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Clinicopathologic features and outcomes of primary vaginal adenosis as a dermatologic and gynecologic burden

A retrospective study

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Abstract

In the recent 20 years, primary vaginal adenosis is extremely rare and the data of clinical presentations, management, and outcome have not been studied systematically.

In this retrospective study, women with vaginal adenosis between January 1997 and June 2017 were identified from the hospital's medical records. Data on patient age, history, symptoms, mass location, size, diagnosis, complications, treatment, and recurrence were analyzed by SPSS 20.0.

Twenty women were histopathologically diagnosed as having vaginal adenosis (mean age, 37.9 ± 10.6 years). All patients denied utero exposure. The most common symptom was vaginal pain or abnormal bleeding. For all patients, the local vaginal lesions were surgically excised. Seven patients had complications with endometriosis. 15 patients lived without recurrence, and 1 patient underwent postoperative local recurrence after 81 months. Primary vaginal squamous cell carcinoma in another patient was confirmed to arise from adenosis; she survived with disease. The remaining 3 patients developed carcinoma of different types in varied periods of a disease-free state (5 months, 30 months, and 23 years, respectively); 1 patient died of progressive disease, and 2 patients survived with disease.

Primary vaginal adenosis is a spontaneous lesion with a propensity for late canceration. Local lesion resection is the primary treatment.

Abbreviations: CCC = clear cell carcinoma, DES = diethylstilbestrol.

Keywords: adenosis, carcinoma, diethylstilbestrol, vagina

1. Introduction

Vaginal adenosis, defined as the development of columnar epithelium in the vagina, is the most common anomaly in young girls and female adults exposed to diethylstilbestrol (DES) in utero.[1] DES was administered to prevent abortion during pregnancy in the United States and European countries from the 1940s to the 1970s.[1,2] Although lacking direct proof, adenosis is widely accepted to be the precursor of clear cell adenocarcinomas, as the presence of adenosis has been found in all daughters exposed to DES with vaginal clear cell carcinoma (CCC).[2] The National Cooperative Diethylstilbestrol Adenosis project registered 4653 patients with utero exposure to DES and analyzed pregnancy complications and the risk of cervical neoplasia or breast cancer, and treated them.[1] However, in China, there is no report on cases of DES exposure, and vaginal adenosis is an uncommon disease. Therefore, this study describes 20 cases of vaginal adenosis and summarizes the data of diagnosis, management, and outcomes. Additionally, pertinent literature was reviewed, and the potential origin and effective management of this disease are discussed.

2. Materials and methods

In this retrospective study, data of patients with vaginal adenosis from the departments of dermatology and gynecology were combined. From 1997 to 2017, 20 cases were retrieved from the electronic databases at Peking Union Medical College Hospital in China. As a case series, this study does not need approval of the Peking Union Medical College Hospital Ethics Committee, but all patients were informed of the study and provided consent.

Clinical information, including age at diagnosis, location of the lesions, symptoms, pathology, and therapeutic procedures, were extracted from the hospital medical records. Follow-up data, including postoperative complications and survival, were collected by telephone and from outpatient records. And there is no loss.

2.1. Statistical analysis

The overall survival or time to recurrence was calculated from the date of operation to the date of relapse, death, or final follow-up (July 13, 2017). Analyses of the data were performed with SPSS, version 20.0 (IBM Corp., Armonk, NY).

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3. Results

During the 20-year study period, 997 patients were treated for primary vaginal diseases, including malignant and benign disease; of these, 20 patients were treated for histopathologically confirmed primary vaginal adenosis, of whom 16 had been diagnosed by a gynecologist and 4 had been diagnosed by a dermatologist initially for vulvar skin irritation. The age at diagnosis ranged from 9 to 61 years (mean age, 37.9 ± 10.6 years) with parity ranging from 0 to 2. The symptoms and signs of primary vaginal adenosis presented among the study patients were variable and included pain, pruritus, discharge, palpable cysts, patchy or diffuse red stippling, granularity or nodularity, and ulcers (Table 1). Four asymptomatic patients were discovered incidentally on routine examination or on the basis of benign gynecologic conditions. Among all patients, 4 had multiple lesions, whereas 14 had a single lesion; the remaining 2 women did not have obvious lesions and were admitted for uterine prolapse and imperforate hymen. The exact locations of the lesions were the lower vagina (9/20), upper part of the vagina (8/20), middle vaginal wall (2/20), and both the lower and upper parts of the vagina (1/20) (Fig. 1). Additionally, most lesions invaded the posterior wall of the vagina (10/20). The diameter of the lesions ranged from 0.5 to 4.8 cm (mean diameter, 2 ± 1.6 cm).

All 20 patients underwent surgical treatment, and vaginal adenoses were histopathologically confirmed by pathologists who specialized in gynecology. Eighteen patients underwent local vaginal resection with negative margins, of whom, case 10 with vaginal squamous carcinoma had stage I disease and underwent total hysterectomy with local vaginal resection. Additional procedures included hysterectomy, salpingo-oophorectomy, and vaginoplasty for other benign conditions, such as leiomyoma (4/20), adenomyosis (2/20), endometriosis (7/20), Müllerian abnormality (1/20), uterine prolapse (1/20), or chronic vulvar dystrophy (1/20). Regarding those with endometriosis, the lesions involved different parts: 1 involved the ovary, 3 invaded the vagina, 1 involved the Douglas pouch, 1 involved the ovary and Douglas pouch, and 1 involved the ovary and vagina.

During the mean follow-up period ranging from 4 to 23 years, 15 patients were alive with no evidence of disease after local vaginal resection. Nevertheless, case 7 with vaginal intraepithelial neoplasia I experienced local recurrence 81 months later from initial treatment, underwent local resection again and then lived free of disease. Case 10 with carcinoma diagnosed initially was included in this study for pathological diagnosis of moderately differentiated squamous cell carcinoma surrounded by adenosis. She experienced local recurrence as the same pathologic diagnosis 2 months later without any intervention and lived with the disease. Three patients (case 4, case 12, and case 19) progressed to vaginal carcinoma at 5 months, 30 months, and 23 years after the initial surgery; their tumor types (the International Federation of Gynecology and Obstetrics [FIGO] stage) were mucinous carcinoma (stage IV), CCC (stage I), CCC (stage I), respectively. Case 4 was treated with adjuvant radiotherapy and tumor debulking after recurrence and then died of advanced disease 13 months after primary surgery. Case 12 underwent local vaginal excision combined with 6 fractions of external radiation at a dose of 45 Gy after recurrence, and then experienced a disease-free status for 7 years; thereafter, she remained alive with disease for 8 years without treatment (per her decision) or regular screening at the date of the investigation. After experiencing alternating symptoms, such as pain, pruritus, ulceration, and bleeding, case 19 underwent regular colposcopic examination every 3 months, by which the diagnosis of vaginal adenosis was histologically confirmed for 18 years. Subsequently, the vaginal lesion progressed to a serous borderline tumor after 5 years, so she underwent regular screening without any treatment. One month from the last follow-up date, she developed CCC in situ.

4. Discussion

Since vaginal adenosis is benign and almost asymptomatic, the presence of this disease is often overlooked by a dermatologist or gynecologist.[3] Vaginal adenosis is mostly a coincidental finding, as the diagnostic criteria and clinical treatment guidelines of this lesion are difficult to find.[4] Although primary vaginal adenosis has been described for more than 100 years, the condition has been rarely reported in the last 20 years due to withdrawal of DES (Table 2). DES was found to have a strong association with the development of CCC or adenocarcinoma from adenosis.[1,4] Other sporadic case reports suggested alternative causes of vaginal adenosis, such as sulfonamide-induced Stevens-Johnson syndrome,[5] carbon dioxide laser treatment, 5-fluorouracil therapy,[6] and tamoxifen uterine-exposure.[7] However, the low incidence rate hindered the study of the etiology of vaginal adenosis. Even if the pathogenesis of vaginal adenosis is still not completely understood, in the cases of adenosis after vaginal inflammation, it is suggested that adenosis develops as a metaplastic process similar to other well-known types of metaplasia that occur as a result of noxious stimuli in other parts of the body.[6] The present study's data might contribute to a better understanding of this rare condition.

All patients denied utero exposure of DES, thus confirming that other aetiological factors may contribute to the development of adenosis.[1] The pathogenesis of vaginal adenosis is unknown, yet some researchers showed that if the biological process of the developing vagina remained incomplete, squamous epithelium during organogenesis of the lower female reproductive tract might switch to a columnar 1.[2] Our cases may shed new light on a possible correlation between vaginal adenosis and endometriosis. Unlike the reported cases, about half the patients had endometriosis in our study; the vaginal glandular epithelium may be derived from heterotopic endometrium without stroma, which is important for differentiation (Fig. 2). Another possibility is that menstruation blocked by the vaginal malformation led to vaginal adenosis. Although it is possible that the coexistence of vaginal adenosis and endometriosis in these cases occurred simply by chance, we believe that it is likely that the endometriosis was a precursor to vaginal epithelial changes. Although never mentioned in several previous reports on this subject, the relationship between endometriosis and adenosis has gained little attention in the literature (Table 2).

According to data of the epidemic period, vaginal adenosis affects less than 4% of DES-unexposed women but 8% to 10% of the general population.[8,9] The mean age of all patients with lesions reported recently is 40.9 years, which is older than that of our patients (37.9 years; Tables 1 and 2). The main populations with DES exposure were born from 1950 to 1959, accounting for 70%, according to Hoover et al.[1] Different from the worldwide distribution, the study at our center showed that most patients (70%) were born from 1960 to 1979 (Table 1). Besides, the effect of vaginal adenosis on infertility had been ruled out in this study, which is in contrast to the findings of another study.[1] In accordance with reported studies,[3,4,6–8,10–13] the common clinical presentations of vaginal adenosis are vaginal pain (7/20) and bleeding (8/20) (Table 1). However, some patients are

Table 1

Clinical features, treatment, and outcome of the 20 study patients.

Case no.	Age, years	G/P	Presentation	Lesion size, cm	Gross findings	Location	Diagnosis	Other finding	Treatment	Outcome
1	50	3/1	Pain	4.5 × 2.1, 4.8 × 0.8	Strip	Upper and lower one-third of the left wall	Vaginal adenosis	Congenital absence of the left kidney	LVR, recurrence and regular colposcopy	ANED, pain
2	9	NA	Bleeding	1.0 × 1.0	Papilla	Lower one-third	Vaginal adenosis	None	LVR	ANED
3	37	2/1	Asymptomatic	0.5 × 0.8	Nodular	Upper one-third of the posterior wall	Vaginal adenosis	None	LVR	ANED
4	47	4/1	Contact bleeding, drainage	0.7 × 1.0	Polypoid	Upper one-third of the posterior wall	Vaginal adenosis	Leiomyoma	LVR, recurrence and then combination RT and CT, and RH/BSO/RV/ pelvic and para-aortic lymphadenectomy/ partial rectal resection	Recurrence as mucinous carcinoma (stage IV) at 5 months, DOD at 13 months
5	45	3/1	Bleeding	4.5 × 1.6	Cystic nodule	Lower one-third of the anterior wall	Vaginal adenosis	Left ovarian endometriosis, leiomyoma	LVR/TH/ oophorocystectomy	ANED
6	37	3/1	Pruritus	4.0 × 1.0	Strip	Lower one-third of the left wall	Vaginal adenosis combined with endometriosis	Vaginal endometriosis	LVR	ANED
7	40	2/1	Bleeding	2.0 × 1.0	Nodularity	Upper one-third of the posterior wall	Vaginal adenosis	VAIN1, anterior rectal endometriosis	TH/BSO/rectal resection	Recurrence at 81 months, ANED after the second resection
8	61	2/1	Pain, Adenomyosis, leiomyoma, chronic vulvar dystrophy	LVR	ANED	depigmentation	NA	Patchy red stippling	Lower one-third of the posterior wall	Vaginal adenosis
9	38	2/1	Asymptomatic	2.0 × 2.0	Nodularity	Lower one-third of the anterior wall	Vaginal adenosis	None	LVR	ANED
10	45	3/1	Pain, bleeding, ulceration	1.0 × 1.0, 1.0 × 1.0	Cauliflower-like	Lower one-third of the anterior wall	Vaginal squamous cell carcinoma (FIGO stage I) arising from adenosis	None	TH/RV	Recurrence at 2 months and refusal of any treatment, TBL until the follow-up date
11	29	0/0	Asymptomatic	3.5 × 2.4	Nodularity	Middle one-third of the left wall	Vaginal adenosis	None	LVR	ANED
12	37	1/1	Bleeding, ulceration	3.0 × 4.0	Nodularity	Middle one-third of the posterior wall	Vaginal adenosis	None	LVR, recurrence and then RT and LVR	Recurrence as vaginal clear cell carcinoma (FIGO stage I) at 30 months and then treatment, 2nd recurrence at 7 years, TBL until the follow-up date

(*continued*)

Table 1
(continued).

Case no.	Age, years	G/P	Presentation	Lesion size, cm	Gross findings	Location	Diagnosis	Other finding	Treatment	Outcome
13	41	1/1	Pain	NA	Diffuse red granular	Lower one-third of the anterior wall	Vaginal adenosis combined with endometriosis	Vaginal endometriosis	LVR	ANED
14	40	4/1	Asymptomatic	2.8 × 2.3	Cystic nodularity	Lower one-third of the right anterior wall	Vaginal adenosis	None	LVR	ANED
15	35	4/1	Pain, bleeding	1.8 × 1.7	Papilla	Upper one-third of the posterior wall	Vaginal adenosis combined with endometriosis	Vaginal endometriosis	LVR	ANED
16	37	NA	Uterine prolapse	Non-lesion	None	Lower one-third of the posterior wall	Vaginal adenosis	Uterine prolapse	TAH	ANED
17	28	0/0	Asymptomatic	0.5 × 0.5	Nodularity	Upper one-third of the posterior wall	Vaginal adenosis	Bilateral ovarian endometrium cyst, leiomyoma, DIE	Oophorocystectomy + DIE + LVR	ANED
18	37	4/1	Pain, bleeding	3.0 × 2.0	Nodularity	Upper one-third of the posterior wall	Vaginal adenosis combined with endometriosis	Adenomyosis, bilateral ovarian endometrium cyst, vaginal endometriosis	LVR	ANED
19	42	5/2	Pain, ulceration, pruritus	2.0 × 1.0	Ulcer surface	Upper one-third of the posterior wall	Vaginal adenosis	None	LVR every 3 months and sirolimus therapy	Pain or pruritus with adenosis for 23 years, serous borderline tumor for 5 years, progression to clear cell carcinoma one month before the follow-up date
20	23	2/1	Asymptomatic	Non-lesion	None	Upper one-third	Imperforate hymen, vaginal adhesive tissue (adenosis)	Imperforate hymen	Vaginoplasty	ANED

ANED = alive with no evidence of disease, CT = chemotherapy, DIE = deep infiltrating endometriosis, DOD = died of disease, G/P = gravida/parity, LVR = local vaginal resection, NA = not available, No. = number, RH = radical hysterectomy, RT = radiotherapy, RV = radical vaginectomy, TAH = total abdominal hysterectomy, TBL = tumor bearing living, TH/BSO = total hysterectomy/bilateral salpingo-oophorectomy, VAIN1 = grade 1 Vaginal intraepithelial neoplasia.

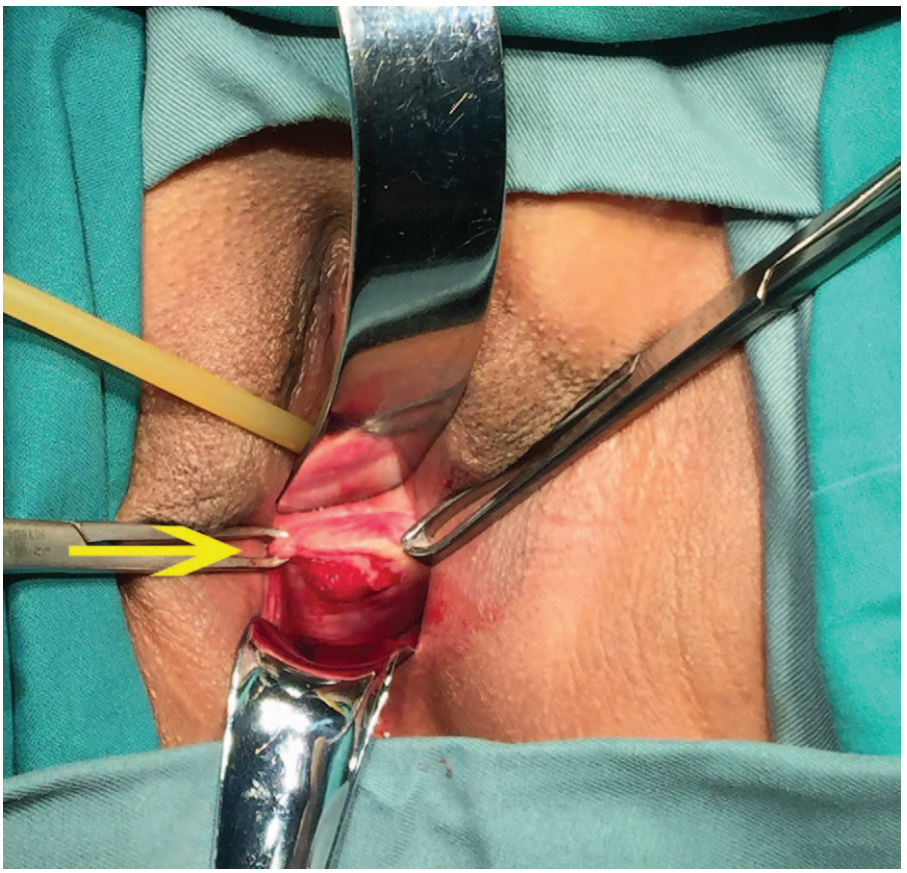

Figure 1. A lesion located in the vaginal os (yellow arrow).

asymptomatic and are diagnosed incidentally during a general physical examination or treatment for other ailments. The location of vaginal lesions may be related with the pathogen: vaginal adenosis caused by Stevens–Johnson syndrome and toxic epidermal necrolysis often occur in the lower one-third of the vagina; nevertheless, DES-induced lesions are usually found in the upper two-thirds of the vagina.[5] In this study, the distribution of lesions was random.

There is a paucity of literature reporting the clinical management and outcome of vaginal adenosis. The carcinogenesis of vaginal adenosis in DES-exposed patients is extremely rare (reported in 0.1% of the cases), and the pathological classification is mostly CCC.[1] Adenosis induced by DES was reported as the precursor of vaginal carcinomas previously; in vaginal CCC, glandular epithelium was identified in 80% of patients.[9,14] However, the incidence of CCC is significantly different from the incidence of adenosis caused by DES exposure. Thus, there may be no direct evidence of a relationship between adenosis with carcinomas, or the risk of malignant transformation from adenosis to carcinoma may be lower with a slow progression. Yet, this study cannot support this hypothesis, as the course of carcinogenesis was discrepant: 5 months, 30 months, or 23 years. Tumor types described in relevant literature include CCC and adenocarcinoma.[4,6,13] In this study, there were 3 types, including mucinous carcinoma, squamous cell carcinoma, and CCC. According to the literature, CCC is associated with vaginal adenosis in DES-exposed women, while mucinous carcinoma and squamous cell carcinoma may arise in a context of chronic inflammation.[15,16] For the clinical treatment of vaginal adenosis, local resection is preferred. Immune response modifiers, such as imiquimod, can achieve ideal goals in the treatment of vaginal lesions, for example, complete response of vaginal intraepithelial neoplasia in 57% to 86% of patients.[17] Another intervention, including lesion resection or cauterization, to control symptoms may be more feasible.[12] Additionally, Vigliani et al[18] suggested that blocking aromatase activity via bilateral oophorectomy or owing to natural menopause would be an effective alternative. Given the potential malignant transformation, follow-up of these patients is mandatory to identify carcinomatous lesions. Most of our patients (16/20) had complete remission after local vaginal excision and are receiving cervical and vaginal cancer screening at recommended intervals, but symptomatic women with or without pathological recurrent lesions undergo a Papanicolaou smear or colposcopy more frequently.

Primary vaginal adenosis is an extremely rare pre-carcinomatous lesion. Currently, there is a lack of clinical strategies for patients with this abnormality. Analysis of the clinical features and outcomes of patients with DES exposure over the past 20 years in this study indicated differences in the pathogen, year of birth, age of onset, fertility, complications, and clinical outcomes. Although a causal association remains to be proven, clinicians should be mindful of the possibility of vaginal glandular alteration when managing patients with endometriosis. This

Table 2

Review of reported cases in the past 20 years.

Author	Patient age, years	DES exposure	Other finding	Presentation	Location	Diagnosis	Treatment	Outcome at follow-up
Lu W et al 2016[10]	52	NA	Endometrial polyp, leiomyoma, pelvic floor relaxation	Asymptomatic	Lower posterior wall	Adenosis	Hysteroscopic surgery and repair of perineal laceration	ANED at 2 months
Talia KL et al 2012[4]	41	No	OVSS, EIN	Lump	NA	Adenocarcinoma	Excision of local vaginal mass + right pelvic nodes	ANED at 2 months
	56	No	None	Mass, palpable inguinal lymph node	Right anterolateral wall of the lower vagina	Adenocarcinoma	Partial vaginectomy and bilateral lymphadenectomy + RT	Recurrence at 9 months and then DOD at 3 years
Accetta SG et al 2001[11]	6	No	None	Persistent vaginal discharge	Left posterior wall of the upper vagina	Adenosis	Biopsy and electrocoagulation	Recurrence at 9 months
Cebesoy FB et al 2007[12]	24	No	ASCUS	Vaginal discharge and dyspareunia	Posterior wall of the upper vagina	Adenosis	Local lesion cauterization	NA
Paczos TA et al 2010[6]	45	No	Low-grade cervical dysplasia	No	Anterior wall of the upper vagina	VAINIII and adenocarcinoma	Hysterectomy + 5-FU cream + estrogen + radical upper vaginectomy + bilateral pelvic lymph node dissection + bilateral salpingo-oophorectomy	NA
Kranl C et al 1988[8]	41	No	No	Soreness of the vagina and introitus, vaginal bleeding	All of the vaginal wall	Vaginal adenosis	Hysterectomy and CO_2 laser coagulation	Recurrence at 2 months
Uehara T et al 2010[13]	54	No	Genitourinary anomalies	Vaginal bleeding	Anterior wall of the upper vagina	Vaginal clear cell adenocarcinoma	Radical hysterectomy and pelvic lymphadenectomy	ANED at 43 months
Ganesan R et al 1999[7]	52	NA	Cervical intraepithelial neoplasia II	Asymptomatic	NA	Adenosis	Repeat smear	Self-resolution at 6 months
Martin AA et al 2013[3]	42	No	Malignant melanoma of the breast	Asymptomatic	Introitus	Adenosis	Local excision	ANED at 3 months
Vigliani MB et al 2017[18]	30	Yes	Cervical intraepithelial neoplasia I	Vaginal bleeding	Upper vagina	Adenosis	Repeat smear	Self-resolution until menopause
	48	Yes	Breast cancer, ovarian teratoma	NA	Upper vagina	Adenosis	NA	Resolution until bilateral oophorectomy for teratoma

5-FU = 5-fluorouracil, ANED = alive no evidence of disease, ASCUS = atypical squamous cells of undetermined significance, CO_2 = carbon dioxide, DOD = died of disease, EIN = endometrial intraepithelial neoplasia, NA = not applicable, OVSS = oblique vaginal septum syndrome, VAINIII = vaginal intraepithelial neoplasia III.

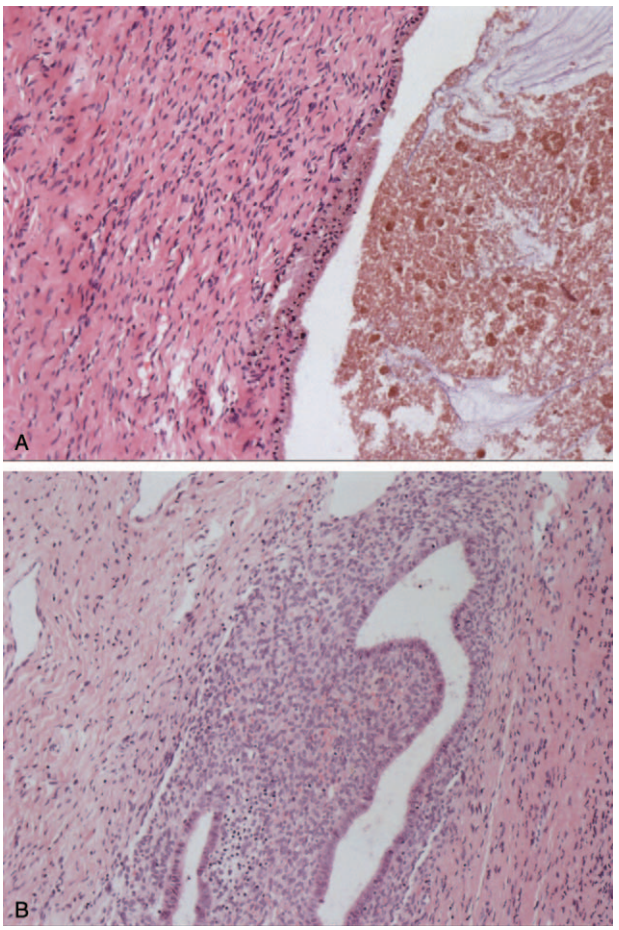

Figure 2. Vaginal adenosis consistent with benign-looking glands (A: H&E 100x). The same sample of endometriosis shows endometrial stroma (B: H&E 100x).

study is the first to document clinical examinations, follow-up data, and ascertainment of outcomes in China. Further large-scale studies on the rarity of spontaneous vaginal adenosis are needed to better inform and establish the optimal treatment.

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