A Case Series Of Poorly Differentiated Carcinoma Endometrium IHC Confirmed Reported at AHRCC Cuttack, State Odisha, Country India

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Abstract- Endometrial carcinoma has a high morbidity in advanced countries of eastern Europe and usa and japan, here its morbidity has increased in recent years . therefore it has become increasingly important to understand the oncogenetic mechanism and prognostic factors of endometrial cancer. It has reported that the gradeof differentiation is one of the critical prognostic factors. Various studies reveal 5 yrs survival decreases ith lower differentiation grades.92% G1 well differentiated, and 86% and 74%respectively in G2 and G3.The poorly differentiated cancer have a higher rate of metastasis, recurrence and loer over all survival. Diagnosis of poorly differentiated cancer of endometrium may sometimes , be difficult and can be confused with other malignancies.here we report to cases of poorly differented carcinoma , confirmed by IHC

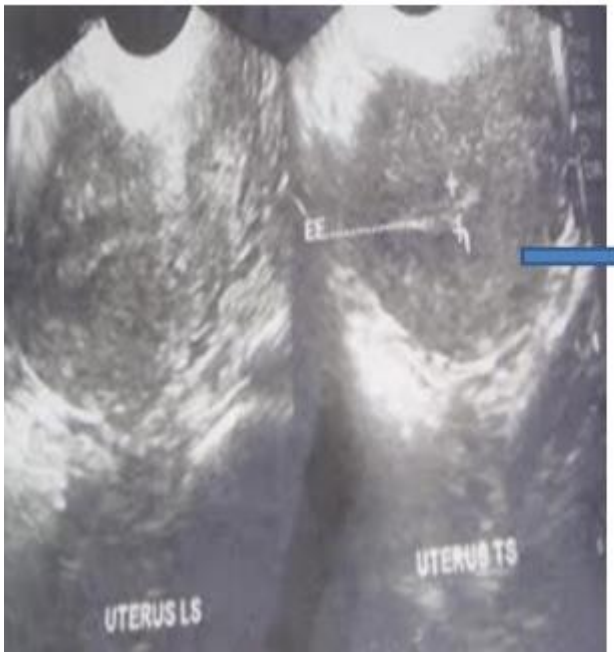
Index Terms- ET- ENDOMETRIAL THICKNESS, SOL- SPACE OCCUPYING LESION, BPLND- B/L PELVIC LYMPHADENECTOMY, BSO-B/LSALPINGOOPHERECTOMY, PDL-1 PROGRAMWDEATH LIGAND

I. INTRODUCTION

1st case-
History – 72 yrs female presented to opd with ,c/o – postmenopausal bleeding for 2 mths , no watery discharge , no pain abdomen.M/h- attained menopause 20 yrs back.O/H – p4l4/ all vd, lcb 32 yrs , Not sterilised .F/h – no family history of cancer .T/H- no history of any hormonal therapy
On/examination– average built , good nutritional status no scln, absensce of pedal oedema ,b/l- breasts normal on examination.P/A - soft ned .P/S- cx and vagina healthy.P/VP/R- Uterus bulky rv, b/l fornices free

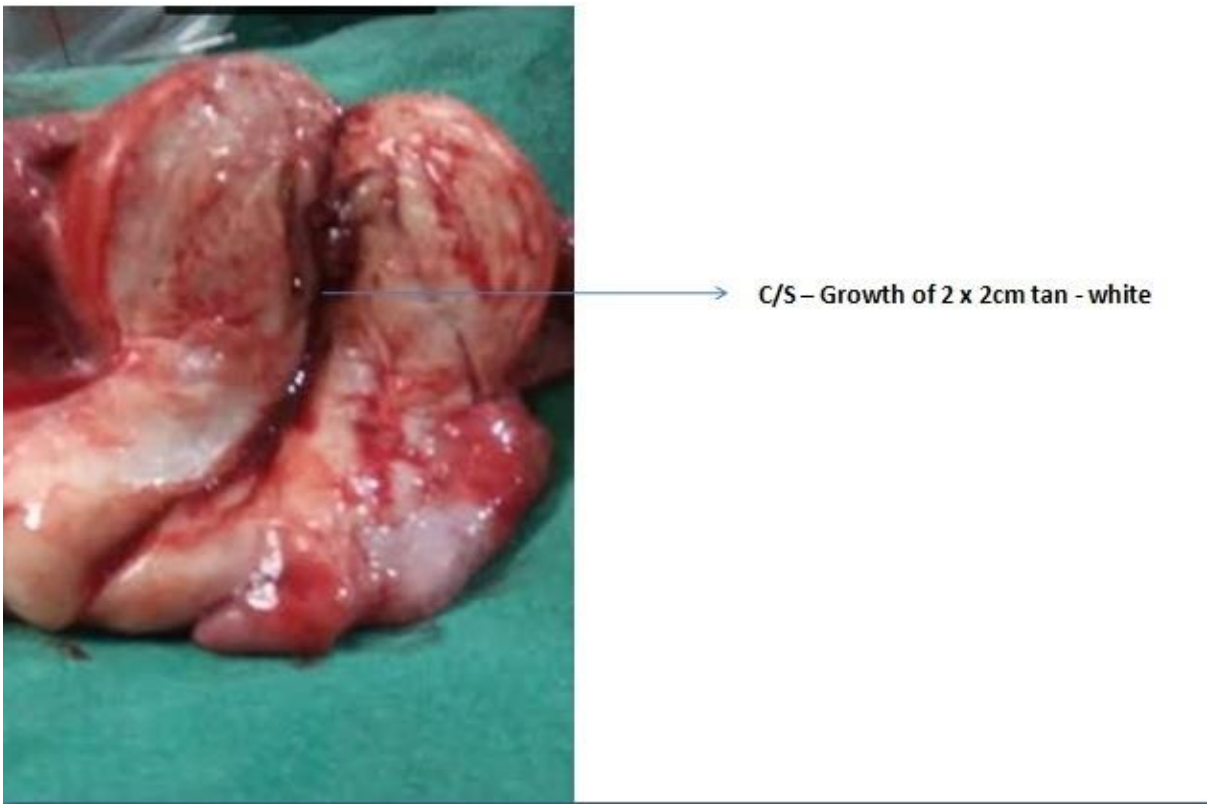
INVESTIGATIONS –

- **PAP SMEAR**- atypical squamous cell can"t exclude hsil
- **USG** - ET- 18mm, no sol



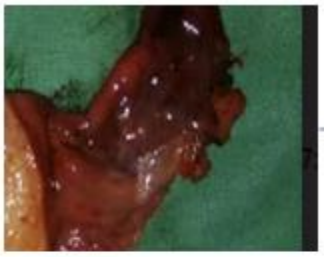
- **DIAGNOSTIC HYSTEROSCOPY ENDOMETRIAL BIOPSY**- growth(2x2) seen in posterior wall in the fundus
- **EB-** Endometrial stroma with fragmented glands with areas haemorrage
  Plan - hysterectomy
- **Procedure** – ndvh
  IOP – uterus bulky +b/l tubes and ovaries normal
- Cut section - 2x2 cm growth at fundus ,>% 50% myo-invasion, myometrium and endometrium could not be differentiated, endocervical cavity normal

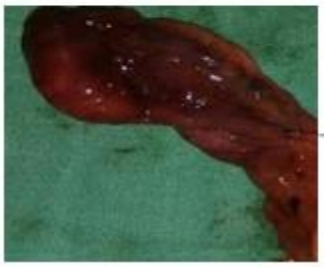
HPS



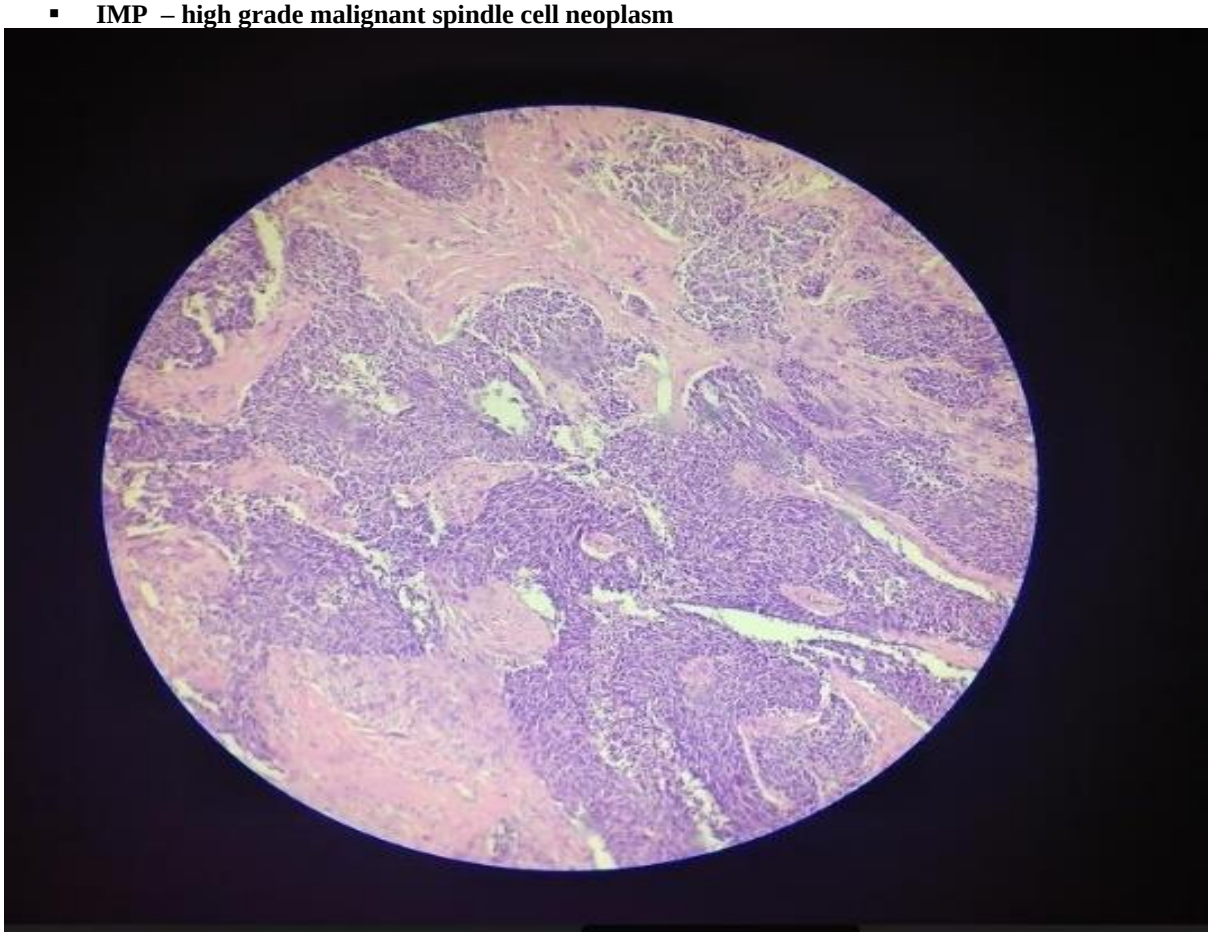
gross

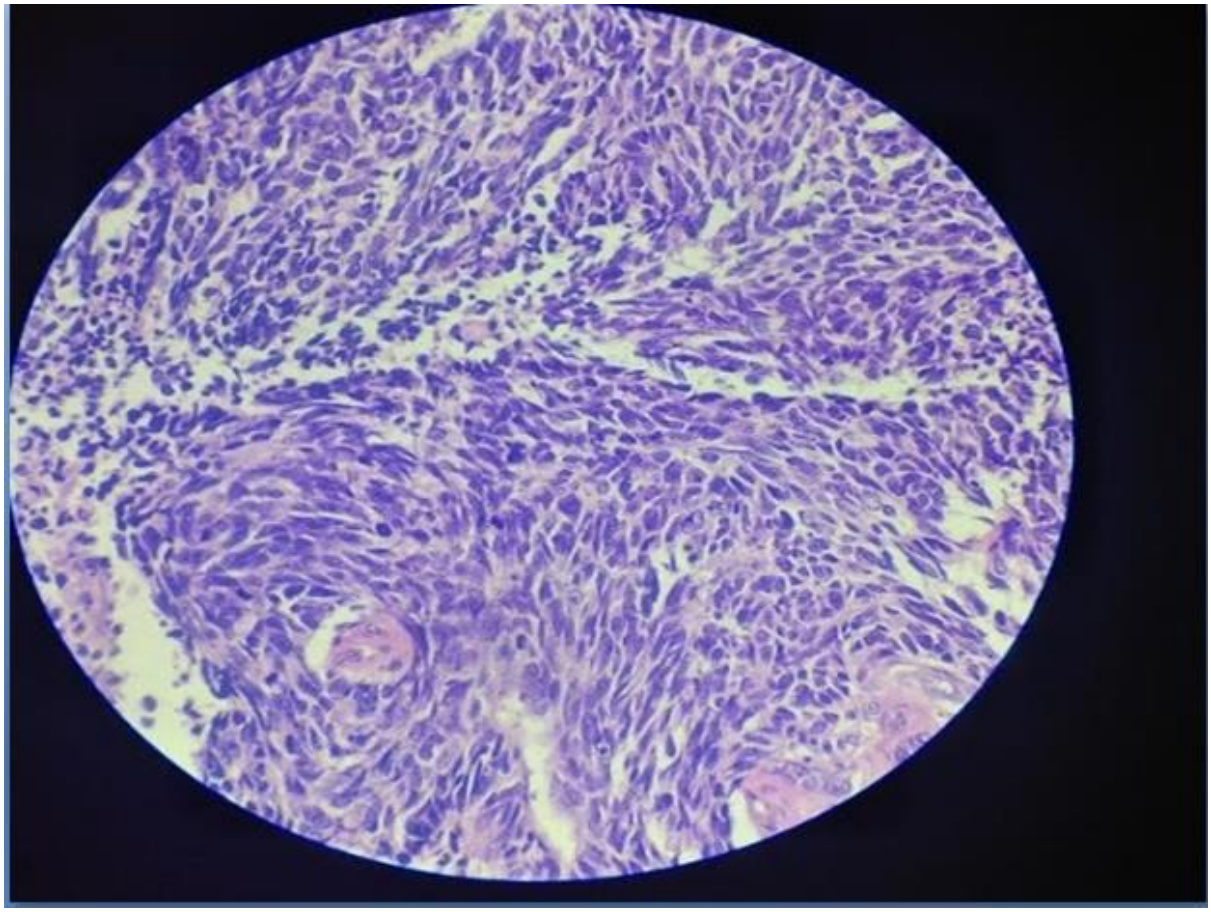
- cervix- chronic cervicitis and free of tumor
- b/l tubes and ovaries were free of tumor





- section from the growth - highly grade malignant tumor consists **of spindloid to oval pleomorphic** cells present in small fasicles , arranged in whroled pattern ,separated by fibrous tissue
- 40-45 / HPF mitotic figures . Both typical and atypical mitotic figures noted
- necrosis seen (<50%), > 50% myo-invasion, uterine serosa free of tumor
- **IMP – high grade malignant spindle cell neoplasm**





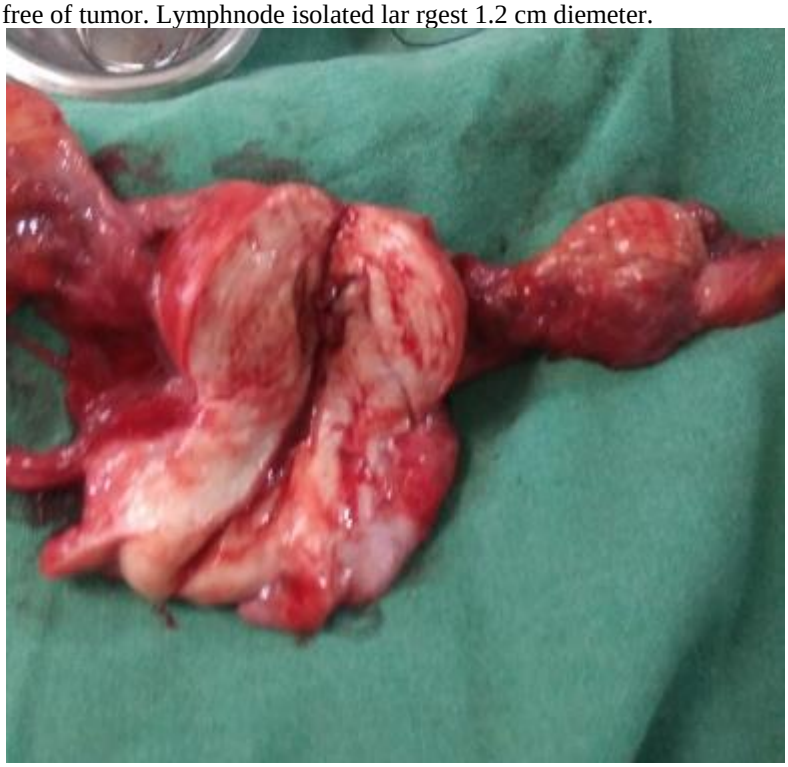
- **D/D – poorly differentiated carcinoma**
  leimyosarcoma
  undifferentiated sarcoma
  uterine stromal cell sarcoma
  carcinosarcoma
  IHC done
- SMA , CD10 , CK , S1OO
- SMA –**NON REACTIVE SCORE 0**
- CD-10 – IMMUNO REACTIVE 1+
- S100 - NONREACTIVE
- CK - **IMMUNO-REACTIVE3+**
- WT-1 – NON REACTIVE
- PAX-8- NON- REACTIVE
- **IMP- poorly differentiated carcinoma with spindle cell morphology, native endometrial tissue**

Post op usg – normal usg of adomen and pelvis
Planning CT and chest xray – normal
DIAGNOSIS – HIGH GRADE POORLY DIFFERENTIATED ENDOMETRIAL CARCINOMA OF SPINDLOID MORPHOLOGY STAGE IB (sarcomatoid variant of endometrial carcinoma)
Treat ment – planned for adjuvant RT(3drt) with CT
presently receiving EBRT

CASE -2
A 63 yrs female presented to opd c/o –pmb- 10 days
o/h p6lcb 40yrs, menopause 20yrs
G/E-NAD
P/D- NAD
P/S- cervix flushed with endocervicitis
P/V- ut rv, para free ,b/l fornices free

Investigations- **USG-** bulky uterus(8.6x4.8x6.1cm) with hyperplastic endometrium
ET- 30mm
Ovaries-not imaged,No adnexal; mass

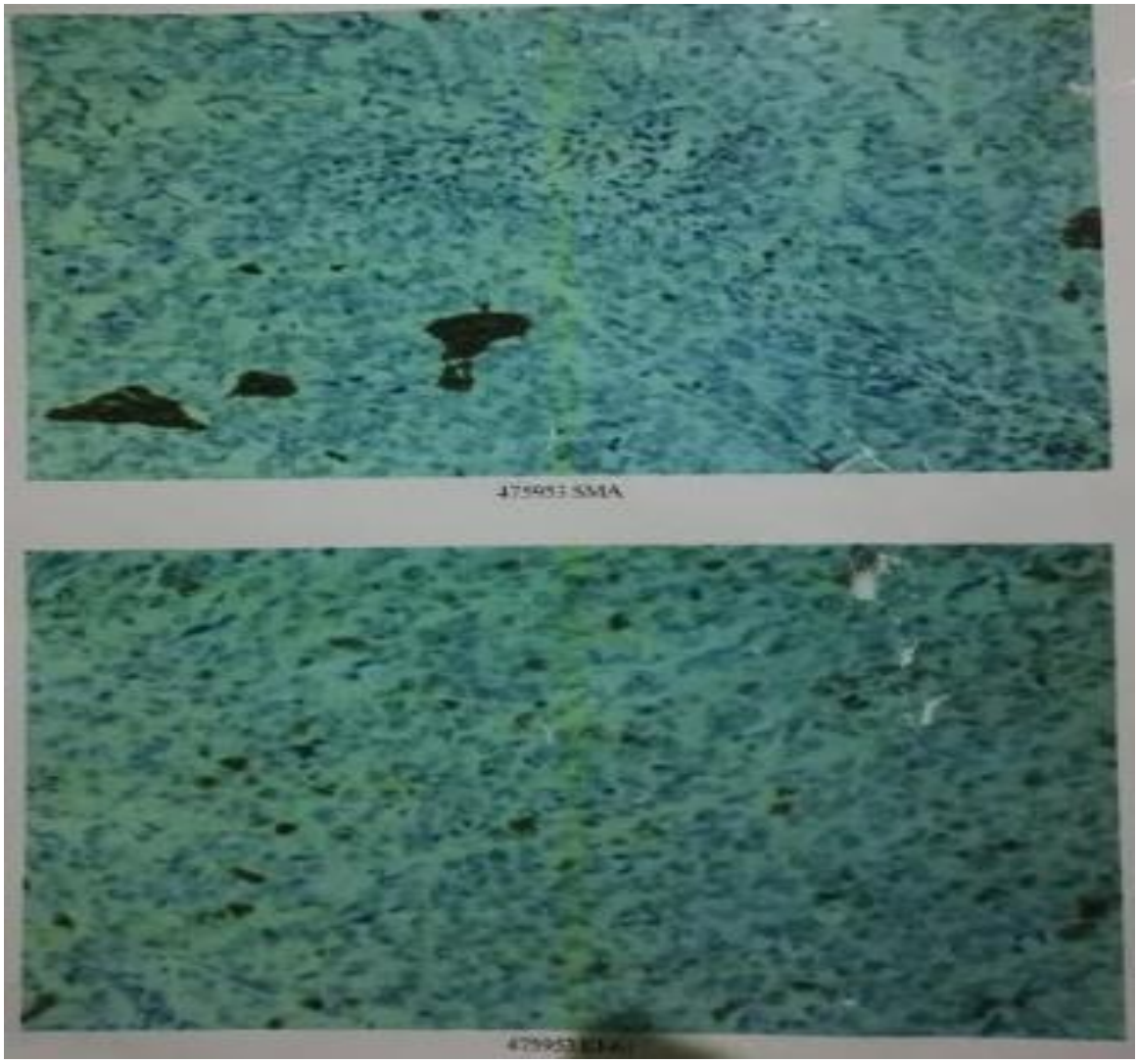
MR I – findings reveals a enhancing mass lesion in the anterior fundic region & involving anterior myometrium(>50%) with peri uterine fat plane and sparing b/l parametrium,sparing cervix, no enlarged lymphadenopathy, normal MRIevaluation of the upper abdomen, finding consistent with ca endometrium.
EB- invasive squamous cell carcinoma cevix,G2
PLAN – COMPREHENSIVE SURGICAL STAGING
IOP-no free fluid
Uterus 8 wks size, b/l adnexa normal
All lymph nodes enlarged
All abdominal organs normal
Omentum normal, mild adhesion
c/s- 5x6 cm mass in the fundus, with >50% myoinvasion ,endo cervix not involved
PROCEDURE – TYPE II RADICAL HYSTERECTOMY+BSO+BPLND
adhesiolysis
perItoneal washings taken
adequate parametrium, vaginal margin taken, hysterctomy done
HISTOPATHOLOGY – gross – cut open section uterus- growth present in fundus 3x2x1, no myometrial invasion, myometrial thickness free of tumor. Lymphnode isolated lar rgest 1.2 cm diemeter.

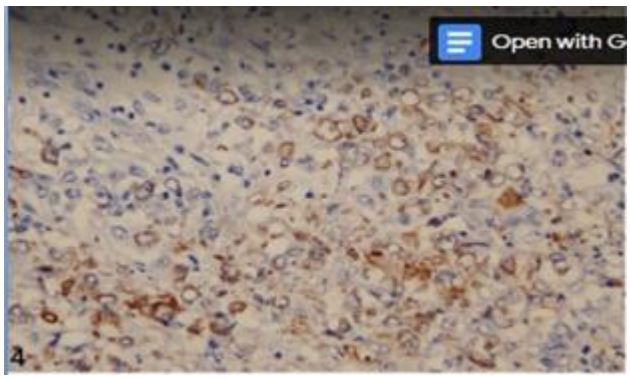


High grade, depth of inavasion. ,50%, lvsi-ve,b/l para and b/l adnexa free of tumor, cx- chronic cervicitis
Imp-features suggestive of undifferentiated high grade sarcoma
d/d- epitheliod leiomyosarcoma

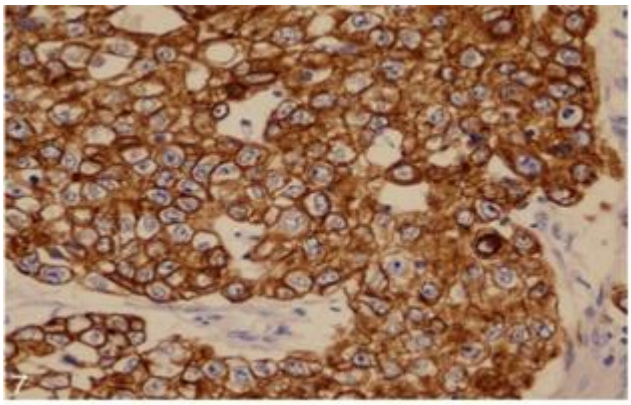
poorly differentiated carcinoma

Ihc - panel CK3+VE, EMA –VE,CD10—VE, SMA-VE
DESMIN-VE, Ki-67 -VE3+
CD-117- VE, INHIBIN- VE, CALRETININ-VE,SOX--VE

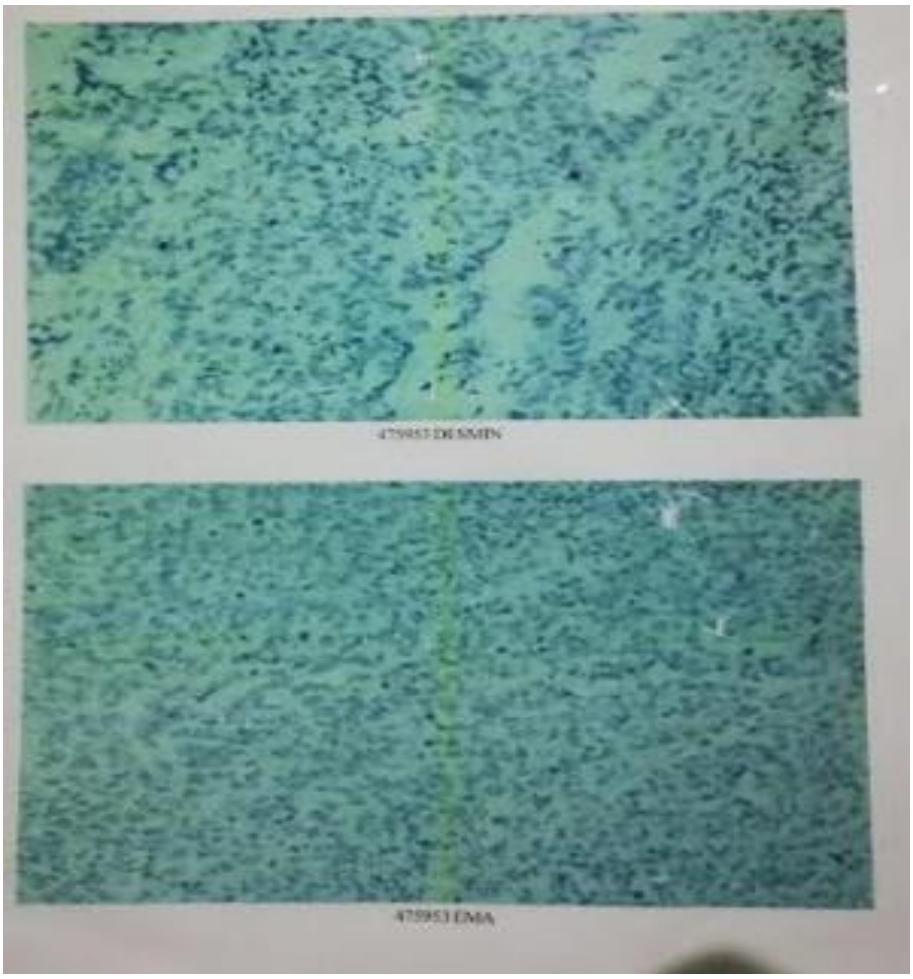




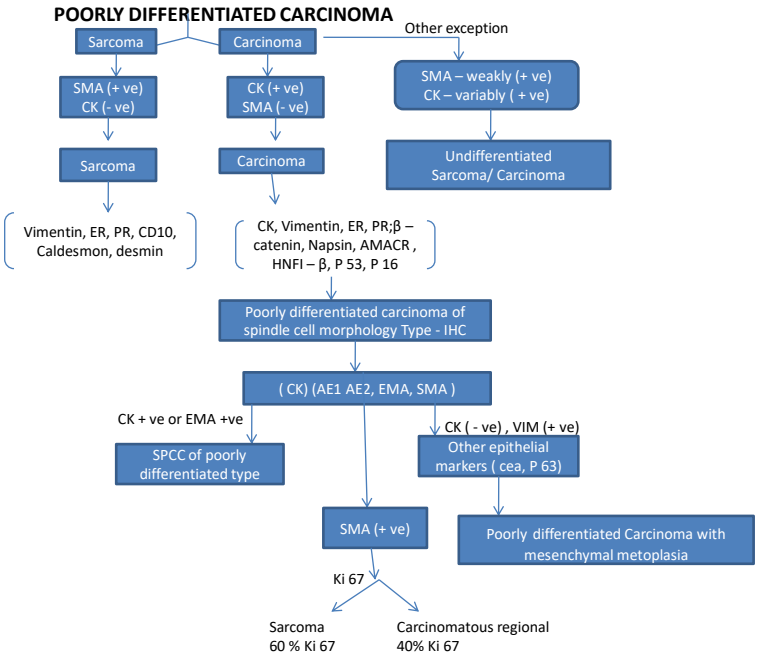
Focal and intense positivity of of cytokeratin in poorly differentiated carcinoma



Intense diffuse positivity of cytokeratin in a poorly differentiated carcinoma



- FLOW CHART TO DIAGNOSE **: UTERINE SPINDLE CELL MORPHOLOGY**



Immunohistochemical (IHC) markers in the differential diagnosis of endometrial carcinomas

	Vim	ER	PR	ARID1A	β – cat	AMACR	HNF 1β	Napsin A	P 53	P 16	Specific
	Endometrial tumours										
EMC	+	+	+	M>wt	M>wt	+/-	-	-	Wt>M	-/+	PTEN & MMR loss
USC	+	-	-	Wt	Wt	-	-/+	-	M	+	CCNE 1 amplification
CCC	+	-	-	Wt	Wt	-/+	+	+/-	Wt>M	-	MMM loss
UC	-	-	-	Wt	M>wt	NA	-	NA	M>wt	-/+	E – cadherun & MMR loss
MMMT	+	-/+	-/+	Wt>M	Wt	NA	-	NA	M	+	WT1, desmin, CD10, S100,myogenin,Myo – D1, h – caldesmon, Biphasic pattern

IHC in favour uterine carcinoma

- **CK- CK-(AE-1/AE-3,8,18)is frequently positive, CK- 18 more frequently positive(1)**
- **CAM5.2 (2)**
- **EMA**- usually focally positive, very rarely diffusely positive

special emphasis should be give **to intensity of staining of keratin AND EMA** than the percentage of staining(3)

- **ER/PR**- CONFLICTING DATA(1)
- **Vimentin –ve** or may be focally positive,
- Focally positive **CD-10.**
- **Focal positivity for S-100, CD- 56**

OTHER IHC MARKERS

- **Synaptophysin, chromogranin,CD56- usually –ve, may be focally positive(4,5)**
- **P-16-is diffusely / stronglypositive +/_ve**

- **P53 wt- weakly nuclear positivity seen**

SPECIFIC- loss of , E- CADHERIN(4,5)

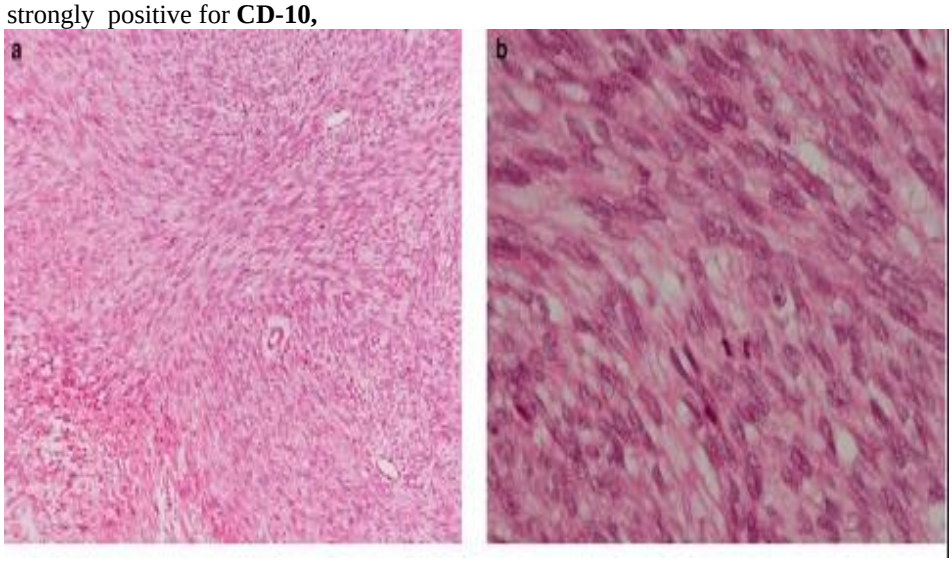
Poorly differentiated carcinoma - is completely negative SMA, desmin ,HMB-45

Differential diagnosis

1.UNDIFFERENTIATED STROMAL SARCOMA /PDEC(9)

CK- Negative , negative of epithelial markers

strongly positive for **CD-10,**



LEIOMYOSARCOMA /UEC(2)

- CD 10 - -VE
- **Sma-+ve**
- Desmin+ve
- Caldesmon +ve
- Negative - **Cytokeratin** except the epetheloid leimyosarcoma may be focally postive
- **RHABDOMYOSARCOMA / UEC (SPINDLE CELL MORHOLOGY)(10)**
- Uniform spindle cell with a **herring bone pattern**
- Negative or else focal reactive FOR CK
- **SMA -+VE**
- **DESMIN+VE, MYOGLOBIN+, CALDESMON**
- **+ve in spcc**BAF-47(INI-1) this protein is lost in rhabdoid tumor,

Carcinosarcoma / PDEC(SPINDLE CELL MORPHOLOGY)(8)

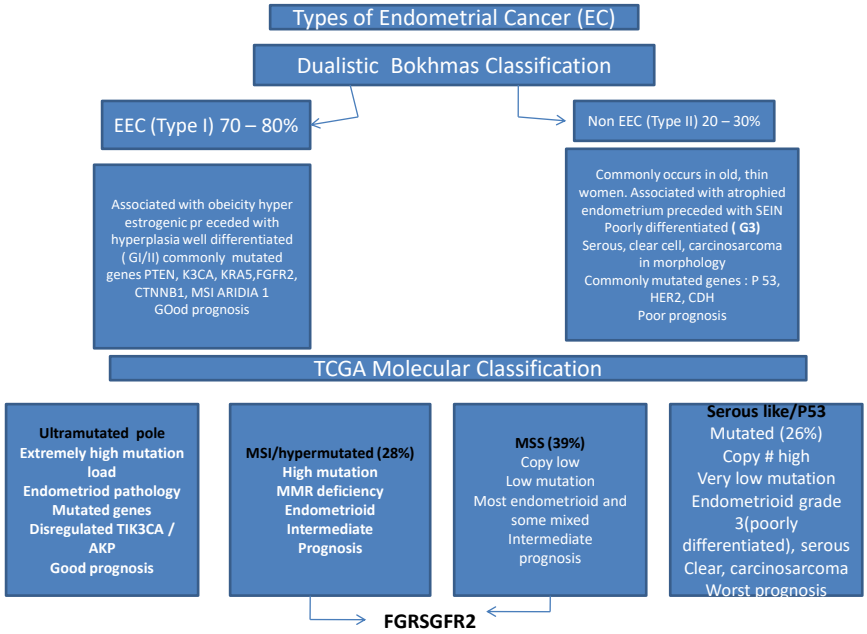
there is disinct compartmentalisation of the carcinoma and sarcomatous component.There are presence of heterologous elements ihc +VE WT-1/P53 is helpful indifferentiating from spindle carcinoma.Morphological features is enough for diagnosis

uec/ grade 3 endometrial (7)

Morphology	**UEC**	**ENDOMETROID**
Growth	Diffuse	solid and glandular
Glands	absent	present in 1-4% of tumor area
Cords trabeculae	vague	
C**omponent**	sharp demacation	intermingled demarcation
Cohesive growth	**dyshesive** squamoid	**cohesive**
Rhabdoid	may present	absent
Myxoid	may be present	absent
IHC – **PANCYTOKERATIN**	patchy /focal	diffuse(b)
EMA	patchy/focal	diffuse(b)
ER/PR	focal	diffuse(b)

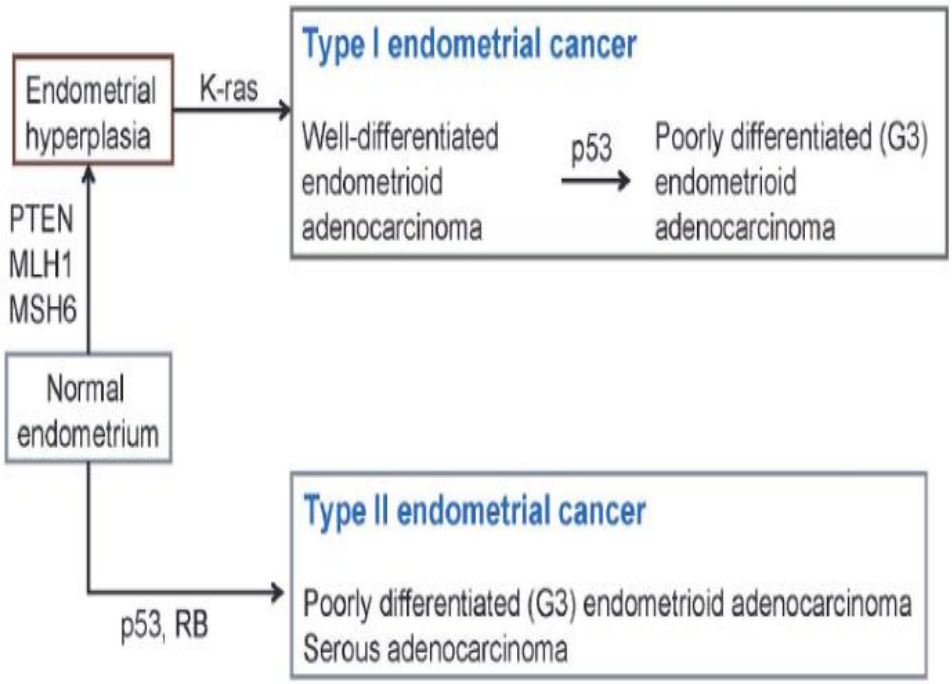
Review literature –

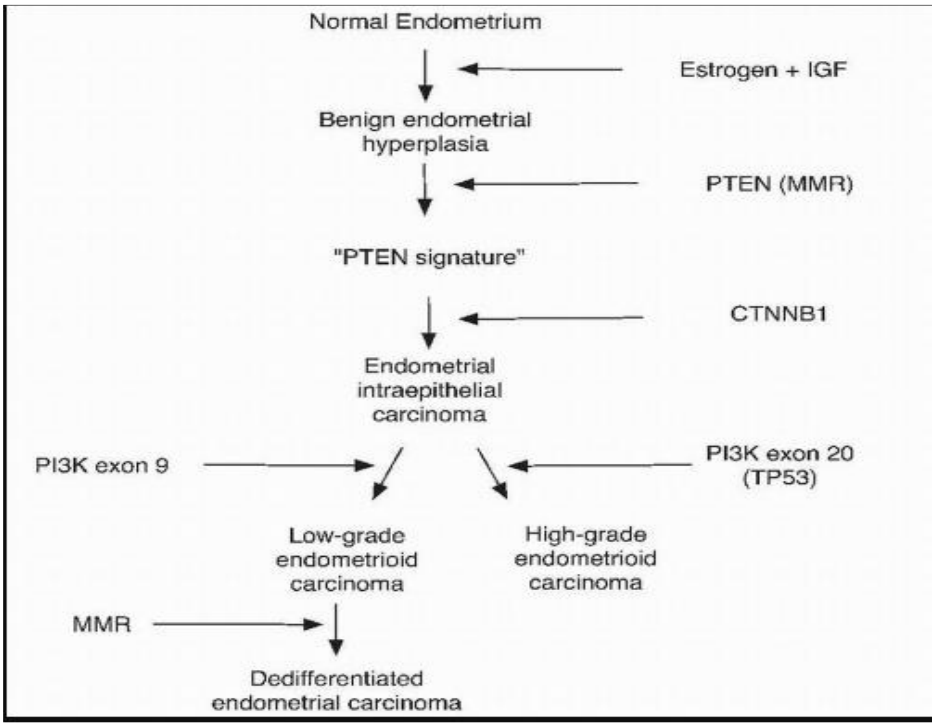
- Poorly differentiated carcinoma is a type II endometrial cancer, about 20% of endometrial cancer(1)



- This group is also associated with hereditary non-polyposis colorectal carcinoma(lynch syndrome).Significant number of patients display loss of 1 more DNA mismatch repair.

Pathogenesis





About half present in higher stage(III AND IV)(2)
GROSS PATHOLOGY- may present as polypoidal fleshy masses with evident of necrosis
Usually involves the lower uterine segment
MICROSCOPICALLY- solid pattern less growth of medium size relatively monomorphic round or polygonal epithelial cells that lack glandular differentiation. Sometimes pleomorphism detected(5)
Very occasionally- spindle cell pattern, alveolar pattern is found in uc(3,4,5)

PROGNOSIS

- **Prognosis is poor irrespective of age, stage, presence an number of tumor infiltrating lymphocytes, any rhabdoid or spindloid morphology**
- **Prognosis depends in MMR mutation,up AND DOWNREGULATION OF MI –RNAS due abberant methylation thus making it sensitive to taxanes.(6)**
- **P53 mutant type i.e mss high copy nos, worse pognosis**
- **variability in expression or of cell adhesive glycoprotein loss e- cadherin can determine the prognosis**
- **Other HER-2, ECAM poor prognosis**
- **ploidy status of these tumors usually aneuploid**
- **High grade g3 has high chances of recurrences in comparison to grade1 and 2.**
- **However there are instances where grade3 endometrial cancers do show a good prognosis**
- **The fact is validated by a japanese study taking 12 prognostic factor of grade 3 carcinoma into consideration . Among them absence of adnexal metastasis, no cervical involvement, low pre-surgery CA602 and a low CA-19.9 carried a favourable prognosis .(7)**

MANAGEMENT –
Currently there is no difference in management of grade3 endometroid, undifferentiated and dedifferentiated endometrial carcinoma all are HIGH RISK CATEGORY (8)

- **TAH +BSO and chemotherapy and radiotherapy**

OR

- **surgical staging(TAH+BSO+ PARTIAL OMENTECTOMY+PERITONEAL WASHINGS+ B/LPLND+B/LPAND FOLLOWED BY EBRT +CT)**
- **PORTEC-3 TRIAL on HIGH RISK PATIENTS IN STAGE I-II OR STAGE III , revealed higher failure free survival and decrease in pelvic recurrences a of chemoradiotherapy(two concurrent cycles of cisplatin in weeks 1 and 4 of ebrt , followed by four cycles of carboplatin and paclitaxel) than EBRT alone**

- **GOG 258 AND GOG 249 greater evidence support EBRT+ CHEMOTHERAPY**
- **E-cadherin is an independent predictor of survival of endometrial cancer, regardless of histology.(9,11)**
- **Loss ofE- cadherin ,is of poor prognosis , advance stage, poor differentiation.**
- **E- caderin has a central role in organisation of epithelial structure(cohesiveness) it also regulates apoptosis.**
- **Presence of e- cadherin almost precludes invasiveness .**
- **It is also related tumor budding(11)**

Miyamato etal studied and compared the expression of E- CADHERIN and cytoplasmic E-cadherin related molecules (alpha-catenin, beta catenin , gamma catenin, in well differentiated and poorly differentiated carcinoma .(11)

- **They reported significant difference in expression between the above two histological types.**
- **The recently used drug DASATINIB Increase the expression of e-cadherin , by repressing slug-mrna**
- **The literatures reveals the presence of E-cadherin**

Increases the sensitivity to EGFR inhibitors (10)

Immunotherapy in poorly differentiated endometrial cancer

- Recent clinical phase II Trials on Nivolumab and **Iplimumab in undifferentiated endometrial cancer**
- **The addition of pembrolizumab with paclitaxel and carboplatin is undifferentiated carcinoma in phase IIItrial**

Immune checkmpoint inhibitors (ANTIPD-1/PD-1 antibody,ANTI CTL-4antibody) could be effective in treatment of poorly differentiated endometrial carcinoma and the presence of MSI may be a bio-marker for good response to PD-L1 immunotherapy

FOLLOW UP –

- **these patients should be on close follow up**
- **3 monthly for first- 3 months with usg , ct vault examination and cytology**
- **6 monthly for next 3 yrys**
- **thereafter once a year**

CONCLUSION – After corelating the hps and ihc we coulfd reach the final diagnosis of poorly differentiated carcinoma of endometrium , accordingly planned her treatment

PURPOSE – The case series will throw some light in area of diagnosis and management of poorly differentiated carcinoma endometrium, keeping in view of its variety of hps morphology a broad differential diagnosis. To help in diagnosis of a poorly differentiated carcinoma , particularly the sarcomatoid or the spindloid morphology can be sometimes be confuse with sarcoma i.e undifferentiated sarcoma or a leimyosarcomaor a rhabdomyosarcoma.Due to the confusing histopathology picture, IHC staining and interpretation may be required , to reach the final diagnosis.

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