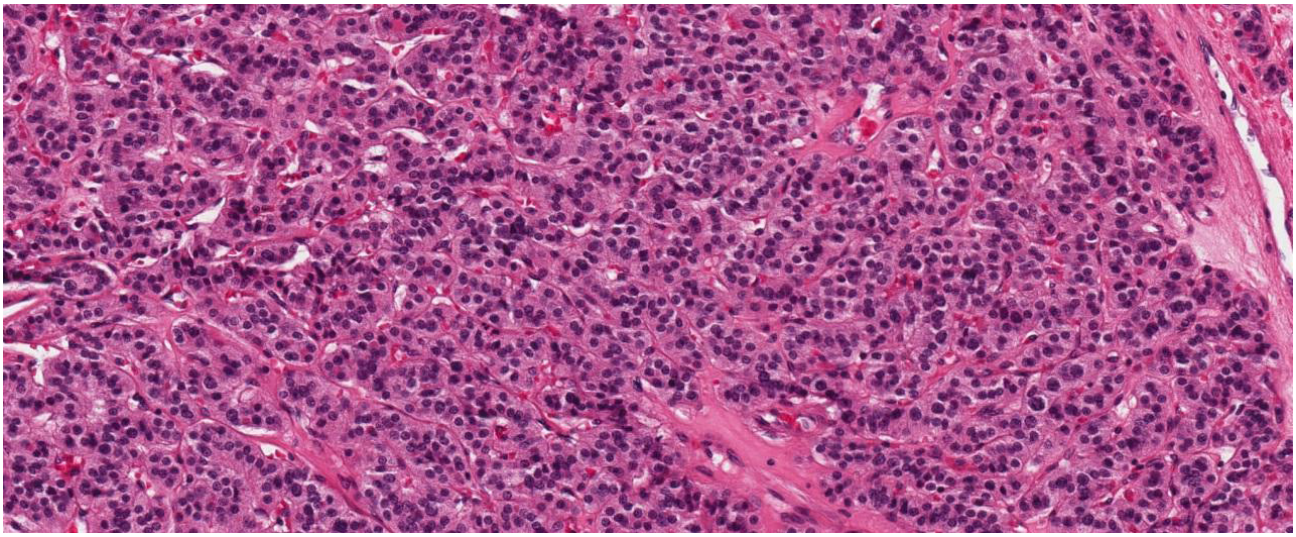

Fig. 1. Poorly differentiated thyroid carcinoma (PDTC) based on the Turin Proposal criteria. Solid/insular growth pattern with thin fibrovascular septa, highly dense small monomorphic cells with high nuclear/cytoplasmic ratio; no nuclear features typical for papillary thyroid carcinoma (H&E, ×200 magnification)

include solid, trabecular or insular growth pattern, absence of nuclear features of papillary carcinoma, and ≥ 3 mitoses per 2 mm^2 or necrotic foci [2] (Fig. 1).

It is important to distinguish the HGFC-NA tumors to clarify the diagnosis and choose the tactics that also includes targeted approaches. These tumors reflect a transitional biological range and require the comprehensive assessment of morphological, immunohistochemical, and molecular features. The HGFC-NA tumors are characterized by solid, trabecular, follicular, and sclerosing structures accompanied by cellular atypia, high Ki-67 index (> 20–30%), and the signs of neoangiogenesis [3–5].

Mutations in the *TERT* promoter, *TP53* и *BRAF* are considered to be the key molecular alterations. These are associated with the poor prognosis, radioiodine-resistance, and metastasis. DHGTC can have any morphological structure, including papillary or follicular, but it is diagnosed with ≥ 5 mitoses per 2 mm^2 and/or necrosis, regardless of differentiation [6, 7].

A clinical case of DHGTC with morphological assessment, immunohistochemistry, and molecular testing is provided below.

Clinical case

The female patient K. aged 62 years presented with complaints of the neck enlargement, moderate difficulty swallowing and hoarseness escalating within six months. She had a history of hyperthyroidism during therapy with antithyroid drugs and stage II hypertension. The patient had no family history of cancer. Examination revealed a dense mass sized up to 3.5 cm in the right lobe of the thyroid gland, which moved when swallowing.

Instrumental methods

Ultrasonography revealed a hypoechoic nodule sized 3.5 × 2.8 cm with uneven contours, hypervascularization, and microcalcifications. The mass TI-RADS score was 5. CT of the neck revealed no invasion of the surrounding tissues and regional lymph nodes. The fine-needle aspiration biopsy was classified as Bethesda V ("suspect for malignancy").

Surgical treatment

The right-sided hemithyroidectomy was performed. There were no complications in the postoperative period.

Macroscopic examination

The tumor had a grey-white color, irregular lobular pattern, foci of necrosis and microcalcifications. Tumor size: 3.4 × 2.8 × 2.5 cm. The section showed alternating solid zones and areas of coagulative necrosis.

Microscopic examination

The tumor showed pronounced architectonic heterogeneity: solid, trabecular, and pseudofollicular structures surrounded by thin fibrous septa. Cell nuclei were hyperchromic, round-oval, with moderate atypia and clearly visible nucleoli. Mitotic activity was high: 8–10 mitoses per 10 fields of view at ×400, which was above the diagnostic threshold for DHGTC. Furthermore, foci of coagulative necrosis and microvascular proliferation with signs of vascular invasion were revealed. There were no typical nuclear features of papillary carcinoma.

To demonstrate the differential diagnosis features, an example of anaplastic thyroid carcinoma (ATC) is provided. ATC can resemble high-grade tumors in terms of morphology, but it is distinguished by higher cellular pleomorphism, the presence of giant multinucleated cells, and a larger number of atypical mitoses (Fig. 2).

The combination of features identified is in this case typical for the solid/trabecular and pseudofollicular structure (Fig. 3A); foci of necrosis and high mitotic activity (Fig. 3B) make it possible to classify the tumor as a highly probable differentiated high-grade follicular thyroid carcinoma (DHGTC) belonging to the HGFC-NA group. Final verification required the use of additional histological assessment, extended immunohistochemistry (TTF-1, PAX8, CK19, p53, Ki-67), and molecular testing methods. The latter included assessment of mutations in the genes *TERT*, *TP53*, and *BRAF* using the NGS-panel method with confirmation by Sanger sequencing.

Immunohistochemistry analysis

Tumor cells expressed TTF-1 and PAX8, which confirmed their origin in follicular cells. The Ki-67 index reached 35%. Galectin-3 expression and focal HBME-reaction were reported; no calcitonin and thyroglobulin were detected.

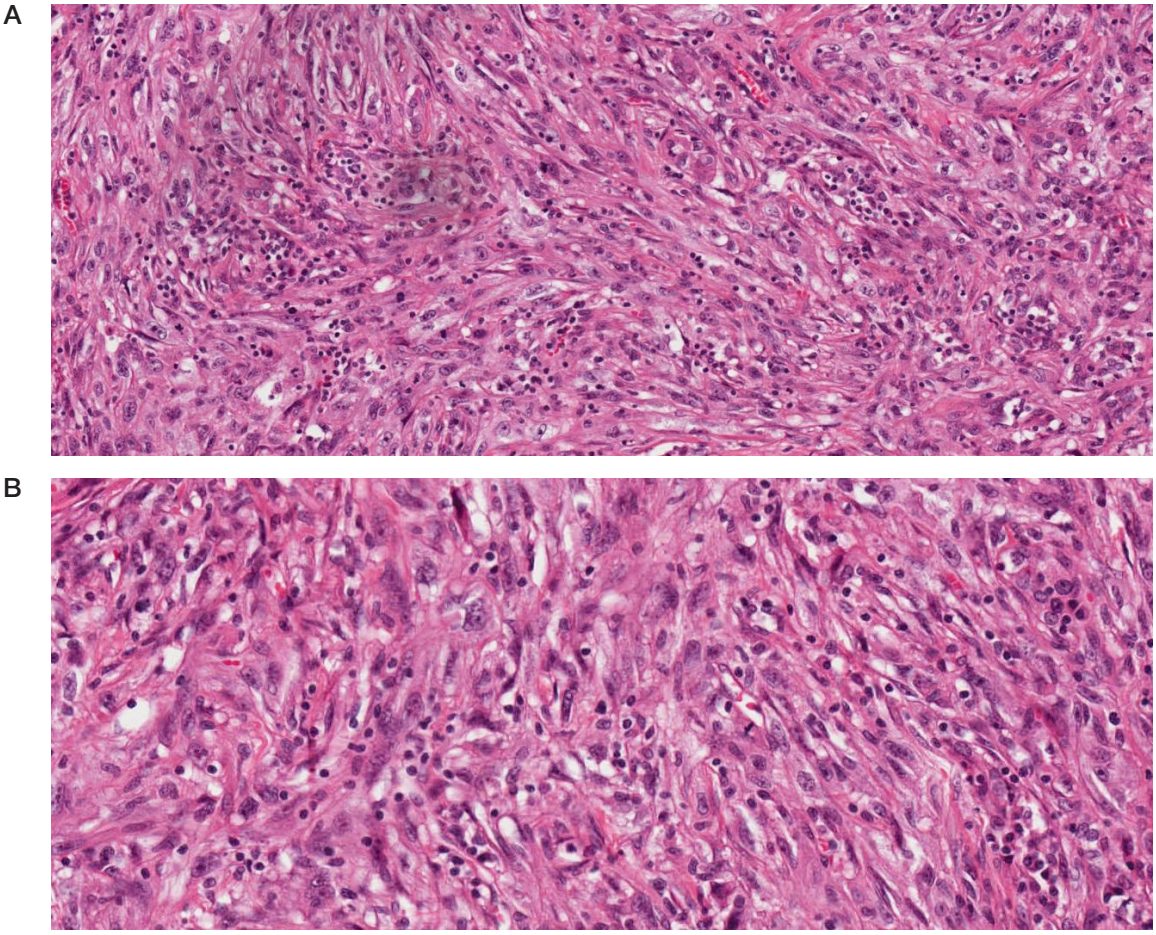

Fig. 2. Spindle cell variant of anaplastic thyroid carcinoma (ATC). **A**. Dense, multidirectional bundles of spindle cells with the pronounced nuclear pleiomorphism, coarsely granular chromatin (H&E, ×100 magnification). **B**. High cellularuty, multiple atypical mitoses, sporadic multinucleated tumor cells (H&E, ×400 magnification)

Molecular testing

The *TP53* mutation with the mutational p53 expression pattern was identified in the tumor, while no *TERT* and *BRAF V600E* mutations were reported. The profile in combination with morphology and immunohistochemistry assessment confirmed the diagnosis of DHGTC belonging to the HGFC-NA group.

Clinical case discussion

The HGFC-NA tumors represent a recently distinguished category showing high diagnostic complexity. These occupy an intermediate position between differentiated and anaplastic carcinomas combining thyroid differentiation with aggressive biological behavior [8, 9].

The pronounced architectonic heterogeneity is the key feature of HGFC-NA tumors. Solid, trabecular, pseudofollicular, and sclerosing structures can be combined in the same tumor, which hampers the diagnosis, especially in small biopsies [10]. According to the WHO classification (2022), the decisive criteria are the presence of ≥ 5 mitoses per 2 mm^2, focal necrosis, and Ki-67 index > 20% with the preserved thyroid differentiation. In the case provided, the Ki-67 index reached 35%, and the *TP53* mutation identified suggested poor prognosis [11].

From a molecular perspective, HGFC-NA tumors are characterized by genomic instability. The most significant are mutations in the *TERT* promoter (35–40% of cases) associated with radioiodine resistance, *TP53* alterations (20–25%) reflecting genomic instability, and the less frequent *BRAF V600E* mutations that are found mainly in DHGTC, which can determine sensitivity to the MAPK cascade inhibitors [12].

In this case, molecular testing revealed the *TP53* mutation, the presence of which confirmed poor prognosis, while there were no *TERT* and *BRAF V600E* mutations. These findings are consistent with the literature data emphasizing that the presence of the combination of *TERT* and *TP53* mutations significantly worsens the prognosis, and an isolated *TP53* mutation also reflects high genomic instability. A negative test for *BRAF* precludes the possibility of using the MAPK cascade inhibitors, which emphasizes the need to search for other therapeutic targets.

For clinical practice it is important to distinguish PDTC and DHGTC, since the diagnostic criteria of those partially overlap. Comparative analysis of morphological, immunohistochemical, and molecular features is provided in Table 1.

From the prognostic point of view, the HGFC-NA tumors are characterized by aggressive course: the five-year survival rate is only 40–60%, it decreases considerably when there are *TERT* and *TP53* mutations. The main risk factors are high Ki-67 levels (>20–30%), micro- and macrovascular invasion, tumor extent at the time of diagnosis. Early detection of these features is of fundamental importance for personalized treatment selection, including targeted drugs, and patient enrollment in clinical trials [13–15].

A practical algorithm to diagnose PDTC and DHGTC can be presented as follows:

1. Morphological analysis: detection of the architectonic heterogeneity, necrosis, and mitotic activity.
2. Quantitative criteria: the number of mitoses ≥ 3 per 2 mm^2

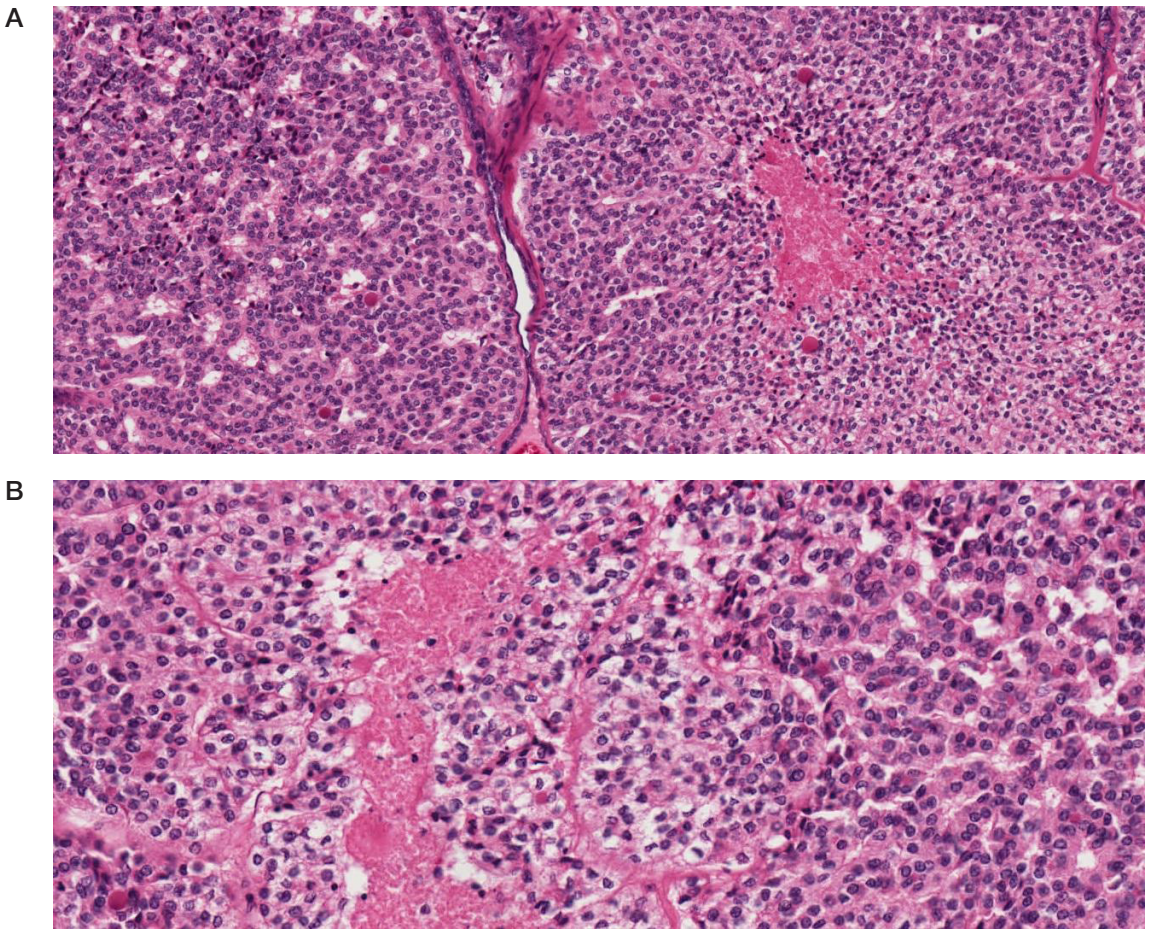

Fig. 3. Differentiated high-grade thyroid carcinoma (DHGTC). **A**. Solid/trabecular and alveolar areas with the zone of comedo/geographical necrosis (H&E, ×100 magnification). **B**. Pronounced increase in cytological atypia and proliferation; frequent mitoses (≥ 5 per 2 mm^2 when counted in the fields with the highest activity) (H&E, ×400 magnification)

suggests PDTC, the number of mitoses ≥ 5 suggests DHGTC.

3. Immunohistochemistry analysis: determination of the Ki-67, p53, TTF-1, PAX8 expression. The high Ki-67 index (>20–30%) and mutational p53 pattern are the signs of high tumor grade.

4. Molecular testing: determination of the *TERT*, *TP53*, *BRAF* mutations. The combination of those determines the prognosis and the targeted therapy options.

5. Data integration: the final classification is based on the combination of morphology, quantitative characteristics, and molecular profile.

Targeted therapy prospects

Identification of the *BRAF V600E* mutations opens the prospects for the use of MAPK cascade inhibitors (dabrafenib, trametinib). The use of appropriate targeted agents can be considered when the PI3K/AKT/mTOR pathway is activated. Participation in clinical trials of new drugs remains a promising area for patients with the combination of *TERT* and *TP53* mutations. Thus, the HGFC-NA tumor molecular profiling is not only of prognostic, but also of therapeutic value, since it allows one to select personalized treatment strategies.

Table. Comparison of morphological, immunohistochemical, and molecular features of poorly differentiated (PDTC) and differentiated high-grade tyroid carcinoma (DHGTC)

Criterion	PDTC	DHGTC
Architecture	Solid, trabecular, insular	Any: papillary, follicular, solid, etc.
Nuclear features of papillary carcinoma	Absent	May be present
Mitotic activity	≥ 3 mitoses per 2 mm^2	≥ 5 mitoses per 2 mm^2
Necrosis	Present (one of the diagnostic criteria)	May be present, strengthens the diagnosis
Turin Proposal criteria (2006)	Essential for making the diagnosis	Not used
Rate of *TERT/TP53* mutations	May be present, more often *TERT*	Often *TERT*, *TP53*, sometimes *BRAF*
Ki-67	Frequently >10–20%	Usually >20%, often >30–40%
Prognosis	Poor, but slightly better, than for DHGTC	Poor, especially when there are TERT- and TP53- mutations
Is ruled out when there are	Nuclear features of papillary carcinoma	No clear exclusive features (quantitative criteria only)

CONCLUSION

High-grade non-anaplastic (HGFC-NA) thyroid tumors represent a rare and clinically significant category requiring a specific diagnostic approach. The case of differentiated high-grade carcinoma (DHGTC) provided showed the features typical for this group: morphological heterogeneity, focal necrosis, high mitotic activity, and the Ki-67 index above 30%, as well as the mutational p53 expression pattern with no *TERT* and *BRAF* alterations. The combination of morphological, immunohistochemichal, and molecular data made it possible to confirm the diagnosis and estimate poor prognosis. This observation emphasizes the need for comprehensive assessment of HGFC-NA tumors involving mandatory consideration of the quantitative criteria (mitotic activity, Ki-67), as well as the *TERT* and *TP53* status. Disregard for these features can result in underestimation of the grade and selection of suboptimal treatment tactics. In the Russian context, the case presented demonstrates the importance of the molecular profiling introduction into routine practice of pathology diagnosis, which will make it possible to improve verification accuracy, enable timely detection of aggressive form and patient management strategy optimization.

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