

E-cadherin expression in thyroid carcinoma and correlation with histologic type and nodal metastasis.

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Abstract :

Background: Thyroid cancer is the fifth most common cancer in women worldwide. The incident of thyroid cancer in both women and men has been increasing in recent years. In many cases, traditional histopathological examination has not been able to predict the aggressiveness and prognosis of thyroid carcinoma. E-cadherin molecules are involved in thyroid folliculogenesis and loss of cell-cell adhesion is a precondition for the invasive behavior of malignant tumors. If down regulation occurs in E-cadherin expression, it correlates with strong invasive potential and poor prognosis of thyroid carcinoma. **Objectives:** Evaluation of E-cadherin expression in various types of thyroid carcinoma and correlation with histologic type and nodal metastasis. **Method:** This is a descriptive cross sectional study which was carried out at the Department of Pathology, Dhaka Medical College, during the period of March, 2017 to February, 2019 with 50 thyroid carcinoma patients attending in Department of ENT, Dhaka Medical College Hospital. All collected samples were processed for routine histopathological study and selected for immunohistochemistry with E-cadherin antibody. Patients' demographic data were collected from patients' file and requisition forms. Statistical analysis was done using SPSS (version 20). **Results and observations:** In this study the mean age was 41.76 ±11.4 and male to female ratio was 1: 2.1. The predominant histologic types were papillary carcinoma (78%) and 92% of all carcinomas were well differentiated. E-cadherin expression was reduced in some follicular and papillary carcinoma and markedly reduced in anaplastic carcinoma. Nodal involvement also showed markedly reduced expression of primary thyroid carcinoma. **Conclusion:** E-cadherin expression is very important for detecting the aggressiveness of thyroid carcinoma. Down regulation in E-cadherin expression correlates with strong invasive potential and poor prognosis of thyroid carcinoma.

Key words: E-cadherin, Nodal metastasis, Thyroid carcinoma

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Introduction:

The thyroid gland is the largest endocrine gland of the body. The major function of the thyroid gland is to secrete thyroid hormone, which maintains the level of metabolism in the tissue that is optimal for their normal function. Thyroid hormone also stimulates oxygen consumption by most of the cells in the body, help to regulate lipid and carbohydrate metabolism, and thereby influence body mass and mentation¹. The incidence and disease

pattern of thyroid varies in different geographic distribution due to dietary, environmental and genetic factors. About 5% of world population are suffering from various thyroid diseases² and endemic goiter is the most common disease pattern throughout the world³, hyperplasia and benign and malignant tumor. Thyroid cancer is the fifth most common cancer in women worldwide⁴. The incident of thyroid cancer in both women and men has been increasing in recent years. Globally in 2012, the estimated number of death from thyroid cancer was 27000 in women and 13000 in men, corresponding to mortality rate approximately 6/100000 in women and 0.3/100000 in men⁵. In USA incidence have been increasing over the last few decades^{6, 7}. If recent trend is maintained, thyroid cancer might become the fourth most common cancer by 2030 in USA⁸. Thyroid cancers comprise a heterogeneous group of malign-

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nant tumors. Differentiated thyroid cancers are usually associated with a good prognosis. Undifferentiated cancer is a highly malignant tumor that usually leads to patient's death. Poorly differentiated thyroid cancers occupy, both morphologically and clinically, an intermediate place between the well differentiated and undifferentiated cancers. In many cases, traditional histopathological examination has not been able to predict which differentiated cancers have the potential to behave aggressively. Adhesive interactions between cells are dynamic and regulated during tissue development and homeostasis. Cadherins are major cell-cell adhesion molecules involved in the development and maintenance of solid tissue. Cadherins are transmembrane glycoproteins localized in the plasma membrane of cells in most of the solid tissue. Most of them mediate Ca^{2+} dependent cell-cell adhesion molecule that contributes to morphogenesis by hemophilic interaction⁹. More than 30 human members of cadherin family are identified. The classic epithelial type cadherin is generally referred to as E-cadherin¹⁰. E-cadherin molecules are involved in thyroid folliculogenesis. Studies in normal thyroid tissue demonstrated a basolateral expression of E-cadherin. Loss of cell-cell adhesion is a precondition for the invasive behavior of malignant tumors. Adherens junctions or desmosome mediated cell-cell adhesion is maintained by members of the cadherin family of transmembrane proteins and their connections to a group of cytoplasmic proteins named catenins¹⁰. If down regulation occurs in E-cadherin expression, it correlates with strong invasive potential and poor prognosis of thyroid carcinoma¹¹. Some studies have been done regarding E-cadherin expression in thyroid carcinoma in various countries but no studies done regarding these parameters in our country. In this present study, evaluation of E-cadherin expression in thyroid carcinoma was done in relation to their histopathologic type, extent of local invasion and lymph node involvement.

Materials and Method:

This is a prospective observational study carried out at the department of pathology, Dhaka Medical College from March 2017 to February 2019. Ethical issues were address accordingly. Fifty cases were taken and routine histology test were done and each histological specimen were examined to determine histological type & grade of the tumor according to the World Health Organization and to select one representative paraffin block for immunohistochemical analysis. Immunohistochemical findings was assessed semi-quantitatively by the evaluation of 1,000 cells in each lesion. The staining was regarded as positive in the case of membrane expression of E-CAD. The results were expressed in an ordinal scale from 0 to 4. 0 = no membrane staining or staining present in 5% of cells, 1 = membrane staining present in 6–30% of cells, 2 = membrane staining present in 31–60% of cells, 3 = membrane staining present in 61–90% of cells, and 4 = membrane staining present in more than 90% of cells. Grades 0 and 1 were classified as markedly reduced. Grade 2 - as reduced, and Grades 3 and 4 - as preserved¹².

Observations and result

A total of 50 cases of thyroid carcinoma sample were enrolled in this study. After detail gross examinations of the specimens, hematoxylin and eosin stained sections were examined under microscope for histological examination and E-cadherin immunostaining were done.

Mean age of the patients were 41.76 ± 11.4 with age range from 18 to 66 years, 16 cases were male (32%) and 34 cases were female (64%) and the male female ratio was 1: 2.1. There are female predominance upto 50 years of age group (36 cases, 72.0%) and after 50 years of age the male and female ratio is equal (14cases, 28.0%). Among

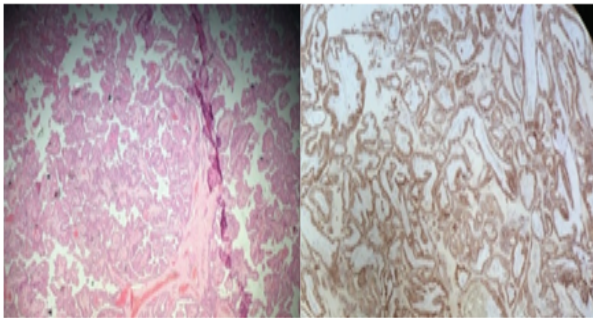


Figure 1: Photomicrography showing Papillary carcinoma of thyroid and showing preserved E-cadherin immunostain.

the 50 cases, the highest number were diagnosed as papillary carcinoma (36 cases, 72 %) followed by follicular carcinoma (7cases, 14%). Follicular variant of papillary carcinoma was observed in 3cases (6%). The number of medullary carcinoma and anaplastic carcinoma were equal (2 cases, 4%) each.

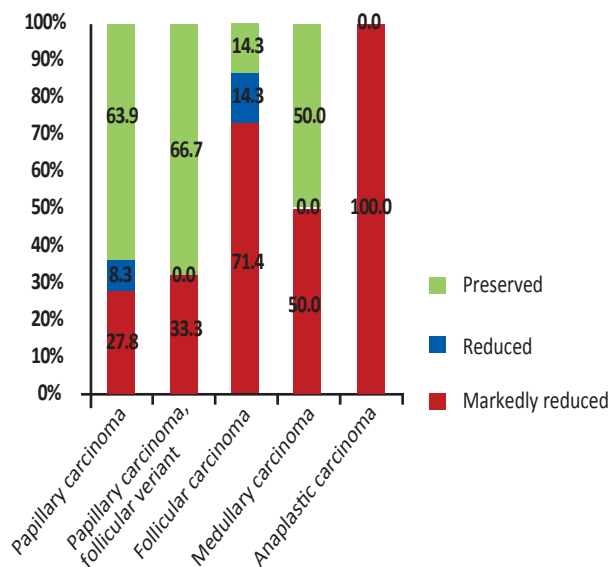


Figure 2: Bar diagram showing Correlation of E-cadherin expression with different histologic type of thyroid carcinoma (%) [p value = 0.269]

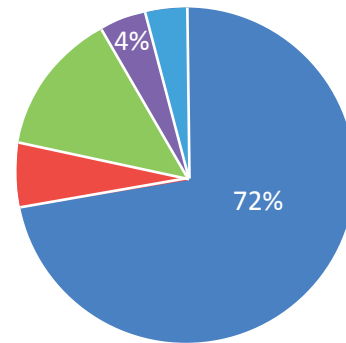


Figure 3: Pie Chart Showing Frequency of histologic type of different thyroid carcinoma.

Among the 50 cases, 46 (92%) were well differentiated and rest 4 (8%) cases were poorly differentiated. Among the well differentiated cases, 26 (56.5%) cases showed preserved, 16 (34.8%) cases showed markedly reduced and 4 (8.7%) cases showed reduced E-cadherin immunostaining. 3(75%) cases of poorly differentiated cases showed markedly reduced and 1 (25%) case showed preserved E-cadherin immunostaining.

Out of 50 cases 7 cases have regional lymph nodes involvement (pN1). All of the cases 100% (5 papillary, 2 follicular) showed markedly reduced E-cadherin immunostaining. Remaining 43 cases (31 papillary, 5 follicular, 2 medullary, 2 anaplastic and 3 follicular variant of papillary carcinoma) showing preserved expression in 27 cases (23 papillary, 2 follicular variant of papillary carcinoma, 1 follicular carcinoma, and 1 medullary carcinoma), reduced expression in 4 cases (3 papillary, 1 follicular carcinoma) and markedly reduced in 12 cases (5 papillary, 1 follicular variant of papillary carcinoma, 3 follicular carcinoma, 1 medullary carcinoma and 2 anaplastic carcinoma).

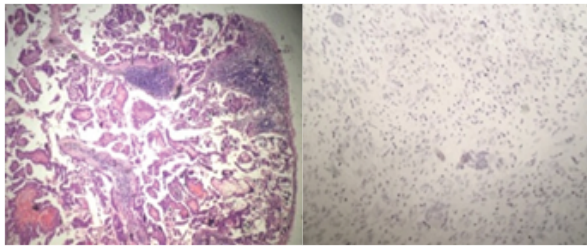


Figure 4: Photomicrograph showing metastatic papillary carcinoma in a lymph node and markedly reduced E-cadherin expression in primary tumor.

Table I: Correlation Of E-cadherin Expression With Different Histologic Parameters Of Thyroid Carcinoma (n=50)

Histopathological parameters		No. of cases	E- Cadherin comment			p-value
			Markedly reduced	Reduced	Preserved	
Histologic type	Papillary carcinoma	36	27.8% (10)	8.3% (3)	63.9% (23)	0.269
	Papillary carcinoma, follicular variant	3	33.3% (1)	0.0% (0)	66.7% (2)	
	Follicular carcinoma	7	71.4% (5)	14.3% (1)	14.3% (1)	
	Medullary carcinoma	2	50.0% (1)	0.0% (0)	50.0% (1)	
	Anaplastic carcinoma	2	100.0% (2)	0.0% (0)	0.0% (0)	
Lymph node involvement	Involved	7	100.0% (7)	0.0% (0)	0.0% (0)	0.001
	Not involved	43	27.9% (12)	9.3% (4)	62.8% (27)	

Discussion

Carcinomas of thyroid are accounting for about 1.5% of all cancers. A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years. The incidence in women are about 6%. In contrast, cases presenting in childhood and late adult life are distributed equally among males and females. Most thyroid carcinomas are derived from the thyroid follicular epithelium and of these, the vast majority are well differentiated lesions³.

E-cadherins a transmembrane glycoprotein has a small cytoplasmic component and the remaining portion of the protein is extracellular. The extracellular domain connects the cytoskeleton through a complex of proteins mainly catenins. E-cadherin-catenin complex has the potential to inhibit mitogenic signaling through growth factor receptors and maintain the molecular determinants of epithelial polarity¹³. E-cadherin is a potent invasive suppressor. If down regulation occurs in E-cadherin expression, it correlates with strong invasive potential and poor prognosis of thyroid carcinoma¹⁴. In this study, total 50 cases were included. The age ranged from 18 to 66 years and the mean age was 41.76 ± 11.4 . Most of the study subject were between 41 to 50 years of age group (14 cases, 28 %) followed by 31 to 40 and 51 to 60 years of age group (12 cases, 24 % each). There was another group 21 to 30 years of age (9 cases, 18%). The fifth group was above 61 years of age (2 cases, 4%). There was no case below 18 years or above 66 years. The least number of sample was below 20 years of age (1 case, 2 %). E-cadherin expression was reduced with increasing the age and expression was preserved at younger age group.

All the cases below 18 years showed preserved E-cadherin staining. The study group in between 21 to 30 years showed 66.7% preserved staining, age group 31 to 40 showed 58.3% preserved staining, age group 41 to 50 and 51 to 60 showed 50% preserved staining. All the cases above 60 years of age showed no preservation of E-cadherin immunostaining and both of them showed markedly reduced staining. So, this result showed an important relation between E-cadherin expression and different age group. Naito⁹ had done similar type of study. But they did not get any correlation between age and E-cadherin expression. Brabant¹⁵ also done E-cadherin expression on thyroid carcinoma and their observation was similar to this study. In this current study, 16 cases were male (32%) and 34 cases were female (64%) and male female ratio was 1: 2.1. No correlation was found

between E-cadherin expression and sex group. Study by Kapran¹⁰ found mean age of the patients were 37.3 ± 11.2 years with male female ratio 1: 4.9. Similar study by Slowinska-Klencka¹² showed mean age of the patient were 50.02 ± 17.45 with a marked female predominance where male female ratio was 1: 7.1. None of them found any correlation between sex group and E-cadherin expression.

All the 50 cases of thyroid carcinoma 72% were papillary carcinoma, 14% follicular carcinoma, 6% follicular variant of papillary carcinoma, 4% medullary carcinoma and remaining 4% were anaplastic carcinoma. Among them 92% were well differentiated and remaining 8% were poorly differentiated.

Out of 36 cases of papillary carcinoma, 23(63.9%) showed preserved immunostaining, 10(27.8%) cases showed markedly reduced and 3(8.3%) cases showed reduced E-cadherin immunostaining. Out of 7 cases of follicular carcinoma 5(71.4%) cases of follicular carcinoma showed markedly reduced, 1(14.3%) case showed reduced and 1(14.3%) case showed preserved E-cadherin immunostaining. Out of 46 cases of well differentiated carcinoma, 36 are papillary carcinoma, 7 cases are follicular carcinoma and 3 cases are follicular variant of papillary carcinoma. Among the well differentiated cases, 26 (56.5%) cases showed preserved, 16 (34.8%) cases showed markedly reduced and 4 (8.7%) cases showed reduced E-cadherin immunostaining. 4 cases are poorly differentiated. 2 cases are medullary carcinoma and 2 cases are anaplastic carcinoma. 3(75%) cases of poorly differentiated cases showed markedly reduced and 1(25%) case showed preserved E-cadherin immunostaining.

Similar study was done in the department of pathology, Samsung Medical Centre, Seoul, Korea by Choi¹⁶. In their study among 150 cases papillary carcinoma were 53.6%, follicular carcinoma 24%, poorly differentiated carcinoma 9.6%, undifferentiated carcinoma 8% and Hurthle cell carcinoma 4.8%. Here E-cadherin staining expression is

similar with our study. Another study by Rocha¹⁷ showed that out of 17% cases of poorly differentiated thyroid carcinoma 15 cases showed reduced E-cadherin expression.

In immunohistochemical studies, tumors with preserve epithelial morphology (Differentiated type) express high amount of cadherin, whereas undifferentiated type have reduced amount of these molecules. There is significant correlation between reduced expression of E-cadherin and loss of tumor differentiation. The impaired expression of E-cadherin is frequently observed in tumors with aggressive histopathologic character that is invasiveness, lymph node involvement and distant metastasis¹⁸.

Out of 50 cases 7 cases have regional lymph nodes involvement (pN1). All of the cases 100% (5 papillary, 2 follicular) showed markedly reduced E-cadherin immunostaining. Remaining 43 cases (31 papillary, 5 follicular, 2 medullary, 2 anaplastic and 3 follicular variant of papillary carcinoma) showing preserved expression in 27 cases (23 papillary, 2 follicular variant of papillary carcinoma, 1 follicular carcinoma, and 1 medullary carcinoma), reduced expression in 4 cases (3 papillary, 1 follicular carcinoma) and markedly reduced in 12 cases (5 papillary, 1 follicular variant of papillary carcinoma, 3 follicular carcinoma, 1 medullary carcinoma and 2 anaplastic carcinoma).

Conclusion:

The incidence of thyroid tumor is increasing about 5% per year and it is fifth most common tumor of women. Well differentiated tumors have good prognosis but undifferentiated tumors are highly malignant and leads to patient death. Routine histopathologic procedures can categorize the tumor in different types but cannot estimate the prognosis in poorly differentiated thyroid carcinoma. So, E-cadherin expression estimation is very important for such cases. In our country no study has been done regarding incidence, histological types and associated biomarkers expression in thyroid carcinoma. The aim of the study

was to evaluate E-cadherin expression in thyroid carcinoma in relation to their histopathological type and lymph node involvement. This cross-sectional study was carried out at the Department of Pathology, Dhaka Medical College, from January 2017 to December 2018. Histopathological examinations of thyroid carcinoma of 50 patients were done followed by evaluation of IHC expression of E-cadherin. In this study mean age were 41.6 ± 11.4 ranges from 18 to 66 years with female predominance where male female ratio was 1:2.1. Papillary carcinoma was the most common type of cancer in this study (72%) followed by follicular carcinoma (14%), Follicular variant of papillary carcinoma (6%), Medullary carcinoma (4%), Anaplastic carcinoma (4%). Papillary carcinoma was common in early age group and anaplastic carcinoma was in late age. 14% cases showed lymph node involvement but no distant metastasis seen. Significant correlation was found between E-cadherin expression histologic type and lymph node involvement.

Recommendation

Immunohistochemical expression of E-cadherin in all type of thyroid carcinoma may be included as part of routine pathological evaluations. Follow up study should be included for proper evaluation of patients

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