Original Article

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Critical Analysis of Cervical and Endometrial Biopsy Specimens.

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ABSTRACT

Introduction: This is a retrospective study done in cervical and endometrial biopsy specimens received in the pathology department of Shree Birendra Hospital over a period of one year from 14th April, 2011 to 13th April, 2012. The aims of this study were to analyze the histological findings of cervical and endometrial biopsies and to identify activities needed to critically evaluate these specimens.

Methods: The histopathological diagnoses of 104 cervical and 84 endometrial biopsy specimens reported by the pathologists were retrieved. The diagnoses were categorized and correlated with age in order to work out a strategy for better patient management.

Results: The majority of 104 cervical biopsies (76.0%) comprised of neoplastic lesions and 83.5% of them were low-grade squamous intraepithelial lesions. Among the nonneoplastic lesions, cervical polyps and cervicitis were in the ratio of 3:2. Of the 84 endometrial biopsies analyzed, proliferative endometrium comprised the majority (61.9%) with disordered proliferative being the most common pattern. Detailed information about the patients was minimal including the absence of age in 8.0% of cases. More than 80% of both cervical and endometrial biopsies were performed in the age group 30-59 years of age.

Conclusions: Neoplastic lesions comprised the majority of the cervical biopsies while all the endometrial biopsies were nonneoplastic. Important clinical information like age of the patient has to be mentioned in the biopsy request form for useful clinical correlation of histological findings.

Keywords: biopsy; cervix; endometrium.

INTRODUCTION

Cancer of cervix makes up about 85% of all gynecologic malignancies in Nepal[1]. The development of cervical cancer is a multistep process that includes a preinvasive precursor stage[2]. Cervical infection with HPV is usually transient, with 70-90% of individuals documented free from the virus within 12-24 months of the infection[3,4] . Some of these lesions may progress to higher grade lesions[5]. Cervical biopsies are usually performed to rule out the coexistence of focal high-grade or invasive lesions.

Endometrial biopsies are commonly performed to explain the underlying cause for abnormal uterine bleeding (AUB)[6]. In the adolescent age group and perimenopausal years such bleeding is usually dysfunctional. Endometrial biopsy is included in the initial evaluation of women when the cause of bleeding is not obvious or who are at high risk for endometrial cancer[7]. Abnormal uterine bleeding after 40 years of age requires further evaluation to exclude endometrial polyp, hyperplasia, fibroid or carcinoma[8] . Endometrial carcinoma may present as AUB in 8 – 50% of cases[9]. This retrospective study was carried out to analyze the various histopathological diagnoses in cervical and endometrial biopsies submitted to the Pathology Department within one year.

METHODS

This retrospective study was undertaken because of a significant load of about 8000 women attending the Gynaecological OPD in Shree Birendra Hospital in a year. Two to eight of these cases are subjected to minor operations in one week. The majority of the minor cases in the operating list are for cervical and endometrial

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biopsy procedures.

The diagnoses of all the cases of cervical and endometrial biopsies performed between 14th April, 2011 to 13th April, 2012 were collected from the histopathology registers stored in the Histopathology Section of the Pathology Department of Shree Birendra Hospital. The age of the patients recorded in the registers were confirmed by checking the duplicate copies of the request forms. This reassurance about documentation of correct age was important because of the wide range of age between 19 to 84 years among the women undergoing the procedure. The slides of all the cases were also collected. Some of the diagnoses were randomly verified by reviewing the slides.

The diagnoses of all cervical and endometrial biopsies were grouped according to age. Cervical neoplasms were classified according to the WHO guidelines[10]. Histological classification of endometrial biopsy findings is presented in a practical manner as in the CHART 2 study[11]. Hyperplasia was classified as originally proposed by Kurman and Norris and sanctioned by WHO[12].

RESULTS

A total of 184 women had biopsies of cervix and endometrium in one year. Ten women had two (both cervical or one endometrial / one cervical) specimens collected in the same sitting. A total of 194 biopsy specimens from 184 women were therefore available for examination. This comprised 9.5% of the 2035 specimens received in the department. As six specimens, three each from cervix (2.8%) and endometrium (3.4%), were insufficient for reporting, the results for 188 out of 194 specimens were analyzed.

Of the total of 188 specimens that could be categorized, cervical and endometrial specimens comprised 55.3% and 44.7% respectively. The cervical lesions are categorized in Table 1. Cervical squamous abnormalities comprising low grade squamous intraepithelial lesions (LSIL) and high grade squamous intraepithelial lesions (HSIL) formed 66.3% (69 of the 104 cases). Carcinomas formed 9.6% of cervical lesions (10 of the 104 cases). The remaining benign cases comprised of polyp and cervicitis (24.0%). All our cases of LSIL exhibited HPV cytopathic effect with or without the presence of low-grade dysplasia. All HSIL lesions exhibited cellular dysplastic features extending beyond the lower two-third of the epithelial thickness with or without the presence of HPV cytopathic effect (Fig1). Invasive squamous carcinomas were equally divided between large cell keratinizing and large cell nonkeratinizing (four each), with one case of papillary squamous cell carcinoma. We had no case of small cell carcinoma. One case of carcinoma in situ (CIS) was recorded during the period. Histopathological diagnosis of cervical biopsies according to age group is depicted in Table 2. The age of the patients ranged from 22 to 77 years. Among the 97 cases in which age was mentioned, 84 (86.6%) were in the 30-59 years age group.

Table 1: Histopathological impressions on cervical specimens.

Histopathological diagnosis	No of specimens	Percentage
LSIL (CIN 1)	66	63.5
HSIL (CIN 2 & 3)	3	2.9
CIS	1	0.9
Carcinoma	9	8.7
Cervicitis	10	9.6
Cervical polyp	15	14.4
Total	104	100.0

LSIL = Low-grade squamous intraepithelial lesion, HSIL = High-grade squamous intraepithelial lesion, CIS = Carcinoma in situ

Table 2: Histopathological impressions on cervical specimens according to age group.

Age group / Histopathological impression (Years)	LSIL	HSIL	CIS	Carcinoma	Cervicitis	Cervical polyp	Total
20-29	1					1	2
30-39	16	2	1		2	6	27
40-49	23	1		4	3	1	32
50-59	16			3	3	3	25
60-69	4			2	1		7
70 and above	2					2	4
No age	4				1	2	7
Total	66	3	1	9	10	15	104

LSIL = Low-grade squamous intraepithelial lesion, HSIL = High-grade squamous intraepithelial lesion, CIS = Carcinoma in situ

Table 3: Histopathological impressions on endometrial specimens.

Histopathological diagnosis	No of specimens	%
Normal proliferative	18	21.4
Disordered proliferative	27	32.1
Stromal crumbling and breakdown associated with anovulation	7	8.3
Normal secretory	14	16.7
Atrophic	4	4.8
Menstrual	2	2.4
Simple hyperplasia without atypia	1	1.2
Complex hyperplasia without atypia	1	1.2
Chronic endometritis	3	3.6
Endometrial polyp	7	8.3
Total	84	100

The cases of LSIL (90.3%), HSIL (100%) and carcinoma (80%) were most prevalent in the above age group. The various endometrial lesions are categorized in Table 3. Endometrium was proliferative in 52 cases (61.9%) with disordered proliferative comprising the majority of these (51.9%), followed by normal proliferative (34.6%) and stromal crumbling and breakdown associated with anovulation (13.5%). Lesions categorized as disordered proliferative endometrium were characterized by variation in the architectural appearance of proliferative glands without approaching or exceeding the gland-to-stroma ratio of 3:1. (Fig 2). Of the remaining 32 nonproliferative cases, normal secretory endometrium comprised the majority (43.6%), followed by endometrial polyp (21.9%), atrophic lesions (12.5%), chronic endometritis (9.4%), menstrual fragments (6.3%) and hyperplasia without atypia (6.3%). Endometrial polyps are histologically characterized by the presence of spindle fibrous stroma with thick-walled vessels though the polypoid architecture is usually not appreciated in small endometrial biopsy pieces. There were no cases of atypical hyperplasia or carcinoma in the present study. Histopathological diagnosis on endometrial biopsies according to age group is shown in Table 4. The age of the patients ranged from 19 years to 59 years except for one 77- year old woman with chronic endometritis. Sixty-three of the 76 patients (82.9%) fell in the age group 30-59 years. Disordered proliferative endometrium (DPE) was the most common biopsy finding in 24 of the 76 cases (31.6%). All the 24 patients were in the age group 40-54 years. Half of the proliferative group comprised of DPE.

Nine of the 12 cases (75%) below the age of 30 years had various phases of normal endometrium and the remaining three cases were of chronic endometritis, endometrial polyp and stromal crumbling and breakdown associated with anovulation.

Age was not mentioned in a total of 15 of the 188 cases (8.0%) comprising of 7 cervical (6.7%) and 8 endometrial biopsies (9.5%). Most of the pathological findings in both the cervical and endometrial biopsies were found in the age group 30-59 years.

DISCUSSION

The high incidence of LSIL (CIN 1) of 63.5% in the present study is due to the fact that almost all of these cases followed recommendations for biopsy confirmation of the lesions after two consecutive Pap smear report of HPV cytopathic
effect (LSIL) at six months' interval. The majority of persistent infections are caused by high-risk HPV

Table 4: Histopathological impressions on endometrial biopsy specimens according to age group.

Age group (Years) / Histopathological impression	NP	DP	SCBA	NS	A	M	SH	CH	CE	EP	Total
<20	1	0	0	0	0	0	0	0	0	0	1
20-29	4	0	1	2	0	2	0	0	1	1	11
30-39	3	0	0	0	1	0	0	0	0	1	5
40-49	8	14	6	9	0	0	1	0	1	2	41
50-59	1	10	0	0	3	0	0	1	0	2	17
60-69	0	0	0	0	0	0	0	0	0	0	0
70 and above	0	0	0	0	0	0	0	0	1	0	1
No age	1	3	0	3	0	0	0	0	0	1	8
Total	18	27	7	14	4	2	1	1	3	7	84

NP = Normal proliferative, DP = Disordered proliferative, SCBA = Stromal crumbling and breakdown associated with anovulation, NS = Normal secretory, A = Atrophic, M = Menstrual, SH = Simple hyperplasia without atypia, CH = Complex hyperplasia without atypia, CE = Chronic endometritis, EP = Endometrial polyp

variants such as HPV 16, 18, 31, 33, 45 or 58[13]. Persistent infection with high-risk HPV is necessary for the development and maintenance of high-grade cervical lesions, and clinical progression is not found in the absence of high-risk HPV[14]. It is useful for patients to be followed by biopsies because a study on 226 women reported as LSIL on Pap smears were shown to have LSIL, HSIL and microinvasive carcinoma in 58.8%, 15.0% and 1.3% of cases on subsequent colposcopic biopsy evaluation[15]. Colposcopically directed biopsies will sample suspicious acetowhite areas more confidently than the blindly directed procedures from different quadrants currently employed. The finding of 67.3% of CIN in the present study is comparable to 54.0% of 133 recorded in Shree Birendra Hospital in 2003[16]. Biopsy proven cases of CIN 1 have to be followed by regular Pap smears because in one study the two-year risk of CIN3 was 10.3% for women with CIN1[17]. Carcinoma in situ formed 10% among cervical cancers in the present study and was nearly five times more than the 2.1% reported in BP Koirala Memorial Cancer Hospital (BPKMCH)[18]. The nine cases of carcinoma of cervix in this study are all squamous cell carcinoma and form 90% of the cervical cancers which is similar to 93.7% of squamous cell carcinoma out of a total of 1293 cervical carcinomas recorded in the same study.

Carcinomas forming 9.6% of cervical lesions is slightly less than the 13.0% recorded in Shree Birendra Hospital in 2003[16]. As only one case out of a total of 79 cases (1.3%) of cervical neoplasia was noted below 30 years of age, it is rational to focus Pap smears screening according to the recommended guideline published in 2012. This guideline advises Pap screening every three years between the ages of 21-29 years of age[19].

Figure 1. HSIL (CIN 2) showing the extension of dysplastic cellular features up to the upper third of the epithelial thickness with associated HPV cytopathic effect.

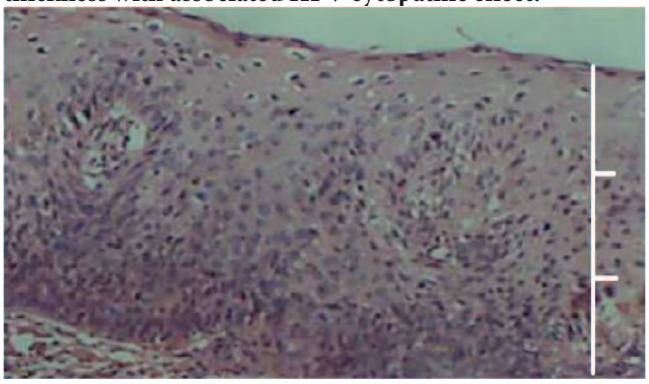
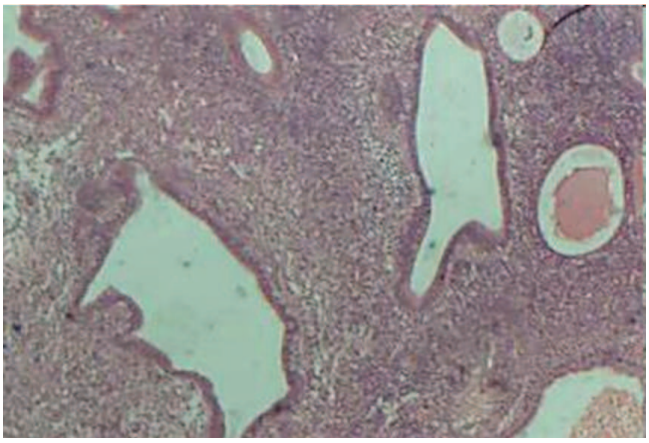


Fig 2. Disordered proliferative endometrium characterized by coexistence of cystically dilated proliferative glands with shallow budding coexisting with small round glands.



Disordered proliferative endometrium (DPE) was the commonest cause for bleeding in our study, accounting for 31.6% of cases. It accounted for 14 of 41 cases (34.1%) in the age group 40-49 years and 24 of 56 cases (42.9%) in the age group 40-54 years. It is comparable to 32% of 80 endometrial biopsies in perimenopausal women analyzed in Helping Hands Community Hospital, Kathmandu[20]. Our 34.1% in age group 40-49 years is almost four times more than the 8.3% recorded in a study of 48 cases in the same age group[21]. Disordered proliferative endometrium resembles normal proliferative tissue in consisting of glands lined by cytologically bland, pseudostratified, proliferative, mitotically active epithelium and in having a roughly normal (unitary) ratio of glands to stroma. It differs from the normal proliferative endometrium in the absence of uniform glandular development. In some areas, the glands may be cystically dilated or may demonstrate varying degrees of shallow budding, whereas in other regions, the glands are tubular, of narrow caliber, and set within abundant stroma. It differs from hyperplasia without cytologic atypia by virtue of its relatively normal ratio of glands to stroma. The significant shift in the glands-to-stroma ratio in favor of glands required for a diagnosis of hyperplasia is absent in DPE. Thus, disordered proliferation serves as a morphologic "bridge" between normal proliferation and hyperplasia. This pattern is considered by some researchers to represent hyperplasia, but hyperplasia also connotes to many clinicians a proliferation that puts the patient at increased risk of endometrial carcinoma. Because there is no evidence that patients with DPE are at any greater risk of endometrial carcinoma than those without this pattern, the label hyperplasia is not appropriate[22,23].

WHO classifies hyperplasias as simple or complex based on the absence or presence of architectural

abnormalities such as glandular complexity and crowding. They are further designated as atypical if they demonstrate cytologic (nuclear) atypia. Only atypical endometrial hyperplasias are clearly associated with the subsequent development of adenocarcinoma. If left untreated, approximately 8% of patients with simple atypical hyperplasia will progress to carcinoma, whereas the progression rate in complex atypical hyperplasia is almost 30% in one study, and as high as 52% in another[24]. In addition, the risk of coexistent cancer may be as high as 20-50%, leading some authors to recommend that all women with atypical hyperplasia should receive definitive surgical management. Hyperplasia accounting for 18.3% of 300 endometrial biopsies in one study and the similar 18.0% of 122 in another is almost about eight times more than our finding of 2.4%[20,21]. Three of our six cases of atrophic endometrium (50%) were in the age group 50-59 years. This is similar to the 44.4% of nine atrophic cases observed in the same age group in another study of 122 cases[21]. Three out of nine cases (33.3%) of chronic endometritis and endometrial polyps in our study occurred in the age group 40-49 years and this age group was also favoured by these two conditions in another study[21]. We did not have any case of endometrial carcinoma in the one year of study. Similar studies on endometrial biopsies have revealed an incidence of 1.0% and 5.7% of endometrial carcinoma[20,21].

The involuntary omission of age in a total of 15 of the 188 cases (8.0%) in our study was of great concern. Age of the patient has proved to be a very important parameter to critically evaluate the biopsy specimens because both cervical and endometrial lesions have favoured the age group 30-59 years. Age specific care especially for cervical screening after 30 years and exploration for cervical pathology after the age of 40 years is important. Endometrial biopsies were performed in women younger than 30 years in 15.8% of cases of which 75% proved to be normal. Findings like hyperplasia, DPE and polyps are clustered between the ages of 40-54 years.

CONCLUSIONS

Cervical biopsies constituted about 55% of all specimens. The ratio of carcinoma to precancerous lesions is found to be 1:7 in cervical biopsies. Disordered proliferative endometrium was the commonest cause for bleeding in our study. All the cases of disordered proliferative endometrium who had their age mentioned were found to be in the age group 40-54 years of age.

The involuntary omission of age in a total of 15 of the 188 cases (8.0%) in our study is of great concern. Age of the patient has proved to be a very important parameter to critically evaluate the biopsy specimens because both cervical and endometrial lesions have favoured the age group 30-59 years.

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