Non diethylstilbesterol induced vaginal adenosis - A case series and review of literature

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Summary

Non diethylstilbestrol induced vaginal adenosis has a reported incidence of about 10% in adult women [1]. Although in some, it may be an insignificant coincidental finding, it is probably under-diagnosed even in symptomatic women. Little is known about the aetiology, pathogenesis, symptomatology and management of this poorly understood condition. Our experience with the four cases of vaginal adenosis unrelated to diethylstilbestrol (DES) exposure and a review of the literature will probably shed some light on this, as it still remains an enigma in gynaecological oncology.

Key words: Vaginal adenosis; Non diethylstilbestrol; Vaginal intraepithelial neoplasia; Cervical glandular intraepithelial neoplasia.

Introduction

Vaginal adenosis is characterised by the presence of glandular tissue or its secretory products in the wall of the vagina [2]. Occasionally, it may extend into the vulva leading to vulval adenosis [1]. The epithelium may be endocervical, endometrial or tubal in type. Sandberg broadened the entity to include the replacement of squamous lining by columnar epithelium without the formation of glands [2]. In upto 90% of women this arises from DES exposure in utero and in the remaining it can be acquired over a long period of time with or without any identifiable trigger [3].

In all cases, either congenital or acquired, there is an inherent risk for development of adenocarcinoma. Hence early recognition of the condition and appropriate vigilance is warranted. Of the four cases described below, there was no known cause found for the development of this condition. Neither was there any histopathological or immunofluorescent evidence of an inflammatory dermatosis.

Case Reports

Case 1

A 42-year-old women, para 2, was referred in November 1992 with a 18-month history of superficial dyspareunia and postcoital bleeding. The cervical smear was negative, but showed atrophic changes despite a regular menstrual cycle. On examination, reddened, granulating areas with contact bleeding were seen affecting the vagina and cervix. Punch biopsies showed submucosal noncaseating epithelioid granulomata. Tuberculosis, Crohn's disease, sarcoidosis and syphilis were excluded and vaginal and endocervical swabs grew no pathogens. Examination at review in August 1998 revealed some inflammatory changes in the posterior vestibule. The vagina was narrowed with similar erosive patches as before. Further vulval and vaginal biopsies showed "mildly inflamed and congested mucosa lined by endocervical-type columnar mucinous eithelium" suggesting vaginal adenosis. Acigel was prescribed in January 1999 and a review appointment arranged for six months.

Case 2

A 42-year-old, para 4, presented in December 1994 with a four month history of deep dyspareunia and postcoital bleeding. On colposcopy, a 5 mm superficial ulcer which bled to touch was noted in the right lower third of the vagina. It stained aceto white on application of 3% acetic acid and there was no iodine uptake. Biopsy showed squamous epithelium with benign tubal glandular epithelium. The cervical smear was normal. In February 1995, colposcopy under general anaesthesia demonstrated islands of "adenosis" extending from the cervix to the lower third of the vagina. The area was treated with superficial CO_2 laser ablation. Two months later, her symptoms had improved and colposcopy showed evidence of resolution. Acigel was prescribed to promote squamous metaplasia of the residual adenosis. Her symptoms returned one year later with vaginal adenosis circumscribing the cervix at the fornix and extending down the vagina virtually to the introitus. The area was again treated with CO_2 laser ablation. Four months later she was symptomfree with no adenosis seen colposcopically. By October 1996 she was experiencing localised superficial dyspareunia and postcoital bleeding. A 1 cm patch of adenosis was noted in the right lower-third of the vagina which was treated with laser as before. In addition, there was a tender erythematours area at the posterior vestibule and biopsy confirmed vulval intraepithelial neoplasia, grade 1 (VIN 1). In December 1998 she remained symptomatic to the point that she was virtually apareunic. Thea rea of VIN had increased in size but there was no overt vaginal adenosis. Laser ablation was carried out to the lesion at the posterior vestibule and she is awaiting further review.

Case 3

A 43-year-old, para 3, had laser ablation for CIN 3 in 1991. In 1994, she was re-referred for colposcopy following a mildly dyskaryotic smear. Punch biopsy confirmed CIN 1 and a large loop excision of the transformation zone (LLETZ) was performed.

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Histology showed squamous metaplasia and severe inflammatory changes with no convincing CIN. Subsequent smears were negative. She presented in April 1998 with a six month history of intermenstrual and postcoital bleeding. On examination, the cervix, upper and lower-third of the vagina was noted to be grossly abnormal in appearance with contact bleeding and sloughing of the epithelium. Colposcopic examination identified glandular epithelial fronds which bled to touch in the upper posterior vaginal wall. Vaginal and cervical smears were normal. Vaginal biopsy confirmed glandular epithelium focally at surface level and subepithelially. A diagnosis of vaginal adenosis was reached and Acigel prescribed.

Case 4

A 53-year-old, para 8, was in February 1997 following a severely dyskaryotic cervical smear. Cone biopsy revealed a FIGO stage 1a1 squamous cell carcinoma and, in addition, cervical glandular intraepithelial neoplasia (CGIN). A total abdominal hysterectomy and bilateral salpingo-oophorectomy was undertaken. There was no residual malignancy or CGIN. While asymptomatic, a vault smear in March 1998 reported glandular neoplasia with a suspicion of invasive adenocarcinoma. This was confirmed by external expert pathology review. Punch biopsies from the vaginal vault revealed vaginal intraepithelial neoplasia grade 2 (VAIN 2). She was referred to us for a second opinion. On colposcopy, an ulcerated are a highly suggestive of malignancy was seen in the left upper vagina. An excisional biopsy revealed CGIN in vaginal adenosis. Follow-up colposcopy in January 1999 identified persisting ulceration at the vault and the smear reported borderline changes in glandular cells. Acigel was prescribed to promote squamous metaplasia. Two months later the ulcerated area was considerably smaller. Further review is due in four months.

Discussion

The abnormal occurrence of metaplastic glandular epithelium in the vagina was first described by Von Preschen in 1877 [3] and Plaut and Dreyfuss proposed the term vaginal adenosis [2]. Two groups of women are known to develop vaginal adenosis. In the first "congenital" group, there is proliferation of the remnant Mullerian epithelium in the vagina due to exposure to DES in utero. The autopsy of 100 DES exposed foetuses and young women up to 25 years, showed a 15% prevalence of vaginal adenosis in subjects younger that one month [2]. In the second "acquired" group, this may occur due to:

a) trauma and inflammation causing spontaneous de novo changes, or changes in an acquired lesion in the vaginal epithelium; b) proliferation of the glandular cells in the remnant Mullerian epithelium of the vagina due to sex hormones; c) idiopathic spontaneous change in epithelium, where no cause has been identified.

Authors of various case reports postulate that trauma to vaginal epithelium in the form of carbon dioxide laser [4], 5 fluorouracil [5, 6], vaginal packs [7] or chronic pessary use [4] act as a trigger for the development of vaginal adenosis. Our first case is in this category as she developed the condition seven years following laser ablation to treat cervical intraepithelial neoplasia. In our series, there was no apparent trigger found in the first two cases. However, the other two cases did have history of trauma to the vaginal epithelium in the form of laser and surgery. Conversely, Singer *et al.* treated cases of adenosis with laser [7]. The aim of treatment was to destroy superficial columnar epithelium and stimulate replacement by metaplastic squamous epithelium which over time become mature squamous epithelium. The second patient in our series was treated with laser and showed remarkable improvement in symptoms without any residual adenosis left following treatment.

The prevalence of vaginal adenosis in girls between 13-25 years of age is 13%. No cases have been identified in prepubertal girls beyond one month of age [4]. This suggests that the production of sex hormones at menarche may cause proliferation of adenosis that had risen from Mullerian epithelium. However, in our series there was no case to support this. In the first two cases, the condition developed spontaneously, without any known trigger. But it was interesting to note that both of them were middle-aged women presenting with dyspareunia and postcoital bleeding. They both had negative smears and had developed an ulcerative lesion. One was treated with acigel to which she responded, while the other patient had laser therapy since she did not respond to acigel. In 1984, the DES-adenosis project found the incidence of CIN and VAIN was twice as high in DES exposed women [9]. In this series of non-DES exposed women three of them had a history of CIN, cervical glandular intraepithelial (CGIN) or invasive cervical disease. Two of them later on developed VIN and VAIN. This suggests that vaginal adenosis without DES exposure is also associated with a higher incidence of lower genital tract neoplasia. To our knowledge there has been no previous case reported of CGIN in an area of vaginal adenosis following hysterectomy for micro-invasive squamous cell carcinoma of the cervix and CGIN. Vaginal adenosis, though rare, should be considered in any middle-aged woman presenting with postcoital bleeding and dyspareunia. A detailed history is to be taken with particular relevance to the known trigger factors. Absence of identifiable risk factors cannot exclude the diagnosis and a thorough examination of the vagina should be performed. Once diagnosed, VA requires regular colposcopic follow-up for the early detection of adenocarcinoma, as its incidence in non-DES exposed women compose up to 10% of vaginal cancers [11].

Women with other genital tract intraepithelial neoplasia may acquire this condition. Conversely, women with vaginal adenosis are at increased risk of developing neoplasm. Acigel may be prescribed in order to promote squamous metaplasia, but this is not guaranteed. There is no ideal treatment at present. Those affected require long-term support and surveillance to allow early detection of malignancy.

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