Original paper

Histopathological Study of Epithelial Metaplasias in Endometrial Hyperplasia

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ABSTRACT **Objective:** The aim of this paperwork is a histopathological study focused on the association of endometrial hyperplasia with epithelial metaplasia to evaluate the ethiopathological relation between these conditions. **Material and methods:** The material we studied was endometrial tissue obtained from biopsies, curetting and hysterectomy specimens from 624 patients investigated in Gynaecologic Ambulatory and hospitalised in Gynaecologic surgery of Emergency Hospital Tg-Jiu and diagnosed with endometrial hyperplasia in a period of 5 years, between 2004 and 2008, cases which were revaluated for epithelial metaplasias. This material was processed by classical technique of paraffin embedding and Haematoxylin-eosin staining in the Laboratory of Anatomopathology in the same hospital. **Results:** From the 624 endometrial hyperplasias, 333 cases were associated with different variants of epithelial changes as follow: ciliated metaplasia (144 cases), eosinophilic metaplasia (107 cases), squamous /morular metaplasia (78 cases), clear cell metaplasia (23 cases) and mucinous metaplasia (7 cases); these epithelial metaplasias were observed either as unique change (more frequently) or associated each other (most frequently ciliated and eosinophilic). Referred to the histological type of endometrial hyperplasia, the ciliated metaplasia and eosinophilic metaplasia were the most frequent epithelial changes associated with simple hyperplasia without atypia (72.90% and 71.02% respectively). In majority, squamous metaplasia and clear cell metaplasia were found in complex hyperplasia without and with atypia (83.33% and 82.60% respectively), while the mucinous metaplasia was associated with atypical complex hyperplasia in all cases. **Conclusions:** The increased frequency of association between endometrial hyperplasia and epithelial metaplasia in this study stand for one common etiopatogenic factor of the two lesion, namely persistent estrogenic stimulus. Generally, the most frequent variants of epithelial changes found in endometrial hyperplasias were ciliated and eosinophilic metaplasias. The significant endometrial lesions, namely atypical complex hyperplasia, have shown an increased propensity to associate squamous and mucinous metaplasia; however, these changes cannot be considered indicators of either synchronous or subsequent endometrial carcinoma.

KEY WORDS *epithelial changes (metaplasias); endometrial hyperplasia; histopathology*

Introduction

The endometrial epithelial metaplasia refers to the process in witch the surface and /or cryptic epithelium is replaced by other cellular types witch are either absent or very rarely seen at this level. Hendrickson and Kempson first described this phenomenon in 1980 [3].

The endometrial metaplastic changes may be the consequence of two processes, namely:

- true metaplastic process, involving most frequently a phenomenon of mullerian differentiation, in which the columnar epithelium can be replaced with a mucosecretory, squamous or ciliated tubal epithelium (epithelia of common mullerian origin) or
- degenerative or regenerative /reparative processes with subsequent changes involving either the surface (most frequently) or glandular epithelium; a good example of this phenomenon is the sincitial eosinophilic change [15]. Therefore, some of these endometrial epithelial changes classified as metaplasias should be designate as "changes", descriptive term that do not imply a specific pathogenic mechanism [8].

The endometrial epithelial metaplasias /changes arise almost always in certain conditions, affecting more often either perimenopausal women or younger women with exogenous or endogenous hyperestrogenism. These endometrial changes may be seen in association with a dishormonal status (anovulatory cycle, polycystic ovaries) or with hormonal therapy (estrogens or tamoxifen), in chronic endometritis or mechanical irritations (IUD); associated with metroragy; associated with endometrial polyps or in endometrial hyperplasias and carcinomas [8].

Histological, there are known some variants of endometrial metaplasias /changes that are variably grouped by different authors but with considerable overlapping between categories. The most comprehensive classification of endometrial epithelial changes include metaplastic and related endometrial changes grouped in 10 distinctive categories [10,13]: 1) squamous /morular metaplasia; 2) mucinous metaplasia; 3) ciliated (tubal) metaplasia; 4) eosinophilic cell change; 5) hobnail cell change; 6) clear cell change; 7) secretory change; 8) surface sincitial change; 9) papilary proliferation; 10) Arias Stella change.

Alternatively, the entities included in this classification are either absent or variably found in other classifications. Therefore, according to other authors, clear cell change and hobnail change are in fact variants of the secretory change or are individually noted without remembering the later one [1,3]. In some of the classifications, the surface sincitial and papilary change is considered a variant of eosinophilic change, the later one being classified more properly as degenerative /regenerative process while the eosinophilic and sincitial changes are considered as separate entities in other classifications [3,8]. Beside, in others opinion, this sincitial and papilary change is different from another distinctive condition namely papilary proliferation that has 2 architectural variants: proliferation with simple papillae and proliferation with complex papillae [4]. For mucinous metaplasia, some authors described 3 architectural subtypes with particular clinical significance: type A (plane architecture), type B (microglandular architecture) and type C (complex architecture and moderate cytological atypia) [9]. Concerning the Arias Stella change, it is not included in other classifications.

The significance of endometrial epithelial metaplasias /changes associated with endometrial hyperplasias emerge from the fact that these conditions frequently mimics the histological and cytological features of hyperplasias making them difficult for histological interpretation.

Material and Methods

This paperwork is an analytical histopathological study, realized retrospectively on endometrial hyperplasias diagnosed in the interval of 5 years between 2004 and 2008, in the Emergency Hospital Tg-Jiu, aiming the assessment of association with different variants of epithelial metaplasias /changes.

The studied material was endometrial tissue from biopsies, curetting and hysterectomy specimens from 624 patients investigated in Gynaecologic Ambulatory and hospitalised in Gynaecologic surgery of Emergency Hospital Tg-Jiu and diagnosed with endometrial hyperplasia. The tissue fragments were processed by classical technique of paraffin embedding and Haematoxylin-eosin staining in Anatomopathology Laboratory from the same hospital.

Results:

This study was realised upon a period of 5 years, 2004 – 2008, on 624 patients in a large range of age (between 22 and 75 years) diagnosed with endometrial hyperplasias; among these, the highest incidence of endometrial hyperplasia was in the fifth decade of life, with 418 cases (66.98%).

The 624-endometrial hyperplasias were classified according with WHO recommendations based on cytological and architectural criteria in: hyperplasia without atypia, simple (515 cases) and complex (81 cases) and hyperplasia with atypia, simple (6 cases) and complex (26 cases) .

Table 1: Histological variants of endometrial hyperplasia according WHO classification.

Endometrial hyperplasia (EH)	EH without atypia	EH with atypia		
	Simple	Complex	Simple	Complex
Nr. cases /percents	511 81.89%	81 12.98%	6 0.96%	26 4.16%

These endometrial hyperplasias were studied for histopathological evaluation of the association with epithelial metaplasias /changes.

The endometrial epithelial metaplasias were found in 333 hyperplasias (53.43%) totalising 359 cases of different histological variants, among in 26 variants were associated each other as two variants per case of hyperplasia.

Table 2: The frequency of endometrial epithelial metaplasia variants

Histological variants of epithelial metaplasias /changes	Nr. cases	Percents %
Ciliated metaplasia	144	40.11%
Eosinophilic change	107	29.80%
Squamous metaplasia	78	21.72%
Clear cell change	23	6.40%
Mucinous metaplasia	7	1.94%

The histological variants of epithelial metaplasias that we found were: ciliated metaplasia (144 cases), eosinophilic change (107 cases), squamous metaplasia (78 cases), clear cell change (23 cases) and mucinous metaplasia (7 cases); these cytoplasmatic alterations were found either as unique finding (more frequently) or

associated each other (26 variants as follow: ciliated and eosinophilic; ciliated and squamous; squamous and eosinophilic; squamous and clear-cells) .

Table 3: Cases of endometrial hyperplasia associated with two variants of epithelial metaplasia per case.

Associations between epithelial metaplasia variants	Cases of endometrial hyperplasia
Ciliated and eosinophilic	7
Ciliated and squamous	3
Squamous and eosinophilic	2
Squamous and clear cell	1

We have also observed the variability of the association between metaplasias and hyperplasias related with the histological type of the later one .

Table 4: The distribution of epithelial metaplasias variants referring to endometrial hyperplasia type

Association endometrial metaplasia (EM)/ hyperplasia (EH)		Total	Ciliated EM	Eosinophilic EM	Squamous EM	Clear cell EM	Mucinous EM
EH without atypia	Simple	511	105	76	12	4	-
	Complex	81	23	20	35	11	-
EH with atypia	Simple	6	2	2	1	-	-
	Complex	26	14	9	30	8	7
Total / % EH associated with EM		624	144 23%	107 17.14%	78 12.50%	23 3.68%	7 1.12%

The ciliated (tubal) metaplasia was the most frequent variant of endometrial epithelial metaplasias (40.11%) found in 144 (23%) cases and most often associated with simple hyperplasia without atypia (105 cases).

In the involved proliferative glands the epithelium was replaced with ciliated columnar cells with pale to eosinophilic cytoplasm and nuclei round to oval in shape with slight nuclear enlargement and often mildly stratified.

These ciliated cells were often interspersed isolated or in small groups among non-ciliated columnar cells, while the glands extensive lined with ciliated epithelium were rare.

Eosinophilic change was present in 107 cases of endometrial hyperplasias (17.14%), more frequent being associated with simple hyperplasia without atypia (76 cases). This variant of endometrial epithelial alteration was the second as frequency (29.80%), followed by the ciliated metaplasia.

As in ciliated metaplasia, eosinophilic change was in majority associated with endometrial hyperplasia without atypia either simple or complex; it was also 8.38 times more frequent in hyperplasia without atypia than in hyperplasia with atypia.

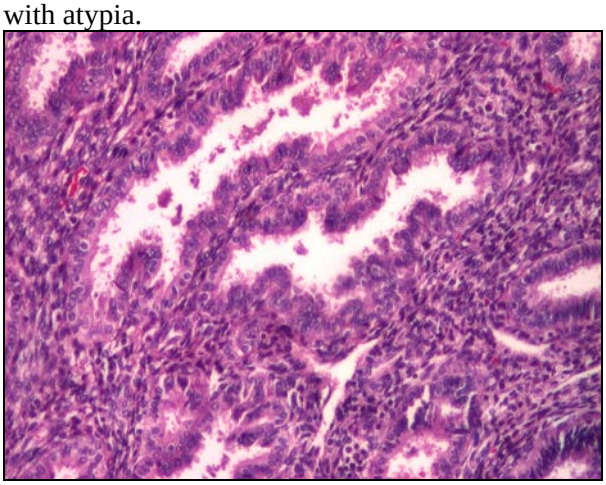

Figure 1: The ciliated (tubal) metaplasia associated with simple hyperplasia without atypia, HE stain, Ob. X 100;

The metaplastic eosinophilic cells were of variable morphology. In some cases, we found cells similar with ciliated cells – columnar, with moderate pale to eosinophilic cytoplasm – but lacking of lumenal cilia.

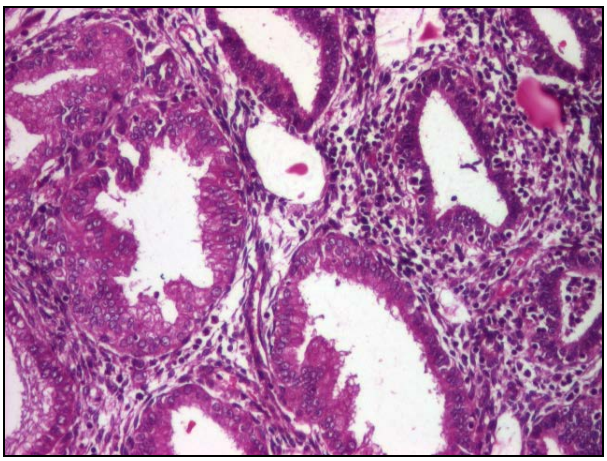

Figure 2: The eosinophilic change associated with simple hyperplasia without atypia, HE stain, Ob. X 100;

A peculiar aspect, seen in 16 cases, was the replacement of surface endometrial epithelium with eosinophilic metaplastic cells having a syncytial and /or papilary growth pattern (the surface papilary syncytial change). In these cases the eosinophilic cells formed cellular aggregates with indistinct cytoplasmatic borders or papillary structures lacking of vascular cores (pseudopapilae).

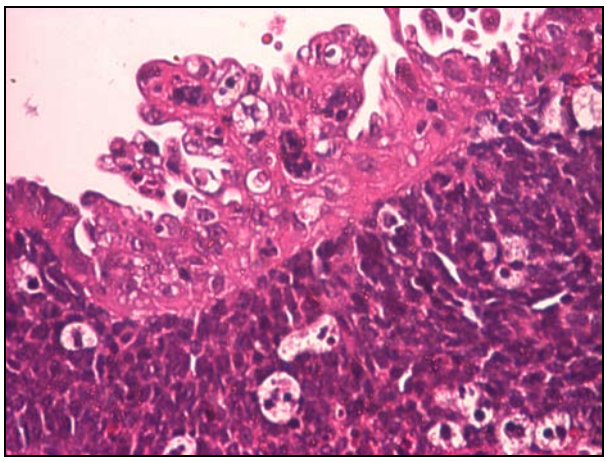

Figure 3: The surface papilary syncytial change associated with simple hyperplasia without atypia, HE stain, Ob. X 200;

Squamous metaplasia was found in 78 cases, representing 21.72% from epithelial metaplasias and associated in 12.50% from endometrial hyperplasias. Distinctive, the squamous metaplasia was more frequent in complex hyperplasia, either without or with atypia (35 and 30 cases respectively).

In majority of endometrial hyperplasia without atypia, simple or complex, the arias with metaplastic squamous epithelium appeared as rounded solid nests filling the glandular lumens and consisted in immature squamous cells (non-keratinised) forming so-called morules. These structures contained uniform rounded, polygonal or, rarely, spindle shaped eosinophilic cells, with indistinct cell borders and less abundant cytoplasm than mature and complete differentiate squamous cells.

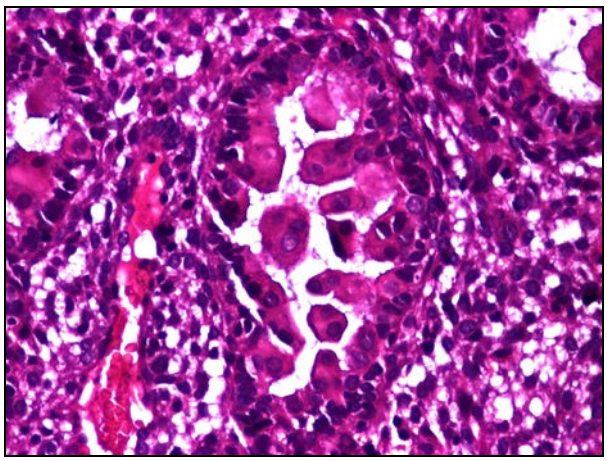

Figure 4: The squamous metaplasia, HE stain, Ob. X 200;

The areas pavement-like of squamous mature metaplasia consist in polygonal keratinised cells with abundant eosinophilic cytoplasm and distinct border cells was more rarely seen (6 cases), all of them in complex hyperplasia either without atypia (1 case) or with atypia (5 cases).

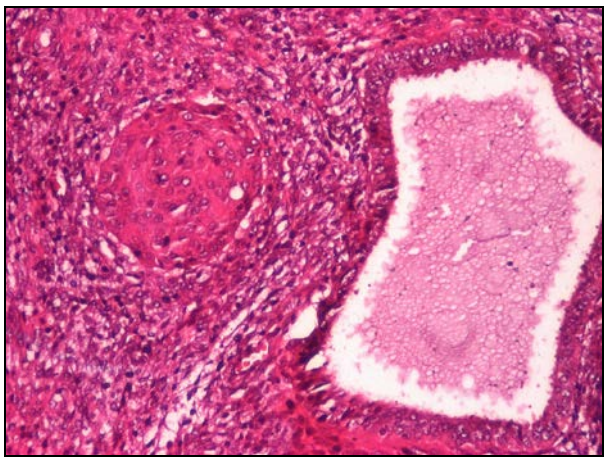

Figure 5: The squamous metaplasia (morules) associated with simple hyperplasia without atypia, HE stain, Ob. X 100;

Another variant of epithelial alteration associated with endometrial hyperplasia was **clear cell change (secretory metaplasia)**, found in 23 cases (6.40%). The epithelium in involved glands was partially or completely substituted by the columnar cells with clear cytoplasm (glycogen rich) and enlarged, basally placed and sometimes hypercromatic nuclei.

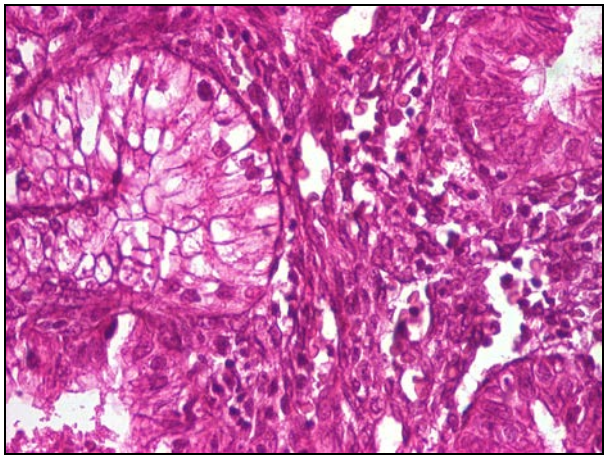

Figure 6: The clear cell change (secretory metaplasia) associated with complex hyperplasia without atypia, HE stain, Ob. X 200;

A peculiar aspect seen in 8 cases was the "hobnail" morphology of metaplastic clear-cell (hobnail clear-cell metaplasia).

As in squamous metaplasia, the clear cell metaplasia was associated with complex hyperplasia, without or with atypia in majority of cases.

The most rare variant of epithelial metaplasia in endometrial hyperplasia was **mucinous metaplasia**, found in 7 cases (1.94%), all of them with focal distribution and associated with complex hyperplasia with atypia.

These cases of mucinous metaplasia corresponded morphologically and architecturally to type C (Nucci). The mucinous metaplastic cells resembling with endocervical epithelium lined architectural complex glands and consisted in tall columnar cells with some nuclear enlargement.

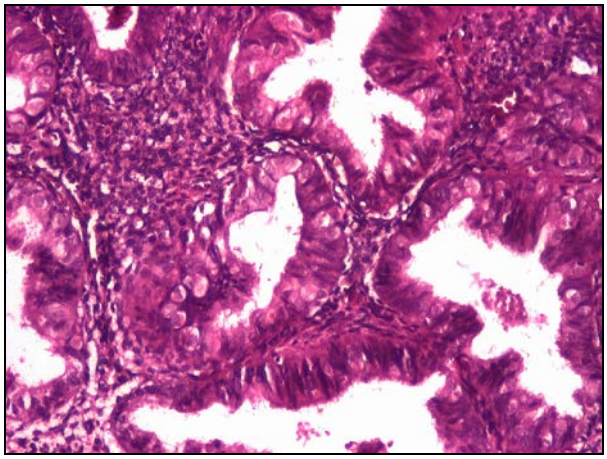

Figure 7: The mucinous metaplasia, associated with complex hyperplasia with atypia, HE stain, Ob. X 200;

Discussion

The association of epithelial metaplasias with endometrial hyperplasias and the association of different variants of the epithelial alterations one another on the background of hyperplasia suggest that many of the later changes are related with the persistent estrogenic stimulus, the most known ethiological factor involved in endometrial hyperplasia **[7]**.

Among the known variants of endometrial epithelial changes, the squamous and ciliated metaplasias are related with persistent estrogenic stimulus, particularly with hyperplasia **[5,7]**. However, the ciliated cells are normally present along the surface epithelium, being most numerous in proliferative endometrium while squamous metaplasia involve frequent the surface epithelium in reparative processes associated with chronic endometritis or IUD **[6,8,12]**. The eosinophilic change is often seen in prolonged estrogenic stimulus, and the surface papilary syncytial change, considered by some authors as variant of eosinophilic change, is most frequent seen as regenerative processes in stromal breakdown and uterine bleeding **[2,11,15]**. The clear cell metaplasia appears more often associated in progesterone uptake than in endometrial hyperplasia; frequently, this epithelial change accompanies the Arias Stella reaction **[8].**

In our study, the epithelial metaplasias /changes were found in 53.43% from endometrial hyperplasias and the most frequent variant was ciliated metaplasia, present in 40.11% cases, followed by the eosinophilic change in 29.80% cases.

These results correspond with the results in similar studies which rapports the same maximal incidence of ciliated metaplasia but contravene to other studies that point out the eosinophilic cytoplasmic transformation as the most frequent metaplastic change **[8,14]**.

Referred to the hyperplasia type, the ciliated metaplasia was by far much more frequent in simple hyperplasia without atypia (72.90%) while 11.11% was associated in hyperplasia with atypia, in majority with complex architecture.

A percent of 71.02% from eosinophilic metaplasias was associated with simple hyperplasia without atypia and only 18.69% was found in complex hyperplasia without atypia; this epithelial alteration was also rare in atypical hyperplasia. The surface papilary and syncytial change was found in simple hyperplasia without atypia in all the cases.

Among the variants of endometrial epithelial metaplasias, the squamous metaplasia was found in majority (83.33%) associated with complex hyperplasias, with and without atypia. These results are congruent with other similar studies which rapport the frequent association of squamous metaplasia with atypical endometrial hyperplasia **[7]**.

The clear cell change (including the variant with hobnail cells) was observed in 3.68% of endometrial hyperplasia, representing 6.40% from all epithelial metaplasias. As in squamous metaplasia, this change was the most frequent in complex hyperplasia, without and with atypia (82.60%).

The most infrequent variant of endometrial epithelial change was mucinous metaplasia that represented 1.94% from all metaplasias. This change was associated with complex hyperplasia with atypia in all the cases that we found and the results were similar with those in other studies which reported the more frequent finding of mucinous metaplasia in complex hyperplasia with atypia than in other types of hyperplasia **[7]**.

The association of more than one variant of epithelial metaplasia with endometrial hyperplasia, noted in some studies was present in our study in 13 cases. In majority of these cases (7 cases), ciliated metaplasia associated eosinophilic

change, in a background of simple hyperplasia without atypia, those epithelial changes being the most frequent among endometrial metaplasias **[14]**. The most rare association was between squamous metaplasia and clear cell change, found in only one case.

Conclusion.

In our study the increased percent of association between endometrial hyperplasias and epithelial metaplasias sustain the common pathogenesis of these conditions involving the persistent estrogenic stimulus. In general, the variant of epithelial metaplasia most frequent associated with endometrial hyperplasia was ciliated metaplasia. This change was followed, as frequency by the eosinophilic change while the mucinous metaplasia was the most rare epithelial change.

Referred to the histological type of hyperplasia, the ciliated and eosinophilic changes were in majority associated with simple hyperplasia without atypia, while the squamous metaplasia was most frequent in complex hyperplasias without and with atypia. All the cases of mucinous metaplasia in our study were observed in complex hyperplasia with atypia, and clear cell metaplasia was most frequent in complex hyperplasia without atypia. In our study, the complex hyperplasia with atypia had a great propensity to associate squamous and mucinous metaplasias; however, it is indicated to avoid considering these variants of epithelial change as indicators of synchronous or subsequent carcinoma.

BIBLIOGRAFIE:

1. Buckley CH, Fox H. -(2002), Biopsy pathology of the endometrium. 2nd ed. London: Arnold;
2. Gersell DJ -(1993), Endometrial papillary syncytial change. Another perspective, Am J Clin Pathol, 99:656-657;
3. Hendrickson MR, Kempson RL.- (1980), Endometrial epithelial metaplasias: proliferations frequently misdiagnosed as adenocarcinoma. Report of 89 cases and proposed classification. Am J Surg Pathol, 4:525–542;
4. Lehman MB, Hart WR.-(2001), Simple and complex hyperplastic papillary proliferations of the endometrium: a clinicopathologic study of nine cases of apparently localized papillary lesions with fibrovascular stromal cores and epithelial metaplasia. Am J Surg Pathol, 25:1347-54;
5. Longacre TA, Kempson RL, Hendrickson MR.- (1995),Endometrial hyperplasia, metaplasia and carcinoma. In: Fox H, ed. Haines and Taylor: obstetrical and gynaecological pathology, 4th ed. New York: Churchill Livingstone, p:421–510;
6. Masterson R, Armstrong EM- (1975), More IAR. The cyclical variation in the percentage of ciliated cells in the normal human endometrium. J Reprod Fertil, 42:537–540;
7. Michael T. Mazur, Robert J. Kurman- (2005), Diagnosis of Endometrial Biopsies and Curettings. A Practical Approach. Springer Science+Business Media, Inc, Second Edition, p: 195-204;
8. Mojgan Devouassoux-Shisheboran- (2003), Pathologie du corps uterin, Metaplasies de l`endometre et leurs pieges. In Bulletin de la Division Francaise de l`AIP, No 38;
9. Nucci MR, Prasad CJ, Crum CP, Mutter GL.-(1999), Mucinous endometrial epithelial proliferations: a morphologic spectrum of changes with diverse clinical significance. Mod Pathol, 12:1137-42;
10. Ronnett BM, Kurman RJ.- (2002) Precursor lesions of endometrial carcinoma. In: Kurman R, ed. Blaustein's pathology of the female genital tract. 5th ed. New York: Springer-Verlag, p: 467–500;
11. Rorat E, Wallach RC- (1984), Papillary metaplasia of the endometrium. Clinical and histopathologic considerations. Obstet Gynecol, 64:90S-92S:
12. Silverberg S.- (1992), Significance of squamous elements in carcinoma of the endometrium: a review. In: Fenoglio C, Wolfe M, eds. Progress in surgical pathology, vol 4. New York: Masson,p:115–136;
13. Silverberg SG, Kurman RJ.-(1992), Tumor-like lesions. In: Rosai J (ed). Tumor of the Uterine Corpus and Gestational Trophoblastic Disease. Armed Forces Institute of Pathology: Washington, DC, p: 191–204;
14. Suzuko Moritani, Ryoji Kushima, Shu Ichihara, Hidetoshi Okabe, Takanori Hattori, Tadao K Kobayashi and Steven G Silverberg- (2005) , Eosinophilic cell change of the endometrium: a possible relationship to mucinous differentiation. Modern Pathology, p: 18, 1243–1248;
15. Zaman SS, Mazur MT.-(1993), Endometrial papillary syncytial change. A nonspecific alteration associated with active breakdown. Am J Clin Pathol, 99:741–745;

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