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Original Article

Correlation between Her2/neu oncoprotein expression and prognostic factors in papillary thyroid carcinoma

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Abstract

Background: *Thyroid cancer is one of the increasing cancers diagnosed in Western as well as Eastern countries. Papillary thyroid cancer (PTC) is the most common thyroid cancer. Few researches are done determining the role of Her 2/neu in PTC diagnosis as well as prognosis which have been contradictory to each other. Thus the present study is aimed at correlation of the Her 2/neu expression with various prognostic factors such as tumour size, different subtypes, multifocality, capsular involvement with extra-thyroidal extension and lymph node metastasis.*

Materials and Methods: *The study period was performed from January 2016 to December 2018 in pathology department of IMS and SUM hospital. Of total 83 total/subtotal thyroidectomy cases received, 25 cases were diagnosed as papillary carcinoma on haematoxylin and eosin histology sections. The detailed clinico-pathological parameters were noted in these patients and were further subjected to immunohistochemistry for Her 2/neu expression.*

Results and Observations: *In the study, female (60%) predominance was there and the age ranged from 14 years to 70 years. Majority of these tumours presented as solitary cold nodules but for 24% cases with multifocality. Total 7 cases (28%) showed Her 2/neu positivity (3+) and majority belonged to low risked group. Strong correlation was found between tumour size, multifocality and lymph node metastasis. No correlation was found with extra-thyroid extension or vascular invasion.*

Conclusion: *Variable Her2/neu positivity was seen in different variants of PTC as well as different clinical parameters*

Study type and design: *Hospital based cross sectional study and is an observational study.*

Keywords: *Her 2/neu, papillary thyroid carcinoma, thyroid neoplasm, prognosis.*

Introduction

Thyroid cancer is the most common endocrine malignancy and PTC is the most common thyroid carcinoma accounting for 70%-90% of thyroid carcinoma.[1] Histologic diagnosis of PTC is based on some specific features such as ground glass nuclei with cleavage, pseudo-inclusion and psammoma bodies.[2] PTC tends to invade the

capsule to adjacent lymph node.[3] Haematogenous involvement is rare. Several factors contribute to the prognosis of PTC including tumour size, variants, capsular invasion, multifocality, lymph node status and distant metastasis.[4,5] Though MAPK plays a major role in PTC pathogenesis, mutation of BRAF and RET/PTC have also been established.[6,7] EGFR2 (Her 2/neu) is a recently studied growth factor receptor detected and well studied in various cancers like breast carcinoma and colo-rectal carcinoma.[8] In 2004, Her 2/neu mRNA expression was found in PTC[9] but in 2007 Balta et al. deduced that no striking correlation existed with prognostic factors like tumour size, type, lymph node status etc.[10] On the other hand Kremser et al. found that Her 2/neu expression could be correlated with size, capsular invasion and lymph node status.[11]

PTC has a heterogenous behaviour which depends on the different clinical parameters like age, sex, size, lymph node status and metastasis.[12] The prognosis also variable in different variants of PTC based on which it is divided in to low risked group and high risked group. The tumours included in low risked group are conventional, follicular, oncocytic and microcarcinoma. The high risked group included are diffuse sclerosing, warthin, columnar cell, solid, angio-invasive follicular, and PTC with hobnail features. Diffuse sclerosing type of PTC has grave prognosis because of multifocality, vascular invesion and early age presentation. Her 2/neu shows variable expression in different subtypes of PTC. [13]

Materials and Methods

Medical records of 83 patients who have undergone thyroidectomy (subtotal/total) during 2016-2018 were obtained. Based on the histopathological finding, 25 cases were established as PTC. 3-5µm sections were made from paraffin sections and were subjected to IHC by DAKO reagent and were evaluated under 40x magnification, taking a breast carcinoma as positive control. Interpretation was done on a standard scale (0 to 3+). Score 0 as no staining in tumour cells, 1+ as weak and incomplete membrane staining in <10% of cells, 2+ as moderate and complete membrane staining in >10% cells and 3+ as uniform intense circumferential staining >10% of tumour cells.[12]

Observation

It was found that out of 25 cases, 15 cases were females and 10 were males patients. Her 2/neu positivity was found in 7 cases (28%). Maximum number of cases were observed between 20 years to 50 years except one cases of diffuse sclerosing variant of PTC which was found in 14 year old girl. The Her 2/neu positivity was more seen in lower age (<45 years) [85.71%] as compared to higher age i.e. >45 years. The size of the tumour varied from 1 cm to 10 cm with multifocality in some tumours, particularly oncocytic variant and diffuse sclerosing variant. Her 2/neu positivity was significantly proportional to size ≥3 cm (85.71%) cases and multifocal tumours (57.14%). Extra-thyroidal extension and associated thyroiditis were found in rare variants which did not show statistically significant correlation. Whereas Her 2/neu prevalence was more seen in lymph node metastasis than confined to the thyroid. [Table 1]. The various histological subtyping was done in the papillary thyroid carcinoma and were subdivided into low risked cases which included conventional type (n=10) [Fig 1], follicular (n=4), oncocytic variant (n=2) [Fig 2a &b], papillary microcarcinoma (n=2). Whereas high risked categories were 7 cases (28%). This was further subdivided into diffuse sclerosing type (n=1) [Fig 3a &b], warthin like (n=1) [Fig 4], columnar cell type (n=1), solid type (n=1), angio-invasive follicular (n=2), and PTC with hobnail features (n=1). It was observed that out of 7 Her 2/neu positivity cases, 6 were low risked group (85.71%) whereas only 1 case of high risked group showed Her 2/neu positivity (14.28%). [Table 2].

Table 1: Relationship between Her 2/neu expression and clinico-pathological characteristics

VARIABLES	HER-2/neu positive (n=07)	HER-2/neu negative (n=18)
Age		
• <45 years	06	14
• ≥45 years	01	04
Size (cm)		
• <3	01	02
• ≥3	06	16
Extra-thyroidal extension		
• Negative	05	15
• Positive	02	03
Lymph node metastasis		
• Present	06	13
• Absent	01	05
Vascular invasion		
• Present	02	03
• Absent	05	15
Concurrent thyroiditis		
• Present	01	07
• Absent	06	11
Multifocality		
• Present	04	02
• Absent	03	16

Table 2: Her 2/neu expression in different subtypes of papillary thyroid carcinoma

HISTOLOGICAL SUBTYPES (n=25)	HER-2/neu positive (n=07)	HER-2/neu negative (n=18)
I. **Low Risked Group** (18)		
• Conventional type (10)	03	07
• Follicular (4)	01	03
• oncocytic (2)	01	01
• papillary microcarcinoma (2)	01	01
II. **High Risked Group** (7)		
• diffuse sclerosing (1)	01	00
• warthin (1)	00	01
• columnar cell (1)	00	01
• solid (1)	00	01
• angio-invasive follicular (2)	00	02
• PTC with hobnail features (1)	00	01

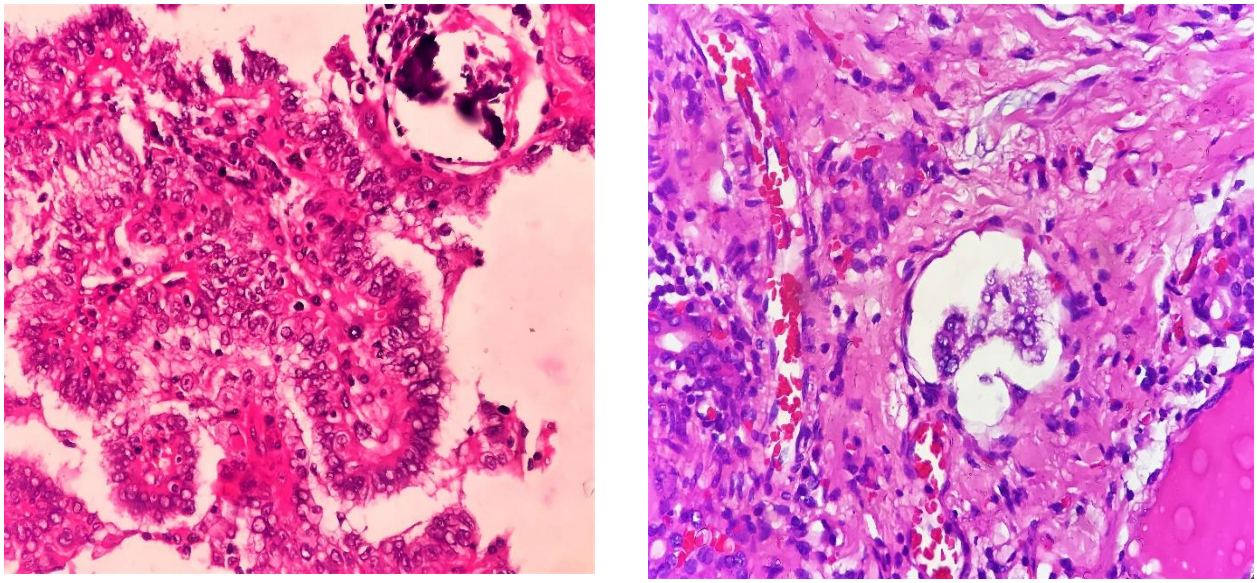

Figure 1: Microphotograph of conventional papillary thyroid carcinoma showing nuclear features and psammoma bodies (a) [H&E] 400X; and lympho-vascular inclusion (b) [H&E] 400X

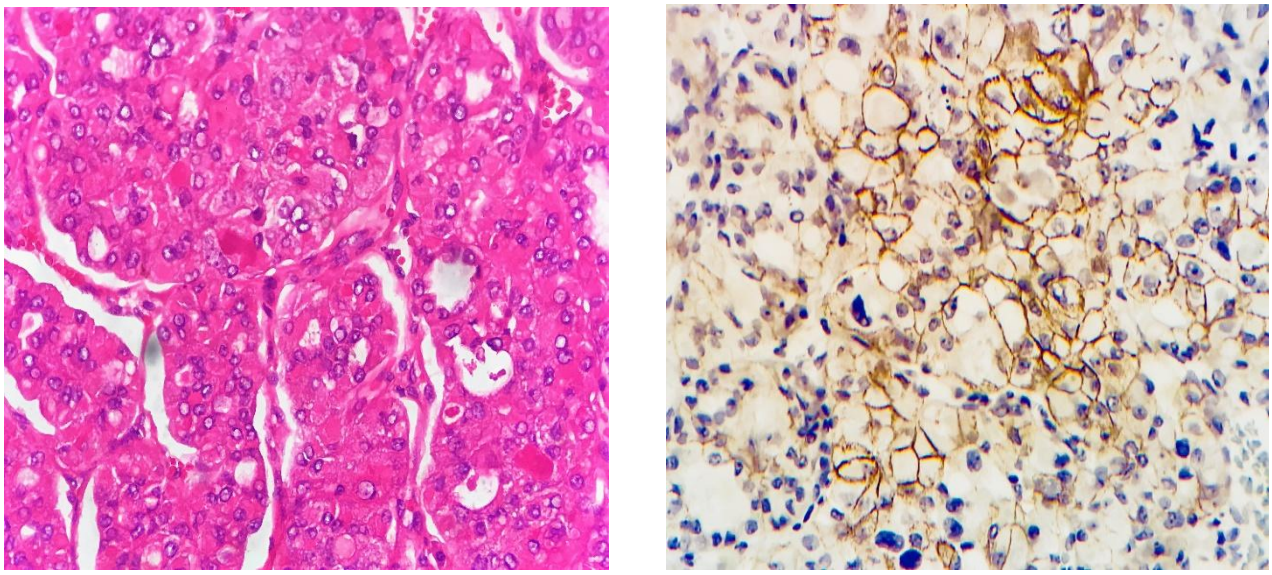

Figure 2: Microphotograph of oncocytic variant of papillary thyroid carcinoma showing eosinophilic cytoplasm and clearing of nuclei (a) [H&E] 400X; and strong and intense Her 2/neu cytoplasmic staining of tumour cells (b) [IHC] 400X.

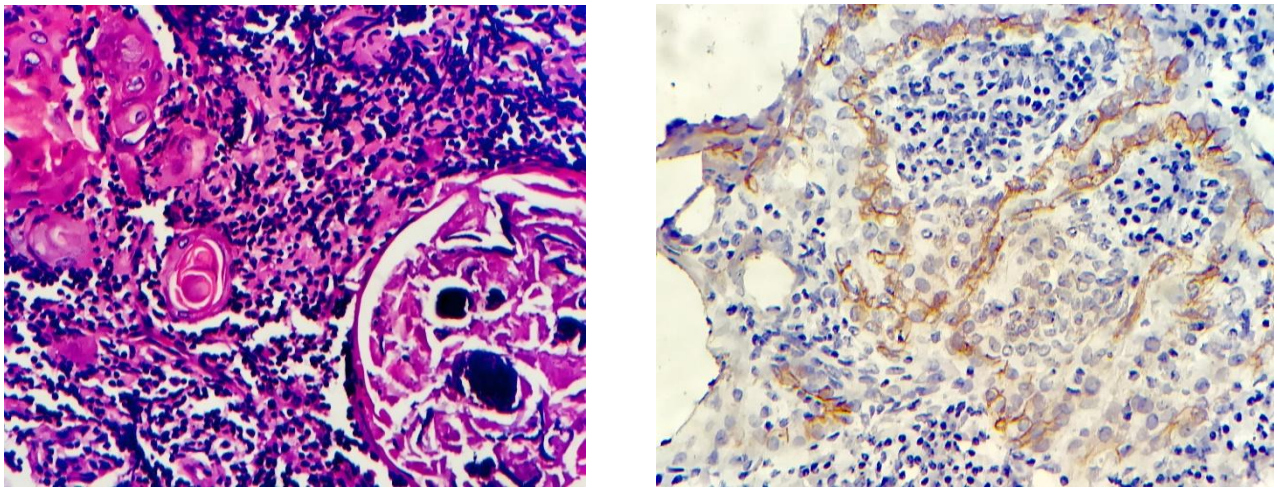

Figure 3: Microphotograph of diffuse sclerosing variant of PTC showing psammoma bodies with extensive squamous metaplasia and lymphoid follicles (a) [H&E] 400X; and strong Her 2/neu cytoplasmic staining of tumour cells (b) [IHC] 400X

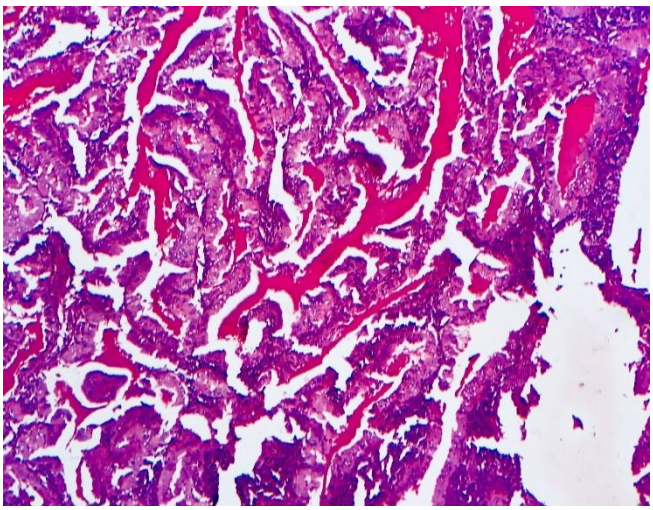

Figure 4: Microphotograph of warthin like PTC showing enlarged papillae with oncocytic change and adjacent lymphoplasmacytic stromal infiltration. [H&E] 200X

Discussion

PTC presented with much heterogeneity because of its variability in presentation, behaviour, and histomorphology.[13] Though it is tumour of adults and aged but cases in adolescents are also noted especially in post radiation exposures. Because of wide range of variants found in PTC, these behaves differently in different subtypes as far as the size, focality and morphology are concerned. Thus the tumour oncogenicity also varies according to different clinico-histologic parameters. Her 2/neu was found in 28% of total PTC in our study which is well correlated with Delia Ciobanu Apostol et al. who found 20.8% cases of Her 2/neu positivity.[13] Our study showed female predominance to male well correlating with Rabiee, et al. who found 88.2% females and 11.8% males.[14] They found no significant correlation between lymph node involvement on contrary to our study where Her 2/neu positivity was found in 6 cases (85.71%) of lymph node metastasis. This is coinciding with Kim Y.S, et al. who found positive correlation of Her 2/neu with younger age (<45 years) and cervical lymph node metastasis.[15] In our study, 6 cases (85.71%) were <45 years. According to Rabiee et al., more positive correlation was found between tumour size and Her 2/neu similar to our study where majority of Her 2/neu positivity cases of size ≥3 cm (85.71%).[14] Out of 25 cases of PTC based on different subtypes, 18 cases were under low risked group whereas 7 cases belonged to high risked group showing extra-thyroidal extension, multifocality and vascular invasion. Her 2/neu was positive in 6 out of 18 cases (33.33%) of low risked group whereas 1 out of 7 cases (14.28%) of high risked group. This is well correlated with Delia Ciobanu Apostol et al. which showed 20 Her 2/neu positive cases out of 72 cases of low risked group (27.77%) whereas Her 2/neu positivity was seen in 5 out of 47 cases of high risked group (10.6%).[13]

Conclusion

Our study showed that Her 2/neu sustains heterogeneity in expression in various types of PTC. The correlation between Her 2/neu expression and different histological subtypes, age, tumour size, focality and lymph node status supports its potential prognostic as well as predictive value with promising application in PTC therapy.

References

1. Hegedus L. Clinicalpractice. The thyroid nodule. N Engl J Med.2004;351:1764-71.
2. Jameson J, Weetman A. Disorders of thyroid gland. In: Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw Hill; 2012. p. 2911- 40.
3. Lal G, Clark O. Thyroid, parathyroid and adrenal. In: Brunicardi F, Anderson D, Billiar T, Dunn D, Hunter J, Matthews J, editors. Schwartz's Principles of Surgery. 9th ed. New York: McGraw- Hill; 2010. p. 2587- 717.
4. Rosai J, Tallini G. Thyroid gland. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology. 10th ed. New York: Elsevier; 2011. p. 488- 565.
5. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab 2005;90:5723- 9.
6. Ciampi R, Knauf JA, Kerler R, Gandhi M, Zhu Z, Nikiforova MN, et al. Oncogenic AKAP9- BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J Clin Invest 2005;115:94- 101.
7. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High

prevalence of BRAF mutations in thyroid cancer: Genetic evidence for constitutive activation of the RET/PTC- RAS- BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 2003;63:1454- 7.

8. Bazley LA, Gullick WJ. The epidermal growth factor receptor family. Endocr Relat Cancer 2005;12 Suppl 1:S17- 27.
9. Kato S, Kobayashi T, Yamada K, Nishii K, Sawada H, Ishiguro H, et al. Expression of erbB receptors mRNA in thyroid tissues. Biochim Biophys Acta 2004;1673:194- 200.
10. Balta AZ, Filiz AI, Kurt Y, Sucullu I, Yucel E, Akin ML. Prognostic value of oncoprotein expressions in thyroid papillary carcinoma. Med Oncol 2012;29:734- 41.
11. Kremser R, Obrist P, Spizzo G, Erler H, Kendler D, Kemmler G, et al. Her2/neu overexpression in differentiated thyroid carcinomas predicts metastatic disease. Virchows Arch 2003;442:322- 8.
12. Wolff AC, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update.Arch Pathol Lab Med. 2018 Nov;142(11):1364-1382.
13. Delia Ciobanu Apostol et al. HER-2/neu expression in different histological subtypes of papillary thyroid carcinoma. Rom J Morphol Embryol 2017, 58(2):439–444.
14. Rabiee S, Nadoushan MJ, Rayeni NM, Ansari I. Correlation between human epidermal growth factor receptor 2 oncoprotien expression and some prognostic factors in papillary thyroid carcinoma. Indian J Microbiol 2017;60:324-7.
15. Kim, Yong-Seon & Kim, Jeong-Soo & Kim, Yong. (2018). EGFR and HER2 Expression in Papillary Thyroid Carcinoma. Journal of Endocrine Surgery. 18. 228. 10.16956/jes.2018.18.4.228.