Postmenopausal Bleeding: Clinical Significance and Histopathological Evaluation

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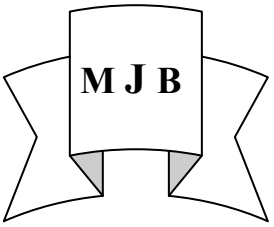

Abstract

Normal menstruation is defined as the bleeding from secretory endometrium associated with an ovulatory cycle not exceeding a length of 5 days. Any bleeding not fulfilling these criteria is referred to as an abnormal uterine bleeding. Some of these are the result of an identifiable pathological lesion, such as endometriosis, submucous myoma, endometrial polyp, or cancer, particularly in the postmenopausal patient.

The aim of the present study was to investigate the clinical significance and endometrial pathology in patients with postmenopausal bleeding (PMB) in terms of etiology, risks factors, incidence of malignancy, and histopathological evaluation.

202 cases of PMB admitted to Basrah Maternity Teaching Hospital from 1990-1999 underwent a detailed history, clinical examination and full investigation, including full laboratory investigation, pelvic ultrasound, and examination under anesthesia (EUA) with dilatation and curettage and tissue sampling.

The age range of the patient was from (35 to 72 years) with a mean of (49 years). The Results showed that Benign pathology was found in (184 / 209) cases. These included senile atrophic endometrium, normal functioning endometrium, endometrial hyperplasia, endometritis, polyps, cervicitis, and cervical polyps. Malignant pathology was found in (18) cases including (8) cases of cancer of the cervix and (10) cases of adenocarcinoma of the endometrium.

It is concluded that postmenopausal bleeding is an important symptom and requires careful and prompt evaluation to eliminate the possibility of malignancy as quickly as possible.

الخلاصة

يهدف البحث دراسة النزف بعد سن اليأس من حيث الأسباب المرضية ،وعوامل الخطورة ،ونسبة الخباثة والآفات المرضية المصاحبة .ضمت المجموعة المدروسة ٢٠٢ حالة إصابة بالنزف بعد سن اليأس .

أجري فحص سريري تضمن فحوص مختبرية كاملة وفحص بالأمواج فوق الصوتية للحوض. تم الفحص تحت التخدير بالتوسيع والتجريف واخذ عينات نسيجية .تمت دراسة العينات النسيجية لمعرفة الأسباب المرضية

تراوحت اعمار المريضات بين ٣٦–٧٢ عاما، بوسطي ٤٩ عاما .كانت الحالات حميدة لدى ١٨٤ من ٢٠٩ حالة وتضمنت التهاب بطانة الرحم او فرط التنسج لبطانة الرحم،أو التهاب عنق الرحم.وجدت الإمراض الخبيثة لدى ١٨ من ٢٠٢ حالة ، تضمنت ٨ حالات سرطان عنق رحم ، و ١٠ حالات سراطانيه لبطانة الرحم الغدية. استنتجت الدراسة إن النزف بعد سن اليأس عرض هام ويتطلب عناية وسرعة في التقييم لاستبعاد التطورات الخبيثة المحتملة.

Introduction

Normal menstruation is defined as the bleeding from secretory endometrium associated with an ovulatory cycle not exceeding a length of 5 days. Any bleeding not fulfilling these criteria is referred to as an abnormal uterine bleeding[1-4]. Some of these are the result of an identifiable lesion, such as endometriosis, submucous myoma, endometrial polyp, or cancer, particularly in the postmenopausal patient[1-5].

The cessation of menstruation is the cardinal symptom of the menopause, and postmenopausal bleeding more than one year after the last menstrual period. Postmenopausal bleeding is considered an important and alarming symptom both to the patient and to the gynecologist, and is requires as complete evaluation as possible in order to ensure the absence of malignancy and to identify and treat high risk patients such as those with endometerial hyperplasia. In most series, approximately 5% to 15% of the cases of postmenopausal bleeding are due to endometrial carcinoma and a similar proportion to endometrial polyps.[2-6]

The only finding on D&C in over half of postmenopausal bleeders is an atrophic endometrium[1-5], vascular degenerative changes in the uterine blood vessels have been suggested as a possible etiology in these cases. The ovarian influence on the endometrium will be absent in a postmenopausal woman due the absence of ovarian follicular unit , but if the estrogen is still available to the endometrium from other sources, it may lead to endometerial proliferation which may develop into hyperplasia or even carcinoma. The purpose of this study was to investigate the clinical significance and endometrial pathology in patients with postmenopausal bleeding (PMB) in terms of etiology,

risks factors, incidence of malignancy, and histopathological evaluation.

Materials and Methods

All cases of PMB were admitted to the Basrah Maternity Teaching Hospital during the period 1990-1999 where detailed history, physical examination and complete laboratory investigation were performed included blood group and Rh factor, fasting blood sugar, bleeding time, clotting time, CBC, urinalysis, diagnostic pelvic ultrasound, ECG, chest x-ray and Pap smear. The patients were evaluated and curettage was performed for histopathological examination.

Results

The patients were analyzed according to the following parameters: age, parity, associated medical disease prior to dilatation and curettage, and various benign and malignant histopathlogical findings. The endometerial histology was then analyzed in terms of patients age, parity, history of blood loss, uterine size, uterine depth, and the interval between menopause and the onset of PMB.

The patients ranged in age from 36 to 72 years with a mean of 49. The most affected ages were between 50 to 64 years of age (68%), table 1. The parity of the patients ranged from 0 to 15. Only 6 patients were nulliparous. Most were grand multiparous (table 2.). Table 3 shows that the most common medical diseases noted were hypertension (36%), obesity (32%), and diabetes (23%). The three condition in combination were found in 20% of the patients. Abnormal premenopausal bleeding, mostly in the form of menorrhagia or polymenorrhagia had been detected in 23% of the patients.

Table 4 demonstrates the patients' history and symptoms at the time of clinical presentation.There was a variable amount of blood loss reported. None of the patients reported feeling a mass. The pain reported by 10 of the patients might be explained on the basis of pelvic congestion, malignant invasion, or incidental benign pathology such as urinary tract infection. The interval between the onest of menopause and PMB was variable. In 38% of the patients it was less than 5 years, while in 62 %of the patients, it was 6 years or more.

The abnormal findings noted on examination are shown in table 5. Atrophy of the vulva, vagina, and cervix and small uterine size are considered normal findings. Uterine size was considered abnormal if it was

felt to be bulky. This was noted in 20 cases. Only on of these cases was proved to have fibroids by scan. In table 6, the histopathological findings are reported. Five specimens could not be processed. Some patients had abnormal pathology at more than 1 site.

Endometrial histopathology was analyzed separately against different clinical parameters. There are four categories of endometrial tissue: Atrophic, normal (proliferative or secretory), hyperplasic (Fig. 1), and endometrial carcinoma (Fig. 2, 3). In table 7, the endometrial findings are analyzed according to patients' age. All cases of endometrial cancer were seen in patients over the age of 50. Endometrial histopathology was analyzed according to parity as seen in table 8. It is of interest that no cases of endometrial carcinoma were found in nulliparous patients.

In table 9 it is shown that two third of patients with atrophic endometrial had scanty blood loss. In the Hyperplastic and carcinoma groups, 31 from 40 patients had moderate to heavy blood loss. Uterine size according to endometrial group is tabulated in table 10. The uterine size was felt to be bulky in 34 of the ٧١ patients in the Hyperplastic or carcinoma group. The one bulky uterus in the atrophic group was attributed to a small sub serous fibroid detected on sonography.

Table 11 shows the measurement of the uterine cavity taken at the external cervical os at the time of EUA. The uterine size was more than 6 cm in 63/71 patients in the Hyperplastic and carcinoma group. More than 1/3 of the Hyperplastic and 2/3 of the carcinoma group had a uterine depth greater than 8 cm. This suggests a strong relationship between increased uterine size clinically and uterine cavity depth detected under anesthesia and abnormal endometrial tissue.

In table 12 The interval between menopause and the onset of PMB is compared. A longer interval is associated with the Hyperplastic and carcinoma group.

Discussion

Diagnostic dilatation and curettage was used to obtain tissue samples. This is the preferred method, according to a number of studies, with a high rate of accuracy [3-7]. Other methods reported in the literature include aspiration of the uterine cavity. [8,9] and Gravelee jet irrigation.[10,11] Histological methods are reported to be superior to

cytological method in the detection of early lesions. [12-13] Some centers are now using hysteroscopy with endometrial sampling on a simple outpatient basis. [14,15] The mean age group (54.29 years), is similar to that reported by Miyazawa and Lidor 6 who reported ages of 55 and 56 respectively. The patients in the endometrial carcinoma group were 60-68 years old. This is similar to the mean ages of 66.3 and 65.6 reported in other studies.[6,16]

The Parity of our patients ranged from 0 to 15 with only 3 nulliparous patients found in the group. Although nulliparity presents a strong risk factor for endometrial carcinoma[17.18] with Gusberg et al12 reporting that 21.6% of their endometrial cancer study group were nulliparous, all seven of our endometrial cancer patients were multigravida (G 7, G8, G9). The three nulliparous patients in this study were found to have cystic endometrial hyperplasic in 2 instances and atrophic endometrial in the third. There was a strong association of hypertension (40%), obesity (35%), and diabetes (28%) in our cases. Obesity is a well-known risk factor for the carcinoma due to the conversion of the adrenal prehormone and ostenedione to estrone by peripheral aromatization in the adipose tissue. Women with an excess of subcutaneous have a higher plasma estrogen level, which leads to abnormal pathology of the edometrium.[1.19.20] almost one third of our patients were obese (32%). The weight of the group ranged from 43 to 119 kg. The ten endometrial cancer patients were all obese with weight of 84, 96, and 108 kg. It is reported that an excess of 10 – 23 kg. of body weight increased the risk of endometrial cancer three fold and that an excess of more than 23 kg. Increased the risk nearly 9 times[2-4]. Other studies have confirmed these findings [21,22]. None of our study group had used estrogen as hormonal replacement therapy (HRT), which has frequently been reported to increase the risk of endometrial disease [22-26]. Other studies have confirmed the obesity associated with PMB [5,6]. The finding of an increase in the amount of blood loss reported in cases of hyperplastic endometrium or carcinoma supports what has been reported by other authors [5,6]. The increase in the interval between menopause and the onset of PMB in patients with hyperplasia and carcinoma has also been reported by others. [5,6,27,28]

The increase in uterine size found in our study in cases of hyperplasia and carcinoma also supported earlier studies [5,6,16]. Pain was reported by 10% of the patients in this study. Kerise et al[28] reported a rate of 3.8 % in an endometrial cancer group. Vaginal discharge with or without bloody staining and foul odor was found in about 10 % of patients, mostly those with cervicitis, cervical polyps, or cervical cancer. Pelvic masses other than uterine, symptomatically unapparent but detectable by bimanual pelvic exam, were found in 4 patients and detected by scan in 4 % patients. This is closed to the rate of 5 % reported by Reid29. The malignancy rate of 10 / 209 (about 5%) in our series contrasts with the malignancy rate ranging from 14.3 % reported by White to about 33 % reported by others28. The incidence of benign atrophic endometrium was higher than that reported by Reid and lower than that reported by others6. Reid also reported fewer cases of proliferative endometrium (9 %) than that (11 %) seen in our cases. Endometrial hyperplasia was 30% of these cases. The simple type was 14 %, cystic 10 %, and adenomatous 3 %. Other studies show less hyperplasia. Cervical polyps were seen in 26 of our patients and Endometrial polyps in 7. This varies from what has been reported by other authors. Lidor7 reported 8 % endometrial and 10 % cervical polyps. The endometrial carcinoma found in only 5% of our patients is much less than that reported by other studies: Miyazawa6 8 %, Lidor7 7 %, 14.3 %, Reid29 5 % and Lee 11 %. The cervical cancer group was again found in only 8 patients who were 47-65 (mean 51.3) years of age. Each was a multigravida .All presented with post coital bleeding and 1 presented with irregular vaginal spotting. All were squamous cell carcinoma in type. Cervical cancer was reported 1 % by Lidor6 or White. Weinstein et al reported 1 % in their study. Much higher rates were reported by Lee (12.9 %), Panda (53 %), and De Albuquerque (59. 26 %).

The distinction between an extreme case of hyperplasia and a well-differentiated adenocarcinoma is very difficult, largely because of the fact that endometrial hyperplasia and carcinoma represent different points in a disease continuum at the morphologic, ultrastructural, biochemical, immunocytochemical, and cytodynamic levels.[30-32] Microscopic features favoring carcinoma include marked

pleomorphism with loss of polarity, complex ramification of disorderly arranged glands, extensive papillary formations, confluent glandular pattern with a solid or cribriform appearance, and desmoplastic stroma .[33-34] Some studies have remarked on the importance of true intraglandular cellular bridges devoid of stromal support and the presence of neutrophils and nuclear debris within glandular lamina. It should be noted that the most superficial portions of the tumor may show microglandular patterns simulating microglandular hyperplasia and other metaplastic patterns.[33,35] Whether quantitative morphology (particularly nuclear morphometry), immunohistochemistry (with the MSN-1 antibody), flow cytometry, PCR for nonrandom X chromosome inactivation, or other techniques will assist or replace conventional morphology in this difficult problem remains to be seen.[32,33,36]

Conclusions

The significance of uterine and cervical carcinoma as a cause for postmenopausal bleeding is well documented in this study. The ten cases of endometrial malignancy in present study were all Adenocarcinoma. The eight cases of cervical carcinoma in this study were all squamous cell in type.. Endometrial hyperplasia and carcinoma were associated with heavier blood loss at the time of clinical presentation, longer interval between menopause and the onset of symptoms, and larger uterine size.

References

1.Pacheco JC, Kempers RD, Obstet Gynecologic 32:40-46, 1968.

2.Rome M, Brown JB, Mason T, Smith MA, Laverty C, CortuneD, Br J Obstet Gynaecol 84:88-97, 1977.

3.MacDonald CD and Silteri PK. , Gynecol Oncol 1974;2:259.

4.Gambrell R D. Clin.Obstet. Gynecol., 1977;4:129.

5.Novak ER. Clin Obstet Gynecol 1964;7:464.

6.Miyazawa. Obstet Gynecol 1983; 61: No. 2 February.

7.Lidor A, Ismajavich B, Confino F and David MP. Acta Obstet Gynecol Scand 1986; 65:41-43.

8.Vupala S. ,Acta Obstet Gynecol Scand Suppl 1977;56:1-72.

9.Isaacs JH, White RW. , Am J Obestet Gynecol 1974; 118:6799-87.

10. Gravlee Lc. , Obestet Gynecol 1969;34:168-72.

11.Schwartz AM, Silverberg SG, Fu YS, Nozawa S, Huang S, Tsukasaki K,

Williams KR, Int J Gynecol Pathol 12:253-258, 1993.

12.Gusberg J and Milano F. Cancer March ,1.1981.

13.Reagen JW, Ng ABP. The cell of uterine adenocarcinoma. Baltimore: William and Wilkins; 1965.

14.Dones F, Maniscalo V, Cadili G. Minerva Gynecol (Italy), 1999;44:433.

15.Gupta JK, Wilson S, Desai P, Han C. , Acta Obstet Gynecol Scand 1996;75:457-9.

16.Cacciatore B, Pentti L. Am J Obestet Gynecol 1989;1960.

17.Beral V. , Clinical Gynecological Oncology. Blackwell, Oxford; 1985:1.

18.Alberico S, Consenti G, Veglio P, Bogatti P, DiBonito L and Mandruzzato G. A clinical and epidemiological study of 255 PMB. Clin Exp Obestet Gynecol 1989;16:113-21.

19.MacDonald CD, Hemsell DL, Porter JC. , Am J Obstet Gynecol 1978; 130:448.

20.Austen H, Austen JJ, Partridge EE, Hatch KD, Shingleton HM. Endometrial cancer, obesity and body fat distribution. Cancer Res 1991; 51:568-72.

21.Henderson BE, Ross PK, Pike MC, Casagrande JT. cancer. Res 1982; 42:3232.

22.Gambrell SB and Mulvihill MN. Clin Obestet Gynecol 1986; 35:168-72.

23.Smith DC, Prentice R, Thompson DJ, Herrmann WL. N Engl J Med 1975; 293:1164-67.

24.Ziel HK. Obestet Gynecol 1982; 60:509.

25.Smith PG and Vessey MP. Jordan Oncology. London RCOG; 1980:91-105.

26.Studd JW and Thom MH. , Oncology. London. RCOG;1980: 911.

27.Kumar V, Cotron R and Robbins SL: Basic Pathology. 6th ed., WB Saunders Co., Philadelphia 1997.

28.Kerise MT. , Postgrad Med 1973; 49:344.

29.Reid PC, Brown VA, Fothergill DY. , Br J Obstet Gynecol 1993; 100.

30.Gordon MD, Ireland K, Oncol 21:64-70, 1994.

31.Jacques SM, Qureshi F, Int J Gynecol Pathol 14:191-197, 1995.

32.Mutter GL, Chaponot ML, Fletcher JA,Am J Pathol 146:501-508, 1995.

33. Schwartz AM, Silverberg SG, Fu YS, Nozawa S, Huang S, Tsukasaki K, Williams KR, Int J Gynecol Pathol 12:253-258, 1993.

34.Mittal KR, Peng XC, Wallach RC, Demopoulos RI, Hum Pathol 26:574-575, 1995.

35.Staros EB, Shilkitus WF Surg Pathol 4:157-166, 1991

36.Spiegel GW, Am J Surg Pathol 19:417, 1995.

Table 1. Age distribution

Age group in years	No.	%
<45	9	4
45-49	32	16
50-54	59	29
55-59	42	21
60-64	40	18
65-69	11	4
60 or>	16	8
Total	209	100%

Table 2. Parity distribution

parity	No.	%
0	6	3
1-5	72	35
6-10	68	32
> 10	63	30
total	209	100%

Table 3: Associated medical conditions .(N.B: Patients might have more than one disease).

Associated disease condition	No.
obesity	73
hypertension	84
Diabetes + obesity + hypertension	59
Thyroid disease	4
Metal illness	0
Anemia (HB< 11g%)	110
Other blood disorders	0
Ischemic heart disease	14
Other heart disease	3
Estrogen hormonal therapy in fertility	15
Abnormal premenopausal bleeding	52
Breast disease	3
renal disease Tuberculosis Bronchial asthma Liver disease	4 4 6 2

Table 4. Clinical symptoms and history at presentation (symptoms may have been multiple).

symptoms	No.
Spotting 1 attack	25
>1 attack	40
Post-coital bleeding 1 attack	2
>1 attack	4
Moderate blood loss l attack	37
>1 attack	43
Severe blood loss 1 attack	41
>1 attack	25
Interval between menopause PMB	
1-5 years	77
6-10 years	85
>10 years	41
pain	20
Obvious abdominal mass	0
Foul smelling discharge	22

Table 5. Abnormal findings detected on physical examination

Clinical findings	No.
Cervix: Growth	4
Erosion	25
Polyp	35
Uterine size: Small	47
Normal	106
Bulky	45
Adnexal mass	
(ovarian): Palpated	6
Detected by scan	12

Table 6. Normal, Benign and malignant histopathology.

histopathology	No.
Inadequate tissue	8
Benign tissue	
Atrophic (inactive) endometrium	39
Cervical polyp	26
Cervicitis	20
Normal endometrium: Proliferative	23
Secretory	7
endometerial: Polyp	7
Hyperplastic endometrial: Simple	31
Cystic	22
Adenomatous	6
Atypical	2
Malignant tissue	
Cervical cancer	8
Endometrial cancer	10

Table 7. Endometerial findings and age categories

Group	No.	Age in years				
		<40	41-50	51-60	61-70	>70
atrophic	39	2	15	16	5	1
normal	30	2	14	8	3	2
Hyperplastic	61	2	29	22	6	2
Carcinoma	10	0	1	3	5	1

Table 8. Endometerial findings and parity.

		Parity			
group	**No.**	**P0**	**1-5**	**6-10**	**>10**
atrophic	39	2	4	23	10
normal	30	0	7	13	10
Hyperplastic	61	4	7	31	19
Carcinoma	10	0	3	5	2

Table (9): Endometrial Findings and Reported Blood Loss

Group	No.	Scanty	Moderate	Heavy
Atrophic	39	25	13	1
Normal	30	10	12	8
Hyperplastic	61	16	24	21
carcinoma	10	4	3	3

Table (10): Endometrial Findings and Uterine Size

Group	No.	Uterine size		
		Small	Normal	bulky
Atrophic	39	27	11	1
Normal	30	3	24	3
Hyperplastic	61	8	33	20
carcinoma	10	-	1	9

Table (11): Endometrial Findings and Uterine Depth.

Uterine depth in cm				
Group	No.	<6 cm	6-8 cm	>8 cm
Atrophic	39	25	14	0
Normal	30	3	26	1
Hyperplastic	61	6	36	19
Carcinoma	10	0	1	9

Table (12): Endometrial Findings and interval after menopause

Group	No.	Interval between menopause and PMB (years)		
		1-5	6-10	>10
Atrophic	39	20	7	4
Normal	30	21	5	4
Hyperplastic	61	12	29	20
carcinoma	10	3	4	3

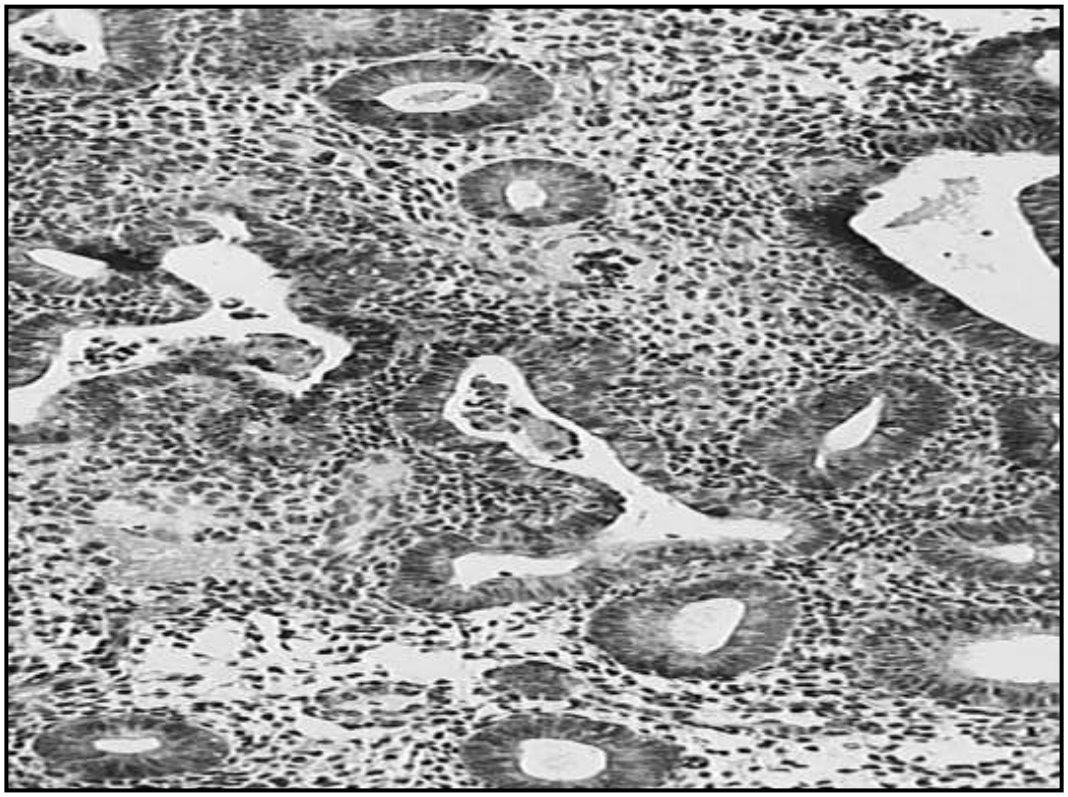

Fig. 1.*Microscopic appearance of endometrial hyperplasia of moderate degree. With increasing severity of disease, cystic changes in glands and amount of stroma diminish, whereas epithelial proliferation becomes more intense.*

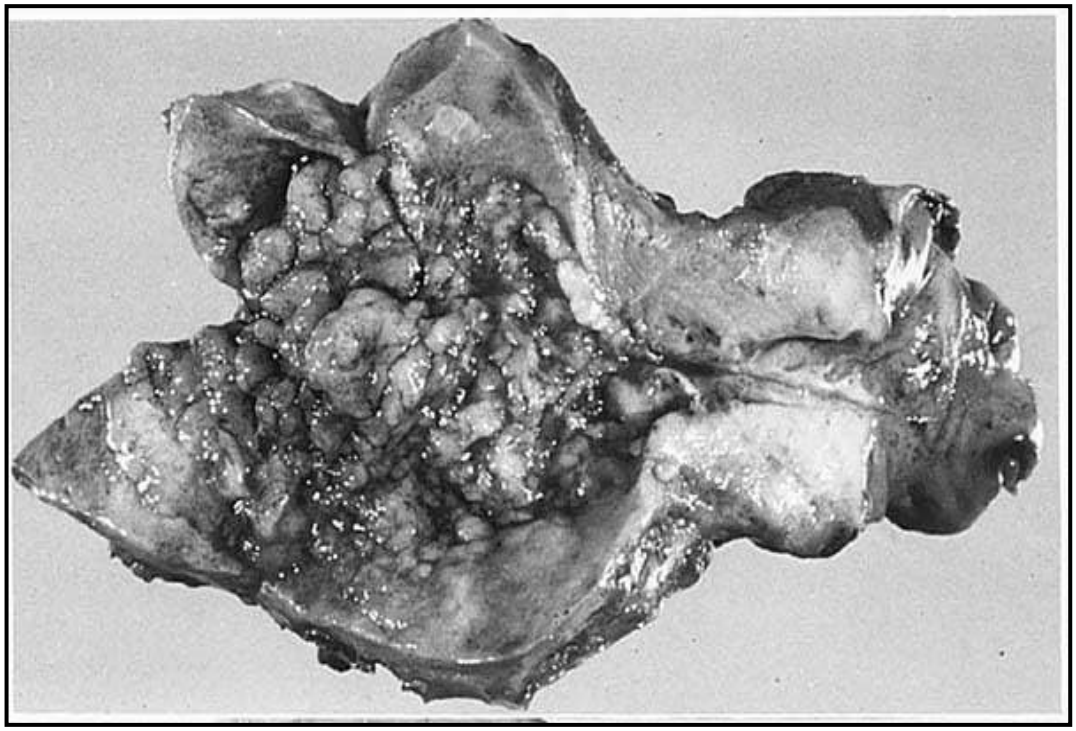

Fig. 2. *gross appearance of endometrial adenocarcinoma. Lesion has a distinctly polypoid appearance involves most of endometrial cavity.*

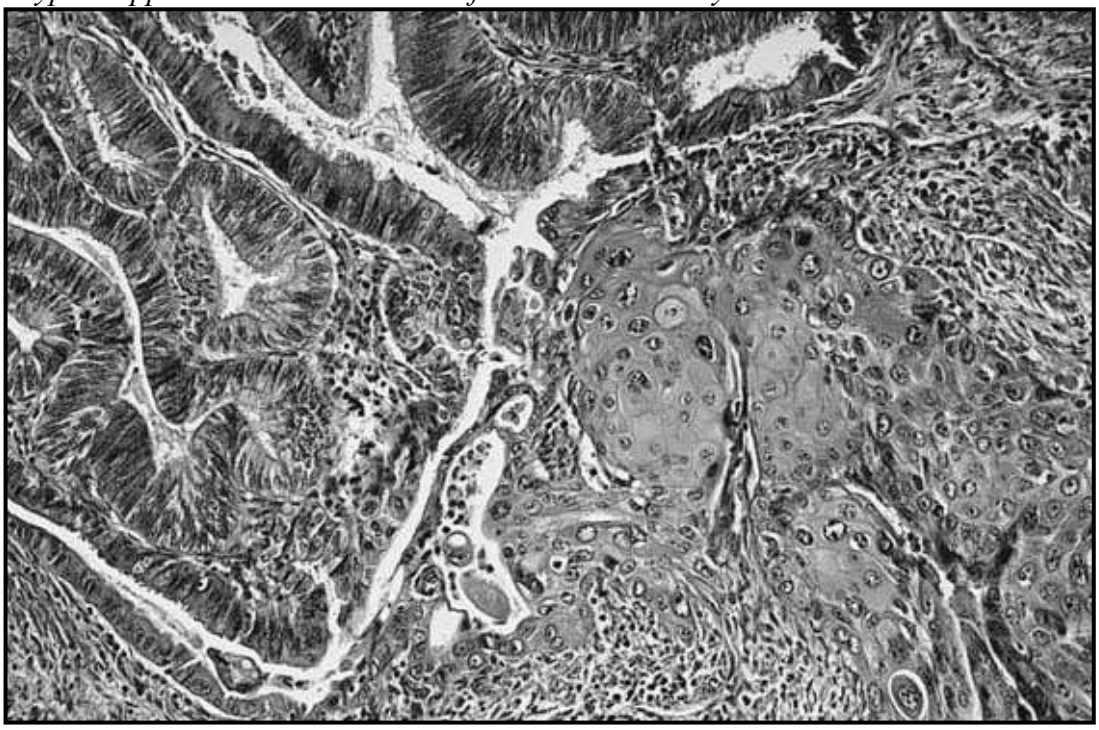

Fig. 3. *Endometrial adenocarcinoma with squamous metaplasia, the squamous component has markedly atypical cytologic features*