DOI: 10.14260/jemds/2014/2882

ORIGINAL ARTICLE

POSTMENOPAUSAL BLEEDING: HISTOPATHOLOGICAL SPECTRUM AND ASSOCIATION WITH AGE AND CLEAR SPAN: CASE SERIES OF 328 CASES

Ruchita Tyagi[1], Roma Isaacs[2], Tapasya Dhar[3]

HOW TO CITE THIS ARTICLE:
Ruchita Tyagi, Roma Isaacs, Tapasya Dhar. "Postmenopausal Bleeding: Histopathological Spectrum and Association with Age and Clear Span: Case Series of 328 Cases". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 26, June 30; Page: 7210-7221, DOI: 10.14260/jemds/2014/2882

ABSTRACT: Introduction: Postmenopausal bleeding is defined as vaginal bleeding occurring after twelve months of amenorrhea in a woman of the age where the menopause can be expected. With increase in life expectancy, a larger proportion of female population will be in postmenopausal age group; hence, the incidence of postmenopausal bleeding is expected to increase. **AIM:** We studied the prevalence of malignancy as well as the histopathological spectrum of genital tract lesions in cases of postmenopausal bleeding. The association between age, period between cessation of menses and onset of bleeding per vaginum (clear span) was also studied. **RESULTS**: Malignant causes were more common (58.5%) than benign causes and included cervical carcinoma, malignant uterine tumors (13.1%), carcinoma vagina (4.3%), malignant ovarian tumors (5.5%), carcinoma vulva (0.9%) and carcinoma fallopian tube (0.3%). Squamous cell carcinoma was the commonest among cervical malignancies. The benign causes included polyps (16.5%), endometrial hyperplasia (4.9%), adenomyosis (2.7%), atrophic endometrium (2.4%), cervicitis (2.1%), leiomyoma (1.8%), proliferative endometrium (1.5%), endometritis (1.5%), secretory endometrium (1.2%), retained IUCD (0.9%) and uterovaginal prolapse (0.6%). The likelihood of malignancy increased significantly with advancing age (p-value 0.042). The clear span of cases with malignant tumors was significantly longer than the clear span of cases with benign lesions. Hence, the likelihood of malignancy increased with length of clear span (p-value 0.00809). **CONCLUSION:** Any postmenopausal patient with vaginal bleeding needs to be investigated thoroughly to determine the cause of the bleeding and should be considered to have abnormal histopathology until proved otherwise.

KEYWORDS: Bleeding, clear span, genital tract, histopathology, menopause, postmenopausal.

INTRODUCTION: Menopause is defined as spontaneous and permanent cessation of menses for more than one year.[1] Throughout the world, the most common age group for attaining menopause is 45-55 years and the average age is 51 years.[2] Postmenopausal bleeding is defined as vaginal bleeding occurring after one year of amenorrhea in a woman of the age where the menopause can be expected.[3] It is a common problem accounting for 5% of cases in gynecological practice.[4] Cancer is the most important cause of this abnormal bleeding.[5-17]

The dictum remains that this alarming symptom indicates malignancy until proved otherwise.[11] Malignant tumors account for 7-49 % of causes of postmenopausal bleeding, depending on genetic, racial, ethnic differences in incidence of malignancy in diverse populations as well as to differences in criterion adopted by different studies. (Table 1) The likelihood of malignancy increases with increase in age of onset of postmenopausal bleeding.

A number of benign pelvic causes like infection (vaginitis, cervicitis, endometritis and salpingitis), traumatic lesions in vagina, foreign bodies, cervical erosions, cervical and endometrial

DOI: 10.14260/jemds/2014/2882

polyps, leiomyomas, endometriosis, and adenomyosis may also cause bleeding in postmenopausal women.

The period between cessation of regular menses and onset of postmenopausal bleeding is called clear span. Clear span has been found to be longer in malignant cases.[11-15]

Most of the studies on postmenopausal bleeding were based on findings in endometrial biopsies. In view of paucity of studies describing the histopathological spectrum of lesions in entire genital tract, this study was undertaken to examine the lesions in genital tract in cases of postmenopausal bleeding. The association of factors like age of onset of postmenopausal bleeding and clear span with malignancy was also studied.

MATERIAL AND METHODS: The study was conducted in a tertiary care centre over a period of five years (September 2004 to August 2009). All menopausal patients presenting with bleeding after one year of amenorrhea were included as having postmenopausal bleeding. None of these women were on any hormonal treatment. No hormonal parameters were used to characterize the women as postmenopausal. The clinical details of the patients were noted from the requisition forms and case files in the medical records department. The specimens were fixed in 10% formalin, gross features noted, and relevant sections taken and routinely processed in histokinette and embedded in paraffin wax. The slides were routinely stained with Haematoxylin and Eosin (H&E). The results were compiled and analyzed using proportion and chi square tests and compared with other studies.

RESULTS: The study comprised of 328 cases of postmenopausal bleeding, which constituted 5% of all gynecological biopsies received during the study period. The age of the patients ranged from 40-85 years (mean 57.62±8.5). More than half (55.2%) of cases had postmenopausal bleeding before the age of sixty years and this was statistically significant (p-value 0.0097). The age of onset of menopause ranged from 36 to 62 years (mean 47.46 ± 4.6). 54.3% of cases had attained menopause in the fifth decade and a majority (83.8%) of patients had attained menopause before the age of 52 years which was statistically significant (p-value<0.00035). Clear span varied from one year to 35 years (mean 10.18±7.6). A statistically significant portion of the study population (65.2%) experienced postmenopausal bleeding within ten years of menopause (p-value<0.00077).

Postmenopausal bleeding was due to malignant lesions in 192 (58.5%) cases; 136 cases (41.5%) had benign lesions. With increasing age, the incidence of postmenopausal bleeding decreased significantly (p-value<0.0097). Distribution of malignant cases according to age showed that the likelihood of malignancy increased significantly with advancing age (p-value<0.0042) (Graph 1). The patients who had postmenopausal bleeding due to malignant lesions were significantly older than patients with benign lesions (p-value<0.0099). The clear span of cases with malignant tumors (mean 11.31±7.8 years) was also significantly longer than the clear span of cases with benign lesions (mean 8.61 ± 7.1 years). Hence, the likelihood of malignancy increased with length of clear span (p-value<0.0081). The incidence of cervical, uterine and ovarian malignant tumors increased significantly after the age of 55 years (p-values<0.0063, 0.0057 and 0.049 respectively).

In our study, only gynecological specimens were received, majority being hysterectomy specimens. (Table 2) None of the patients were uncertain of the origin of the bleeding and no case of hematuria or bleeding from rectum was confused with vaginal bleeding. The problem of inadequate biopsies with only fibro muscular tissue was encountered more often (88.2%) in older patients above

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fifty years of age The spectrum of genital tract lesions in our cases of postmenopausal bleeding and their frequency of occurrence is depicted in Tables 3, 4. Postmenopausal bleeding was due to uterine causes in 86.3% and non-uterine causes in 13.7% of patients.

Most (81.3%) of the malignant tumors comprised of cervical or uterine malignancy. The ratio of malignant tumors in cervix to those in uterus was 2.6:1. One case of squamous cell carcinoma of cervix also had granulomatous salpingo-oophoritis.

In three cases of endometrioid adenocarcinoma of the uterus, the tumor had invaded more than half of the myometrium (FIGO stage I B). Most cases of endometrioid adenocarcinoma belonged to FIGO stage I, two belonged to FIGO II and four cases had tumor deposits in bilateral adnexae (FIGO stage III A). The two cases of squamous cell carcinoma of the uterus showed invasion upto less than half of the myometrium (FIGO stage I A).

There was no co-existent adenocarcinoma of endometrium; the cervix was free of tumor with no evidence of squamous cell carcinoma, cervix. The two cases of uterine adenosquamous carcinoma had infiltrated more than half of the myometrium (FIGO stage I B). One case of MMMT presented with simultaneous occurrence of uterine and ovarian malignancy, making it FIGO stage III.

Postmenopausal bleeding was seen in patients with surgically induced menopause due to prior hysterectomy due to recurrence of previous carcinoma in the vaginal vault.

Out of the ovarian tumors, malignant tumors formed 75% and benign ovarian tumors formed 25% cases. The benign tumors of ovaries comprised of three cases of mucinous cystadenoma, one case of serous cystadenoma and two cases of thecoma. One case of Granulosa cell tumor had endometrial hyperplasia due to estrogenic stimulus provided by the tumor. The associated hysterectomy specimens in other cases had chronic cervicitis, proliferative to atrophic endometrium and intramural leiomyoma. Two cases of serous papillary cystadenocarcinoma had tumor deposits on serosa of the uterus while the two cases of mucinous cystadenocarcinoma had tumor deposits on ipsilateral fallopian tubes (FIGO II A).

The percentages of benign lesions added up to more than 100% as these lesions overlapped i.e. one specimen had more than one lesion. Three hysterectomy specimens had both endocervical polyp as well as endometrial polyp and two cases with endometrial hyperplasia also had endometrial polyp. Hence, percentages of lesions are calculated out of total cases for comparative analysis. Out of three cases with retained IUCD causing postmenopausal bleeding, one case had partial perforation of the uterus with Lippe's loop in situ; chronic cervicitis and atrophic endometrium.

The other case had acute and chronic necrotizing inflammatory granulation tissue in the endometrium. The third patient had pyometra due to impacted Lippe's loop. The two patients of uterovaginal prolapse were found to have chronic cervicitis and atrophic endometrium. One patient with endometrial polyp also had bilateral granulomatous salpingitis and miliary tuberculosis in the omentum.

DISCUSSION: With increase in life expectancy, women spend one third of their life as postmenopausal. [12] As women over fifty years of age are forming an increasingly large part of our population, postmenopausal bleeding has become a frequent cause of gynecological visits. [3] In our study, postmenopausal bleeding accounted for 5% of gynecological specimens. Women with amenorrhea for at least a year were taken as postmenopausal, similar to criterion in some studies.[17, 18] The patients with amenorrhea of less than a year generally experience irregular bleeding

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due to breakthrough or withdrawal bleeding. The choice of one year was preferable to two years after the last menstruation because of the high frequency of cancer in such patients and the urgency of making a prompt diagnosis.

The age of the cases was comparable with other studies. (Table 5) In the present study, majority of the cases presented with postmenopausal bleeding before the age of 60 years and only thirteen percent of cases were older than 70 years, similar to findings by other authors.[12,19] As the age of onset of postmenopausal bleeding increased, the likelihood of malignancy also increased. This phenomenon has also been observed by others.[11-13, 17-19] Hence, increasing age is a significant risk factor for development of carcinoma in patients of postmenopausal bleeding.

Clear span, the period between cessation of periods and occurrence of postmenopausal bleeding, ranged from one to 38 years. Lee et al (1995) have reported this interval from one to 44 years.[12] The patients with malignancies had a significantly longer clear span than cases with benign cause of postmenopausal bleeding. Similar results have also been observed in various studies. [12, 13, 15] None of the cases had postmenopausal bleeding due to non-gynecological causes, unlike a study where hematuria due to cystitis was mistaken as vaginal bleeding.[12]

Any postmenopausal patient with vaginal bleeding should be considered to have abnormal histopathology.[3] The dictum is "Postmenopausal bleeding is due to malignant causes unless proved otherwise''.[11] Thus there is an urgency to investigate each and every case of postmenopausal bleeding. Comparison between incidences of malignancy as a cause of postmenopausal bleeding ranged from 7-49% in various studies. (Table 1) This variation in results can be attributed to genetic, racial, ethnic differences in incidence of malignancy in diverse populations as well as to differences in criterion adopted by different studies.

The incidence of cervical malignancies being more than twice the incidence of uterine malignancies, was a significant finding, unlike Lee et al (1995) who found only marginal increase in incidence of cervical cancers as compared to uterine malignancies.[12] (Table 6) The low incidence of cervical cancer in Western studies could be due to effective methods for screening and diagnosis of cervical carcinoma and its precursor lesions that has reduced the incidence of cervical carcinoma as a cause of postmenopausal bleeding in developed countries. On the other hand, in countries where effective cervical screening programme is not in place, especially in a developing country, cervical carcinoma still accounts for a majority of cases with postmenopausal bleeding.

Although routine Papanicolaou smears are easily available and widely encouraged, our system depends on opportunistic screening of women who seek medical care and misses out on many women, especially the elderly and those in high risk groups, who may not be aware of serious implication of postmenopausal bleeding and significance of routine Papanicolaou smears. Hence, there is need to intensify cytology screening programmes and to increase the awareness in general population about the value of periodic gynecological examination and adoption of healthy, hygienic practices.[12-14]

Majority of our cases experienced bleeding due to uterine causes, similar to findings of other workers. (Table 7) Though non-uterine causes formed a small proportion of cases, nonetheless they must also be kept in mind while investigating the underlying cause for postmenopausal bleeding. The spectrum of lesions in postmenopausal bleeding in different studies is depicted in Table 8.

Ovulation can occur sporadically after menopause. An inadequate corpus luteum thus formed may lead to formation of an imperfect secretory endometrium, which may result in abnormal postmenopausal bleeding. According to Novak, thin and atrophic epithelial lining of endometrium is

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susceptible to infections, resulting in endometritis and consequent bleeding.[20] There were three cases with bleeding due to retained IUCD causing either trauma or pyometra. Pyometra, caused by intrauterine retention of infective material either due to cervical stenosis and fibrosis or because of obstruction by a tumor in cervix may result in abnormal bleeding.[12] Uterine perforation by a retained IUCD can also cause postmenopausal bleeding.[21]

Bleeding in endometrial polyps may be due to injury to thin walled veins present just below the surface epithelium or thrombosis of vessels. The mechanism by which leiomyoma may cause postmenopausal bleeding include increased pelvic congestion or atrophy and thinning of the overlying endometrium and myometrium predisposing to ulceration and bleeding.[22,23] Some myomas become submucosal during involution of uterus after menopause and begin to bleed.[20]

The relatively low incidence of endometrial hyperplasia as a cause of postmenopausal bleeding was due to strict selection of postmenopausal women with a clear span of one year or more; hence we did not include perimenopausal patients who reported bleeding within one year of amenorrhea and are likely to have dysfunctional uterine bleeding due to adenomatous endometrial hyperplasia; none of our patients were on hormone replacement therapy, and also due to the fact that we received more hysterectomies than endometrial curetting.[24,25]

Thus chances of reporting endometrial adenocarcinoma as complex atypical hyperplasia were less in our study. Endometrial hyperplasia in postmenopausal patients may develop in response to excessive estrogen, the possible sources of which are obesity, functioning granulosa-theca cell tumors, thecomas, iatrogenic estrogen administration, or estrogen production by adrenal glands or the residual ovarian stroma.[16, 26] In our study, there was one case each of endometrial hyperplasia resulting from excessive estrogen production by Granulosa cell tumor and thecoma of the ovary.

The malignant uterine tumors were the second most common malignant cause of postmenopausal bleeding after cervical carcinoma. This percentage was higher than those found in other studies as the number of hysterectomy specimens in our study was more than the number of endometrial biopsies. Blind curettage may result in incomplete sampling of the uterine cavity and cases of hyperplasia and cancer may be missed.[27]

Serous cystadenocarcinomas and Granulosa cell tumors of the ovary have also been associated with postmenopausal bleeding.[12,28,29] In our study, abnormal bleeding was found to be due to Atypical proliferative mucinous tumor in two cases and endometrioid ovarian carcinoma in one patient, as also reported by Gredmark et al (1995).[16]

CONCLUSION: With increase in life expectancy, patients with postmenopausal bleeding comprise a frequent cause of gynecological visits. The present study displayed a wide spectrum of both neoplastic and non-neoplastic conditions of female genital tract in such patients with malignant causes being more common. With advancing age, the incidence of postmenopausal bleeding decreased but the likelihood of malignancies increased significantly. The likelihood of malignancy increased with increase in clear span.

Among the malignant tumours, cervical carcinoma was the commonest followed by malignant uterine tumours. Squamous cell carcinoma was the commonest malignant cervical tumour causing postmenopausal bleeding. Thus, there is need for intensive comprehensive cervical cytology screening programmes and more awareness among the general population especially the elderly women who may not be aware of the importance of routine Papanicolaou screening.

The uterine causes of postmenopausal bleeding showed endometrioid adenocarcinoma as the most frequent cause followed by endometrial polyp and hyperplasia. Since methods of screening for asymptomatic endometrial carcinoma are not as effective as that for cervical carcinoma and postmenopausal bleeding is often the first indication of its occurrence, the importance of a thorough evaluation should be realised.

Though lesions in uterus and cervix accounted for 86.3% of cases of postmenopausal bleeding, non-uterine causes viz. tumours of ovary, fallopian tube and vulva must also be kept in mind while investigating the underlying cause for postmenopausal bleeding.

Postmenopausal bleeding indicates malignancy until proved otherwise and justifies a thorough evaluation of patients along with histopathological confirmation.

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Study	Malignant Causes (%)
Choo et al (1985)	7
Lidor et al (1986)	7
Gredmark et al (1995)	15.00
Lee et al (1995)	25.8
Asim and Akhtar (2004)	22.5
Naik et al (2005)	49.1
Cheema et al (2008)	30.0
Present study (2010)	58.5

Table 1: Incidence of malignant tumors as a cause of postmenopausal bleeding in various studies

DOI: 10.14260/jemds/2014/2882

Specimen	No. of cases	Percentage (%)
Biopsy vagina	16	4.88
Biopsy vulva	03	0.92
Vulva + endometrium	01	0.30
Biopsy Cervix	108	32.93
Fractional curettage	11	03.35
Endometrial curetting	45	13.72
Only Hysterectomy	27	8.23
Hysterectomy with adnexae	117	35.67
Total	**328**	**100.00**

Table 2: Types of specimens received

Type of Lesion	No.	Percentage (%) of total cases	% of malignant cases	Mean Age± SD(years)
Non- malignant conditions	136	41.5	-	56.3±7.9
Carcinoma vulva (Squamous cell carcinoma)	3	0.9	1.6	62.7±6.4
Carcinoma vagina	14	4.3	7.3	61.3±10.1
Squamous cell carcinoma	11			
Adenocarcinoma	2			
Undifferentiated	1			
Carcinoma cervix	113	34.5	58.8	57.6±9.4
Cervical intraepithelial neoplasia	7			
Squamous cell carcinoma	90			
Adenocarcinoma	8			
Adenosquamous carcinoma	4			
Undifferentiated	4			
Malignant uterine tumors	43	13.1	22.4	60.0±6.9
Squamous cell carcinoma	2			
Adenocarcinoma	32			
Adenosquamous carcinoma	2			
MMMT	6			
Undifferentiated	1			
Carcinoma fallopian tube (papillary serous adenocarcinoma)	1	0.3	0.5	56.0
Malignant ovarian tumors	18	5.4	9.4	58.8±7.5
Granulosa cell tumor	7			
Serous papillary cystadenocarcinoma	6			
Mucinous papillary cystadenocarcinoma	2			
Atypical proliferative mucinous tumor	2			
Endometrioid adenocarcinoma	1			
Total	**328**	**100.0**	**100.0**	**58.6±8.8**

Table 3: Diagnosis of cases with postmenopausal bleeding

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Non-malignant cause	No. of cases	Percentage (%) of total
Cervicitis	07	2.1
Cervical polyp	25	7.6
Endometrial Polyp	29	8.8
Endometrial hyperplasia	16	4.9
Endometrial Atrophy	08	2.4
Proliferative endometrium	05	1.5
Secretory endometrium	04	1.2
Endometritis	05	1.5
Adenomyosis	09	2.7
Leiomyoma	06	1.8
Retained Intrauterine Contraceptive Device	03	0.9
Uterovaginal prolapse	02	0.6
Endometriosis ovary	01	0.3
Benign ovarian tumors	06	1.8
Inadequate/non-diagnostic	17	5.2

Table 4: Diagnosis and number of cases with non-malignant causes of Postmenopausal bleeding

Study	Age range (years)	Mean age (years)
Lidor et al (1986)	40-81	58
Lee et al (1995)	43-84	58
Giusa-Chiferi et al (1996)	45-84	60.8
O'Connell et al (1998)	42-80	59.7
Present study (2010)	40-85	57.6

Table 5: Age range and mean age of onset of postmenopausal bleeding in various studies

Study	Ratio of cervical and uterine cancer
Lee et al (1995)	1.2:1
Present study (2010)	2.6:1

Table 6: Ratio of Cervical and Uterine cancer in different studies

Study	% of cases with lesions in uterus
Gredmark et al (1995)	82.6
Lee et al (1995)	56.5
Naik et al (2005)	95.2
Cheema et al (2008)	96
Present study (2010)	86.3

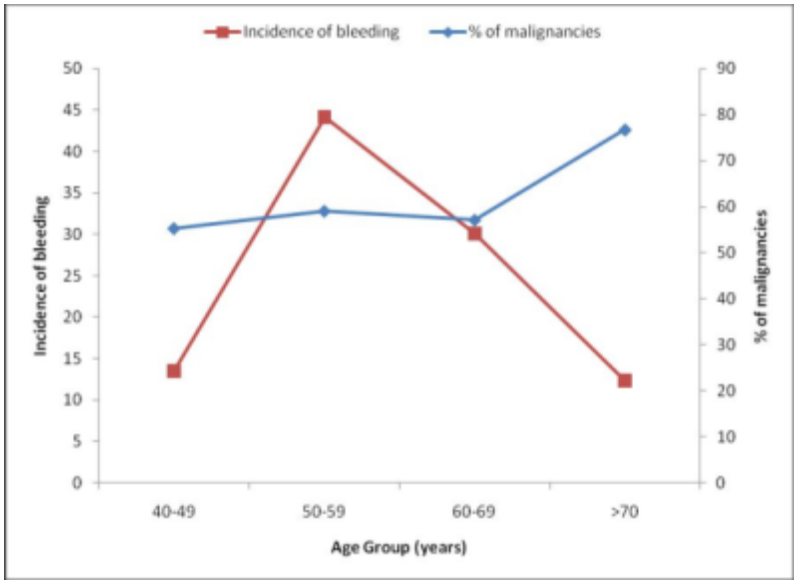
Table 7: Frequency of uterine lesions as cause of postmenopausal bleeding in different studies

DOI: 10.14260/jemds/2014/2882

Lesion	Lee 1995	Gredmark 1995	Asaf 1997	Escoffery 2002	Asim 2004	Ghazi 2005	Naik 2005	Sarfraz and Tariq 2007	Cheema 2008	Present study (2010)
Carcinoma vagina	0.6									4.3
Cervical ca	12.9		25.55	6.8		8.8	39.4		14	34.5
Malignant uterine tumors	11	8	1-1.44	9.5		11.1	9.6	6	10	13.1
Malignant ovarian tumors	1.2	1.75					0.96		6	5.5
Cervicitis	12.9						0.96		68	2.1
Cervical polyp	6.7			4.5			2.8			7.6
Endometrial sarcoma				3.5						1.8
Endometrial polyp	1.8	9					2.8	8	16	8.8
Endometritis	1.2		16.66					13		1.5
Proliferative endometrium		4	3.88	3.2			8.6	6	8	1.5
Secretory endometrium		1	3.33					5	14	1.2
Atrophic endometrium		50		21.3	50		16.3	27	32	2.4
Endometrium hyperplasia	3.1	10	16.1	22.3	10	11.1	13.4	27	2	4.9
Leiomyoma	4.3									1.8
Non-diagnostic	24.5	14	5.55	19.9				8	4	5.2

Table 8: Spectrum of lesions in postmenopausal bleeding in various studies

Graph 1: Association between advancing age with decreased incidence of postmenopausal bleeding and increased likelihood of malignancy:



Graph 1

DOI: 10.14260/jemds/2014/2882

Figure 1: Squamous cell carcinoma, cervix (A&B).A- Hysterectomy specimen showing ulceroproliferative growth with variegated appearance on cut section. B- Photomicrograph depicting keratin pearls in well differentiated squamous cell carcinoma. H&E 100x.C&D- Endometrioid adenocarcinoma, uterus. C- Hysterectomy specimen showing friable growth arising from uterine cavity. D- Photomicrograph showing anaplastic cells arranged in papillae; H&E 100x. Inset shows multilayering in glands and nuclear pleomorphism; H&E 200x.

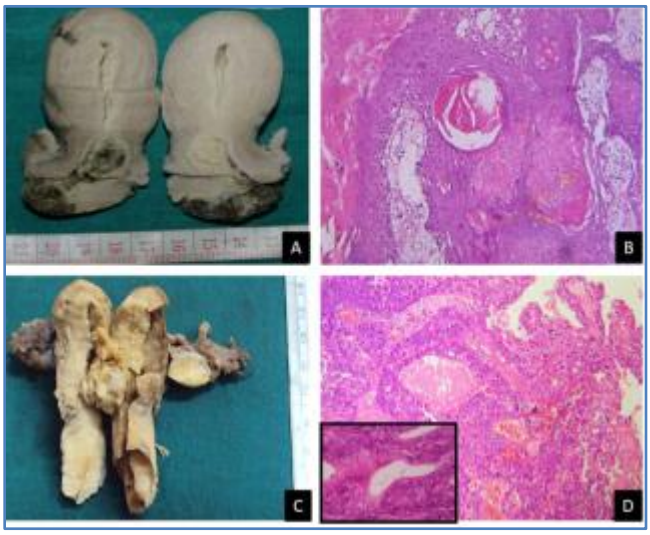


Figure 1

Figure 2: Malignant mixed Mullerian tumor of uterus. A- Nodular mass distending the uterine cavity and infiltrating both the adnexae; B-Photomicrograph showing sarcomatous component: markedly pleomorphic, bizarre spindle shaped cells (red arrows), multinucleated giant cells (black arrow) and brisk mitoses (blue arrows) H&E 100x; C-cells of sarcomatous component with striations seen on PTAH stain; D- Photomicrograph of carcinomatous areas with foci of glandular differentiation; H&E 100x.

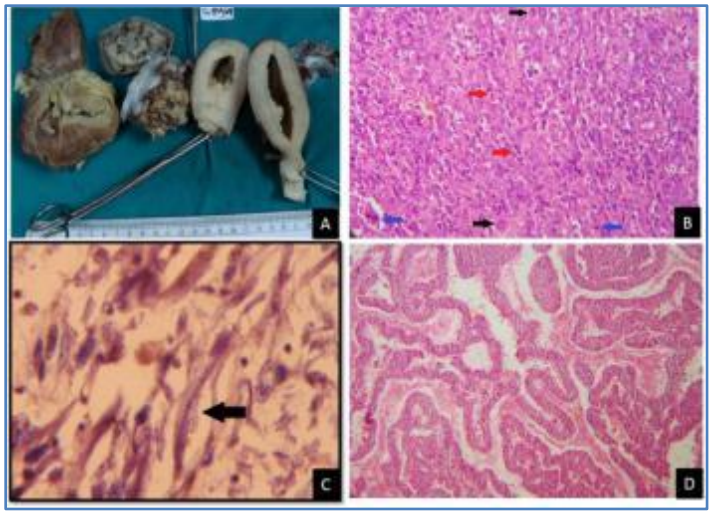


Figure 2

DOI: 10.14260/jemds/2014/2882

Figure 3: Granulosa cell tumor, ovary (A&B) A- Hysterectomy with bilateral salpingo-oophorectomy, pale tan appearance on cut section; B- Microscopy showing cells arranged in trabecular pattern; H&E 100x. Inset shows nuclear grooving in tumor cells; H&E 400x; C & D: Bilateral Serous Papillary Adenocarcinoma. C - Hysterectomy specimen with bilateral salpingo-oophorectomy and omentum: Enlarged ovaries replaced by tumor with solid areas and cystic areas having papillary excrescences (inset); D- Photomicrograph showing cribriform arrangement of tumor cells and foci of psammomatous calcification (arrows); H&E 100x.

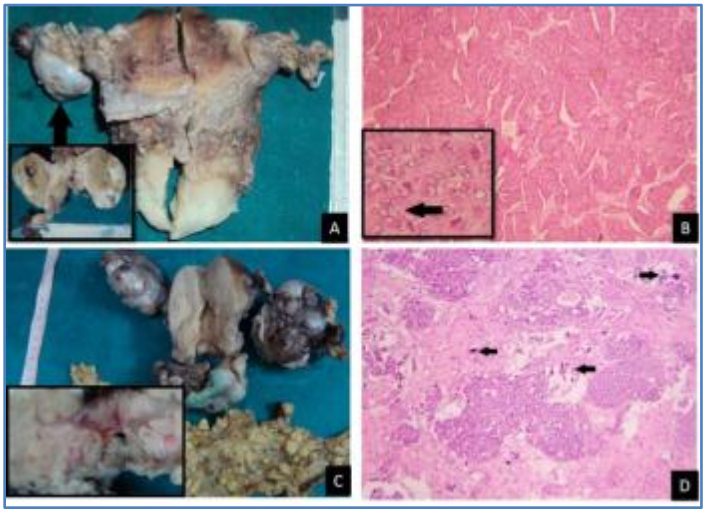


Figure 3

AUTHORS:

1. Ruchita Tyagi
2. Roma Isaacs
3. Tapasya Dhar

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Pathology, Post Graduate Institute of Medical Education and Research, Chandigarh.
2. Professor, Department of Pathology, Christian Medical College and Hospital, Ludhiana.
3. Professor, Department of Obstetrics and Gynaecology, Christian Medical College and Hospital, Ludhiana.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Roma Isaacs,
Professor,
Department of Pathology,
Christian Medical College and Hospital,
Brown Road,
Ludhiana, Punjab.
Email: drromalhmc@yahoo.co.in

Date of Submission: 13/06/2014.
Date of Peer Review: 14/06/2014.
Date of Acceptance: 24/06/2014.
Date of Publishing: 27/06/2014.