Original Article

IMMUNOHISTOLOCALIZATION OF c-erbB-2 PROTEIN: A PROLIFERATIVE MARKER IN BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT:
Objective: To examine possible role of c-erbB-2 in the development of benign prostatic hyperplasia.
Design: A retrospective study of 25 patients suffering from benign prostatic hyperplasia.
Setting: BMSI, Jinnah Postgraduate Medical Centre, Karachi.
Subjects: Twenty five patients between the ages of 51-80 years were selected for the period of 2001 suffering from benign prostatic hyperplasia.
Results: Results of study show that overall frequency of c-erbB-2 expression was not found. Maximum numbers of BPH among total cases were in age group 61-70 years i.e 13 tumours (52% of total cases).
Conclusion: Results of current study and work of previous researchers indicate a lot of controversy over c-erbB-2 immunostaining in benign prostatic hyperplasia. Further study is required to elucidate the precise role played by this protein marker in the benign growth of prostatic tissue.

KEY WORDS: c-erbB-2 protein, prostatic hyperplasia, immunohistochemistry.

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INTRODUCTION

Benign prostatic hyperplasia is common disorder in men over the age of fifty. It is characterized by hyperplasia of stroma and epithelial cells, resulting in formation of nodules in periurethral region of prostate, which may compress and narrow the urethral canal to cause partial or complete obstruction of the urethra.[1] It can be seen in 20% of men 40 years of age, 70% by age of 60 and to 90% by age of 70.[2]

Critical aspect of the biology and molecular basis for prostate tumours remain poorly understood. One form of prostatic enlargement is related to action of androgens.[3] Dihydrotestosterone, a metabolite of testosterone, is the ultimate mediator of prostatic growth. It binds to nuclear androgens receptors of epithelial and stromal cells and signals the transcription of growth factors that are mitogenic to epithelial and stromal cells. The fact that all patients do not benefit from androgen depriving therapy suggest that prostatic hyperplasia may be etiologically heterogeneous, and in some cases, factors other than androgens may be more important.

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It is well established that activation of cellular genes may trigger uncontrolled cell growth and cancer development. Previous reports suggest that epidermal growth factor receptor and c-erbB-2 receptor may be implicated in the development of benign prostatic hyperplasia.[4] c-erbB-2 is a component of four member family of closely related growth receptors including epidermal growth factor receptor (EGFR) or HER-1 (erbB1), HER-2 (erbB2), HER-3 (erbB3) and HER-4 (erbB4). The designation HER is made in reference to structural similarity to human EGFR.[5] The genes called Neu, c-erbB-2 and HER-2 were isolated independently, but subsequent analysis and chromosomal mapping studies revealed all three genes to be same. c-erbB-2 gene generates a messenger RNA of 4.8Kb. Like epidermal growth factor receptor c-erbB-2 receptor has an extracellular domain, Transmembrane domain, and intracellular domain, indicating that it is also likely to be a cellular receptor for an as yet unidentified legend (Growth factor)[6]. Once activated, intracellular signals transmitted to cell nucleus, resulting in transcription of genes involved in controlling cellular replication and differentiation.

MATERIALS AND METHODS

This study was performed on formalin fixed paraffin embedded blocks of all cases diagnosed as benign prostatic hyperplasia (BPH), at Department of Pathology Basic Medical Sciences Institute Jinnah Postgraduate Medical Centre Karachi Pakistan. Blocks and slides of 25 cases of BPH reported from year 2001, were retrieved. All slides were stained for immunohistochemistry to see over expression of c-erbB-2 / HER-2 (Zymed kit, polyclonal antibody). c-erbB-2 staining was considered positive, cells show intense circumferential cell membrane staining. It was read under 10x objectives. In all these cases it was proposed that staining would be observed in majority (>50%) of the hyperplastic cells. Cells in which there was cytoplasmic staining without distinct cell membrane staining were scored as negative. Results were compared with positive and negative controls.

RESULTS

In this study, 25 cases of benign prostatic hyperplasia were subjected to immunohistochemistry staining for c-erbB-2 overexpression. Table-I shows distribution of 25 cases of Benign Prostatic Hyperplasia into different age groups. Maximum number of BPH among total cases were in age group ranging from 61-70 years i.e. 13 BPH (52% 0f total cases). Table-II show frequency of c-erbB-2 expression in twenty five cases of Benign Prostatic Hyperplasia. Overall frequency of c-erbB-2 expression was found 0%. It was observed that all 25 cases demonstrated no membranous staining (Figure 1).

TABLE-I
Age Group
Benign Prostatic Hyperplasia

Age group		*No.*	*%*
A	51-60	8	32
B	61-70	13	52
C	71-80	3	12
D	81+	1	04
	Total	25	100

TABLE-II
Overall frequency of
overexpression of c-erbB-2 in
Benign Prostate Hyperlpasia

Group	*Over expression*	*No.*	*%*
A	Positive	0	0
B	Negative	25	100
Total	25	100	

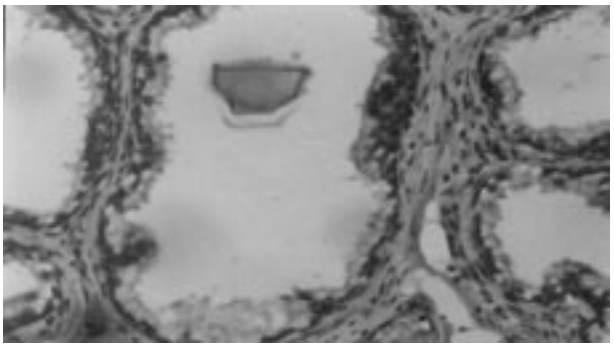

Figure 1: Benign prostatic hyperplasia.C-erbB-2 / Her-2 negative immunohistochemical staining. Magnified 20X.

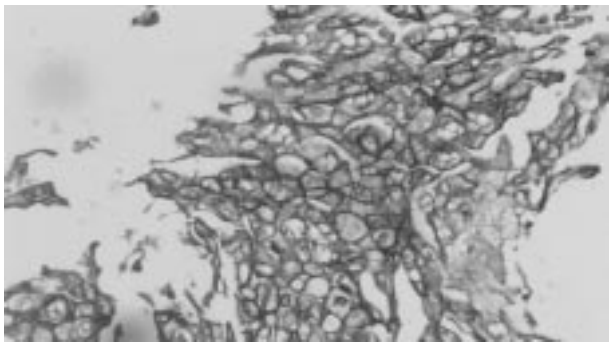

Figure 2: c-erbB-2 / neu, Positive control, Breast, Magnified 20X

DISCUSSION

Benign Prostatic Hyperplasia is etiologically heterogeneous, and in some cases, factors other than androgens may be more important. This study was undertaken as a step toward a more understanding of the biology of BPH. It should help to disclose the molecular mechanisms underlying prostate growth and to identify molecular markers for prognostic and therapeutic use.[7]

c-erbB-2 is a member of the epidermal growth factor receptor family and is known to be associated with cellular growth and differentiation. The role played by this factor in BPH is not clearly known.[8] In the present study, expression of this factor was investigated immunohistochemically in formalin fixed prostate tissue suffering from BPH. The results are comparable with those of previous studies.

In the present study, frequency of c-erbB-2 over expression in prostatic hyperplasia is 0%. No immunoreactivity was found in 25 cases of hyperplasia. This finding is similar to Visakorpi[9], Scwartz[10], Sadasivan[11] and Zhau.[12] Contrary to our findings immunoreactivity was reported by different researchers, like Ware[14], Giri[15], Ibrahim[16] and Grobe[17].

Previous authors have studied the expression of c-erbB-2 in BPH. Iwamura M,[18] states that prostatic neuroendocrine cells play an important role in the growth and differentiation of prostate. Neuroendocrine cells may be regulated by the c-erbB-2 protein family, probably in a ligand-specific fashion. Shwartz S,[19] demonstrated a role for EGFR and c-erbB-2 in the development of BPH.

Torring K[20] found minor changes in the expression of c-erbB-1 and c-erbB-2 after finasteride (a well known steroid 5alpha-redutase inhibitor) treatment. Haussle O[21] studied expression of c-erbB-2 in BPH, but absent or low in cancer and adenosis. Giri DK,[15] states that available data indicate that prostatic tumours as well as a high percentage of prostatic hyperplasia tissues express c-erbB-2 protein, however, its role in cellular proliferation needs further study. Ibrahim Gk[16] found that c-erbB-2 immunoreactivity was present at significantly higher degree in BPH than in malignant prostate epithelium.

Visakorpi T,[9] found that non of the normal, hyperplastic or malignant prostate tissues showed clearly positive c-erbB-2 immunoreactivity. Schwartz S Jr,[10] detected no c-erbB-2 genomic content in the BPH samples. Sadasivan R[11] states that using a monoclonal antibody directed against human c-erbB-2 protein product and an immunohistochemical staining method, no c-erbB-2 expression was noted with Benign Prostatic Hyperplasia.

Our results regarding frequency of c-erbB-2 over expression in Benign Prostatic Hyperplasia are almost similar to many of previous studies and discordance between results of current study and some of previous studies may be partially explained on the basis of technical variables like tissue fixation protocols, antigen retrieval, primary antibody, immunodetection system and scoring system used in the studies (Cote[22] and Jacob[23]).

Like many previous studies, the exact role of c-erbB-2 protein is unclear, but its potential usefulness in prognostication and therapy must be explored. Further study is required to elucidate the precise role played by this factor in benign growth of prostate.

REFERENCES

1. Steers WD, Zorn B. Benign Prostatic Hyperplasia. Dis Mon 1995;41:437.
2. Arrighi HM, et al. Natural history of Benign Prostatic Hypeplasia and risk of prostectomy: The baltimore longitudinal study of aging. Urology 1991; 38 (suppl): 4.
3. Droller MJ. Medical approaches to the management of prostate diseases. Br J Urol 1997; 79: 42.
4. Schwartz S Jr, Cacceres C, Morote J, et al. Overexpression of epidermal growth factor receptor and c-erbB2 / neu but not of int-2 genes in Benign Prostatic Hyperplasia by means of semi-quantitative PCR. Int J Cancer 1998;76(4): 464-7.
5. Wisecarvar JL. Her / neu testing comes with age. Am J Clin Pathol 1999; 111: 299-301.
6. Salmon DR,et al. Studies of HER / neu oncogen in human breast and ovarian cancer. Science (Wash DC) 1989; 24: 707-13.
7. Jun Luo, David , Duggan et al.Advances in breif human prostate cancer and Benign Prostatic Hyperplasia. Cancer Research 2001; 61: 4683-8.
8. Giri Dk, Pal R, Widhwa SN, Talwar GP. Immunohistochemical localization of transforming factor-alpha, epidermal growth factor receptor and c-erbB-2 protein in hyperplasic human prostates. Carcinogenesis 1995; 16(4): 729-33.
9. Visakorpi T, Kallioneimi OP, Koivula T, Harvey J, Isola J. Expression of epidermal growth factor receptor and erbB-2(HER-2 / neu) oncoprotein in prostatic carcinoma. Mod Pathol 1992;5(6):643-8.
10. Schwartz S Jr, Caceres C, Morote J et al. Gains of the relative genomic content of erbB-2 in prostate carcinoma and their association with metastatsis. Int J Oncol 1999;14 (2):367-71.
11. Sadasivan R, Morgan R, Jennings S, et al. Overexpression of Her-2 / erbB-2 may be an indicator of poor prognosis in prostate cancer. J Urol 1993; 150(1): 126-31.
12. Zhau HE, Wan DS, Zhau J, et al. Expression of c-erbB-2 oncoprotein in human prostate cancer tissues and cell lines. Mal. Carcinog 1992; 5:32.
13. Eric J Kuhn, Richard A, Kurnot et al. Expression of c-erbB-2 oncoprotein in human prostate carcinoma. J Urol 1993;150: 1427-33.
14. Ware JI, Maygarden SJ, Knootaz WW Jr. Immunohistochemical detection of c-erbB-2 protein in human benign and neoplastic prostate. Hum Pathol 1991;22(3): 254-8.
15. Giri DK, Widhwa SN, Uppadhawa SN, Talwar GP. Expression of HER-2 oncoproein in prostate Tumours: an immunohistochemical study. Prostate 1993;23(4):329-36.
16. Ibrahim GK, MacDonald JA, KernsBJ, et al. Differential immunoreactivity of HER-2 / neu oncoprotein in prostate tissues. Surg Oncol 1992;1(2):151-5.
17. Grob B, Schelhammer PF, Wright GL. Expression of c-erbB-2 oncogen in human prostate carcinoma. J Urol 1991;145, 294A, abstract 325.
18. Iwamura M, Koshiba K, Cockett AT. Receptors for Benign Prostatic Hyperplasia growth factors are located in some neuroendocrine cells. Prostate Suppl 1998;8:14-7.
19. Schwartz S Jr, Caceres C, De Torres I et al. Androgen-independent basal cell re-epithelialization, c-erbB-2 mRNA expression and androgen-dependant EGFR mRNA expression in Benign Prostatic Hyperplasia explant cultures treated with finasteride. Int L Cancer 1998; 76(4): 519-22.
20. Torring K, Moller-Ernst Jensen, L Lund JE. Possible autocrine loop of the epidermal growth factor system in patients with Benign Prostatic Hyperplasia treated with finasteride. Br J Urol 2002; 89(6):583.
21. Haussler O, Epstein JI, Amin MB, Hetz PU, Hailemariam S. Cell proliferation, apoptosis, oncogene, and tumour suppressor gene status in adenosis with comparison to Benign Prostatic Hyperplasia, prostatic interaepithelial neoplasia, and cancer. Hum Pathol 1999;30(9): 107-66.
22. Cate RJ,Taylar CR. Immunohistochemistry and related marketing techinques In:Damjanove I,Linder J(eds). Anderson's Pathology. 10th ed. New York: Mosby 1996:136-175.
23. Jacob WT,Gown MA,Yazgi H,Barnes MJ,Schint SJ.Her-2 / neu protein expression in breast cancer evaluated by immunhistochemistry. Am J Clin Pathol 2000; 113: 251-8.