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TROP-2 AND THE HISTOMORPHOLOGICAL SPECTRUM OF THYROID LESIONS

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ABSTRACT

Background: Thyroid lesions encompass a broad histomorphological spectrum, ranging from benign lesions to low-risk neoplasms and various malignant neoplasms, with considerable morphological overlap among certain entities. TROP-2, a transmembrane glycoprotein implicated in tumour progression, has demonstrated variable expression in thyroid neoplasms. Evaluation of its immunoexpression across different histomorphological patterns may provide insights into its relationship with the morphological spectrum of thyroid lesions.

Aim: To evaluate the pattern and intensity of TROP-2 immunoexpression across the histomorphological spectrum of thyroid lesions and to assess the differences in its expression among various thyroid lesion categories and histological subtypes.

Materials and Methods: Our prospective observational study included 44 surgically resected thyroid specimens representing a spectrum of histomorphologically distinct thyroid lesions. Histopathological examination was performed to classify the lesions based on their morphological features. TROP-2 IHC was assessed by evaluating membranous staining intensity and H-score. Cases were categorized as benign (n=16), low-risk thyroid neoplasms (n=6), and malignant lesions (n=22). The pattern and degree of TROP-2 expression were compared across the different histomorphological categories and histological subtypes. Statistical analyses were performed to determine the association between TROP-2 expression and the histomorphological spectrum of thyroid lesions.

Results: TROP-2 immunoexpression showed a progressive increase across benign, low-risk, and malignant thyroid lesions. Benign lesions demonstrated minimal expression, with positivity in only 1 of 17 cases (5.9%) and a mean H-score of 11.76 ± 48.51. Low-risk lesions showed limited and heterogeneous expression, with positivity in 33.3% of cases and a mean H-score of 25.83 ± 46.32. Malignant lesions demonstrated markedly higher expression, with positivity in 77.3% of cases and a mean H-score of 137.27 ± 113.73. A statistically significant association was observed between TROP-2 expression and lesion category ($p < 0.001$).

Conclusion: TROP-2 immunoexpression varies across the histomorphological spectrum of thyroid lesions, with minimal expression in benign lesions and substantially higher expression in malignant lesions, particularly PTC and its variants. The heterogeneous expression observed among different histological subtypes highlights the variable relationship between TROP-2 and thyroid tumour morphology. These findings suggest that TROP-2 may serve as a useful adjunctive immunohistochemical marker for characterizing thyroid lesions across a diverse histomorphological spectrum.

KEYWORDS: Trophoblast cell surface antigen- 2 [TROP-2], thyroid lesions, papillary thyroid carcinoma [PTC], immunohistochemistry [IHC], follicular tumor of uncertain malignant potential (FT-UMP), diagnostic marker, follicular-patterned lesions.

INTRODUCTION / BACKGROUND

Thyroid cancer is the most common endocrine malignancy worldwide, with its incidence increasing largely due to improved detection and changing environmental and lifestyle factors. It ranks 7th globally in cancer incidence but has relatively low mortality. It occurs about three times more often in women, with a mean age at diagnosis of approximately 51 years. Despite rising incidence, mortality remains low, with fewer than 1 death per 100,000 population in most countries. [1]

Thyroid cancer risk factors are classified as non-modifiable and modifiable. Non-modifiable factors include female sex, increasing age, family history, genetic syndromes, and benign thyroid disorders. The major modifiable risk factor is childhood exposure to ionizing radiation; other factors include obesity, abnormal iodine intake, environmental pollutants, and endocrine-disrupting chemicals.[2]

TROP-2 (TACSTD2) is a transmembrane glycoprotein expressed in normal epithelium and various epithelial malignancies. It regulates cell proliferation, migration, and invasion through pathways such as MAPK and PI3K/AKT. Its overexpression is associated with tumour progression and aggressiveness. In thyroid cancer,

TROP-2 shows potential as a diagnostic biomarker and therapeutic target, including antibody-based and antibody–drug conjugate therapies. [3]
Our study aims to evaluate TROP-2 expression in various thyroid lesions, including benign, low-risk, and malignant neoplasms. It aimed to assess the expression pattern of TROP-2 across these categories and determine its value in distinguishing PTC from its benign as well as low-risk mimics.

MATERIALS AND METHOD
This prospective observational study included 44 FFPE thyroid specimens from surgically resected benign and malignant lesions. Routine H&E examination was followed by TROP-2 immunohistochemistry using a standardized immunoperoxidase method. Cases were classified based on histopathological diagnosis, and TROP-2 expression was assessed and correlated with the clinicopathological features. Ethical approval was obtained, and patient confidentiality was maintained throughout the study.

INTERPRETATION OF IMMUNOSTAINING
TROP-2 expression was evaluated based on:
- Localization: membranous staining
- Intensity: weak, moderate, strong
- Extent: percentage of positive tumor cells

STATISTICAL ANALYSIS
Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics for Windows, Version 29.0 (Armonk, NY: IBM Corp.). Categorical variables were expressed as frequencies and percentages. Correlations between TROP-2 expression and clinicopathological parameters were assessed using the Chi-square test. Results were presented and two-tailed p-value <0.05 was considered statistically significant.

RESULTS
Our study included 44 patients with thyroid lesions. Mean age at presentation - 41.75 ± 13.48 years (range: 20–72 years), with most patients belonging to the middle-aged age group. A marked female predominance was observed, with 84.1% (n = 37) females and 15.9% (n = 7) males.
Total thyroidectomy was the most commonly performed procedure, accounting for 39 cases (88.6%), while hemithyroidectomy was performed in 5 cases (11.4%). The right lobe was the most frequent site of involvement (54.5%, n = 24), followed by the left lobe and bilateral involvement, each comprising 20.5% (n = 9), whereas the isthmus was involved in 4.5% (n = 2) of cases.

TROP-2 Expression
Our study evaluated TROP-2 expression across benign, low-risk, and malignant thyroid lesions.
Benign lesions: TROP-2 expression was largely absent, with positivity in only 1/17 cases (5.9%) and a low mean H-score of 11.76 ± 48.51. Hashimoto thyroiditis showed moderate positivity, while follicular adenoma and nodular disease were negative. [Fig 1A,1B]
Low-risk neoplasms: TROP-2 positivity was seen in 2/6 cases (33.3%), with a mean H-score of 24.17 ± 46.09. Expression was heterogeneous, with no strong (3+) staining. One NIFTP showed high expression, while most cases were negative or weakly positive.
Among malignant thyroid lesions, TROP-2 expression was frequent but heterogeneous. The mean percentages of weak (1+), moderate (2+), and strong (3+) staining were 8.64 ± 6.58%, 17.73 ± 17.44%, and 31.36 ± 32.96%, respectively, while 22.73% of cases showed no staining. The mean H-score was 137.27 ± 113.73, and TROP-2 positivity was observed in 17/ 22 cases (77.3%), whereas 5 cases (22.7%) were negative.
Strong TROP-2 expression, with H-scores up to 280, was predominantly observed in classic PTC [FIG 2A,2B & 3A,3B], infiltrative follicular subtype PTC and several cases of follicular variant PTC (FVPTC). Among FVPTC (n = 7), 42.9% of cases each showed moderate (2+) and strong (3+) staining, 14.3% demonstrated weak positivity, and one case was negative. No expression was observed in one case each of classic PTC and infiltrative subtype PTC, as well as in encapsulated angioinvasive follicular carcinoma, medullary carcinoma, and poorly differentiated carcinoma Although higher expression was noted in papillary carcinoma variants, the association between tumor subtype and TROP-2 expression was statistically significant ($\chi^2 = 21.6$, $p < 0.001$). Overall, TROP-2 expression was higher in malignant follicular-pattern lesions than benign and low-risk entities ($\chi^2 = 38.9$, $p = 0.003$).

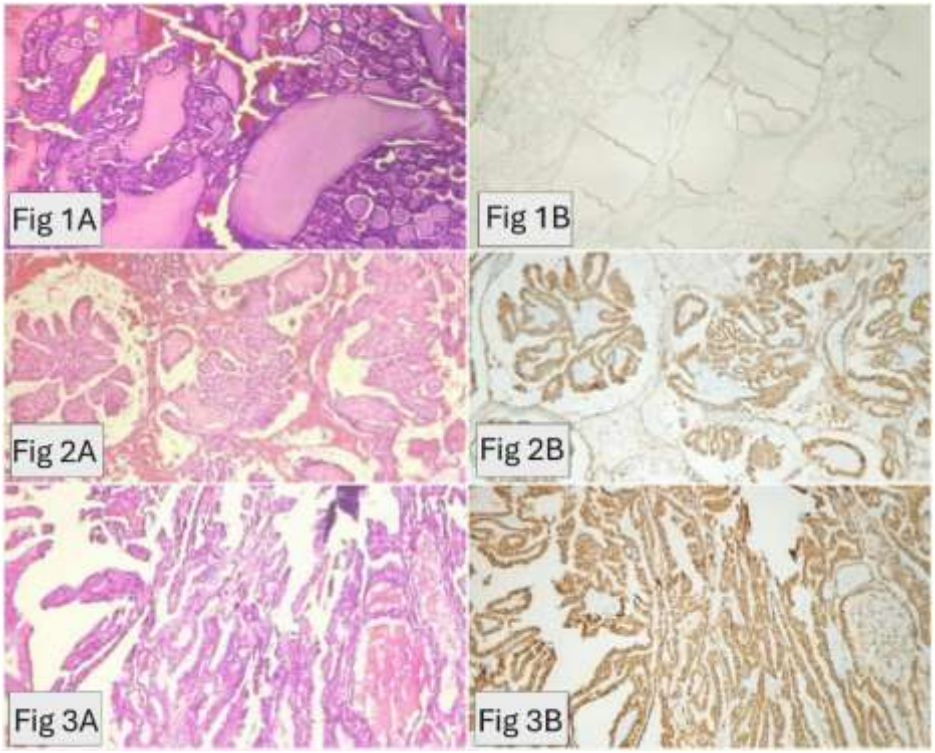

Figure 1: A) Multinodular goiter – Thyroid [H & E x 40]; B) Negative staining of TROP2 in MNG [IHC x 40]. Figure 2 & 3: A) Papillary Carcinoma of thyroid – Classic type [H & E x 40]; B) Strong membranous positivity 3+ of TROP2 in PTC – Classic type [IHC x 40].

DISCUSSION

Our study comprehensively evaluated the clinicopathological profile of thyroid lesions and assessed TROP-2 immunohistochemical expression across benign, low-risk, and malignant thyroid neoplasms. Although histopathology remains the diagnostic gold standard, differentiating follicular-patterned lesions with overlapping morphology remains challenging. In this context, TROP-2 has emerged as a promising ancillary biomarker because of its reported overexpression in PTC and other epithelial malignancies. [Trop2 expression in Thyroid neoplasms consolidated in Table 1]

Parameter	Benign Lesions	Low-Risk Lesions	Malignant Lesions
Number of Cases (n)	16	6	22
TROP-2 Positivity (%)	5.9%	33.3%	77.3%
Mean H-Score (±SD)	11.76 ± 48.51	25.83 ± 46.32	137.27 ± 113.73
Weak Staining (1+) (%)	Minimal	Predominant	Moderate
Moderate Staining (2+) (%)	Rare	Occasional	Significant
Strong Staining (3+) (%)	Absent	Rare	Predominant
Overall Expression Pattern	Negligible / Absent	Predominantly negative with focal weak expression	Strong & Diffuse
Biological Interpretation	Non-neoplastic / benign proliferation	Intermediate / borderline Behavior	Malignant Transformation
Diagnostic Utility	Limited	Supportive (context- dependent)	Highly useful marker of malignancy

Table 1: Comparative Analysis of TROP-2 Expression Across Thyroid Lesion Categories

The major objective of our study was to evaluate TROP-2 expression across various thyroid lesions. TROP-2 said to be involved in cell proliferation, tumour progression and has gained importance as diagnostic and therapeutic biomarker.

Benign lesions of thyroid demonstrated minimal TROP-2 expression, with a positivity rate of only **5.9%** and a mean H-score of **11.76 ± 48.51**. Most benign lesions were negative, with occasional positivity in Hashimoto thyroiditis, possibly related to oncocytic (Hurthle cell) change. Similar findings were reported by **Vani et al. [4]**, supporting minimal TROP-2 expression in benign thyroid tissue.

Low-risk neoplasms showed variable TROP-2 expression, with **33%** positivity and a mean H-score of **25.83 ± 46.32**. Focal positivity in a single case suggests that TROP-2 upregulation may occur during early malignant transformation but is not consistently expressed. These findings are in accordance with **Liu et al. [5]**, who reported predominantly weak or absent staining in non-PTC thyroid neoplasms.

Malignant thyroid lesions exhibited significantly higher TROP-2 expression, with **77.3%** positivity and a mean H-score of **137.27 ± 113.73**. Moderate-to-strong membranous staining (2+ and 3+) predominated, supporting the association of TROP-2 with thyroid carcinogenesis. Similar observations were reported by **Zargari et al. [6]**.

Among malignant tumours, **PTC** and its variants showed the strongest and most diffuse membranous staining, similar to reports by **Simms et al. [7]** and **Addati et al. [8]**.

However, TROP-2 expression was not uniform. Two PTC cases were negative, indicating intratumoral heterogeneity and reinforcing that TROP-2 should be interpreted as an adjunct rather than a standalone marker. Absent staining in follicular, medullary thyroid and poorly differentiated thyroid carcinomas may reflect differences in tumour biology, although focal positivity in two follicular carcinoma cases suggests possible overlap with PTC-associated molecular pathways.

Table 2: Comparative Study of Trop2 Sensitivity & Specificity

Study	Sensitivity (%)	Specificity (%)
Vani D et al.^4	85.7%	94.4%
Nooshin et al.^6	93%	74%
Simms et al.^7	90%	95.2%
Addati et al.^8	87%	89%
Nesreen et al. 9	93.8%	94.4%
Our Study	**77.3%**	**86.4%**

TROP-2 diagnostic performance of our study showed **77.3% sensitivity** and **86.4% specificity**, indicating good specificity but moderate sensitivity. Therefore, TROP-2 should complement routine histopathological evaluation rather than replace it. [Table 2]

Overall, our study revealed increasing TROP-2 expression across benign, low-risk, and malignant thyroid lesions., indicating a positive association with malignant potential. **Nesreen et al. [9]** as well as **Liu et al. [5]** also reported same. **Simms et al. [7]** as well as **Addati et al. [8]** also highlighted the value of diffuse membranous TROP-2 expression in differentiating PTC from morphologically similar lesions.

Our study is limited by its relatively small sample size and single-centre design, which limits generalizability of the findings. Larger multicentric studies are required to validate the diagnostic performance of TROP-2 and establish standardized criteria for its routine clinical application.

CONCLUSION

TROP-2 is a valuable immunohistochemical marker in thyroid pathology, demonstrating high sensitivity and specificity for papillary thyroid carcinoma (PTC). Its expression is significantly higher in malignant lesions compared with benign lesions and most follicular-patterned neoplasms, making it a useful adjunct for differential diagnosis. However, occasional negative staining in PTC and focal positivity in some follicular carcinomas highlight the need to interpret TROP-2 expression alongside histomorphological findings rather than as an independent diagnostic marker.

Overall, TROP-2 can improve diagnostic confidence in distinguishing PTC from its histological mimics, particularly in morphologically challenging cases, and may serve as a useful adjunct in routine thyroid pathology practice.

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