Original Research Paper

Volume-9 | Issue-4 | April-2019 | PRINT ISSN No 2249-555X

Pathology

VALUE OF ECADHERIN EXPRESSION IN PROSTATE CANCER

Dr. V. Nithyananthinie* MD, DNB, Assistant Professor In Pathology, Government Theni Medical College, Kanavilakku Post, Theni, Tamilnadu. *Corresponding Author

Dr. G. Leelavathy MD, Assistant Professor In Pathology, Government Medical College And ESI Hospital, Varadharajapuram, Coimbatore.

ABSTRACT E-cadherin, low expression is associated with progression to higher grades of prostate malignancy and in assessing the metastatic spread of prostate cancer.

Aim: To study prostatic carcinomas with altered E-cadherin expression and to correlate with Gleason score and PSA levels.

Materials and methods: 25 cases of prostate cancer specimens, were selected and paraffin embedded formalin fixed sections in coated slides were subjected for immunohistochemical expression with E-cadherin antibodies by the peroxidase- antiperoxidase method. Membranous positivity for E-cadherin was observed based on the staining pattern, strength of staining and population of stained cells.

Results: E-cadherin was negative in 28% cases and 56% cases showed weak positivity, indicating a considerable loss of E-cadherin as the lesions are progressing and suspected extra prostatic extension.

Conclusion: To detect extra prostatic extension, without any major symptoms, E-cadherin can be used even in minimal tissue samples and anticipate the progression.

Keywords : E-cadherin, Prostate Cancer, Metastatic Deposits

INTRODUCTION

Cancer of the prostate-one among the top ten malignancies in men, showing increase in incidence and prevalence rates, even with advanced technology. The morbidity and mortality rate, on the other hand, has led some to conclude that many of the prostate cancers are harmless, and perhaps, would better be left undetected. Nevertheless, the present trends of the increasing life expectancy continue, given the current age-specific incidence, morbidity and mortality rates of prostate cancer, this disease will become a far greater public health problem in the near future.

This study was done to identify prostatic carcinoma with altered expression of E-cadherin for treatment strategies and to correlate these findings with PSA levels and Gleason scoring.

E-cadherin is a calcium dependant cell adhesion molecule that determines development in the embryo and maintains adult differentiated epithelium and homeostasis. Aberrant or decreased expression has been reported to be associated with prostate carcinoma progression.

AIM

To study the value of expression of immunohistochemical marker E-Cadherin in prostate cancer specimens and their correlation with Gleason` scoring and serum PSA levels.

MATERIALS AND METHODS

A prospective study done for a period of 1year in our institution which included all prostate cancer specimens with detailed evaluation. Specimens were processed in formalin and paraffin embedded sections in coated slides were subjected to immunohistochemical evaluation based on antigen retrieval by microwave, avidin biotin peroxidase method and 3,3`diaminobenzene chromogen marker. IHC scores were done based on the strength and percentage of antibody expression on the cells.

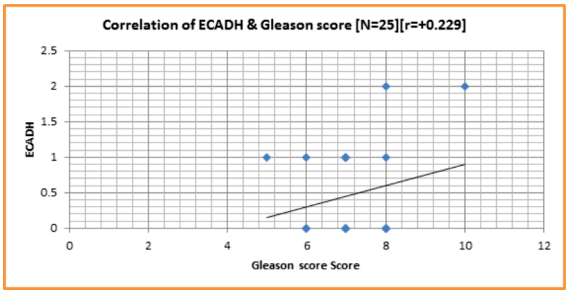
OBSERVATION AND RESULTS

Table No.:1 Comparing Ihc Expression Of E-cadherin Marker

ECADH	n	(%)
1+	14	56%
2+	4	16%
Negative	7	28%
Total	25	100%

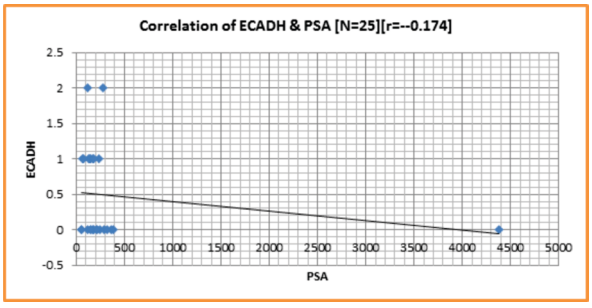
As with table-1, on studying the expression of E-Cadherin in the biopsy specimens, it was found that 56% of the cases showed 1+ intensity in staining and about 28% cases showed negative staining, indicating the more malignant nature of the cancer in the specimens received

Chart No.:1 Correlation Of E-cadherin And Gleason's Score.



The scatter diagram in chart no.1, shows a linear plot of Gleason's scoring with that of E-Cadherin expression with increasing scores mostly seen with 1+ intense expression.

Chart No.:2 Correlation Of E-cadherin And Psa Values

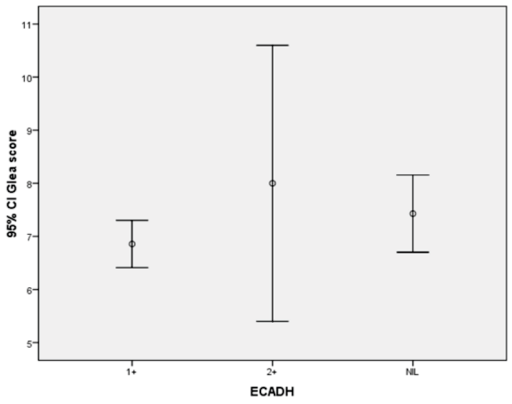


The scatter diagram shows that even with minimal elevation of PSA values, the expression of E-cadherin tends to become weaker in most of the cases and the case with maximum PSA value has negative E-Cadherin expression, vide chart no.2.

Table No.:2 Mean Of Gleason Score With E-cadherin

				95% CI for Mean				
	ECADH	Mean	SD	Lower	Upper	Minimum	Maximum	Sig
Gleason	1+	6.9	0.77	6.41	7.3	5	8	
score	2+	8.0	1.63	5.4	10.6	6	10	
	NIL	7.4	0.79	6.7	8.16	6	8	>0.05
	Total	7.2	1.00	6.79	7.61	5	10	

Chart No.:3 Mean Of Gleason Score With E-cadherin

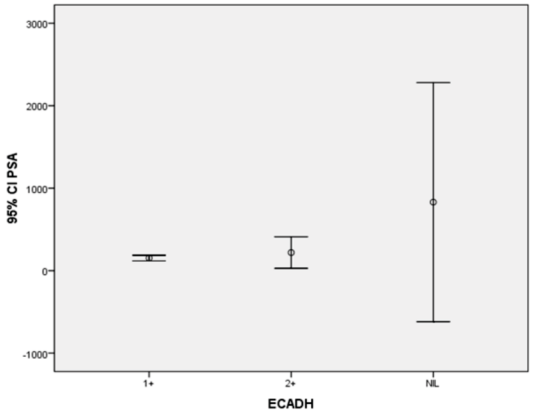


On comparing the Gleason's score and the expression of E-Cadherin, maximum score of 10 had weak 2+ expression of E-Cadherin and likewise minimum score of 5 also had 1+ expression, thus giving a nil significant p value of >0.05 vide chart no.3 and table no.2

Table No.:3 Comparison Of Mean Of Psa With E-cadherin

				95% CI for mean				
	Ecadherin	Mean	SD	Lower	Upper	Minimum	Maximum	Sig
PSA	1+	152.4	58.86	118.37	186.34	53	243	
	2+	219.5	120.56	27.66	411.34	118	360	
	NIL	830.9	1566.88	-618.26	2279.98	53	4376	>0.05
	Total	353.1	842.93	5.14	701.02	53	4376	

Chart No.:4 Comparison Of Mean Of Psa With E-cadherin



As with table no.3 and chart no.4, analysing the PSA values and E-Cadherin expression, the maximum PSA value had negative expression, but the other moderately high values had weak expression of E-Cadherin giving a p value of >0.05, making the significance nil between the two.

Statistical Analysis:

The datas here are reported as the mean +/- SD or the median.
Frequencies are expressed in percentages.

The differences in quantitative variables between groups were assessed by means of the unpaired t test.

Comparsion between groups was made by the Non parametric Mann - Whitney test
ANOVA was performed.

The chi square test used to assess differences in the categoric variables between groups.

A p value of <0.05 using a two-tailed test was taken as being of significance for all statistical tests.

All data were analysed with a statistical software package. (SPSS, version 16.0 for windows)

DISCUSSION

Earlier diagnosis and management even before the tumour metastasises, is very critical for improving the patient survival. Most cases of cancer prostate that present with organ confined cancer are managed by surgery, radiation or androgens. But development of metastatic disease is ultimately lethal. Despite newer systemic therapies, metastatic phenotype is characterised by inevitable development of resistance, disease progression and death, ultimately[7,8].

The 5 year survival rate is higher in case of organ confined prostate cancers, but with metastatic deposits, the same is reduced to about 33% In various studies it had been found that with radical prostatectomy specimens, done for organ confined prostate cancers, 17% had extra-prostatic extension that was detected later[1,2]. Likewise in the current study, where of the 25 cases taken for study, nearly 32% had suspicious extra prostatic extension that was identified by immunohistochemical studies done in the trucut biopsies received.

Cadherins are a group of type-1 transmembrane proteins. They play very important role in the process of cell adhesion, forming adherens junctions to the binding cells, within tissues. They are dependent on calcium ions to function, hence they get their name. Cell-cell adhesion is being mediated by extracellular cadherin domains, whereas those of the intracellular cytoplasmic tail associate with a large number of adaptor and signalling proteins, which are collectively referred to as the cadherin adhesome.[9]

E-cadherin is a calcium-regulated adhesion molecule that is expressed in most of the normal epithelial tissues. The E-cadherin gene is located on the chromosome 16q22. E-cadherin is thus associated with gland formation, stratification and causes epithelial polarization.[26] E-cadherin knockout mice are found to be non-viable and result in abnormal epithelial morphogenesis. Selective loss of E-cadherin results in dedifferentiation and invasiveness in the human cancers. In the various cell lines studied, a reciprocal relationship has been shown between the levels of E-cadherin expression and the invasiveness of the tumour. Thereby reduced expression of E-cadherin was observed in the aggressive tumours of the oesophagus, ovary and the stomach. Mechanisms by which the expression of E-cadherin protein is lost would include E-cadherin gene mutation and the loss of the wild-type allele by the loss of its heterozygosity. These studies indicate that E-cadherin is a classical tumour suppressor gene.[12,13]

The functional role of E-cadherin in tumor progression was studied following the frequent loss of E-cadherin in most of the malignant tumors in various studies. The forced expression of E-cadherin using tumor cell lines in culture, it was demonstrated by various studies that re-establishing the functional cadherin complex, resulted in a reversion from an invasive to the benign, epithelial cell phenotype.[14]

Several of these experiments have clearly demonstrated that there has been a critical role for E-cadherin in suppressing the tumor invasion in cultured cells. However, it has remained elusive if the loss of E-cadherin mediated cell adhesion has been a prerequisite for the progression of tumor or if it has been the result of the consequence of de-differentiation in the process of tumor progression.[11] It has recently been shown that the expression of Ecadherin will be lost during the transition from a well differentiated adenoma to the more invasive carcinomas in the studies in transgenic mouse model of pancreatic β-cell tumorigenesis (RIP1TAG2). It was noted that there was an arrest of tumor progression at the adenoma stage, when there was e-cadherin expression persistent by β cell tumorigenesis.[29] But in contrast, there was early invasion and metastasis with expression of a dominant negative E-cadherin. Thus, these studies demonstrate that when there is a loss of E-cadherin mediated cell-cell adhesion which, is one of the rate-limiting steps from the progression of adenoma to carcinoma in vivo and it will highlight the role of E-cadherin, as a suppressor of tumor invasion.[29] Normal epithelium is being organized by a number of specific intercellular tight junctions, adherens-type junctions, and desmosomes, which are then intimately interconnected with the actin and intermediate filament, cytoskeleton. [14,15]

In a study by L.Cheng and M.Nagabhushan, on expression of E-Cadherin in primary and metastatic prostate cancer, 53 primary prostate cancers and 14 patients with metastases were taken up for study. Among the organ confined prostate cancer patients a maximum of 21 patients had moderate staining of E-Cadherin and others had heterogeneous expression. But the expression was decreased in the

poorly differentiated cases as well as when the Gleason increased, the expression of E-Cadherin declined (p=0.03). "Among the patients with metastases 86% of them showed negative or weak expression of E-Cadherin. The expression of E-Cadherin in metastatic prostate cancer was reduced compared with that in primary prostate cancer".[14]

Finally, it was concluded in their study that the "expression of E-Cadherin is decreased in less well differentiated prostate cancers and in metastases".

The current study shows that there is an equal incidence in prostate cancer in accordance with the national cancer registry. Also the Gleason score and the serum PSA values are also significantly correlating with the clinical diagnosis of prostate cancer and with extra- prostatic extension.

Immunohistochemical analysis always has been a valid aide in the diagnosis or exclusion of prostate carcinoma in doubtful cases. This in addition will help us in keeping a step forward by diagnosing advanced stages of prostate cancer using immunohistochemical markers like E-Cadherin, which is an important predictor of metastases or progression, as proved by various studies stated above. Thus in conjunction with such studies, the present study has also shown that there is loss of E-Cadherin expression in cases of advanced malignancy stages in contrast to the benign conditions like benign hyperplasia of prostate, where there will be moderate to strong expression in the glandular cells.

CONCLUSION

The expression of E-Cadherin is lost in about 28% of the cases, whereas in a majority of 56% of the cases showed weak or moderate positivity, indicating that as the lesions are progressing, there is considerable loss of E-Cadherin. Also cases with suspected extra prostatic extension, either absent or very weak expression of E-Cadherin was observed.

There is no significant correlation between the expression of E-Cadherin in comparison with Gleason score and serum PSA values (value>0.05).

ACKNOWLEDGEMENT

The authors have reported that there is no conflict of interest and there has been no funding received for this work.

Fig.1 ecadherin weak positivity in malignant glands (10x)

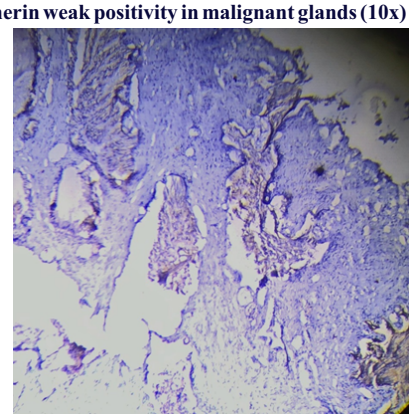
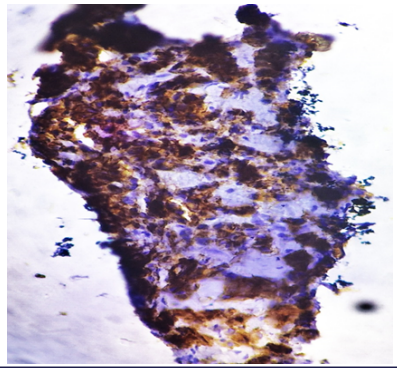


Fig.2 ecadherin strong positivity in benign glands(10x)



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