

Great mimickers: Tumor-like lesions of uterine corpus

Divya Shekhar Shetty,
Alka Vikas Gosavi,
Prashant Shankarrao Murarkar,
Kalpana Ranjitsingh Sulhyan

Department of Pathology, Government Medical
College Miraj, Miraj, Maharashtra, India

Address for correspondence:

Dr. Divya Shekhar Shetty,
Department of Pathology,
Government Medical College Miraj,
Miraj, Sangli - 416 410, Maharashtra, India.
E-mail: divya_shetty61@yahoo.com

WEBSITE: ijhs.org.sa

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ABSTRACT

Objective: The objective of the study was to evaluate the relative occurrence of uterine corpus tumor-like lesions and to establish a clinicopathological correlation.

Methods: A 5-year study was conducted on histopathologically diagnosed cases of tumor-like lesions of the uterine corpus. The lesions were classified according to the recent World Health Organization classification. Relevant clinical findings and histomorphologic details were noted and analyzed.

Results: A total of 85 cases of tumor-like lesions were included in the study. Multiparous women (88.2%) were most commonly affected and endometrial polyp (89.4%) was the most common lesion. Endometrial polyp showed a definite predilection during the 3rd and 4th decades of life (56.6%) whereas Arias-Stella reaction was seen in pregnant women and squamous metaplasia was seen in peri and postmenopausal women. Patients with endometrial polyp presented mostly with heavy menstrual bleeding (HMB) (32%) and Arias-Stella reaction with HMB. Two cases of squamous metaplasia one presented with HMB and pain in the abdomen. Most of the endometrial polyps were single (90.8%) and sessile (68.4%), hyperplastic type (56.6%) and the adjacent endometrium were mostly atrophic (42.1%) or in proliferative phase (34.2%). The mean age in years of premenopausal women was 39.34 ± 5.01 and postmenopausal women were 62.66 ± 7.26 . The mean size of the polyp, parity, number of polyps and association with leiomyoma was not significantly different between premenopausal and postmenopausal women. Adenomyosis was seen in 11 cases of the endometrial polyp.

Conclusions: Although tumor-like lesions of the uterine corpus as the name suggests tend to mimic the tumors, certain clinical and histopathological features can help in making the accurate diagnosis and thus avoid unnecessary radical surgeries.

Keywords: Arias-Stella reaction, differential diagnosis, endometrial polyp, recent classification, squamous metaplasia

Introduction

Endometrial curettage and biopsy account for a major proportion of the workload in surgical pathology. The most common indication is abnormal uterine bleeding (AUB). The main role of the pathologist is to accurately exclude endometrial cancer or a precancerous lesion. AUB is a common complaint in all age groups, including adolescents.^[1]

The World Health Organization (WHO) classification of uterine corpus tumors 2014 includes tumor-like lesions – endometrial polyp, metaplasia, Arias-Stella reaction, and lymphoma-like lesion.^[2] These tumor-like lesions mimic malignant tumors clinically and even on histopathology. Hence, awareness of these lesions is essential to avoid over-diagnosing them.

By definition, endometrial polyp^[3,4] protrudes into the uterine cavity and shows a biphasic growth of endometrial glands

and stroma along with blood vessels. They occur in pre- and postmenopausal women and present as AUB.^[5] They are thought to be related to hyperestrogenism.^[6] Polyps may be single or multiple, sessile or broad based, pedunculated, or attached to the endometrium by a slender stalk. They usually have a smooth surface and small cysts may be seen on sectioning. They can arise anywhere in the endometrium, including the lower uterine segment, but are most common in the fundus.

Endometrial metaplasias^[2,4] are non-neoplastic and show replacement of normal endometrial epithelium by another type of differentiated epithelium. Metaplasias are associated with endometrial polyps, exogenous hormone therapy, intrauterine device, chronic endometritis, and pyometra. Progestin therapy given for endometrial hyperplasia or endometrioid adenocarcinoma may result in various epithelial metaplasias within the malignant or premalignant lesion. By itself, it is

not associated with clinical symptoms. The various types of metaplasia include squamous, mucinous, papillary syncytial, eosinophilic and ciliated cell, hobnail, secretory, and papillary metaplasia, of which squamous being the commonest.

Arias-Stella reaction^[2,3,4] is also known as Arias-Stella phenomenon. It refers to hypersecretory glands in the gestational endometrium. The hallmark features are the cells with nuclear atypia exhibiting enlargement, hyperchromasia, and irregularity.^[2] The importance of this change is the difficulty that occurs in distinguishing it from hyperplasia and adenocarcinoma.^[2] It is almost always associated with pregnancy, either intrauterine or ectopic, or with the trophoblastic disease. It rarely occurs secondary to hormone therapy, especially progestins; occasionally, there is no obvious cause.^[7] The diagnosis is exclusively done on microscopy. They resemble, but should not be mistaken for clear cell carcinoma.^[3,4]

Lymphoma-like lesions^[2,3] are more common within the cervix but have rarely been described in the endometrium.^[8] Histologically, they are characterized by dense aggregates of lymphoid cells, often with large numbers of blasts and a starry-sky appearance, forming a superficial band-like infiltrate. Lymphoid follicles with germinal centers, which may be large and ill-defined, are typically present. Lymphoma-like lesions represent an exaggerated form of chronic endometritis. The polymorphic nature of the infiltrate together with the presence of germinal centers and the superficial location of the inflammation helps to distinguish lymphoma-like lesion from malignant lymphoma, as does the absence of a mass lesion grossly.

The aim of this study is to classify tumor-like lesions as per the WHO 2014 and to establish a clinicopathological correlation. An attempt has been made to re-emphasize on their histopathological features and also their differential diagnosis to avoid the common mistake of over-diagnosing these cases.

Methods

The present study was a retrospective study conducted on 85 cases in the department of pathology of our institution for a study period of 5 years after taking permission and clearance from the ethical committee of the institution. The study was started by data collection from histopathology department and retrospectively, the patient's record was reviewed. All specimens with unequivocal histopathology diagnosis of tumor-like lesions of the uterine corpus as per the WHO classification 2014 were included in the study. All histopathology cases which were tumors and precursor lesions without any associated tumor-like lesions were excluded from the study. The specimens types received were endometrial curettage, biopsy, polypectomy, and hysterectomy. Conventional tissue processing, standard staining by hematoxylin and eosin, and examination by light microscopy were done.

Clinical data were obtained, and the tumors were classified as per the WHO classification of tumors of the uterine corpus, 2014. The data thus compiled were analyzed for various parameters such as age, parity, clinical features, clinical diagnosis, histopathological features, and incidence of the different histological types. The limitation of the study was that some of the cases had missing data and incomplete documentation. The obtained parameters were evaluated using descriptive statistical analysis and presented in terms of percentage. Chi-square test was used for comparison of categorical variables and Students t-test was used for numerical variables.

Results

During this 5-year period, a total of 85 tumors like lesions were observed. Of these, endometrial polyp 76 (89.4%) was the most common tumor-like lesion of the uterine corpus followed by Arias-Stella reaction 7 (8.2%) and metaplasia 2 (2.4%), as summarized in Table 1.

Distribution of tumor-like lesions with respect to age and parity is summarized in Table 2. Tumor-like lesions were more common in multiparous females ($n = 67$, 88.2%). The youngest patient with endometrial polyp was 30 years old and the oldest was 80 years old. Endometrial polyp showed a definite predilection during the 3rd and 4th decades of life ($n = 43$, 56.6%). Thirty-one cases (40.8%) occurred after 50 years and only 2 cases (2.6%) before 30 years. Arias-Stella reaction was seen in pregnant women whereas squamous metaplasia was seen in peri and postmenopausal women.

Patients with endometrial polyp presented mostly with HMB ($n = 27$, 35.5%), followed by mass descending per vaginam ($n = 21$, 27.6%), pain in abdomen ($n = 18$, 23.1%), postmenopausal bleeding ($n = 7$, 14.1%), white discharge per vaginam ($n = 2$, 2.6%), and premenstrual spotting ($n = 1$, 1.3%). All ($n = 7$, 100%) patients with Arias-Stella reaction were pregnant (amenorrhea) and presented with HMB. Out of the 2 cases of squamous metaplasia, one presented with HMB and the other with pain in abdomen. The distribution with respect to clinical features is summarized in Table 2.

The clinical diagnosis of the patients with endometrial polyps was mostly dysfunctional uterine bleed (DUB) ($n = 45$, 59.2%). All the patients with Arias-Stella reaction were pregnant and hence the clinical diagnosis was amenorrhea whereas the cases of squamous metaplasia were clinically diagnosed as under evaluation for white per vaginam discharge.

Table 1: Distribution of tumor-like lesions of the uterine corpus

Lesions	Number (%)
Endometrial polyp	76 (89.4)
Arias-Stella reaction	7 (8.2)
Squamous metaplasia	2 (2.4)
Total	85 (100)

Table 2: Distribution of tumor-like lesions with respect to age, parity, and clinical features

Demographics and clinical features	Endometrial polyp	Arias-Stella reaction	Squamous metaplasia	Number (%)
Age (years)				
≤30	2	4	-	6 (7.1)
31–40	24	3	-	27 (31.8)
41–50	19	-	1	20 (23.5)
51–60	8	-	-	8 (9.4)
≥61	23	-	1	24 (28.2)
Parity				
Nulliparous	2	0	-	2 (8.8)
Uniparous	7	2	-	9 (3)
Multiparous	67	5	2	74 (88.2)
Clinical features				
Heavy menstrual bleeding	27 (35.5)	7 (100)	1 (50)	35 (41.2)
Pain in abdomen	18 (23.1)	-	1 (50)	19 (22.4)
Postmenopausal bleeding	7 (14.1)	-	-	7 (8.2)
Premenstrual spotting	1 (1.3)	-	-	1 (1.2)
Mass descending per vaginam	21 (27.6)	-	-	21 (24.7)
White discharge per vaginam	2 (2.6)	-	-	2 (2.4)

The mean age in years of premenopausal women was 39.34 ± 5.01 and postmenopausal women was 62.66 ± 7.26 . The mean size of the polyp was not significantly different ($P = 0.23$) between premenopausal (1.93 ± 1.02) and postmenopausal women (1.69 ± 0.63). In addition, parity ($P = 0.54$), number of polyps ($P = 0.29$) and association with leiomyoma ($P = 0.60$) not significantly different between premenopausal and postmenopausal women. These findings are summarized in Table 3.

Gross and microscopic features

Endometrial polyp

In the present study, endometrial polyp was either single or multiple, sessile or pedunculated mass with size ranging from 0.5 cm to 5 cm [Figure 1a]. Single ($n = 69$, 90.8%) and sessile ($n = 52$, 68.4%) were more common. Microscopy showed polypoidal tissue lined by cuboidal epithelium. The core of the polyp showed endometrial glands and stroma. The stroma showed areas of fibrosis, thick-walled blood vessels and infiltration by mononuclear cells [Figure 1b]. Most of the polyps were hyperplastic type ($n = 43$, 56.6%) and the adjacent endometrium was mostly atrophic ($n = 32$, 42.1%) or in proliferative phase ($n = 26$, 34.2%). Out of 76 endometrial polyps, five were polypectomy specimens hence, the status of the adjacent endometrium and whether they were sessile or pedunculated could not be evaluated. The distribution of the gross features, microscopic type and status of the adjacent endometrium is summarized in Tables 4 and 5, respectively. Adenomyosis was seen in 11 cases of the endometrial polyp.

Arias-Stella reaction

The microscopic examination of the endometrial curettage specimens showed bits of endometrium composed of

Table 3: Clinical features of endometrial polyp among premenopausal and postmenopausal women

Clinical diagnosis	Premenopausal	Postmenopausal	P-value
Number of cases	41	35	-
Mean age in years (standard deviation)	39.34 ± 5.01	62.66 ± 7.26	-
Parity			
Nulli/Uni-parous	4	5	0.54
Multiparous	37	30	0.29
Number of polyps			
Single polyp	39	31	
Multiple polyp	2	4	
Mean size in cm	1.93 ± 1.02	1.69 ± 0.63	0.23
Associated with leiomyoma	14	10	0.60

Table 4: Distribution of gross features of endometrial polyp

Gross	Single	Multiple	Total (%)
Sessile	48	4	52 (68.4)
Pedunculated	16	2	18 (23.7)
Both	-	1	1 (1.3)
Not known	5	-	5 (6.6)
Total (%)	69 (90.8)	7 (9.2)	76 (100)

endometrial glands separated by compact stroma. The glands were lined by tall columnar cells with abundant pale to vacuolated cytoplasm and large bulbous nuclei with irregular outline, smudged or vesicular chromatin, and showed focal pseudostratification. At places hobnail cells were seen. In areas tufting, budding and papillary infoldings of the epithelium were noted [Figure 1c].

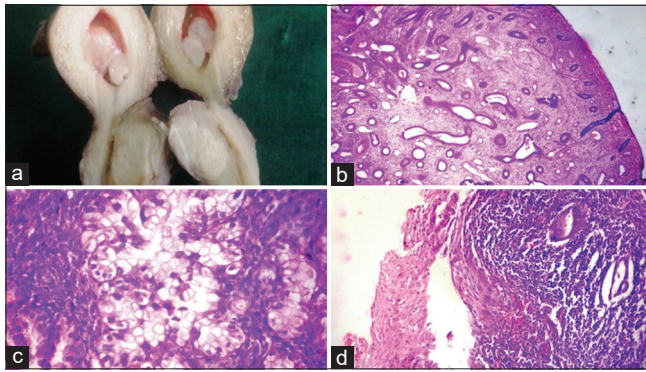


Figure 1: (a) Gross photograph of the endometrial polyp with a leiomyoma in cervix, (b) microphotograph of endometrial polyp (hematoxylin and eosin stain, $\times 10$), (c) photomicrograph of Arias-Stella reaction showing irregularly dilated glands along with decidua (hematoxylin and eosin stain, $\times 10$), (d) photomicrograph showing foci squamous metaplasia of surface endometrium (hematoxylin and eosin stain, $\times 10$)

Table 5: Distribution of types of endometrial polyp and status of adjacent endometrium in an endometrial polyp

Histopathological features	Number (%)
Types of endometrial polyp	
Hyperplastic polyp	43 (56.6)
Atrophic polyp	22 (28.9)
Functional polyp	11 (14.5)
Type of endometrium	
Autolytic	4 (5.3)
Basal	1 (1.3)
Endometritis	2 (2.6)
Proliferative phase	26 (34.2)
Secretory phase	6 (7.9)
Atrophic	32 (42.1)
Not known	5 (6.6)

Metaplasia

On gross examination, the endometrium was unremarkable. The microscopic examination of both the cases showed evidence of acute on chronic nonspecific endometritis (which explains the pain in the abdomen) and the surface endometrium at places showed round to polygonal cells with dense eosinophilic cytoplasm [Figure 1d]. The nuclei showed no atypia.

Discussion

In the year 2003,^[9] the WHO classified tumors of the uterine corpus as epithelial tumors and related lesions, mesenchymal tumors, mixed epithelial and mesenchymal tumors, gestational trophoblastic disease, miscellaneous tumors, lymphoid and hematopoietic tumors, and secondary tumors. Epithelial tumors and related lesions were further subclassified as endometrial carcinoma, endometrial hyperplasia, endometrial polyp, and tamoxifen related lesions. In 2014^[2] classification, the WHO replaced the term epithelial tumors and related lesions with

epithelial tumors and precursors. Under this endometrial carcinomas and a new sub-classification tumor-like lesions were introduced. Polyp, metaplasias, Arias-Stella reaction, and lymphoma-like lesion were included under tumor-like lesions.

Endometrial polyp

The age range showing that the greatest frequency of endometrial polyp in the present study was 40–59 years. This finding was similar to the studies done by Peterson and Novak,^[10] Van Bogaert,^[11] and Costa-Paiva *et al.*^[12] About 97.4% of endometrial polyps in the present study were seen in multiparous females which were similar to the findings by Costa-Paiva *et al.*^[12] (91.4%).

In the present study, the sizes of endometrial polyps ranged from 0.5 to 5 cm. About 49.4% of the polyps were <2 cm and 50.6% were 2 cm or more in size. Hafizi *et al.*^[13] studied 82 polyps and observed that polyps which were <2 cm in size were 46.3% and those that were 2 cm or more in size were 53.7%. These findings were analogous to our study. They also observed that 46.3% had a narrow base and 53.7% had a wide base. The mean polyp size was 2.39 ± 2.63 cm. In terms of location in the uterus, the posterior wall was the most common. The mean size in our study was 1.74 cm.

The mean age in years of premenopausal women was 39.34 ± 5.01 and postmenopausal women were 62.66 ± 7.26 . The mean size of the polyp, parity, number of polyps, and association with leiomyoma was not significantly different between premenopausal and postmenopausal women. Hence, the pathogenesis of endometrial polyp is multifactorial and excess of estrogen may not be the sole causative agent.

In the present study, the number of endometrial polyps varied from one to three. Solitary endometrial polyps (89.5%) were more common, which were analogous with other studies.^[10,14,15]

In the present case, all the polyps were lined by cuboidal epithelium. The core of the polyp showed endometrial glands and stroma. The stroma showed areas of fibrosis, thick-walled blood vessels and infiltration by mononuclear cells. Hyperplastic endometrial polyp (56.6%) was the most common type.

The differential diagnosis includes adenomyoma, which may also present as a polypoidal mass and show the presence of glands without atypia. It was ruled out because their stroma is predominantly composed of smooth muscle. It also needs to be differentiated from atypical polypoidal adenomyoma which shows atypical endometrial glands set in a predominantly smooth muscle stroma.^[3,4]

Arias-Stella reaction

The diagnosis is typically straightforward, particularly since the sampling will often contain other gestational features

such as decidua, placental, and fetal tissue. However, Arias-Stella reaction can be present in the endometrium following a spontaneous abortion; in such cases, the patient may not even know she was pregnant and an endometrial sampling performed after a time of bleeding may only contain a bit of residual involuting endometrium that does not contain features of well-developed decidualization. In the absence of a good clinical history and in the absence of good decidualization, the presence of striking cellular and nuclear atypia of cells of Arias-Stella reaction in involuting endometrial glands may be mistaken for clear cell carcinoma.^[3,4]

It is differentiated from adenocarcinoma on the following basis, Arias-Stella reaction occurs in females who experienced a recent pregnancy or are pregnant, whereas clear cell carcinoma is almost always postmenopausal. Furthermore, in Arias-Stella reaction, the cells are not mitotically active or show rare mitotic figures and the chromatin is smudged rather than coarsely granular. In addition, the stromal decidual reaction is often associated with the glands demonstrating Arias-Stella reaction.^[2,3,4] Glandular epithelium of the cervix and fallopian tube may show Arias-Stella reaction and it may also involve endometriosis or vaginal adenosis.^[16]

Squamous metaplasia

Squamous metaplasia of endometrium may range from highly keratinized epithelia that exfoliate anucleate squames to sheet-like proliferation of cells with indistinct cytoplasmic margins, no obvious keratinization and often a rounded contour (morules) and are intimately mixed with benign or malignant endometrial glands. It has been described in various benign conditions, including hyperplasia, endometritis, and endometrial polyps and it may also be seen in low-grade adenocarcinoma of the endometrium. In India, approximately 6% of the adult population suffers from sexually transmitted infections/reproductive tract infections and present with per vaginam discharge. Hence, they are an important differential diagnosis.^[17]

Ichthyosis uteri is a rare condition in which the entire surface of the endometrium is replaced by stratified squamous epithelium and was studied by Murhekar *et al.*^[18] and Bewtra *et al.*^[19] However, in our case, only focal areas of the surface endometrium showed stratified squamous epithelium.

The epithelioid appearance of trophoblast cells in a placental site nodule (PSN) can mimic squamous metaplasia of the endometrium. PSN is usually found in young women. Typically, the trophoblast is embedded in a hyalinized eosinophilic background, which helps to differentiate it from squamous metaplasia.

Endometrial involvement by cervical squamous cell carcinoma can also be a mimicker. Cervical cancer is quite common and, therefore, is a very important differential diagnosis.^[20,21] As in the case of cervical squamous dysplasia, the nuclear features

should be evident. Irregular contours of cell aggregates, premature cytologic differentiation, and necrosis should also raise concern for carcinoma. As in the case of cervical squamous dysplasia, evaluation of the cervix and use of immunostaining for p16 and MIB-1 may be helpful.

Before dismissing endometrial alterations as benign, it is important to determine whether the pathology correlates with the clinical presentation. Postmenopausal female, prior history of atypical hyperplasia or carcinoma or radiological findings suggestive of uterine mass should prompt further diagnostic evaluation of the endometrium. Therefore, checking into the detail of the clinical history or direct communication with the gynecologist is a prudent step when faced with any of these endometrial alterations and is more than compensated by the increased chance to enable the correct management of a patient and avoid patient mismanagement. Histologic findings of foamy histiocytes in the endometrial stroma and presence of large amounts of necrosis should also prompt caution.

Conclusions

Multiparous women are most commonly affected with tumor-like lesion of the uterine corpus and endometrial polyp was the most common lesion. Endometrial polyp showed a definite predilection during the 3rd and 4th decades of life whereas Arias-Stella reaction was seen in pregnant women and squamous metaplasia was seen in peri and postmenopausal women. The clinical diagnosis of the patients with endometrial polyps was mostly DUB, Arias-Stella reaction was amenorrhea whereas squamous metaplasia as under evaluation for white PVD. The clinical features of endometrial polyp do not differ between premenopausal and menopausal women. A number of benign entities may be difficult to distinguish from neoplasms in the female genital tract. The suspicion of malignancy increases in the postmenopausal age group. Hence, being aware of the spectrum of such lesions may allow their correct diagnosis and prevent overdiagnosis and excessive treatment.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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