Case Report

Endometrial Serous Carcinoma Arising From Adenomyosis: A Clinico-Pathological Insight

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Abstract

Objective: Endometrial cancer (EC) is the most commonly diagnosed malignancy and has the second-highest mortality rate among gynecological cancers. Adenomyosis is well-known for abnormal uterine bleeding and is a widely reported entity; however, an EC arising from the adenomyosis is a rare event; even rarer is the occurrence of serous endometrial carcinoma.

Case report: A 60-year post-menopausal female presented with post-menopausal bleeding. Subsequently, she underwent a hysterectomy, which showed atrophic and cystic endometrium with extensive adenomyosis and atypical endometrial glands, which are diffusely P53 positive with intervening negative benign and focally positive dysplastic endometrial glands. A final diagnosis of serous endometrial carcinoma arising from adenomyosis was rendered. In a table format, previously reported serous endometrial carcinoma Arising cases from adenomyosis using PubMed search had been described.

Conclusion: Serous endometrial carcinoma arising from adenomyosis (<20 cases reported) and has a slightly more dismal prognosis than those deriving from the endometrial cavity. Hence, this case report highlights the occurrence, rarity, and importance of such an entity.

Keywords: Endometrial Neoplasms; Adenomyosis; Menopause; Carcinoma in Situ; Endometrium; Carcinoma

Introduction

Among the gynecological cancers, the second most common cause for mortality in females is caused by endometrial cancer (EC) (1). As stated by Bokhman et al. (2) in 1983, EC is divided into two essential categories. The subgroups I and II of EC are represented by the endometrioid and serous carcinoma, respectively. The endometrioid subgroup has a favorable prognosis, whereas serous subgroup II cancers have a dismal prognosis. This traditional classification is based on clinical, endocrinological, and histopathological features (2). Adenomyosis is defined as ectopic endometriosis, which invades the endometrial glands into the uterine myometrium (3). The prevalence of adenomyosis ranges widely from 18 to 66%, and hysterectomy is the treatment for the

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patient with persistent severe pain and not responding to hormone medication (4). Endometrial adenocarcinoma and adenomyosis are common findings in the uterus. However, endometrial cancer arising in adenomyosis is a rare event (1-4). It is estimated that there are approximately up to several dozens of type I endometrial cancers arising in adenomyosis (5, 6). However, it is infrequent to have type II endometrial cancers reported as occurring in lesions of adenomyosis (7). Overall, less than 20 cases have been reported in the literature of serous endometrial carcinoma (SEC)/ Serous endometrial carcinoma in situ (SEIC) arising from adenomyosis.

Hence, we present the index case so that both clinicians and pathologists will be aware of this phenomenon as they deal with adenomyosis cases in day-to-day practice. Therefore, adenomyosis patients should be investigated and examined thoroughly, both clinically and histopathologically, to rule out the malignancy.

Case report

A 60-year post-menopausal female with para (number of births of viable offspring) 3, living children 3 [P3L3] presented to the postgraduate institute of medical sciences (PGIMER) Ram Manohar Lohia (RML) Hospital, New Delhi in gynecology outpatient department (OPD) with complaints of bleeding per vagina for four years in March 2020. She had been menopausal over the previous 07 years and was known for hypothyroidism and hypertension on medication with no other relevant clinical history. On examination patient's abdomen was soft, no lump was identified. Per-vagina uterus was anteverted, size 6-8 weeks with bilateral fornices free. Hysteroscopy showed a fibroid of 1.5x1.5cm in the anterior wall. Endometrial biopsy was done and received at our department in multiple small bits. Microscopy showed both benign endometrial glands along with glands lined by atypical epithelium with hobnail nuclei, moderate nuclear pleomorphism, coarse chromatin, and prominent nucleoli with mild to moderate amount of eosinophilic to clear cytoplasm. Brisk mitotic activity was noted, and the surrounding stroma showed moderate mixed inflammatory infiltrate (Figure 1a). The atypical glands on immunohistochemistry (IHC) showed diffuse nuclear positivity for p53 (Figure 1b) with a Ki-67 labeling index of >70% in the highest proliferative area (Figure 1c) and were negative for estrogen receptor (ER) and Wilm's tumor-1 (WT1) (Figure 1d).

An MRI done following this showed a hypointense lesion of 15x17x 18mm arising from the anterior uterine wall suggestive of an intramural fibroid. Endometrial thickness was measured to be about 7.6 mm.

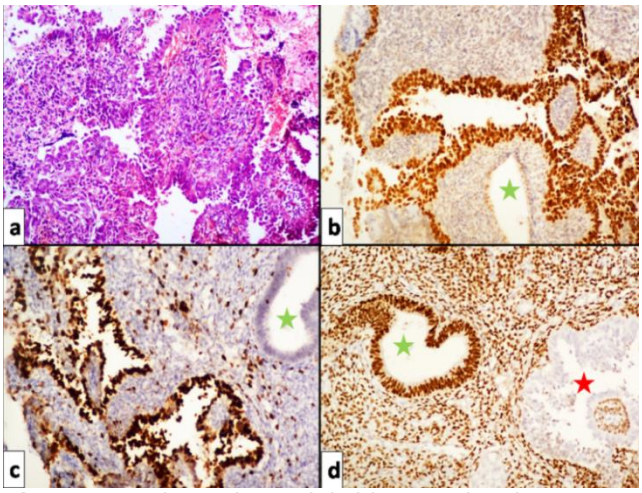

Figure 1: a) Endometrial biopsy showing tumor composed of short branching papillary structures with high-grade nuclei and scalloped apical borders. These fibrovascular papillae are lined by epithelial cells with large atypical nuclei, prominent nucleoli, and scant eosinophilic to clear cytoplasm. b) Tumor cells showing diffuse nuclear immunopositivity for P53 while the interspersed resting benign endometrial glands are negative (green star). c) The Ki-67 proliferating index is high in the tumor cells, while the resting endometrial glands are negative (green star). d) Estrogen receptor (ER) shows positivity in resting endometrial glands (green star), while tumor cells are negative (red star)

No other ovarian or pelvic growth was noted. Subsequently, the patient underwent hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and lymph node dissection. The patient did not receive any neoadjuvant chemo-radiotherapy. On gross examination, the uterus and cervix were enlarged and distorted, measuring 14.5x 10.5x 4cm. On serial slicing through the uterus, an intramural fibroid was identified, measuring 1cm in diameter along with diffuse thickening of endometrium measuring 3.5x1.5x1.5 cm. Myometrium also showed tiny pinpoint hemorrhage like areas. Extensive sampling of the endometrium and myometrium was done.

Endometrium revealed an atrophic, cystic, weak proliferative endometrium. Myometrium showed extensive adenomyosis (Figure 2a) with foci of glands lined by atypical columnar cells showing

hyperchromatic nucleus, moderate nuclear pleomorphism, and a moderate amount of eosinophilic to clear cytoplasm (Figure 2 b-d). There were areas of endometrial glandular dysplasia (DG), serous endometrial intraepithelial carcinoma (SEIC), along foci of invasion into the myometrium (Figure 2 e, f). On IHC, the areas of SEC in the adenomyotic glands showed diffuse staining by p53 (strong nuclear) and high Ki-67, while dysplastic glandular areas show weak patchy nuclear staining for p53 and low Ki-67 and resting Endometrium (BE) was negative (Figure 2 g-h). Estrogen receptor showed positivity in resting endometrium while tumor cells were negative, and dysplastic endometrial glands show patchy positivity (Figure 2 i). In view of the biopsy and subsequent hysterectomy findings, a final diagnosis of endometrial serous carcinoma arising from extensive adenomyosis was rendered.

Discussion

More than 100 years ago, carcinoma arising from adenomyosis was described; however, in the 1950s, Colman et al. (5) had put forwarded diagnostic criteria for the carcinomas arising from adenomyosis. These encompass: "I) the endometrial cavity or pelvis should not contain a tumor; II) the source of origin of the tumor must be seen arising from the epithelium within the focus of adenomyosis instead of invasion from another source, and III)

The diagnosis of adenomyosis should be supported by the presence of endometrial (adenomyotic) stromal cells. Even though our case doesn't fit all three criteria word by word, we believe that this case should be considered as that of serous carcinoma arising from adenomyosis. Firstly, multiple foci of adenomyosis, both involved and uninvolved by malignant serous cells, were present in the uterus. Benign, resting endometrial glands, and benign endometrial stromal cells were present surrounding the malignant glands. Secondly, no direct connection could be established between the areas of adenomyosis with either the invasive component of ESC or the noninvasive serous EIC within the endometrial cavity.

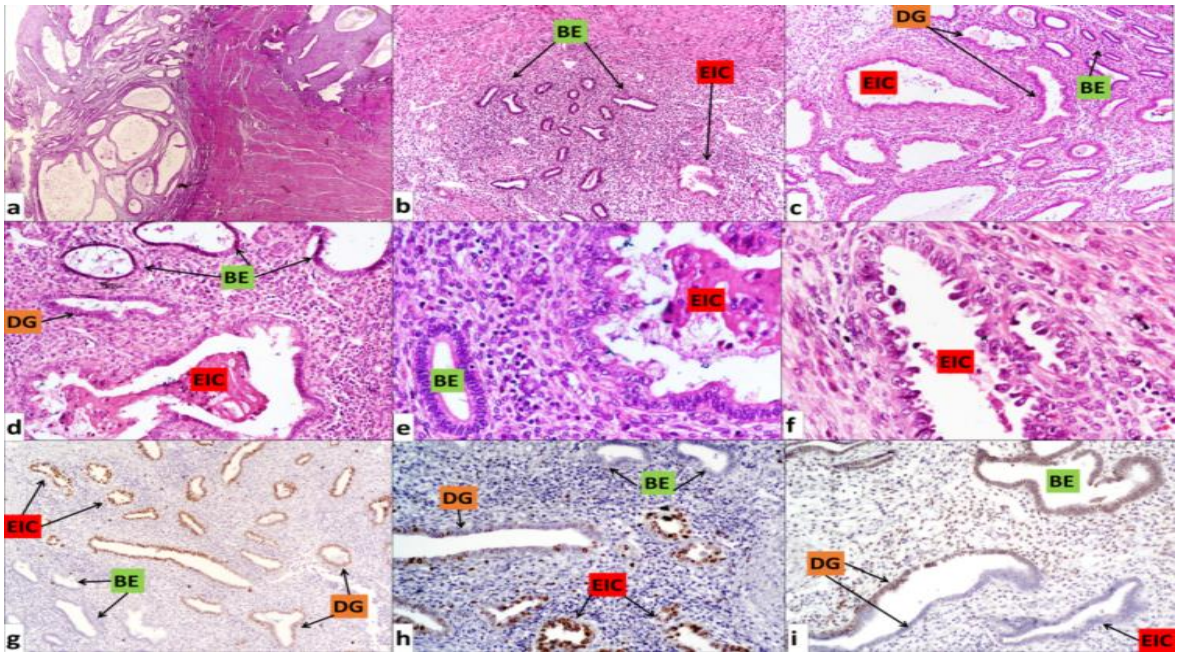

Figure 2: a) Hematoxylin and eosin (H&E) section showing eutopic atrophic, cystic endometrium with foci of adenomyosis. b-d) Higher magnification showing BE along with EIC having high-grade nuclei, coupled with the scalloped apical borders clinching towards the serous carcinoma. e, f) These adenomyotic areas showing numerous benign resting endometrial glands (BE) along with endometrial glandular dysplasia (DG) and foci of endometrial glands of serous intraepithelial carcinoma (EIC) surrounded by bands of smooth muscles. g) EIC area showing diffuse strong nuclear positivity for P53 while DG having weak nuclear positivity and BE are negative for P53. h) Similarly, the Ki-67 proliferative index is diffuse and robust in the EIC area, while DG showing weak activity and BE is negative. i) Estrogen receptor staining showed positive in resting endometrial (BE), whereas partially loss in DG and almost complete loss of expression in EIC

Furthermore, IHC for P53 established SEIC in foci of the glandular lining of the adenomyosis, hence canceling out the possibility of an invasion from another source. Put together; the findings suggest that the lesions of serous EIC may likely have arisen from adenomyosis (1-5).

Endometrial adenocarcinoma and adenomyosis are frequent findings in the uterus (2-5). However, endometrial cancer arising in adenomyosis is an uncommon phenomenon (5-7). There are many reports available in the literature on type 1 endometrial cancers arising in adenomyosis. However, it is infrequent to have type 2 endometrial cancers reported as occurring in lesions of adenomyosis (3-5).

Only a few uterine papillary serous carcinoma cases, which is also called ESC, arising in a background of adenomyoma or adenomyosis have been reported (1-3). Hence, our case of serous endometrial carcinoma arising in the foci of adenomyosis is a rare event, and aware clinician and pathologists to investigate promptly and look adenomyosis focus in microscopic examination carefully to rule out the chances of malignancy in adult women.

Carcinomas arising from adenomyosis are predominantly of the endometrial type. Kucera et al. (8) studied 219 cases, of which only 88 had adenomyosis. Six of these 88 cases had malignant change arising from the adenomyosis, all of the endometrial type. A thorough review of the literature was performed, and we came across less than 20 reported cases of serous carcinoma and/ or serous carcinoma in situ arising from adenomyosis with or without association with endometrial cavity serous carcinoma (Table 1). Colman et al. (5) published an article titled Carcinoma developing in areas of adenomyosis in 1959; however, histological typing of the carcinomas is not clear. In 1996, Griffin et al. (9) published a single case of papillary serous carcinoma arising in adenomyosis. Koshiyama et al. (10) reviewed 564 patients and found 4 cases of adenocarcinoma arising in adenomyosis. Only one of them was of the serous subtype. Abushahin et al. (11) reported five cases of serous carcinoma arising from adenomyosis with additional features of SEIC and endometrial glandular dysplasia. Bingjian et al. (12) reported 3 cases with similar findings; however, in one case, they found serous endometrial carcinoma in the uterine myometrium and the left ovary. Also, in another, they observed microscopic serous EICs in the adenomyotic cysts of the cervical stump. Following is a table of all the reported cases from the year 1996 onwards.

Machida et al. (13) conducted a systematic literature search for cases of endometrial carcinoma arising in adenomyosis (EC-AIA) and came across 46 cases. They also followed 350 cases of endometrial carcinoma with adenomyosis (EC-A) from a historical cohort of hysterectomy-based patients in two of their institutions. They concluded that EC-AIA remained an independent prognostic factor associated with decreased disease-free survival (DFS) compared to EC-A.

Till the last follow-up (January 2021), the index case-patient is doing fine after hysterectomy. However, as per the literature available, the prognosis of the serous endometrial carcinoma arising from adenomyosis is bad (14).

Conclusion

Awareness of the possibility of carcinoma arising from adenomyosis and their subtypes, howsoever rare, is essential not only for the diagnostic but also prognostic point of view. It is difficult to make a preoperative diagnosis of serous cancer arising from adenomyosis. Hence, clinicians and pathologists should do thorough investigations and histopathological examination of the endometrium in adult hysterectomy for adenomyosis. The myometrium should be critically looked for foci of glandular dysplasia or SEIC. Also, the knowledge of this entity shall help plan the therapy of the patient accordingly.

Table 1: Previously reported cases SEC with SEIC in adenomyosis

Author	Year	Journal	SEIC In Adenomyosis	Serous Carcinoma in Adenomyosis
Griffin M et al (9)	1996	Acta Cytologica	ND	Present
Koshiyama et al. (10)	2002	International Journal of Gynaecological Pathology	ND	Present in one case
Izadi-Mood N et al. (7)	2007	Archives of Iranian Medicine	ND	Present
Abushahin N et al. (11)	2011	International Journal of Gynaecological Pathology	All 5 cases	Present in one case
Bingjian Lu et al. (12)	2016	Diagnostic Pathology	One case	Present in 2 cases
Liu et al. (14)	2017	Taiwanese Journal of Obstetrics & Gynecology	ND	Present

SEC- Serous endometrial carcinoma; SEIC- Serous endometrial intraepithelial carcinoma; ND- Not described

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