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Study of Histopathological Association of Tensin 4 Antibody in Colorectal Carcinoma in A Tertiary Care Centre

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ABSTRACT

Tensin 4, a cell adhesion molecule, is known to be implicated in various carcinomas including colorectal carcinoma. Overexpression of Tensin 4 or CTEN (C-TerminalTensin like) was reported in several human cancers, such as thymoma, melanoma, hepatocellular carcinoma, lung, breast, pancreatic, ovarian, and gastric carcinoma. This cross-sectional study was conducted in a tertiary care centre including 30 formalin-fixed, paraffin-embedded (FFPE) colorectal carcinoma (CRC) tissue samples. Routine hematoxylin and eosin (H&E) staining was performed for histopathological grading and Immunohistochemical (IHC) staining using Tensin 4 antibody using standard laboratory protocols. The expression patterns of Tensin 4 were assessed and correlated with histopathological grades of CRC. In CRC cases, increased expression of Tensin 4 was noted, particularly in higher-grade tumours. This study demonstrates an association between Tensin 4 overexpression and higher histopathological grades of CRC. These findings suggest a potential role of Tensin 4 as a potential biomarker in tumour progression and aggressiveness.

Keywords*: Tensin 4, Colorectal Carcinoma, Histological Grade, Prognosis*

INTRODUCTION

Colorectal carcinoma is the third most common form of cancer and the second most common cause of cancer-related death in the Western world [1]. Tensin 4, a cell adhesion molecule, is known to be implicated in various carcinomas including colorectal carcinoma [2]. Tensin family consists of four members which encode proteins localizing to focal adhesions. Three genes (*TNS1, TNS2, TNS3*) are highly homologous and encode multi domain proteins that bind to several structural and signalling molecules (such as vinculin, paxillin, Src, Actin) [3]

Tensin-4/CTEN was the last member identified in the Tensin family. Despite tensins being known to localize to focal adhesions, Tensin-4 is also found in the cytoplasm and the nucleus, and it is positively regulated by several growth factors. Tensin-4 is responsible for controlling multiple proteins and signalling pathways, regulates cell invasion, migration, adhesion, growth, metastasis, apoptosis, and epithelial to mesenchymal transition (EMT). Activation of Epidermal growth factor receptor (EGFR) signalling in breast cell lines stimulates cell motility and upregulates Tensin-4 expression while simultaneously downregulating the expression of Tensin 3, known as the Tensin switch [1].

Since Tensin-4 mediated cell migration was not regulated by a Tensin switch mechanism in CRC, other mechanisms of cell migration were sought [2]. In CRC, Tensin-4 signalling downregulates E-cadherin expression. This has prompted the investigation of its role in epithelial to mesenchymal transition (EMT) signaling[3]. Over expression of Tensin-4 was reported in several human cancers, such as thymoma, melanoma, hepatocellular carcinoma, lung, colon, breast, pancreatic, ovarian, and gastric which suggests role of Tensin-4 in carcinogenesis, and is considered to be a putative biomarker and a therapeutic target, although its role and its expression are poorly understood [4].

OBJECTIVE

This was a cross sectional study on CRC samples to study the Tensin 4 expression pattern in CRC and to associate its relationship with the grading of the cancer to assess its role as a possible prognostic biomarker.

METHODS

This was a cross-sectional observational study conducted to evaluate the expression of Tensin-4 in CRC samples and to analyze its association with clinic-pathological parameters. The study was carried out in the Department of Pathology at a tertiary care teaching hospital in India. Histopathological evaluation and Immuno histochemistry (IHC) were performed in the departmental laboratory. A total of 30 formalin-fixed, paraffin-embedded (FFPE) tissue blocks of CRC samples were included. Histopathological grading was performed using routine Hematoxylin and Eosin (H&E) staining. IHC staining for Tensin 4 (TNS4 Recombinant Antibody, Bioss Antibodies, bsm-60276R, Rabbit, Recombinant IgG, conc 25µg/mL) was carried out following standard laboratory protocols. Following deparaffinization, Heat-induced epitope retrieval (HIER) Tris-EDTA buffer (pH 9.0) for 20 minutes at 95°C. On cooling and blocking the endogenous peroxidase primary antibody (TNS4) was added and incubated for 1 hr at room temperature. This was followed by secondary antibody and counter stain with Hematoxylin.

The expression patterns of Tensin 4 were analysed and correlated with histopathological grade of the tumour. The Tensin 4 antibody staining was cytoplasmic. Interpretation of staining was semi quantitative with staining of ≥20% tumour cells was considered positive. The intensity of staining was compared with adjacent normal colonic tissue which showed weak positive and in comparative tumour cells with higher intensity of staining was considered strongly positive [4,5]. Clinical data including age, sex, site of tumour were obtained from medical records. Relevant pathological parameters such as tumour grade and histological subtype were noted from the H&E and IHC slides. The IHC findings were recorded in a structured proforma.

The Results were then analysed using descriptive statistics such as, Mean, Median, standard deviation, inter-quartile range, percentages, tables, graphs wherever necessary and correlated using the Chi-square and Fisher's exact tests on the cases. The study was conducted in accordance with the ethical standards of the Institutional Ethics Committee.

RESULTS

The expression of Tensin 4 in adjacent normal colonic tissue served as internal control. The normal colonic tissue was negative or weakly positive for Tensin 4. However, in CRC of higher grade (Moderately differentiated and poorly differentiated) tumours showed an over-expression of Tensin 4 indicating a positive relationship. The expression of Tensin 4 antibody in different histological grade of CRC is shown in Figure 1. The association between Tensin 4 expression and Histological stages of CRC and lymph node involvement are as shown in Table 1. Fisher's exact test demonstrated a statistically significant association between histopathological grade of CRC and Tensin 4 expression (two-sided $p = 0.003$). Most of the CRC with lymph node involvement showed a significant association with Tensin 4 expression in Chi Square test ($\chi^2 = 11.43$, $df = 1$, $p = 0.0007$) and Fisher's exact test (two-sided $p = 0.0017$). Most of the cases showing positive Tensin 4 expression were from the age group of 51-60 years and the most common affected gender were the male population.

Table 1 - Association with Tensin 4 Status and Tumour size, LN involvement and Histopathological Grade (H&E)

Variable	Category	Tensin 4 Negative	Tensin 4 Positive	Total	Chi-square (df)	p-value	Fisher's Exact (2-sided)
LN Involvement	Yes	3	18	21	11.43	0.0007	0.0017
	No	7	2	9			
Histopathological Grade (H&E)	Mod. Diff	4	10	14	11.70	0.003	-
	Poorly Diff	zero	5	5			
	Well Diff	9	2	11			

Figure 1: Showing Histological grade of CRC with Tensin 4 expression

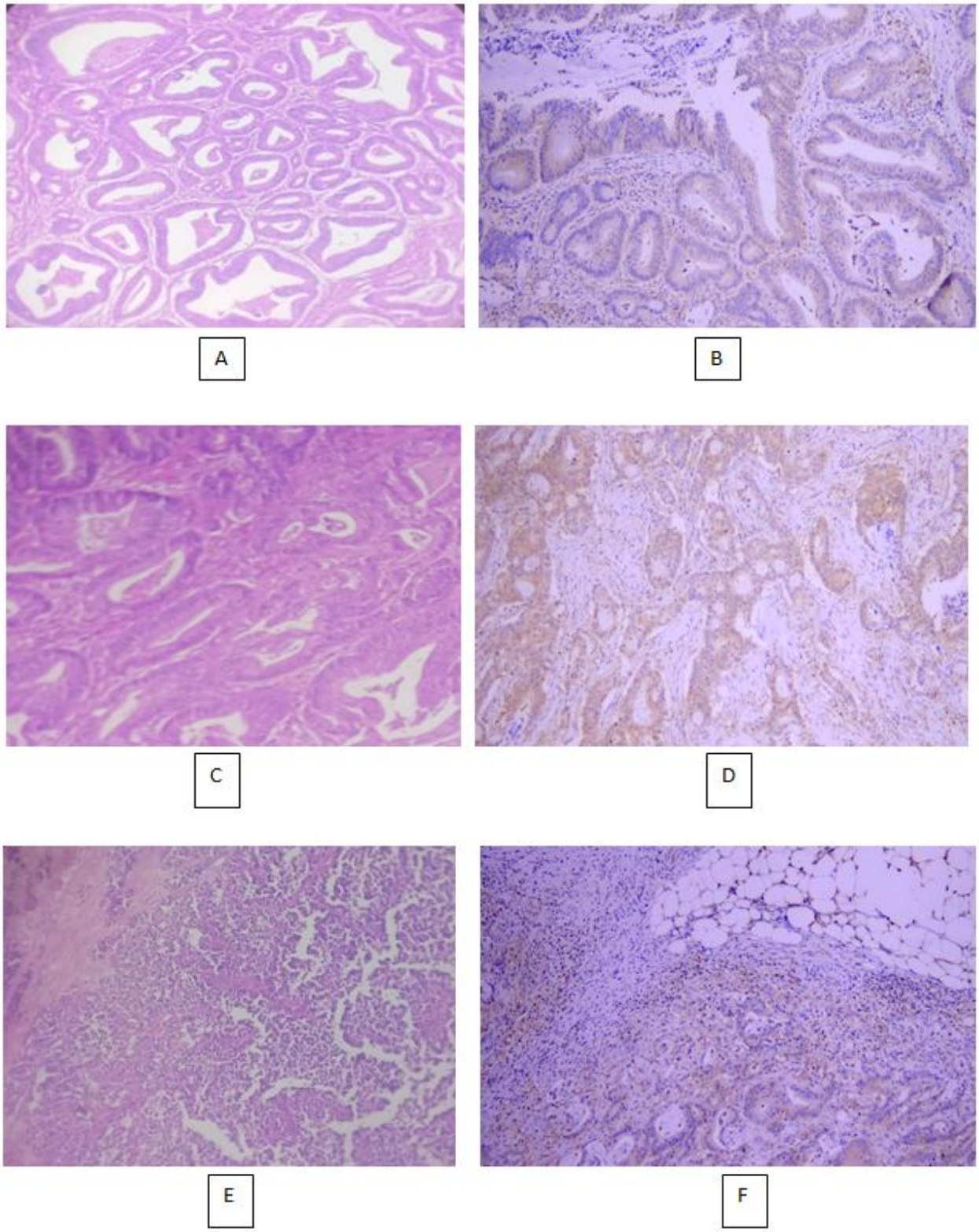

Figure 1: H & E stain showing well Differentiated, Moderately differentiated and Poorly differentiated CRC in A, C and E respectively. The IHC of Tensin 4 antibody shows cytoplasmic staining of well Differentiated, Moderately differentiated and Poorly differentiated CRC in B, D and F respectively.

DISCUSSION

Recent advances in Histopathology and molecular oncology have highlighted the role of cytoskeletal and focal adhesion proteins in tumor progression and metastasis, among which the tensins family has gained increasing attention [3]. Tensins are integrin-associated adaptor proteins that link the actin cytoskeleton to extracellular matrix signalling, thereby

regulating cell adhesion, migration, and survival. According to the WHO Classification of Tumours of the Digestive System, CRC progression is driven not only by architectural distortion and cytological atypia but also by molecular alterations that enable invasion and metastatic spread [1]. Within this context, Tensin 4 has emerged as a key oncogenic protein influencing aggressive tumour behaviour. Structurally, Tensin 4 differs from other members of the Tensin family by lacking the N-terminal actin-binding domain, which alters its functional role from maintaining cytoskeletal stability to promoting cellular motility and invasion [5]. This unique molecular configuration allows Tensin 4 to act predominantly as an oncogene rather than a structural protein. Experimental studies have demonstrated that Tensin 4 modulates focal adhesion dynamics and enhances migratory capacity of malignant cells, thereby facilitating tumor progression [6]. Tensin 4 is an important biomarker and serves as an oncogene in the progress of colorectal cancer. It channels its effect through Epithelial – mesenchymal transition (EMT) which detaches the cells from its architecture and allows easy embolization of the tumor cells to distant sites thus triggering metastasis to distant sites. EMT involves loss of epithelial polarity and cell–cell adhesion, coupled with acquisition of mesenchymal traits that promote motility and invasiveness. A study demonstrated that Tensin 4 overexpression in colorectal cancer represses E-cadherin expression, thereby weakening intercellular adhesion and enhancing cell motility [2]. This disruption of epithelial architecture enables tumor cells to detach from the primary lesion, invade surrounding stroma, and access lymphovascular channels. The expression pattern of Tensin 4 across normal and malignant tissues further supports its role in tumor progression rather than initiation. One of the studies demonstrated that Tensin 4 is upregulated in CRC tissues compared to adjacent normal mucosa [7]. Minimal or absent expression in normal colonic epithelium and well-differentiated tumours suggests that Tensin 4 overexpression represents a later event in colorectal carcinogenesis [3,7]. This stepwise upregulation mirrors observations in other gastrointestinal malignancies, including gastric cancer, where increased Tensin 4 expression has been associated with specific histological subtypes and advanced disease stages. [3,7,8]

Several molecular studies have explored the downstream signaling pathways regulated by Tensin 4. Another study demonstrated that Tensin 4 promotes invasion and migration through activation of the AKT/GSK-3β/Snail signalling pathway, thereby reinforcing EMT and enhancing metastatic potential [9]. More recently, a study showed that Tensin 4 facilitates aerobic glycolysis and tumour cell invasion via activation of the β-catenin/c-Myc pathway in CRC, linking metabolic reprogramming with aggressive tumour behaviour. [2] These findings provide mechanistic support for the clinico-pathological associations observed in human tumours.

In the present study, increased Tensin 4 expression showed a statistically significant association with lymph node involvement. Lymph node metastasis represents a critical step in systemic dissemination of CRC. The observed association aligns with prior studies reporting higher Tensin 4 expression in node-positive tumours and poorer clinical outcomes. [2,8] Tensin 4–mediated EMT and focal adhesion remodelling may enhance the ability of tumour cells to invade lymphatic vessels and survive within the nodal microenvironment thereby contributing to disease progression.

A significant association was also observed between Tensin 4 expression and histopathological grade of the tumor. Moderate to poorly differentiated tumors demonstrated higher Tensin 4 expression compared to well-differentiated carcinomas. Histological grade reflects the degree of loss of glandular differentiation and epithelial characteristics, both of which are hallmarks of EMT-driven tumor progression. Similar correlations between Tensin 4 expression and poorly differentiated tumor have been documented in gastric cancer and other epithelial malignancies, reinforcing the concept that Tensin 4 expression parallels tumor dedifferentiation and aggressiveness. [5, 10, 11]

The oncogenic role of Tensin 4 has also been explored in relation to phosphatase and tensin homolog (PTEN) signaling pathways. Loss of PTEN gene expression is a well-established event in colorectal carcinogenesis, contributing to uncontrolled PI3K/AKT signalling.[12,13] Studies have suggested that Tensin 4 may interact with or modulate downstream pathways influenced by PTEN loss, thereby amplifying oncogenic signaling cascades.[6,14] Additionally, epigenetic activation of Tensin 4 has been shown to promote tumor progression in gastric cancer, indicating that transcriptional and epigenetic mechanisms may regulate its expression in malignancies [11].

In our study, tumour size did not show a significant association with Tensin 4 expression. This finding suggests that Tensin 4 expression may be independent of primary tumor growth and is more closely linked to invasive and metastatic potential. Tumor size alone may not accurately reflect biological behaviour as smaller tumour may harbour molecular alterations that predispose to early metastasis. This observation emphasizes the importance of molecular biomarkers such as Tensin 4 in complementing conventional pathological parameters.

Beyond human oncology, IHC expression of Tensin 4 has been demonstrated in aggressive tumors across species, including squamous cell carcinoma in dogs, further supporting its conserved role in tumor invasion and progression [15]. Moreover, Tensin 4 dependent stabilization of MET signalling has been shown to be essential for carcinoma cell survival and proliferation, underscoring its role in maintaining malignant phenotypes [16].

From a clinical perspective, the association of Tensin 4 expression with lymph node metastasis and higher histological grade suggests its potential utility as a prognostic biomarker in CRC. Incorporation of Tensin 4 IHC assessment into routine histopathological evaluation may aid in identifying patients with biologically aggressive tumors who may benefit from closer surveillance or adjuvant therapy. Furthermore, given its involvement in multiple oncogenic pathways, Tensin 4 represents a potential therapeutic target, although further functional and clinical studies are required to explore targeted interventions.

CONCLUSION

The over expression of Tensin 4 showed to have a positive association of with higher stages of has CRC and with lymph node involvement, suggesting its role in prognostic value. Further larger studied may help clarify its role in risk stratification and prognostication. Understanding the molecular pathways involving Tensin 4 could open ways for targeted therapeutic approaches aimed at limiting tumour invasion and metastasis. Overall, the study provides a foundation for future research exploring Tensin 4 as a clinically relevant biomarker in colorectal carcinoma.

Conflict of interest: The authors disclose no conflict of interest

Acknowledgement: Nil

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