Clinicopathological study of 112 cases of benign, pre-invasive and invasive lesions of the vagina: a 15-year review

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Summary

Objective: Benign vaginal lesions are mainly asymptomatic and often diagnosed during routine screening gynecological examinations. Additionally, vaginal intraepithelial lesions are asymptomatic and diagnosis is often confirmed after vaginal biopsy under colposcopic evaluation in cases of abnormal cytological Papanicolaou examination or synchronous cervical intraepithelial neoplasia. On the other hand, primary vaginal cancer is rare representing approximately 1 - 2% of all gynecological cancers. Metastatic invasion of the vagina is common especially in cases of advanced stage cervical cancer. The aim of this study was to examine the diagnostic approach, the management strategy, and the pathological findings in cases of benign, pre-invasive and invasive vaginal lesions that were diagnosed and treated in our Department. *Materials and methods:* This was a 15-year retrospective study. Cases of benign, pre-invasive, and invasive vaginal lesions diagnosed during the last fifteen years at Aretaieion Hospital of the University of Athens, were analyzed. *Results:* During this study period 40 cases of vaginal cysts (35.7% of all vaginal lesions) were diagnosed. Surgical excision of the lesions was decided in all cases and histology showed that the most frequent cyst type was mucus-secreting Mullerian (30%). During the study period, 23 cases of vaginal intraepithelial neoplasia (VAIN, 20.5% of all vaginal lesions) were detected. In 43.5% of the cases, histological diagnosis revealed low grade VAIN, while the remaining cases were classified as high grade VAIN. Furthermore, 11 cases of primary vaginal cancer (9.8% of all vaginal lesions) were diagnosed. The vast majority of them (91%) were squamous cell carcinomas. Additionally, histology confirmed the diagnosis of metastatic invasion of the vaginal wall in 38 cases (34% of all vaginal lesions). In the majority of these cases (55.2%), primary cancer was located in the cervix. *Discussion:* Benign, pre-invasive and invasive vaginal lesions are relatively uncommon and usually accompany lesions in other sites of the lower genital tract. Their diagnosis is based on gynecological or colposcopical examination. Treatment depends on the type of the lesion and the progression of the disease.

Key words: Vaginal cancer; VAIN; Vaginal cysts; Colposcopy.

Introduction

Benign vaginal cysts are in the majority of cases asymptomatic and are often incidentally discovered during gynecological examination for other purposes [1]. Several classifications have been proposed based on histologic and histochemical features of cyst epithelium [2]. According to a functional classification, vaginal cysts are divided into mucus-secreting Mullerian cysts lined mainly by endocervical and occasionally by Fallopian tube epithelium, Bartholin's duct cysts, Gartner's duct (mesonephric) cysts, and epidermal inclusion cysts of surface mucosa.

The histogenesis of Mullerian cysts remains uncertain. Perhaps some are derived from adenosis and their distinction is made by microscopic examination. They are usually small and located anywhere in the vagina. The pathogenesis of Bartholin's gland cysts is also uncertain, involving occlusion of the duct and are located in the region of the ducts of Bartholin glands. Gartner's duct cysts are usually located at the anterior-lateral wall of the vagina, resulting from secretion by small isolated epithelial remnants after incomplete regression of the mesonephric duct. Epidermal inclusion cysts of surface mucosa are reported as the most common, but usually without any clinically significance type of vaginal cysts, resulting from the entrapment of fragments of mucosa during colporrhaphy or episiotomy and most commonly occur in the distal portion of the vagina.

Additionally, vaginal intraepithelial neoplasia (VAIN) is uncommon, representing 1% of lower genital tract intraepithelial neoplasias [3]. The median age at diagnosis of VAIN is 41 years (range 16 - 87 years) [4-6]. However VAIN is now being diagnosed in younger women and this rise seems to be associated with the increased incidence of human papilloma virus (HPV) infections of the lower genital tract. Generally, most patients are asymptomatic. If present, symptoms may include postcoital spotting, vaginal bleeding, unusual vaginal discharge and odor [4, 5, 7]. The majority of lesions are located in the upper one-third of the vagina and are often multifocal [4-6]. VAIN is classified in a similar manner as cervical intraepithelial neoplasia (CIN) and HPV is the primary initiator of these lesions [7, 8]. Final diagnosis is confirmed by histological examination after vaginal biopsy under colposcopy. In the majority of the cases, an abnormal cytological Papanicolaou examination or the diagnosis of CIN leads to the colposcopic evaluation of the vagina and the vulva. Also, diagnosis of VAIN is reported after hysterectomy among other reasons, and histological examination of vaginal specimens.

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Primary vaginal cancer is a rare malignancy accounting for about 2% of all gynecological cancers with a rate of 0.5 / 100,000 women [9]. Most of the women are more than 60 years old, with mean age of 64 years at diagnosis. Histopathologically, most common are the squamous cell carcinomas (80-90%) and adenocarcinomas (4-10%). Most common symptoms include: vaginal bleeding, unusual vaginal discharge, or dysuria. Risk factors for the development of primary vaginal cancer are considered to be HPV infection, immunosuppression, irradiation, and squamous neoplasia occurring elsewhere in the lower genital tract [10, 11].

Finally, secondary spread of malignant neoplasms to the vagina is quite common, in contrast to the primary vaginal cancer. Metastatic invasion of the vagina is either by direct extension, vascular or lymphatic embolization, or infrequent direct implication. The most frequent primary sites include: cervix, vulva, endometrium, ovaries, rectum, and colon.

Materials and Methods

The present was a 15-year retrospective study. Cases of benign, pre-invasive, and invasive (primary or metastatic) vaginal lesions diagnosed during the last 15 years at the Pathology Laboratory, Aretaieion Hospital of the University of Athens, were analyzed. Pathological findings were related to the clinical parameters, including patients' age and symptoms.

Results

During the study period, 40 cases of benign vaginal cysts were diagnosed (40 / 112, 35.7% of all vaginal lesions) (Table 1). There were 12 cases of Mullerian cysts (30%), 11 cases of Bartholin's duct cysts (27.5%), ten cases of epidermal inclusion cysts (25%), five cases of Gartner's duct cysts (12.5%), one endometrioid cyst (2.5%), and one unclassified cyst (2.5%). Patient's age ranged from 20 to 75 years with a mean age of 35 years and a peak incidence between 31 - 40 years (13 cases, 32.5%). The majority of patients were asymptomatic (31 cases, 77.5%). The cyst type which was most frequently associated with symptoms was Bartholin's duct cyst. Most lesions were located in the left-lateral vaginal wall (13 cases, 32.5%). Mullerian cysts were lined by columnar endocervical-like or cuboidal epithelium, whereas Gartner's duct cysts were all lined by cuboidal epithelium. Epidermal inclusion cysts were lined by stratified non-keratinizing squamous epithelium. Bartholin's duct cysts were lined by transitional, mucin-rich columnar or squamous epithelium and were frequently accompanied by inflammation.

Thenty-three cases of VAIN (23 / 112, 20.5% of all vaginal lesions) were diagnosed during this period. Ten cases were classified as VAIN I (43.5%) aged 19 - 51 years with a mean age of 36.9 years, while six patients aged 18 - 73 years with a mean age of 46.8 years were diagnosed with VAIN II (26.1%). Additionally, histology revealed VAIN III in seven patients (30.4%) aged 50 - 75 years with a mean age of 62.1 years. Two patients diagnosed with VAIN I (20% of VAIN I and 8.7% of all VAIN's), two patients with VAIN II (33.3% of VAIN II and 8.7% of all VAIN's) and three patients with VAIN III (42.8% of VAIN III and 13% of all VAIN's) had previous or coexisting squamous carcinoma of the cervix. Patients with vaginal intraepithelial neoplasia were generally asymptomatic and the changes were initially detected by cytology or colposcopy. When symptoms were present, they included: postcoital spotting, vaginal bleeding, unusual vaginal discharge, and leucorrhea. In low-grade vaginal intraepithelial neoplasia (VAIN I), hypercellularity, disorganization, and increased mitotic activity occurred especially in the deep layers, but the cells maintained orderly maturation from the parabasal to the superficial layers. In high-grade vaginal intraepithelial neoplasia (VAIN II and III), more histological changes occurred. In VAIN II squamous differentiation in the upper third of the epithelium was still maintained, but there was a greater degree of proliferation, higher mitotic activity, and loss of polarity in the lower two thirds of the epithelium when compared with VAIN I. VAIN III consisted of disorderly arranged immature cells with scanty cytoplasms, hyperchromatic and irregular nuclei having a coarse chromatin pattern. Mitotic figures, including abnormal forms, were found in all layers. Squamous differentiation was absent or limited to the most superficial layers.

Eleven cases of primary vaginal cancer (22.4% of invasive vaginal lesions and 9.8% of all vaginal lesions) were histologically confirmed during this study period. Ten patients (91%), aged 50 - 86 years with a mean age of 69 years were diagnosed with squamous cell carcinoma, while one 30 year-old patient (9%) was diagnosed with primary vaginal adenocarcinoma. The majority or 60% of the squamous cell carcinomas were moderately differentiated (non-keratinized), while the remaining 40% of these cases were well differentiated (keratinized). These neoplasms were composed of typical squamous cells. Their nuclei showed low or greater pleomorphism and well-developed or less distinct intercellular bridges, depending on the degree of their differentiation. The vast majority of the patients complained of abnormal vaginal bleeding or discharge and only two patients were asymptomatic. The case of adenocarcinoma was referred to a patient with a history of prenatal exposure to diethylstilbestrol (DES). It was a low differentiated clear cell adenocarcinoma, located in the lateral wall of the upper vagina, and consisted of tubules and cysts and solid areas lined by clear cells due to the presence of glycogen and fat.

Thirty-eight cases of metastatic invasion of the vagina (77.6% of invasive vaginal lesions and 34% of all vaginal lesions) were diagnosed through histology during this ten-year study period (Table 2). Most of the cases were diagnosed during gynecological examination for clinical staging of cervical cancer. In the vast majority of the cases, primary cancer was located in the cervix (21 cases aged 43 - 88 years with a mean age of 60 years, 55.3%).

Table 1. — *Classification of benign vaginal cysts according to histological type*.

Histology of benign vaginal cysts	No. cases	%
Mullerian cysts	12	30
Bartholin's duct cysts	11	27.5
Epidermal inclusion cysts	10	25
Gartner's duct cysts	5	12.5
Endometrioid cysts	1	2.5
Unclassified	1	2.5

Table 2. — *Primary cancer's location in cases of metastatic invasion of the vagina*.

Primary cancer	Histological type	No cases	%
Cervical cancer	Squamous cell carcinoma	21	55.3
Ovarian cancer	Serous papillary adenoCa	8	21
Endometrial cancer	AdenoCa (serous papillary or endometrioid)	5	13.2
Colon cancer	AdenoCa	4	10.5

In the remaining cases, vaginal metastasis was diagnosed in eight patients with ovarian cancer (21%) aged 39 - 71 years with a mean age of 55.5 years, in five patients with endometrial cancer (13.2%) aged 71 - 84 years with a mean age of 74, years and in four patients with colon adenocarcinoma (10.5%) aged 41 - 80 years with a mean age of 62 years. All cervical tumors were squamous cell carcinomas characterized by neoplastic squamous cells showing either individual cell keratinization (non-keratinized tumors, 3 / 21 of the cases) or real keratin pearls (keratinized tumors, 18 / 21 of the cases). Neoplastic cells had round to oval nuclei, coarse chromatin, and numerous mitotic figures. All ovarian cancers were low-differentiated serous papillary adenocarcinomas characterized by nuclear atypia, high mitotic activity, stratification, glandular complexity, branching papillary fronts, and stromal invasion. Two out of these five endometrial cancers were low-differentiated endometrioid adenocarcinomas consisting in malignant-appearing squamous elements and glands that displayed papillary infoldings and branches. In addition, the cytoplasm of the glandular cells was diminished, granular, and lacked mucin. The remaining three cases of endometrial cancer represented serous papillary adenocarcinomas, a highly aggressive histological type with morphological characteristics similar to ovarian serous papillary adenocarcinomas. The colon adenocarcinomas (half of them were low-differentiated and the other half were moderately differentiated) consisting in neoplastic cells that represented a combination of columnar and goblet cells, with occasional participation of endocrine cells.

Discussion

Benign vaginal cysts are rare pathological lesions. The pathogenesis of most types of vaginal cysts remains to be clarified. In this study, benign vaginal cysts represented 35.7% of all diagnosed vaginal lesions. Mullerian cysts were found to be the most common type (30%). These data are in agreement with other studies supporting that the most frequent vaginal cyst type is mucus-secreting Mullerian [12]. In contrast, other studies suggest that epithelial inclusion cysts are more common [2]. Differential diagnosis between Mullerian and Gartner's duct cysts requires histochemical evaluation of epithelial mucin production. The vast majority of the patients diagnosed with vaginal cysts in this study were asymptomatic, as reported in the majority of the literature. Symptoms are usually represented by swelling or mass in the vagina, accompanied in some by stress urinary incontinence, dyspareunia or abnormal vaginal bleeding [12]. There was no case of vaginal cyst neither in this study nor in that of Pradhan *et al*. [12] diagnosed with malignant change or disclosed intraepithelial neoplasia. The treatment of choice is surgical excision, although marsupialization may be indicated with good outcome in cases of Bartholin's duct cysts.

In contrast to the high prevalence of intraepithelial lesions of the cervix and the vulva, vaginal intraepithelial neoplasia is relatively rare. VAIN may occur as an isolated lesion or as a lesion associated with CIN (65%) or vulvar intraepithelial neoplasia (VIN) (10%) [6]. These lesions may occur at the same time (synchronous lesions) or up to several years after the initial CIN lesion (metachronous lesions) [4, 13]. Most VAIN lesions occur in the vaginal vault after radical hysterectomy for invasive cervical cancer [4, 6, 7, 14] therefore long-term cytological follow-up after surgery for early or advanced-stage cervical cancer is strongly recommended. In cases of low-grade VAIN, management is conservative with regular cytological and colposcopy follow-up. Treatment of choice in cases of high-grade VAIN is the excision of the lesion. There are several surgical procedures (local excision, laser surgery, loop electrosurgical excision procedure LEEP, cavitational ultrasonic surgical aspiration) with excellent outcome, although other non-surgical methods, such as: topical medical therapy (5% 5-fluorouracil, imiquimod), immunotherapy (interferon), or radiation therapy have been used [3, 4, 15-20]. In this study, all patients diagnosed with high-grade vaginal intraepithelial neoplasia (VAIN II or III) underwent surgical excision of the lesion with laser surgery or loop electrosurgical excision procedure.

Primary vaginal cancer is a rare gynecological malignancy accounting for about two percent of all malignant neoplasms of the female genital system. In the study of Platz *et al*. [21], squamous cell carcinoma represents about 80% of primary vaginal carcinomas. In the same study, the incidence of primary squamous cell carcinoma of the vagina in the United States was about 1,000 cases / per year. The incidence is 0.42 / 100,000 cases in Caucasian women and 0.93 / 100,000 cases in black women. The mean age at diagnosis of invasive squamous vaginal cancer according to the published literature is about 64 years. However, vaginal adenocarcinomas more commonly affect younger women with a documented history of DES exposure in utero. The average age in which primary vaginal adenocarcinoma is diagnosed is about 19

years. The data resulting from this study seem to be in agreement with the literature. In this study, the squamous cell vaginal carcinoma (91%) was more common than the adenocarcinoma (9%). Patients diagnosed with squamous cell carcinoma aged from 50 to 86 years with a mean age of 69 years in this study, is close to what the literature reports. Similarly, the patient with vaginal adenocarcinoma was a 30-years-old young woman with a history of embryonic DES exposure.

On the other hand, secondary spread of malignant neoplasms to the vagina by direct extension or lymphatic or hematogenous metastasis is quite common. It is considered that only about 15% of vaginal cancers are primary, while the remaining 85% are metastatic. The most common primary cancer that leads to metastatic invasion of the vagina is cervical cancer by direct extension. The results of this study are in agreement with the literature as only 11 out of 49 cases (22.4%) in which histology confirmed the diagnosis of cancer were primary vaginal neoplasms. The remaining 38 cases (77.6%) were metastatic tumors originated from the cervix (55.3%), ovaries (21%), endometrium (13.2%), or the colon (10.5%).

Conclusions

Benign, pre-invasive, and primary invasive vaginal lesions are relatively uncommon and usually accompany lesions in other sites of the lower genital tract. They are usually asymptomatic and diagnosis is often incidental during a routine gynecological examination or after an abnormal cytological Papanicolaou examination that leads to colposcopic evaluation of the cervix and the vagina. Treatment of these lesions depends on the type of the lesion and the progression of the disease.

References

[1] Kondi-Pafiti A., Grapsa D., Papakonstantinou K., Kairi-Vassilatou E., Xasiakos D.: "Vaginal cysts: a common pathologic entity revisited". *Clin. Exp. Obstet. Gynecol.,* 2008, *35*, 41.

[2] Deppisch L.M.: "Cysts of the vagina: Classification and clinical correlations". *Obstet. Gynecol*., 1975, *45,* 632.

[3] Sillman F.H., Seldis A., Boyce J.G.: "A review of lower genital intraepithelial neoplasia and the use of topical 5-fluorouracil". *Obstet. Gynecol. Surv*., 1985, *40*, 190.

[4] Aho M., Vesterinen E., Meyer B., Purola E., Paavonen J.: "Natural history of vaginal intraepithelial neoplasia". *Cancer,* 1991, *68,* 195.

[5] Sillman F.H., Fruchter R.G., Chen Y.S., Camilien L., Seldis A., McTigue E.: "Vaginal intraepithelial neoplasia: risk factors for persistence, recurrence, and invasion and its management". *Am. J. Obstet. Gynecol.,* 1997, *176*, 93.

[6] Dodge J.A., Eltabbakh G.H., Mount S.L., Walker R.P., Morgan A.: "Clinical features and risk of recurrence among patients with vaginal intraepithelial neoplasia". *Gynecol. Oncol*., 2001, *83,* 363.

[7] Terzakis E., Androutsopoulos G., Zygouris D., Grigoriadis C., Arnogiannaki N.: "Loop electrosurgical excision procedure in Greek patients with vaginal intraepithelial neoplasia and history of cervical cancer". *Eur. J. Gynaecol. Oncol.,* 2011*, 32*, 530.

[8] Boonlikit S., Noinual N.: "Vaginal intraepithelial neoplasia: a retrospective analysis of clinical features and colpohistology". *J. Obstet. Gynaecol. Res*., 2010, *36,* 94.

[9] Watson M., Saraiya M., Wu X.: "Update of HPV-associated female genital cancers in the United States, 1999-2004". *J. Womens Health (Larchmt)*, 2009, *18,* 1731.

[10] Brunner A.H., Grimm C., Polterauer S., Hefler L., Stani J., Heinze G., Horvat R.: "The prognostic role of human papillomavirus in patients with vaginal cancer". *Int. J. Gynecol. Cancer,* 2011, *21,* 923.

[11] Ikenberg H., Runge M., Goppinger A., Pfleiderer A.: "Human papillomavirus DNA in invasive carcinoma of the vagina". *Obstet. Gynecol.,* 1990, *76,* 432.

[12] Pradhan S., Tobon H.: "Vaginal cysts: a clinicopathological study of 41 cases". *Int. J. Gynecol. Pathol.,* 1986, *5*, 35.

[13] Vinokurova S., Wentzensen N., Einenkel J., Klaes R., Ziegert C., Melsheimer P. *et al*.: "Clonal history of papillomavirus-induced dysplasia in the female lower genital tract". *J. Natl. Cancer Inst.,* 2005, *97,* 1816.

[14] Diakomanolis E., Stefanidis K., Rodolakis A., Haidopoulos D., Sindos M., Chatzipappas I., Michalas S.: "Vaginal intraepithelial neoplasia: report of 102 cases". *Eur. J. Gynaecol. Oncol.,* 2002, *23*, 457.

[15] Haidopoulos D., Diakomanolis E., Rodolakis A., Voulgaris Z., Vlachos G., Antsaklis A.: "Can local application of imiquimod cream be an alternative mode of therapy for patients with high-grade intraepithelial lesions of the vagina?". *Int. J. Gynecol. Cancer,* 2005, *15*, 898.

[16] Terzakis E., Androutsopoulos G., Zygouris D., Grigoriadis C., Derdelis G., Arnogiannaki N.: "Loop electrosurgical excision procedure in Greek patients with vaginal intraepithelial neoplasia". *Eur. J. Gynaecol. Oncol.,* 2010, *31*, 392.

[17] Patsner B.: "Treatment of vaginal dysplasia with loop excision: report of five cases". *Am. J. Obstet. Gynecol.,* 1993, *169,* 179.

[18] Diakomanolis E., Rodolakis A., Boulgaris Z., Blachos G., Michalas S.: "Treatment of vaginal intraepithelial neoplasia with laser ablation and upper vaginectomy". *Gynecol. Obstet. Invest.,* 2002, *54,* 17.

[19] Robinson J.B., Sun C.C., Bodurka-Bevers D., Im D.D., Rosenshein N.B.: "Cavitational ultrasonic surgical aspiration for the treatment of vaginal intraepithelial neoplasia". *Gynecol. Oncol.,* 2000, *78*, 235.

[20] Woodman C.B., Mould J.J., Jordan J.A.: "Radiotherapy in the management of vaginal intraepithelial neoplasia after hysterectomy". *Br. J. Obstet. Gynaecol.,* 1988, *95*, 976.

[21] Platz C.E., Benda J.A.: "Female genital tract cancer". *Cancer,* 1995, *75* (1 suppl.), 270.

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