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IMMUNOHISTOCHEMICAL EVALUATION OF TROP-2 IN THYROID LESIONS: DIAGNOSTIC IMPLICATIONS AND HISTOPATHOLOGICAL CORRELATION

Histopathology

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ABSTRACT

Thyroid nodules are among the most common endocrine abnormalities encountered in clinical practice and encompass a wide spectrum of benign and malignant lesions. Although the majority of thyroid nodules are benign, accurate distinction from malignant neoplasms remains a critical challenge because of overlapping histomorphological features, particularly in follicular-patterned lesions. Papillary thyroid carcinoma (PTC), the most common thyroid malignancy, is characterized by distinctive nuclear features; however, these changes may be subtle or focal and can occasionally be observed in benign lesions, leading to diagnostic uncertainty. The recent recognition of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has further emphasized the need for reliable ancillary diagnostic tools. Immunohistochemistry has emerged as an important adjunct to routine histopathological evaluation, with markers such as CK19, HBME-1, and Galectin-3 being widely studied. However, their diagnostic utility is limited by variable sensitivity and specificity. Trophoblast cell surface antigen-2 (TROP-2), a transmembrane glycoprotein involved in cellular proliferation, adhesion, migration, and oncogenic signaling, has recently gained attention as a potential diagnostic biomarker in thyroid pathology. Several studies have demonstrated strong membranous expression of TROP-2 in papillary thyroid carcinoma and its variants, while benign thyroid lesions generally exhibit absent or minimal staining. The characteristic staining pattern and high specificity reported in previous studies suggest that TROP-2 may serve as a valuable adjunct in distinguishing benign from malignant thyroid lesions. This study was undertaken to evaluate the immunohistochemical expression of TROP-2 in thyroid lesions and to assess its diagnostic utility in differentiating benign and malignant thyroid neoplasms.

KEYWORDS

Trop-2, Thyroid Lesions, Papillary Thyroid Carcinoma, Immunohistochemistry, Thyroid Neoplasms, Diagnostic Marker.

INTRODUCTION:

The thyroid gland is the largest endocrine organ in the human body and plays a central role in the regulation of metabolism, growth, cellular differentiation, and maintenance of physiological homeostasis. Thyroid disorders are among the most prevalent endocrine diseases worldwide and encompass a broad spectrum of conditions ranging from developmental abnormalities and inflammatory diseases to hyperplastic lesions, benign neoplasms, and malignant tumors. Thyroid nodules represent one of the most common clinical manifestations of thyroid disease and are frequently encountered in routine clinical practice. Palpable thyroid nodules are identified in approximately 4-7% of adults, whereas high-resolution ultrasonography can detect nodules in up to 60–70% of the general population. Although the majority of thyroid nodules are benign, a small but clinically significant proportion harbor malignancy, making accurate diagnosis essential for appropriate patient management and prognostication.[1,2]

The incidence of thyroid neoplasms has increased steadily over the past several decades. While improved detection methods and heightened clinical awareness have contributed to this trend, thyroid cancer remains the most common endocrine malignancy worldwide. Papillary thyroid carcinoma (PTC) is the predominant histological subtype and accounts for nearly two-thirds of all thyroid cancers. Other malignant thyroid tumors include follicular thyroid carcinoma (FTC), medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, and anaplastic thyroid carcinoma. Despite the generally favorable prognosis associated with differentiated thyroid carcinomas, accurate classification remains crucial because management strategies, recurrence risk, and long-term outcomes vary significantly among different thyroid tumor types.[2,3]

Thyroid Neoplasms and Diagnostic Challenges:

Recent advances in molecular pathology and tumor classification have significantly refined the understanding of thyroid neoplasia. The 5th edition of the World Health Organization (WHO) Classification of Thyroid Neoplasms has emphasized the biological continuum of follicular-cell derived tumors and introduced important conceptual changes in the categorization of thyroid lesions. One of the most significant developments has been the recognition of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) as a distinct low-risk neoplasm. This reclassification reflects a growing appreciation that not all tumors exhibiting papillary thyroid carcinoma-type nuclear features behave aggressively and highlights the importance of accurate morphological assessment in avoiding overtreatment.[3] [4]

In addition, molecular alterations such as **BRAF V600E mutations, RAS mutations, RET/PTC rearrangements, and TERT promoter mutations** have significantly enhanced the understanding of thyroid tumorigenesis and tumor progression. These molecular markers provide valuable diagnostic and prognostic information; however, molecular testing may not be readily available in all diagnostic settings, particularly in resource-limited institutions. Consequently, reliable and cost-effective ancillary techniques such as immunohistochemistry continue to play a vital role in routine diagnostic thyroid pathology.

Despite substantial advances in diagnostic pathology, differentiation between benign, borderline, and malignant thyroid lesions continues to pose significant challenges. This difficulty is particularly pronounced in follicular-patterned lesions, which encompass nodular hyperplasia, follicular adenoma, follicular thyroid carcinoma, follicular variant papillary thyroid carcinoma (FVPTC), and NIFTP. These entities frequently exhibit overlapping architectural and cytological characteristics, making definitive diagnosis difficult in a subset of cases. Because treatment strategies differ considerably between benign and malignant lesions, accurate diagnosis is of paramount clinical importance.[3,5]

Papillary thyroid carcinoma is defined primarily by its distinctive nuclear morphology rather than by its architectural pattern. The characteristic nuclear features include enlargement, elongation, chromatin clearing, irregular nuclear contours, nuclear grooves, and intranuclear cytoplasmic pseudoinclusions. However, these changes may be subtle, focal, or unevenly distributed, particularly in FVPTC and NIFTP. Furthermore, similar nuclear alterations may occasionally be encountered in benign lesions such as nodular hyperplasia and follicular adenoma, resulting in diagnostic ambiguity. Consequently, significant interobserver variability has been reported among pathologists when assessing borderline or follicular-patterned thyroid lesions.[6,7]

Challenges in Follicular-Patterned Thyroid Lesions:

The diagnosis of follicular thyroid carcinoma presents an additional challenge because it depends largely upon demonstration of capsular and/or vascular invasion. Thorough sampling of the tumor–capsule interface is therefore essential. Failure to identify foci of invasion may result in underdiagnosis, whereas processing artefacts can

occasionally mimic invasive growth and lead to overdiagnosis. These diagnostic complexities have become increasingly important following the introduction of NIFTP, which requires strict histopathological criteria including complete encapsulation, follicular growth pattern, papillary carcinoma-type nuclear features, and absence of invasion, tumor necrosis, or increased mitotic activity.[3] [8]

Role of Immunohistochemistry in Thyroid Pathology:

Given these challenges, ancillary diagnostic techniques have assumed an increasingly important role in thyroid pathology. Immunohistochemistry (IHC) has become an indispensable adjunct to routine histopathological examination, particularly in lesions exhibiting equivocal morphological features. Although hematoxylin and eosin-stained sections remain the cornerstone of diagnosis, immunohistochemical markers provide additional objective evidence that may assist in distinguishing benign from malignant lesions and reduce observer variability. The primary role of immunohistochemistry is not to replace histomorphological assessment but rather to complement and refine diagnostic interpretation.[9]

Several immunohistochemical markers have been investigated in thyroid pathology. Among the most widely studied are Cytokeratin-19 (CK19), HBME-1, and Galectin-3. CK19 is frequently overexpressed in papillary thyroid carcinoma and demonstrates high sensitivity; however, focal positivity may also be observed in benign lesions, thereby limiting specificity. HBME-1 exhibits membranous and cytoplasmic staining in many malignant thyroid tumors but may occasionally be expressed in benign follicular lesions. Similarly, Galectin-3 has been reported to be positive in a substantial proportion of malignant thyroid neoplasms but lacks absolute specificity. Consequently, no single marker has achieved universal acceptance as a definitive diagnostic tool, and combinations of markers are often employed to improve diagnostic accuracy.[9,10]

Biology and Oncogenic Role of TROP-2:

Trophoblast cell surface antigen-2 (TROP-2), also known as tumor-associated calcium signal transducer-2 (TACSTD2), has recently emerged as a promising immunohistochemical marker in thyroid pathology. Originally identified on trophoblastic cells, TROP-2 is a 35-kDa transmembrane glycoprotein encoded by the TACSTD2 gene located on chromosome 1p32. Structurally, the molecule consists of an extracellular domain, a transmembrane region, and a short intracellular tail that participates in signal transduction. Functionally, TROP-2 acts as a calcium signal transducer and is involved in cellular proliferation, migration, adhesion, invasion, and survival.[11]

The biological significance of TROP-2 extends beyond its role as a structural membrane protein. Experimental studies have demonstrated that overexpression of TROP-2 activates multiple oncogenic pathways, including the MAPK and PI3K/AKT signaling cascades, thereby promoting tumor growth, cellular proliferation, and metastatic potential. Increased expression of TROP-2 has been documented in numerous epithelial malignancies, including cancers of the breast, lung, pancreas, gastrointestinal tract, ovary, and thyroid. Moreover, elevated TROP-2 expression has frequently been associated with aggressive biological behavior, advanced tumor stage, and unfavorable clinical outcomes.[11] [12]

TROP-2 Expression in Thyroid Neoplasms:

The restricted expression of TROP-2 in normal tissues, combined with its consistent overexpression in malignant epithelial tumors, provides a strong biological basis for its use as a diagnostic biomarker. In recent years, several studies have explored the utility of TROP-2 in thyroid neoplasms. Liu et al. demonstrated strong membranous TROP-2 expression in 94% of conventional papillary thyroid carcinomas and 81% of follicular variant papillary thyroid carcinomas, while benign thyroid lesions showed no significant staining. Similar observations have been reported by Nesreen et al., Eid et al., Zargari et al., and Abu-Seadah et al., all of whom documented high sensitivity and specificity for TROP-2 in distinguishing papillary thyroid carcinoma from benign thyroid lesions.[13,17]

An important observation across these studies has been the absence or minimal expression of TROP-2 in common histological mimickers of papillary thyroid carcinoma, including nodular hyperplasia, follicular adenoma, oncocytic adenoma, Hashimoto thyroiditis, and NIFTP. This finding is particularly relevant because these lesions frequently exhibit overlapping morphological features that can complicate routine histopathological interpretation. The characteristic strong membranous staining pattern observed in papillary thyroid carcinoma further enhances the diagnostic utility of TROP-2 and facilitates reproducible interpretation.[13,17]

Furthermore, comparative analyses have suggested that TROP-2 may demonstrate greater specificity than several conventionally employed markers, including CK19, HBME-1, and Galectin-3. The high specificity of TROP-2, particularly in distinguishing papillary thyroid carcinoma from benign follicular lesions and NIFTP, has generated considerable interest in its incorporation into routine diagnostic immunohistochemical panels. Emerging evidence suggests that TROP-2 may substantially improve diagnostic confidence in morphologically challenging cases and reduce interobserver variability among pathologists.[10,17]

Rationale for the Present Study:

Despite advances in thyroid pathology, accurate distinction between benign and malignant follicular-derived thyroid lesions remains a significant diagnostic challenge owing to overlapping morphological features and the limitations of currently available immunohistochemical markers. Although markers such as CK19, HBME-1, and Galectin-3 are widely used, their diagnostic performance is limited by variable sensitivity and specificity. Recent studies have demonstrated promising results for TROP-2, particularly in papillary thyroid carcinoma and its variants, suggesting superior diagnostic accuracy when compared with conventional markers.

In view of the persistent diagnostic difficulties encountered in follicular-derived thyroid lesions, the limitations of currently available immunohistochemical markers, and the encouraging results reported for TROP-2 in previous studies, further evaluation of this marker is warranted. Therefore, the present study was undertaken to assess the immunohistochemical expression of TROP-2 in a spectrum of thyroid lesions and to evaluate its utility as a diagnostic marker in differentiating benign from malignant thyroid neoplasms.

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