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ORIGINAL RESEARCH

To study immune histochemical expression of CD34 and CD117 in benign and malignant prostaticlesions

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ABSTRACT
Aim:
ToevaluateandcomparetheexpressionpatternsofCD34andCD117inbenignandmalignantprostatictissuesandtheirrelationtotheclinicopathologicalfeatures.
Methodology:The present study has been conducted at Department of Pathology, atOsmaniaGeneralHospitalfromAugust2017toJuly2019.total100caseswerecollected.RoutineprocessingandHaematoxylinandEosinstainingofreceivedspecimensweredonefollowed byimmunohistochemicalanalysiswithCD34andCD117.
Results:
Inthisstudy,thepredominantpopulationwasinthe6th to7th(41%)decadeofage.Mostofthepatientspresentedwithdifficultyinmicturition(85%). Immunohistochemical results showed no significant correlation betweenexpression of endothelial cell marker CD34 and mast cell marker CD117 with theage.Our findings showed that there is an increased expression of CD34 in PCa samplescompared to benign prostate tissues. Overexpression of CD34 was also found in PCacases with advanced Gleason score and high total sPSA level. On PCa samples,CD117expressionwasincreasedinadvancedGleasonscoreratherthanearlyGleason score.CD34High/CD117Highphenotypewasmorefrequentin PCacasesthanbenignprostate tissues.Positivesignificantassociationwasalsoobservedbetween CD34High/CD117High phenotype withadvanced Gleason score andtotalsPSA level. AS the overexpression of CD34 and CD117 markers seen in an advancedstageandhightotalsPSAlevelofPCa,itcanindicatesthatCD34High/CD117Highphenotypecanconfertumorprogressionandaggressivebehavioron PCa.
Conclusion: TheroleofCD34andCD117markersintumorigenesisandtargetedtherapycan be clearly studied with the help of western blotting data. Thus, the level ofthesemarkerscanbe analyzedinprostatecancer cell lines, benign prostate tissues andPCasamplesusingwesternblottinginfuturestudies.
Keywords: CD34, CD17, Prostate Cancer, Westernblotting, PCa, Gleasonscore, Malignant lesions

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common urological condition in men.Benign hyperplasia and carcinoma of the prostate are frequently increasing withadvancing age. The prevalence of BPH increases from 20% at 40 years of age to90% by the eighth decade of life

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[1]. Globally, prostatic carcinoma is the secondfrequentlydiagnosedcancerandthesixthleadingcauseofcancerdeathinmales [2].ItconstitutesabOut5%ofallmalecancersinIndia [3].

The most commonly used tools to screen for prostate cancer are digital rectalexamination,Prostaticspecificantigen(PSA),andtransrectalultrasound.However, histopathological examination remains the gold standard for the finaldiagnosis [4].Histologicaldiagnosisofprostatecancerisusuallybasedonmorphological features such as growth pattern, nuclear atypia and absence ofbasalcells.

Although the application of prostate-specific antigen (PSA) has enhanced thedetectionpowerofearlystageprostateadenocarcinoma (PCa),approximately40% of patients with localized disease manifested metastasis, distant seeding anddrugresistance [5].

As the incidence rate of Prostatic carcinoma has shown an alarming trend inalmost all countries; therefore, development of novel therapeutic approaches toovercomeitscellularinvasionandaggressivenessseemsnecessaryandchallengeg [6].

However,histologicaldiagnosiscanbechallengingparticularlywhenthemalignanttissueislimitedandismixedwithbenignprostaticgland,orbecauseofmimickersofcarcinoma [7].Theapplicationofimmunohistochemistrymaybeessentialtoconfirmthediagnosisand/ordistinguishprostaticcarcinomafromthebenignmimics.

One feature distinguishing cancer mimics from prostate cancer is that benignglands contain basal cells,whichareabsentincancerous glands.Pathologistoftenuseimmunohistochemicalmarkerstolabelbasalcellswhenfacedwithambiguous lesion [8]. The most commonly used marker is high molecular weightcytokeratins (34bE12) and more recently, markers such as P63, CK5, CK5/6 andCK14havebeenproposed [9-13].

The accurate pathological evaluation of prostatic lesion is essential, becausethesubjectoftheprostaticdiseaseisfraughtwithdoubts,uncertaintiesandapparentcontraindications [2].

ThisstudywasundertakentostudytheroleofCD34andCD117indifferentbenignandmalignantlesionsofprostate.

AIM & OBJECTIVE

ToevaluateandcomparetheexpressionpatternsofCD34andCD117inbenignandmalignantprostatictissuesandtheirrelationtotheclinicopathologicalfeatures.

MATERIALSANDMETHODS

STUDYDESIGN

Prospectivestudy

PERIODOFSTUDY

24months(August2017–July2019)

PLACEOFSTUDY

UpgradedDepartmentOfPathology,OsmaniaGeneralHospital,Afzalgunj,andHyderabad.

SAMPLESIZE

Atotalof100casesaretakenupforthestudy.

INCLUSIONCRITERIA

1. TURPChips.
2. SurgicallyexcisedbiopsyspecimensofBPHandprostaticcancers.

3. Adequatetumortissueforanalysis.

EXCLUSIONCRITERIA

1. Inadequatetumortissue.
2. Granulomatousprostatitisandprostaticcaliculicases.

Thespecimenswerereceivedin10%formalin.Aftergrossexamination,sections were processed for one day and later embedded in paraffin which was cut atfivemicronthickness.SectionswerestainedwithconventionalHaematoxylinandEosin(H&E)stains.

A total of 100 cases were included in the study. Out of 100 cases, 50 are benignand 50 are malignant. The H and E stained slides of all the cases were reviewed anddiagnosis was made. All these 100 cases were subjected to immunohistochemicalmarkerCD34andCD117.

SCORINGANDEVALUATION

Immunostained slides ofCD34 and CD117 were observed and evaluatedunderlightmicroscope.

ForscoringtheCD34positivemicrovasculardensity(MVD),highlyvascularized areas were selected at low magnification (10X) and micro vessels werecountedin10non-overlappingselectedfieldsathighmagnification(400X).

Asinglecountablemicrovesselwasdefinedasanyendothelialcellorendothelial cell cluster positive for CD34 and clearly separated from an adjacentcluster. For scoring mast cell any cell with membranous and cytoplasmic staining forCD117wascountedasmastcell.

ForapatientwithPCa,theintratumoralareawasselectedformastcellevaluation.TheCD34+vesselsandCD117+mastcellswerecountedin10highpower fields(400X magnification)andtheaveragenumber ofpositivemastcellsandmicrovesselwasfinallyevaluated.

The median of H-scores were considered as a cut-off value to classify thespecimensasloworhighexpressionlevelsofCD34orCD117whichwere25and9,respectively.

STATISTICALANALYSIS

The relationship of CD34 and CD117 markers with clinicopathological factorsandtheassociationbetweenCD34/CD117phenotypesandclinicopathologicalfactors were evaluated using Pearson's chi-square test. A value of $P < 0.05$ wasconsideredstatisticallysignificant.

RESULTS

Outof100cases,therewereBenignprostatichyperplasia-50(50%).Prostaticadenocarcinoma-50(50%).

AGEWISEDISTRIBUTION

Theageofthepatientsincludedinthestudywererangebetween29-90years.Theaveragemeanagewas65years.

Table1:AgeDistributionofpatients

Age	Benign	Malignant
<50Years	05	02
51-60Years	15	17
61-70Years	21	20
71-80Years	07	10
81-90Years	02	01

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Total	50	50

Table-2:correlationofCD34expressionwithAge

Meanage	No.ofcases	CD34	
		Low	High
≤65	55	24	31
>65	45	21	24
Total	100	45	55

Table-3:CorrelationofCD117expressionwithAge

Meanage	No.ofcases	CD117	
		Low	High
<65	55	26	29
>65	45	27	18
Total	100	53	47

CLINICALFEATURES

Patients included in this study presented with combinations of symptoms i.e.,85% ofpatients presentedwithDifficulty inmicturition (85%), frequency (10%),andpain(5%).Themostcommonsymptomobservedinbothbeginprostatichyperplasiaandprostaticadenocarcinomapatientsisdifficultyinmicturition.

SERUMPSALEVELS

Table:4-SerumPSALevelsinallcases

SerumPSALevels	Benign	Malignant
<4	18	-
4-10	24	7
>10	08	49

Table-5:CorrelationofCD34expressionwithPSAlevels

PSAlevels	No.ofcases	CD34	
		Low	High
<4	18	11	07
4-10	25	17	08
>10	57	17	40
Total	100	45	55

Table-6:CorrelationofCD117expressionwithPSAlevels

PSAlevels	No.ofcases	CD117	
		Low	High
<4	18	08	10
4-10	25	09	16
>10	57	36	21
Total	100	53	47

BENIGNPROSTATICHYPERPLASIA

Theresultsinthepresentstudyindicatethatoutof50benignprostatichyperplasia,36and14casesshowedLowandHighexpressionofCD34respectively. Out of 50 cases ofBPH,31 and 19 casesshowedLow andHigh expression ofCD117respectively.

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Table-7:ExpressionofCD34andCD117inBenignProstaticHyperplasia

	LOW	HIGH
CD34	36/50	14/50
CD117	31/50	19/50

PROSTATICADENOCARCINOMA

Inpresentstudy,outofthe50casesofprostaticadenocarcinomas,10,22and18casesshowedGleasons coreof≤6,7and8-10respectively.

Outofthe50casesofprostaticadenocarcinomas,9and41casesshowedLowandHighexpressionofC D34respectively. 22and28casesshowedlowandhighexpressionofCD117respectively.

Table-8:ExpressionofCD34andCD117inProstaticadenocarcinoma

	Low	High
CD34	9/50	41/50
CD117	22/50	28/50

Table-9: Correlationof Expression of CD34andCD117 in Prostaticadenocarcinoma withGleasonScore

GleasonScore	No.ofCases	CD34		CD117	
		Low	High	Low	High
≤6	10	05	05	08	02
7	22	02	20	04	18
8-10	18	02	16	10	08
Total	50	09	41	22	28

TABLE-10:CorrelationbetweenCD34andCD117expressionandclinicopathologicalfeaturesinprostaticadenocarcinomacomparedwithbenignprostatichyperplasia

Patientsandtumorcharacteristics		No.ofCases (%)	Expressionof CD34		P-Value	Expressionof CD117		P-Value
			Low	High		Low	High	
Meanage	≤65	55	24(44)	31(56)	0.76	26(47)	29(53)	0.20
	>65	45	21(47)	24(53)		27(60)	18(40)	
PSA Levels	<4	18	11(61)	07(39)	**0.0018**	8(44)	10(56)	0.055
	4-10	25	17(68)	08(32)		9(36)	16(64)	
	>10	57	17(30)	40(70)		36(63)	21(27)	
Tumor Type	Benign	50	36(72)	14(28)	**0.00001**	31(62)	19(38)	0.071
	Malignant	50	9(18)	41(82)		22(44)	28(56)	
Gleasonscore	≤6	10	5(50)	5(50)	**0.012**	8(80)	2(20)	**0.002**
	7	22	2(9)	20(91)		4(18)	18(82)	
	8-10	18	2(11)	16(89)		10(56)	8(44)	

Thenumbersinboldindicatetheyarestatisticallysignificant.

TABLE-11:CorrelationbetweenCD34/CD117phenotypesandclinicopathologicalfeaturesinprostaticadenocarcinomacomparedwithbenignprostatichyperplasia

atientsandtumorcharacteristics		No.ofCases (%)	CD34/CD117phenotype				P-Value
			Low/Low	High/Low	Low/High	High/High	
Meanage	≤65	55	18(33)	8(14	6(11)	23(42)	0.47

	>65	45	16(36)	11(24)	5(11)	13(29)	
PSA Levels	<4	18	9(50)	1(5)	2(11)	6(34)	**0.011 (significant)**
	4-10	25	11(44)	2(8)	6(24)	6(24)	
	>10	57	14(25)	16(28)	3(5)	24(42)	
TumorType	Benign	50	28(56)	3(6)	8(16)	11(22)	**0.00001 (significant)**
	Malignant	50	6(12)	16(32)	3(6)	25(50)	
Gleasonscore	≤6	10	4(40)	4(40)	1(10)	1(10)	**0.0030 (significant)**
	7	22	1(5)	3(13)	1(5)	17(77)	
	8-10	18	1(6)	9(50)	1(6)	7(38)	

Fig1-Transurethralresectedspecimenofprostate

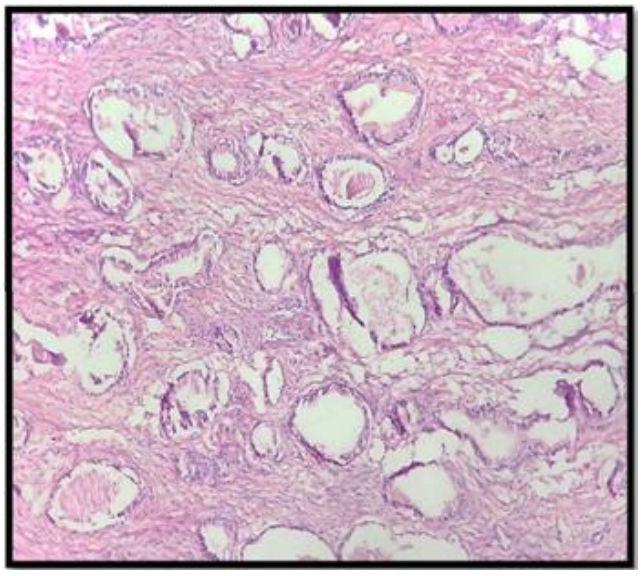

Fig2-BPHshowingbothglandsandstromaH&E(10x)

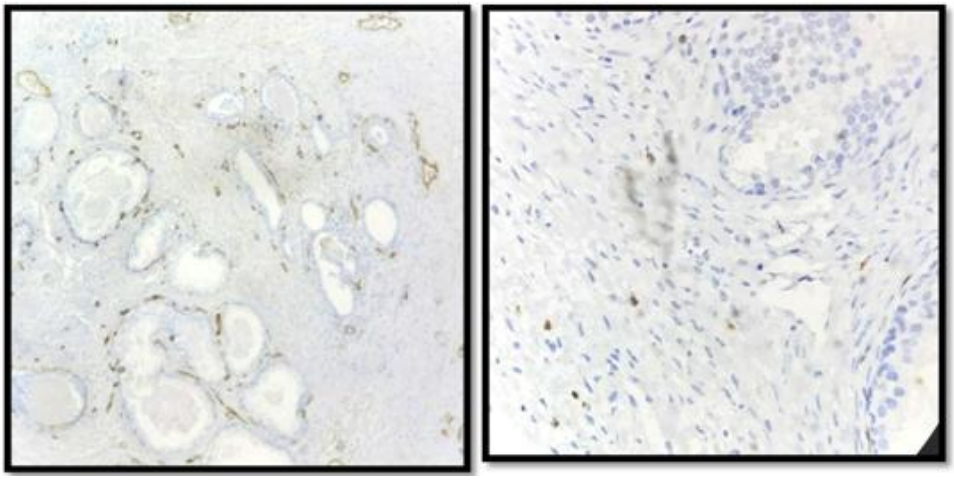

Fig3-BPHshowinglowexpression ofCD34(10X)
Fig-4.benignprostatichyperplasiashowinglowexpressionofCD117(40X)

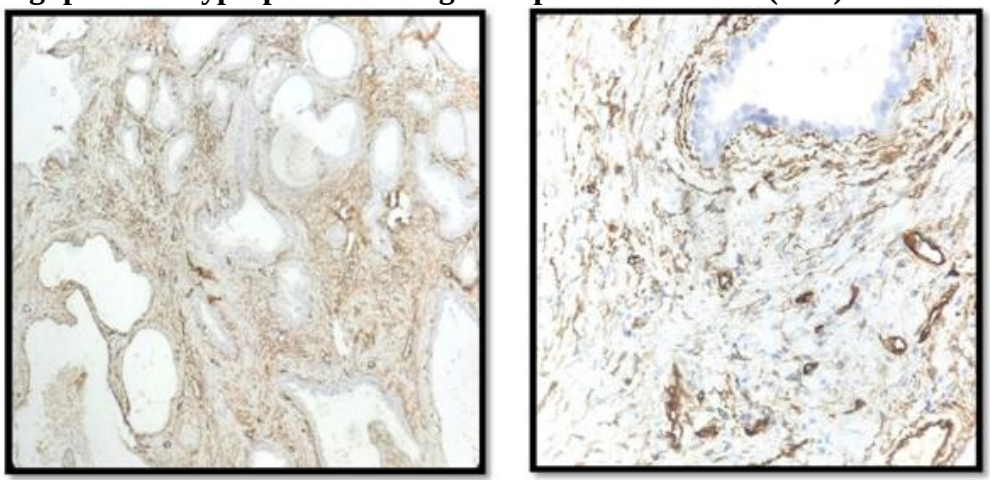

Fig5-BPHshowinghighexpressionhyperplasiaofCD34(10X)
Fig6-benignprostaticshowinghighexpressionofCD117(40X)

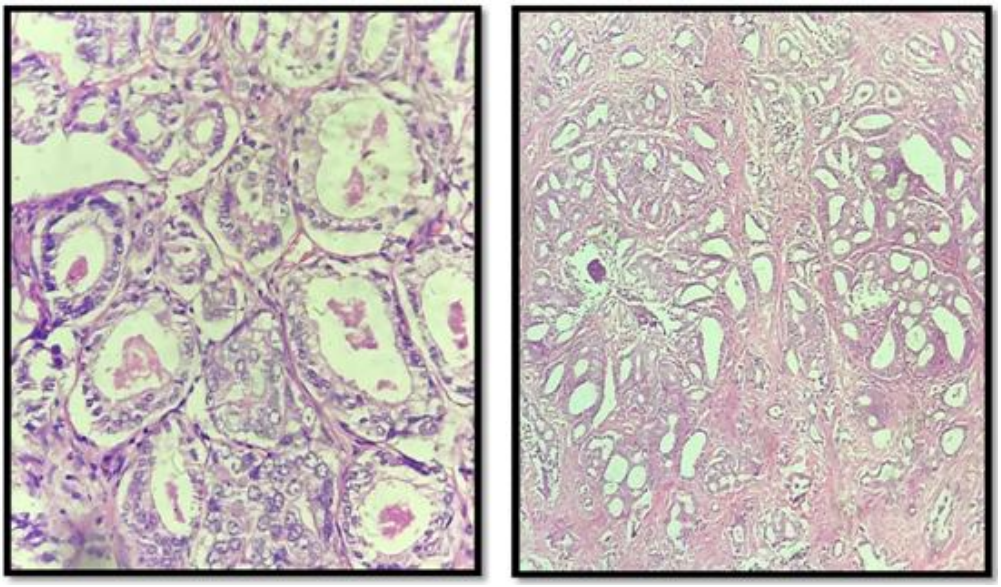

FIG:7-H&ESectionofprostatic adenocarcinomawithGleason score-3+3(40X)

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Fig:8-H&ESectionofprostatic adenocarcinomawithGleason score-4+3(10x)

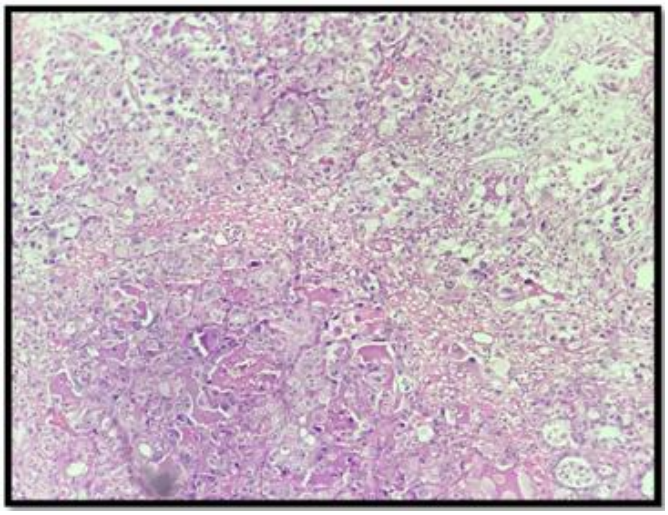

Fig:9-H&ESectionofprostaticadenocarcinomawithGleasonscore-5+4(10x)

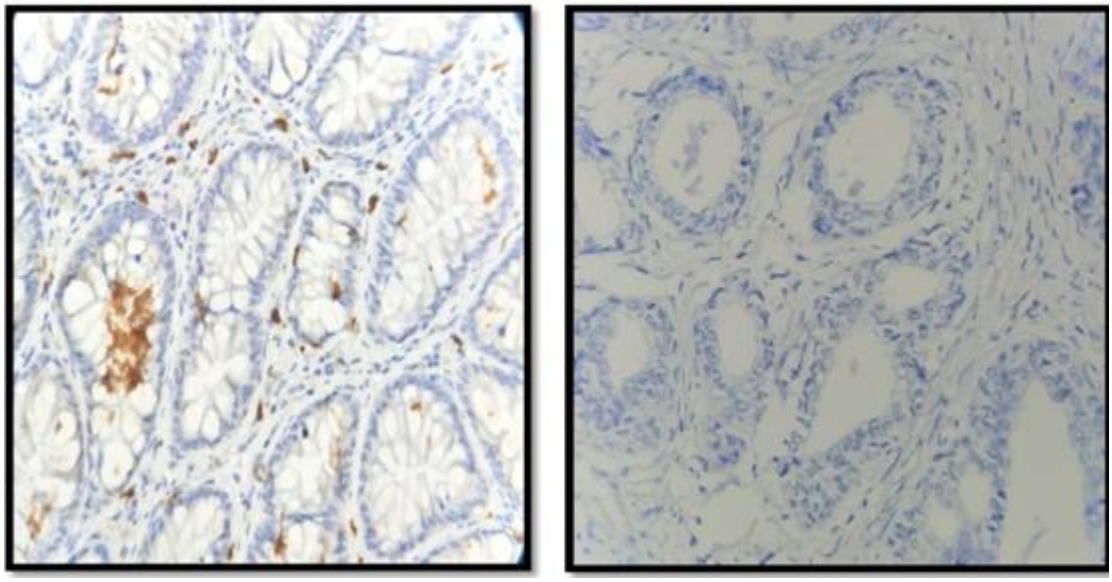

Fig10-prostaticadenocarcinomashowinglowexperessionofCD34
Fig11-prostaticadenocarcinomashowinglowexpressionofCD117

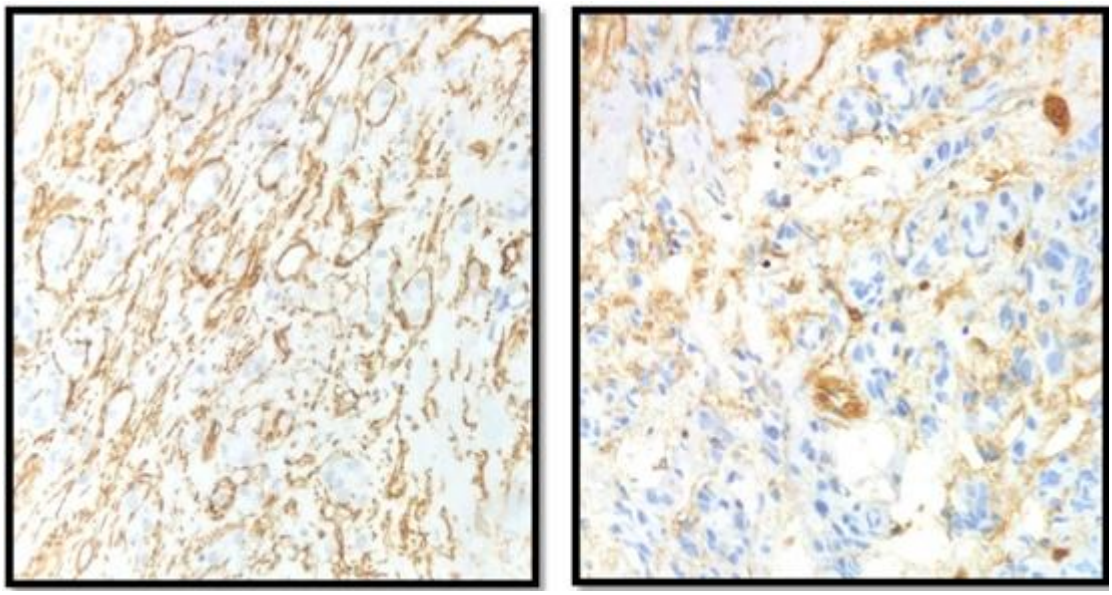

Fig.12-prostaticadenocarcinomashowinghighexpressionofCD34
Fig.13- prostaticadenocarcinomashowinghighexpressionofCD117

DISCUSSION

The present study is carried over in the Upgraded Department of Pathology,Osmaniageneralhospital,Afzalgunj.TheExpressionsofCD34&CD117wereevaluated andcomparedinbenignprostatichyperplasiaandprostaticadenocarcinoma.

Prostate is an accessory male reproductive organ which secretes proteolyticsolution that is expelled into the urethra during the time of ejaculation. It is associatedwith three types of disorders namely, prostatitis, benign epithelial hyperplasia (BPH)and prostate cancer (PCa). Epidemiologically, prostate cancer is more common in thewesternpopulation [14].Whereas,BPHismoreprevalentinAsianpopulation [15]

BothBPHandprostatecancerarecomplexandmultifactorial.Thefactorspredisposingtothedevelopmentofthesediseasesincludehormonalimbalance,aging,oxidativestress,inflammation,environmentalpollution,hereditaryandmostparticularly,stromaltoepithelialcellcrosstalk [16].

In prostate cancer, histopathological analysis has great clinical relevance [17]. Serological and Histological exams describe a number of important changes, allowingmonitoringofthediseaseprogression [18].

Despitethegaininepidemiologyandbiomolecularknowledgeofprostatecancer, one cannot predict which patients will develop clinically significant disease andwhichwillremainwithrestrictedtumour [19].However,upto30%ofpatientsundergoingradicalprostatectomyforclinicallylocalizeddiseasewillexperiencebiochemicalrecurrence.

AGEDISTRIBUTION

The age of the patients in our study ranged from 29 to 90 years. However,thepredominantpopulationwasin6thand7thdecadewithameanageof65years.Nosignificantdifferencewasnotedinthemeanageofthenon-neoplasticandneoplastic groups. The results of present study agree with the studies by Foroozanet.al [20],Barakzaiet.al [21],GeorgeHaffizMuhammadaslam et al. [22] the declinein the number of cases beyond the age of80 years reflectstheaveragelifespanofpeopleinourcountry.

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PSALEVELS

PSA is an enzyme in the form of 237 amino acid glycoprotein producedprimarily by cells lining the acini and ducts of the prostate gland. Its main biologicalfunctionis thedissolution ofthe gel forming proteins inthe freshly ejaculatedserum.Itispresentinsmallquantitiesinnormalmaleserumandisoftenelevatedinprostate cancer. However, it is nonspecific to prostate cancer as it elevated in other conditionssuchasbenignprostatichyperplasia,urinaryinfections,inflammationandtrauma.

Inthe presentstudy PSA levels werecategorizedinto<4, 4-10 &>10ng/ml. Out of 100 cases, 18 cases had total serum PSA levels < 4ng/ml, whereas 25and57caseshadtotalserumPSAlevels4-10ng/mlandgreaterthan10ng/mlrespectively.

Table12-ComparisonofSerumPSAlevelsofpresentstudywithotherstudies:

studies	No.ofcases	<4ng/ml	4-10ng/ml	>10ng/ml
Presentstudy	**100**	**18**	**25**	**57**
Foroozanetal [20]	90	05	47	38
Biswadeepetal [23]	100	35	37	28

GLEASONSCORE

Outof50casesofprostaticadenocarcinoma,10(20%)caseshadGleasonscoreof<6whereas22(44)and18(36)casesshowedGleasonscoreof7and8-10respectively.MajorityofcasesshowedGleasonscoreof7i.e44%.

Table13-ComparisonofGleasonscoreofpresentstudywithotherstudies:

	No.ofcases	≤6	7	8-10
Presentstudy	**50**	**10(20%)**	**22(44%)**	**18(36%)**
Foroozanetal [20]	45	9(20%)	18(40%)	18(40%)

EXPRESSIONOFCD34andCD117INBENIGNPROSTATICHYPERPLASIA

Our results revealed that, out of 50 cases of benign prostatic hyperplasia,36(72%) & 31(62%) cases showed low expression of CD34 & CD117 respectively.whereas, 14 (28%) &19(38%) cases showed high expression of CD34 and CD117respectively. Majorityofcasesshowedlow expression ofCD34 &cd117andwhichwas also found to be statistically significant (p <0.00001). The results of present studyweresimilartoresultsofForoozanet.al [20]

ThecorrelationbetweenimmunohistochemicalexpressionCD34&CD117wasdone.TheCD34/CD117phenotypesweredividedinto4groups,includinglowexpressionofbothmarkers(CD34Low/CD117Low),highexpressionofbothmarkers (CD34 High/CD117 High), CD34 Low/CD117 High and CD34 High/CD117Low.

The results in our study showed that 28 (56%)cases are CD34Low/CD117Low, 3 (6%) cases are with CD34High/CD117 Low phenotype . whereas, 8(16%) &11(22%) cases showed CD34 Low/CD117 High &CD34 High/CD117High phenotypesrespectively.

EXPRESSIONOFCD34andCD117INPROSTATICADENOCARCINOMA

Our results revealed that, out of 50 cases of prostatic adenocarcinoma,9(18%) & 22(44%) casesshowedlow expressionofCD34 & CD117 respectively.whereas,41(82%)&28(56%) cases showedhighexpression ofCD34 andCD117respectively. Majority of cases showed High expression of CD34 & cd117and whichwas also found to be statistically significant (p

<0.00001). The results of present studyweresimilartoresultsofForoozanet.al [20].
Thecorrelationbetweenimmunohistochemicalexpression CD34&CD117wasdone.TheCD34/CD117phenotypesweredividedinto4groups,includinglowexpressionofbothmarkers(CD34Low/CD117Low),highexpressionofbothmarkers (CD34 High/CD117 High), CD34 Low/CD117 High and CD34 High/CD117Low.
The results in our study showed that 06 (12%)cases are CD34Low/CD117Low,16(32%)casesarewithCD34High/CD117Lowphenotype.whereas,03(06%)&25(50%)casesshowedCD34Low/CD117High&CD34High/CD117Highphenotypesrespectively.

COMPARISON OFEXPRESSION CD34 & CD117 IN BPH AND PROSTATICADENOCARCINOMA

The results in our study revealed that 56% of BPH cases showed lowexpression of both CD34 &CD117 whereas, only 12% of prostatic adenocarcinomacasesshowedlowexpressionofbothCD34&CD117.While,50%ofprostaticadenocarcinoma cases showed high expression of both CD34 &CD117 whereas, only11% of BPH cases showed high expression of CD34 & CD117. Thus, in our study highexpression CD34 and CD 117 seen in prostatic adenocarcinoma compared to BPH.ThereisasignificantdifferenceinCD34expressionbetweenprostaticadenocarcinoma and BPH indicating prostatic cancer tissues are more vascularizedthan benign prostate tissues. The results in our study were similar to Foroozan et.alstudy [20].
In Foroozan et.al study 53% of BPH cases showed low expression of bothCD34&CD117whereas,only6%ofprostaticadenocarcinomacasesshowedlow expression of both CD34 &CD117. While, 47% of prostatic adenocarcinoma casesshowed high expression of both CD34 &CD117 whereas, only 11% of BPH casesshowedhighexpressionofCD34&CD117.

CORRELATIONBETWEENCD34ANDCD117EXPRESSIONANDAGEINPROSTATICADENOCARCINOMAANDBENIGNPROSTATICHYPERPLASIA

Inourstudymeanagewas65years.Outof100cases,55arebeloworequalto65yearsand45areabove65yearsofage.Outof55caseswhichare≤65 years,44and56%ofcasesshowedlowandhighexpressionofCD34respectively .whereas, 47 & 53% of cases showed low and high expression of CD117. Out of 45cases which are >65 years, 47 and 53% of cases showed low and high expression ofCD34 respectively .whereas ,60& 40% of cases showed low and high expression ofCD117.Therewas nostatistically significant correlation was observed between ageandCD34andCD117expression.
Markers used to distinguish Prostate cancer from benign tissues includeCD117 and CD34, CD113, CXCR4 [24]. Immunohistological staining of these markerscorrelatedwithaggressivetumorsandincreasedresistancetochemotherapyandradiotherapy [25].
Lutz Trojan et.al [26] studies showed expression of CD34, as most specific markerforendothelialcellsinmalignantprostatictissue,reflectedasimilar,significantcorrelationbetweenhistomorphologicalgradingandMVDasanindexforangiogenesis.Inaddition,theGleasonsumscoreshowedatrendtowardsanassociation with angiogenesis in prostate cancer. Thus, tumor dedifferentiation wouldseemtobeassociatedwithanincreasedpro-angiogenicactivity.
Bonoetal
[27]studiesonMVDinProstaticcarcinomausingCD34showedpositiverelationbetweenMVDand pathologicalstageandalsowithGleason'sscore.DelaTailleetal
[28]showeddirectassociationofMVDwithstageofProstate CarcinomausingCD34and31.
Microvessel density has been correlated with tumor aggressiveness, advancedstage, higher

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potential for metastasis and poor survival in malignant tumors, especiallyPCa [29].
Our results aresimilar to Foroozanet.alstudies showed that synergistic effectofCD34andCD117ontumorprogressionandaggressivebehaviorofprostatecancer.Thus,thesemarkersmaybepotentialmarkersinstudyingofprostatetumorigenesisandmetastasisaswellastargetedtherapy.
TheroleofCD34andCD117markersintumorigenesisandtargetedtherapycan be clearly studied with the help of western blotting data. Thus, the level of thesemarkerscanbe analyzedinprostatecancer cell lines, benign prostate tissues andPCasamplesusingwesternblottinginfuturestudies.

CONCLUSION

Ourfindingsshowedthatangiogenesiswassignificantlyhigherincarcinomathaninbph.Increased MVDwassignificantlyassociatedwithhigh-gradecarcinoma.CD34issuitablemarkerfortheimmunohistochemical visualization ofmicrovesselinbenignandmalignantprostatictissue.Itisausefulmarkerin differentiatingbenignfocifrommalignantfociinatypicalcases.
ExpressionofmarkersCD34andCD117hadasynergisticeffectonPCaprogression andaggressiveness. These molecules can be considered as potentialcandidatesfortargetedtherapyofPCa.
TheroleofCD34andCD117markersintumorigenesisandtargetedtherapycan be clearly studied with the help of western blotting data. Thus, the level ofthesemarkerscanbe analyzedinprostatecancer cell lines, benign prostate tissues andPCasamplesusingwesternblottinginfuturestudies.

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CONFLICT OF INTEREST

None

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