Therapeutic Management of Vaginal Intraepithelial Neoplasia and Clinical Experience in South Western Sydney of Australia

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Abstract: *Background*: VAIN is consistently associated with prior or concurrent neoplasia elsewhere in the lower genital tract. Studies have shown 50-90% of patients with VAIN had or currently have either intraepithelial neoplasia or carcinoma of the cervix or vulva. VAIN represents 1% of all intraepithelial neoplasia and vaginal cancers account for 1-3% of all gynecological malignancies.

Aim: This article is aimed to give an overview of the current therapeutic management options of VAIN. In addition, all available clinical cases of VAIN among South Western Sydney area's hospitals were pooled to compare its treatment with the current therapeutic options as identified from the literature review.

Method: A literature search was conducted using the Medline and Pubmed databases. All available clinical cases of VAIN among South Western Sydney area's hospitals were pooled from the clinical databases within the network hospitals

Results: Between July 1999 to February 2009, 61 patients aged 18 to 88 years (median = 42, average =44.3) were diagnosed with VAIN I to III at the Sydney South West Area Health Services (SSWAHS) in Sydney, Australia. Of these 10 patients, forty percent had a previous hysterectomy for cervical neoplasia. This is in keeping with the current literature regarding VAIN aetiology.

Conclusion: Due to the rarity of this disease, many authors have identified the available literature on the natural history, aetiology and management of VAIN to be limited. Most of the studies on the management of VAIN were single-centre retrospective studies carried out on relatively small groups of patients. Further, the results of the success rates of the different management options vary greatly between each treatment centre. In order for our patients at SWSAHS may be managed optimally, higher levels of evidence are required in the future for standard recommendations on the management of VAIN.

Keywords: Vaginal intraepithelial neoplasia, Human Papilloma Virus, Australia.

BACKGROUND

Vaginal intraepithelial neoplasia (VAIN) is a premalignant condition of the vagina [1]. VAIN is defined by the presence of squamous cell atypia without invasion. The disease is classified according to the depth of epithelial involvement (as shown in Table **1**): VAIN 1 and 2 involve the lower one-third and two-thirds of the epithelium respectively, and VAIN 3 involves more than two-thirds of the epithelium [2].

Table 1: VAIN Classification [2]

VAIN Class	Involvement of epithelium (Depth of disease)
I	One-thirds of epithelium
II	Two-thirds of epithelium
III	More than two-thirds of epithelium to whole epithelium

Despite the steady increasing diagnoses of VAIN, it is still considered a rare condition [2, 3]. VAIN represents 1% of all intraepithelial neoplasia and vaginal cancers account for 1-3% of all gynecological malignancies [3, 4]. In the US, estimated figures of the incidence of VAIN are currently around 0.3 to 0.7 cases per 100,000 women [5]. The average age at diagnosis is between 43 and 60 years old.

METHODOLOGY

A literature search was conducted using the Medline and Pubmed databases. "Vaginal neoplasms" was selected as the subject heading, including the following subheadings: diagnosis, drug therapy, epidemiology, etiology, prevention and control, radiotherapy, surgery and therapy. Further limits were added to the search including, "English Language", "Humans" and "between 1990 to 2009". One hundred and fourteen articles were found within these search criteria. The articles were then evaluated based on their suitability for this literature review.

In order to compare our findings from the literature search to actual clinical practice, a database of patients with VAIN was also obtained from the pathology records at Sydney South West Area Health Services (SSWAHS) in New South Wales, Australia. This area

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health service is a network of five different teaching hospitals of University of New South Wales and University of Western Sydney, namely Liverpool, Campbelltown, Fairfield, Bankstown and Camden Hospitals and serves a population of about 800,000. The patient data available was limited and a focused analysis of the VAIN patient population at SSWAHS has been included in this review.

Aetiology

VAIN is consistently associated with prior or concurrent neoplasia elsewhere in the lower genital tract. Studies have shown 50-90% of patients with VAIN had or currently have either intraepithelial neoplasia or carcinoma of the cervix or vulva [2]. VAIN was first reported in the literature by Graham and Meigs in 1952. Subsequently, there have been scattered reports citing history of cervical or vulvar neoplasia with either simultaneous or subsequent neoplasia in the vagina. It has been suggested that there might be a "field-effect" of the cervix, vagina and vulva [3]. In a retrospective study of 3,030 women with cervical intraepithelial neoplasia (CIN) 2 and 3, up to 7.4% of patients who underwent hysterectomy for CIN 2 and 3 developed VAIN a few months to several years after surgery [6]. Prior hysterectomy for cervical neoplasia represents the main risk factor for VAIN [7].

VAIN shares a number of important risk factors with CIN, notably the Human Papilloma Virus (HPV) [8]. A population-based study of 156 women conducted by Daling *et al.* found over 50% of patients with VAIN or invasive vaginal neoplasia were positive for HPV 16 or 18 antibodies and 82% of patients with VAIN were positive for HPV [9]. In a separate study of 71 vaginal specimens with VAIN, no predominant HPV type was found in VAIN [10]. The disparity between the relatively high incidence of CIN and rarity of VAIN in women who test positive for HPV may be due to increased susceptibility of the metaplastic transformation zone of the cervix to oncogenic stimuli. In contrast, the mature, stable, squamous epithelium of the vagina may be less vulnerable to the same stimuli [2].

Smoking is a significant environmental risk factor for the diagnosis of high grade VAIN. The risk was highest in women who had smoked 30 years or more [11]. In addition, sexual behaviour, immunosuppression, previous history of pelvic radiotherapy and low socioeconomic status have been implicated in the aetiology of VAIN [8, 9].

Clinical Features

VAIN is generally asymptomatic and detection depends primarily on cytologic screening. Most commonly seen changes are observed in post-hysterectomy patients who have undergone therapy for intraepithelial disease of the cervix [1]. When symptoms are present, women may complain of post-coital spotting or unusual vaginal discharge [12].

Fifty-four percent of VAIN are in the upper third which may be partly related to the association with more cervical lesions [3]. Thirty-two percent of VAIN are in the lower third and only 14% in the middle third of the vagina. In most cases, VAIN is located on the posterior vaginal wall and the lesions are generally multifocal [4].

Colposcopy, effective in identifying lesions on the cervix may also be used in the vagina. However, due to its length, surface area and redundancy, viewing the vagina on colposcopy is much more difficult and time consuming. Schiller's or Lugol's iodine staining of the vagina can be helpful in identifying non-staining areas in the vagina that can then be biopsied [2]. Colposcopically the lesion can have many characteristics indicative of an intraepithelial lesion – raised, white and well-defined areas; as seen on the cervix. Increased vascularisation such as punctuation may also be seen. Identified lesions may be very small, restricted to the upper vagina particularly at the cuff area in a patient who has had a previous hysterectomy, or they can be quite large, involving the upper vagina. Skip lesions involving all levels of the vagina can also be present. Adequate biopsies should be taken so that an early invasive lesion is not missed [3].

Management

Progression of high grade VAIN to invasive malignancy has been estimated from 10-20% [8]. Treatment can halt oncogenesis in the vagina but efficacy rates depend on modality used. High success rates have been reported for cold-knife and loop excision, laser ablation, chemotherapy, radiotherapy and immunotherapy [13]. Choice of therapy is usually based on the number of lesions, the location, previous radiation therapy, previous VAIN treatment, desire for future sexual activity, operator experience and patient preference [12].

Surgical Therapy

Surgical excision is the most preferable therapy since it combines accurate diagnosis and treatment [2,

14]. Surgical options include local excision, partial vaginectomy, and rarely, total vaginectomy for extensive and persistent disease. A single-well localized lesion should be managed with local excision of the involved area. Small lesions can be removed entirely with the biopsy forceps in an outpatients setting. If a larger area is involved, then an upper colpectomy can be used with good results. Most excisions are performed transvaginally, although at times an abdominal approach is favoured. Partial vaginectomy is often required when VAIN is buried in the post-hysterectomy vaginal vault recesses. It has been called the standard method for treatment but disadvantages include risk of haemorrhage, injury to bladder or rectum and vaginal shortening or stenosis [12]. In a retrospective review of 121 women with VAIN, partial vaginectomy conferred the highest cure rate [15]. Pre-surgical administration of topical 5-Flurouracil (5-FU) may allow loosening of epithelial-stromal adherence, enabling VAIN to be stripped from the underlying tissue during local excision [2].

The CO_2 laser is the preferred technique for local tissue ablation. It has been reported to have a success rate of 80% [1]. One-third of patients will require more than one treatment. The procedure is generally well-tolerated, heals satisfactorily and results in minimal sexual dysfunction [2].

Ultrasonic surgical aspiration (USA) has been investigated for the use of VAIN therapy. It is a relatively new surgical technique in the treatment for VAIN. It creates a cellular disruption for precise tissue removal by the application of rapid mechanical movement by the formation then collapse of vapour pockets in a flowing liquid media. USA has been shown to have minimal morbidity compared with other non-surgical treatment modalities and is useful for treating VAIN in difficult anatomic areas, such as the upper vagina [1].

Topical application of 5-fluorouracil (5-FU) cream has the advantage of treating the entire vaginal mucosa with good coverage of multifocal disease and disease in folds and recesses of the vagina. 5-FU essentially causes desquamation of the vaginal epithelium, to be replaced by normal epithelium. It is an appropriate first-line therapy in women with early lesions and multifocal disease or those who are poor surgical candidates [3]. 5-FU is relatively inexpensive and can be administered in an ambulatory setting [2]. However, it is often highly irritant leading to non-compliance and has shown failure rates of up to 50% [8].

Radiation Therapy

Intracavitary radiation therapy may be an effective form of treatment but is associated with higher rates of morbidity than other therapies. It has been recommended for patients who have failed previous treatments, are poor surgical candidates or with

Table 2: VAIN Management Options [2, 8, 12]

Mode	Description	Cure rates	Advantages	Complications/disadvantages
Surgery	Surgical options: Local excision Partial vaginectomy Total vaginectomy	68-88%	Histological diagnosis can be obtained from excised specimen	Shortening/stenosis of vagina in wide local excisions Post-operative morbidity Risks increases in previously irradiated patients
Ablation	CO_2 laser tissue ablation	70%	Generally well-tolerated procedure Heals satisfactorily Minimal sexual dysfunction	Pain Bleeding
Topical chemotherapy	Application of 5-Fluorouracil	50%	Can treat entire vaginal mucosa – good coverage of multifocal disease and in disease in fold s and recesses of vagina. Relatively inexpensive Can be administered in ambulatory setting	Vaginal irritation, burning and ulcerations
Radiation	Intracavitary radiation therapy	77%	For patients who have failed previous treatments, are poor surgical candidates or with extensive, multi-focal disease.	Higher rates of morbidity Vaginal atrophy, stenosis and shortening Sexual dysfunction Bowel and bladder changes Poor wound healing

extensive multifocal disease (Graham *et al.,* 2007). Complications arising from intracavitary radiation include vaginal atrophy, stenosis and shortening. The risk of severe toxicity is low, but there is the likelihood of mild to moderate toxicity resulting in premature menopause and potential sexual dysfunction [2, 8].

Table **2** summarises the management options currently available, their indications and cure rates. Following therapy, gynecologic examination and vaginal cytology should be performed at three-month intervals to evaluate for persistent or progressive disease. Thereafter, patients can be followed at six-month intervals [2].

Prevention and Current Guidelines

The survival of patients with vaginal cancers is generally poor - Stage I disease has a five-year survival rate of 64% [5]; highlighting the importance of early detection of VAIN through screening. As mentioned above, the highest incidence of VAIN occurs in post-hysterectomy women with a history of CIN (Matsuo *et al.,* 2008). Women who have had a hysterectomy for high-grade cervical abnormalities require continued screening because of their increased risk of vaginal neoplasia [16].

The rate of primary vagina cancer in women who have undergone a total hysterectomy for benign reasons (e.g. menorrhagia, fibroids) is exceedingly low in the general population – three per year [16], rendering Pap smear screening for VAIN after total hysterectomy for benign disease not cost-effective [17]. However, in a retrospective study of 33 patients who have had a hysterectomy for benign disease, up to 28% of the women who developed VAIN had a previous hysterectomy for benign indications. They recommended that Pap smear should be performed periodically on patients who have undergone hysterectomy, regardless of its indications [4]. By nature of the low incidence of VAIN, screening for these individuals comes down to a matter of cost versus benefit [3].

HPV has been established as one of the key aetiological factors of VAIN. In a study of 71 vaginal biopsy specimens with VAIN, all 71 cases harboured a single HPV type at more than 1000 viral copies per cell [10]. This suggests that HPV testing may play a role in instances where women have received a hysterectomy.

Patient Population at South Western Sydney Hospitals

Between July 1999 to February 2009, 61 patients aged 18 to 88 years (median = 42, average =44.3) were diagnosed with VAIN I to III at the Sydney South West Area Health Services (SSWAHS) in Sydney, Australia. Of these patients, only 10 histopathology reports were retrievable from the database. The records of these patients were dated between September 1999 and December 2008. All 10 reports revealed that patients with VAIN had a prior or concurrent history of CIN (n=9) or cervical cancer (n=1). Table **3** presents the summary of patients at SSWAHS with VAIN.

Of these 10 patients, forty percent had a previous hysterectomy for cervical neoplasia. This is in keeping with the current literature regarding VAIN aetiology. Figure **1** represents the population of patients who have VAIN 1 to 3 and their previous histories.

Table 3: Patients at SSWAHS Diagnosed with VAIN between September 1999 to December 2008

PATIENT	AGE	DATE	HYSTERECTOMY	CIN	VAIN
1	71	17.09.99	Y	3	3
2	41	20.10.03	Y	2	2
3	63	23.11.06		3	3
4	18	23.01.07	Y	3	3
5	47	07.02.07	Y	Cx Ca	3
6	24	05.02.08		2	2
7	43	04.03.08		1	1
8	20	04.03.08		2	1
9	27	05.03.08		3	1
10	20	15.12.08		3	3

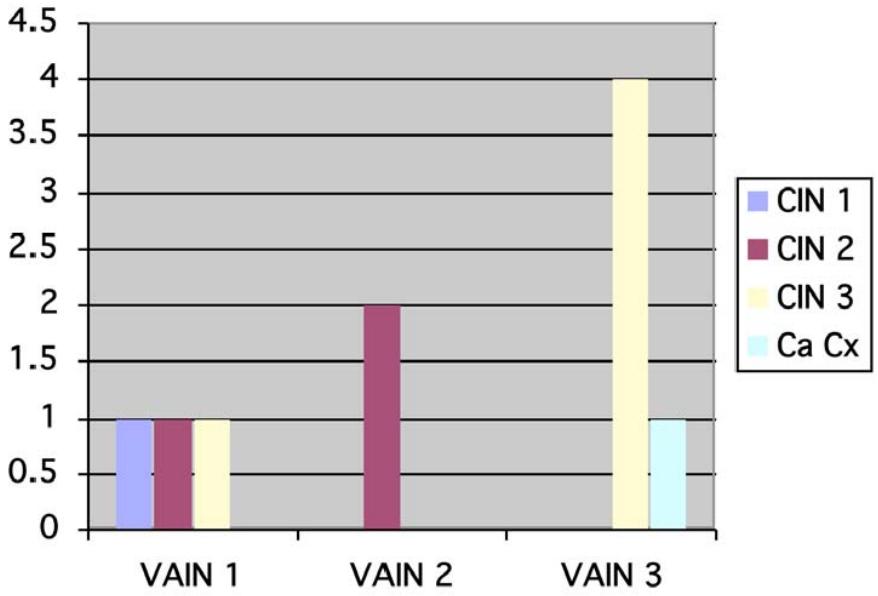

Figure 1: Patient population at SSWAHS.

Due to the rarity of this disease, many authors have identified the available literature on the natural history, aetiology and management of VAIN to be limited. Most of the studies on the management of VAIN were single-centre retrospective studies carried out on relatively small groups of patients. Further, the results of the success rates of the different management options vary greatly between each treatment centre. In order that our patients at SWSAHS may be managed optimally, higher levels of evidence are required in the future for standard recommendations on the management of VAIN.

SUMMARY

- VAIN is a rare pre-malignant condition of the vagina, and little is known about its natural history.
- Factors identified to be associated with VAIN include previous anogenital neoplasia, history of hysterectomy and HPV infection, smoking and immunosuppression.
- VAIN is usually detected asymptomatically following a Pap smear. Colposcopy and biopsy can be helpful in establishing a diagnosis.
- Surgical excision is the mainstay of therapy for VAIN but choice of therapy is based on the number of lesions, the location, previous radiation therapy, previous VAIN treatment, desire for future sexual activity, operator experience and patient preference.
- The current screening guidelines recommend that women who have had a hysterectomy for high-grade cervical abnormalities require continued screening for VAIN. In contrast, due to its rarity screening is not indicated for women who have undergone a total hysterectomy for benign disease.

CONFLICT OF INTEREST

Nil.

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