Vulvar Intra-Epithelial Neoplasia Associated with other Genital Tract Neoplasia Four Case Reports and Discussion

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SUMMARY: It is recognised that a significant number of patients who develop vulvar intra-epithelial neoplasia (VIN) will have had previous genital tract neoplasia. This has resulted in speculation that there may be a common aetiology and in particular, on the possibility of an infective element. Four such cases from the Vulva Clinic at the Western Infirmary, Glasgow are presented for discussion.

Introduction

Multifocal intra-epithelial neoplasia of the female genital tract has become an ever increasing problem for gynaecologists¹. Some authors, recognising its frequency and the association with human papilloma virus (HPV) as an aetiological consideration, have called this syndrome Genital Neoplasm-Papilloma Syndrome (GENPS)². In this, there is probably considerable merit as it is now well recognised that condylomata caused by HPV types 16 and 18 have malignant potential³. Until we have a simple and more widely available typing test to identify those viruses with malignant potential and, therefore, to be selective in treatment, it makes sense to treat them all. There is some evidence that such a typing test may become more widely available in the near future⁴. Hard epidemiological evidence on causal relationships is still lacking, and, as a result, although most authors would treat viral change at least with suspicion, there remain some who counsel a conservative approach⁵.

The four case reports presented from the Vulva Clinic at the Western Infirmary, Glasgow are used as examples of multi-focal genital tract neoplasia, possibly associated with pre-existing viral changes, and to discuss the diagnosis and management of vulvar intra-epithelial neoplasia (VIN), the major research interest in the Vulva Clinic⁶.

Patients, Materials and Methods

Patients are referred to the clinic from a variety of sources, and general practitioners, genito-urinary physicians and gynaecologists are the major ones. Referral of suspicious genital lesions, such as those illustrated in Figures 1 & 2, for colposcopic assessment and directed outpatient biopsy under local anaesthetic⁷ is the initial management. Most, if not all colposcopists nowadays will be looking at the genital tract as a whole rather than just at the cervix, and the ability to interpret these clinical findings continues to improve. In the experience of the vulva clinic, 30% of patients with VIN had pre-existing or previously treated genital tract neoplasia (Table 1). All the cases described below, were colposcoped with a Zeiss OPMI 6-H colposcope and the vulvar disease was treated with a Coherent System 450

CO2 Laser to the second surgical plan (Table 2)⁸. At high power, and under colposcopic and vital staining guidance, a rapid skinning method is used to move through to the second surgical plane i.e. through the epidermis to the papillary dermis. It is the ability to recognise these planes which controls depth and permits healing without significant scarring.

Fig 1. Colposcopic appearance of vulvar intraepithelial neoplasia (VIN) after staining with 5% acetic acid. Note the dull non-reflective appearance (X30).

Fig 2. Vulvar intraepithelial neoplasia (VIN) may appear as a raised and pigmented area. This was formerly called Bowen's Disease and histologically there is usually evidence of viral change (Bowenoid papulosis). (X30).

Table 1

**The Incidence of Pre-Existing Neoplasia
in the Vulva Clinic**

**Western Infirmary, Glasgow
In a 12 Month Period**

	Number of patients	Associated Neoplasia
*VIN I	5	0
VIN II	0	0
VIN III	8	4
		Cervical carcinoma (2) + CIN III (2)

*VIN – vulvar intraepithelial neoplasia
+CIN – cervical intraepithelial neoplasia

Case No 1. Mrs A B was a 29 year old lady referred to the vulva clinic for follow-up of VIN III. She had previously had multiple genital warts when pregnant. A localised vulvar lesion presenting as pruritis vulvae one year ago had been excised and was histologically described as "severe degree of vulval dysplasia amounting to epithelial carcinoma-in-situ (CIS)". (This we would now call VIN III). At cervical colposcopy a Stage IIb carcinoma was found, and other areas of VIN were also found on vulvar biopsy.

Wertheim's hysterectomy was performed and the vulva were subsequently treated with laser to the second surgical plane. She continues to attend for follow up and repeat outpatient vulvar biopsy has shown no recurrence of disease although one persistent area of itch was treated with laser under local anaesthetic to the first surgical plane.

Case No 2. Mrs C D was a 42 year old lady who was referred to the vulva clinic for a second opinion as to the nature of an irritating erythematous patch of vulvar skin. She had previously been found to have histologically diagnosed "Bowen's Disease" in a patch of vulvar skin overlying a cyst in 1981 but no treatment was prescribed. Also in 1981 she had had a total abdominal hysterectomy for cervical intra-epithelial neoplasia (CIN) diagnosed on cone biopsy following abnormal cervical cytology. On colposcopic examination, unilateral lesions were initially seen but with the application of 5% acetic acid lesions on both sides were visible. Partial laser vulvectomy to the second surgical plane under colposcopic control was subsequently performed and she continues to be followed up at the vulva clinic.

Case No 3. Mrs E F was a 79 year old lady referred to the vulva clinic with a long history of pruritis vulvae. A stage IIb cervical carcinoma had been treated with radiotherapy, and unfortunately this was subsequently complicated by radiation necrosis resulting in excision of the sigmoid colon and colostomy. She had also had vulvar warts treated in the past. A year before referral an itchy vulvar lesion had been diagnosed as Lichen Sclerosus et Atrophicus and was treated with dienoestrol cream. As no real improvement ensued, she was referred to vulvar biopsy which was performed under general anaesthetic. Histologically this was seen to be VIN III.

Colposcopic assessment, aided by the application of 5% acetic acid and 1% toluidine blue, showed that the lesion was well circumscribed and confined to the left labia. Colposcopically directed laser treatment to the second surgical plane was performed, and she continues to be followed up in the vulva clinic.

Case No 4. Mrs G H was a 28 year old lady with Letterer-Siwe Disease. She was noted to have a suspicious warty lesion on the left labium when undergoing suction termination of pregnancy, and she had previously complained of pruritis vulvae. A biopsy was taken and proved to be VIN III. At colposcopy CIN III

Table 2

Summary of the Salient Features of the Four Surgical Planes that can be used for More Accurate Control of Depth during Carbon Dioxide Laser Operation

Parameter	Surgical plane			
	First	Second	Third	Fourth
Target tissue	Surface epithelium	Dermal papillae	Pilosebaceous ducts	Pilosebaceous glands
Zone of vapourisation	Proliferating layer	Superficial papillary dermis	Upper reticular	Midreticular dermis
Zone of necrosis	Basement membrane	Deep papillary	Midreticular	Deep reticular
Type of healing	Rapid cosmetic	Rapid cosmetic	Usually cosmetic May hypertrophy	Atrophic or hypertrophic. Needs grafting
Visual landmark	Opalescent cell debris	Scorched basement membrane	Coarse collagen fibres	"Sand grains" (skin appendages)

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was also detected and confirmed histologically. Further colposcopic examination revealed the presence of vaginal intra-epithelial neoplasia (VAIN). She underwent colposcopically directed diathermy to the cervix, and the vulvar and vaginal lesions were biopsied again for further assessment. At review 3 months later multifocal intra-epithelial disease was present in all three sites. Under general anaesthesia, these areas were vapourised with the CO₂ laser. At review one month later, she appeared colposcopically to be free of disease but continues to be followed up.

Discussion

Two of these patients had a history of genital condylomata and one a history of Bowen's Disease. The latter is a descriptive term and the International Society for the Study of Vulval Disease (ISSVD) no longer recommends the use of this eponym (Table 3). It is now classified as VIN 3 under the recommendations of the ISSVD (Table 4)⁹. Although HPV typing was not available to the clinic, the history gives some credibility to the theory of the existence of some causal relationship between viral infections and the subsequent development of intra-epithelial neoplasia.

It is interesting to note that all the cases presented with pruritis and that this is the commonest presenting complaint in those referred to the clinic.

Perhaps the most important point is that illustrated by Case No 1. Had not this patient been subjected to a full gynaecological investigation when she was referred with pruritis, a Stage IIb carcinoma of cervix would have been missed. If there is a lesson to be learned from this paper, it is that anyone presenting with recurrent or chronic vulvar irritation should have a careful and

thorough colposcopic and gynaecological examination of the whole genitalia. This is particularly so when a history of condylomata is given, or when VIN is suspected.

All the cases had some degree of cervical neoplasia and this has been associated with pre-existing vulval disease¹⁰. It is notable that this was associated with the worst grade of VIN (Tables 1 & 4). The cervical disease was treated in an orthodox and well accepted manner.

Table 3

**Vulvar Disease Terminology to be Deleted
*(ISSVD 1976)**

Lichen sclerosis et atrophicus
Leukoplakia
Neurodermatitis
Leukokeratosis
Bowen's disease
Erythroplasia of Queyrat
Carcinoma simplex
Leukoplakic vulvitis
Hyperplastic vulvitis
Kraurosis vulvae

*International Society for the Study of Vulval Disease

Table 4

International Society for the Study of Vulval Disease (ISSVD 1983)

New Classification of Vulvar Intra-epithelial Neoplasia (VIN)

I. Squamous type (with or without koilocytosis). Histological categories.

- a) VIN I (mild atypia/dysplasia)
- b) VIN II (moderate atypia/dysplasia)
- c) VIN III (severe atypia/dysplasia)

Although histological categories may represent an increasing risk of developing invasive lesion, patient age and immune status may play an important role.

II. Non-squamous type.

- a) Paget's disease
- b) Melanoma *in situ*.

and sufficient has been written elsewhere about the management of cervical disease to make further discussion of this unnecessary.

The management of VIN and vaginal intra-epithelial neoplasia (VAIN) is not, however, so well documented, and will therefore be discussed in more detail.

Although the ability to diagnose the disease is improving with the use of colposcopy, vital staining and directed biopsy, it is still contentious as to which grades of disease need treatment. CIN has been sufficiently studied to give a reasonable idea of the natural history but the same cannot be said of VIN or VAIN. Nevertheless, it would be tempting to assume that they exhibit a similar pattern (although this remains to be proven) and to treat on the basis of a progressive spectrum from mild atypia to invasive disease as is seen in the cervix. VIN I and II may, however, revert to normal⁹ in many cases, and follow-up only may be the best management. Most cases do complain of itch, however, and treatment is often indicated because of this.

The initial step is to make a firm diagnosis. Examination is performed colposcopically assisted by vital staining with 5% acetic acid⁶; this will demonstrate the dull grey, non-reflective often velvety appearance usually seen in cases of VIN (Fig 1). Directed biopsy gives a satisfactory sample for histological diagnosis (Fig 3). Outpatient biopsy of the vulva under local anaesthetic is a simple procedure, relieves pressure on bed occupancy and theatre time, and is without significant morbidity⁷.

VIN is best treated using the carbon dioxide laser and all the vulvar lesions in the cases described were treated in this way. It will be appreciated that laser treatment to the second surgical plane does not treat the bases of the

Fig 3. Histological features of vulvar intraepithelial neoplasia, grade III (VIN III). Note the full thickness loss of differentiation, minimal keratin coating and prominent papillae. (X200). (H&E).

pilosebaceous glands and this epithelium will remain abnormal in some cases^{11, 12}. This means that scrupulous colposcopic follow-up is mandatory and that re-treatment will sometimes be required. It is, however, likely that this remaining epithelium contributes to the speed of healing of the vulvar epithelium¹³. Some authorities suggest that, where disease is found in the base of the glands, wide local excision is required¹⁴. This is potentially very mutilating, and this fact must be borne in mind as the age of the patients at presentation appears to be falling¹. Local anaesthetic may be used for the

treatment of small lesions¹⁵ and colposcopy and staining will help delineate disease; larger areas will still require general anaesthesia.

VAIN is even more of an unknown quantity but fits logically into the pattern of events suggesting an infective association. The argument for treating is exactly that for the vulva. The laser is the ideal tool for treatment and its versatility is exemplified by Case No 4 where disease in three sites was treated with the laser without the need to resort to conventional surgery.

Unfortunately not enough is yet known about the natural history of VIN and VAIN and long term follow-up is therefore essential, not only to detect any recurrent disease but also to add to the slowly developing body of knowledge of the epidemiology of these diseases.

Conclusions

Genital tract pre-malignancy continues to be an increasing and worrisome problem. Many questions remain unanswered. The relationship with HPV infec-

tion appears to be established and this necessitates positive action to increase public and medical awareness so that patients suffering from these diseases may be referred, treated and followed up. Improving ability with genital tract colposcopy, improvements in the speed and accuracy of viral typing, and research into immunological aspects of intra-epithelial neoplasia will continue to enhance the capability to detect, treat and therefore to prevent serious situations such as that seen in Figure 4, where a vulvar carcinoma, which had been missed at biopsy under general anaesthesia, was readily identified colposcopically.

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Fig 4. Carcinoma of the vulva detected colposcopically. Toluidine Blue stain. (X30).

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1987 SMITH & NEPHEW SERVICE DOCTOR AWARD

Wing Commander Graham M N Holloway, FRCS, Consultant in Orthopaedic Surgery at Princess Alexandra Hospital, RAF Wroughton, has been awarded a Smith & Nephew Foundation travelling scholarship of £5,000.

He will begin his study tour in October when he plans to use the award to visit major military and civilian centres in North America specialising in the management of knee ligament problems.

W/Cdr Holloway explains: "Assessment and treatment of knee ligament injuries is very important in the military context. Evaluation of these injuries is difficult, the treatment complex, and there is considerable controversy concerning management of these problems".

His visits will include: West Point Military Academy in New York to see how they approach the problems; Burlington, Vermont, to spend time with Mr Bob Johnson who has undertaken considerable research into

knee injuries; Toronto to meet Mr Bob Jackson who has been repairing the anterior cruciate ligament arthroscopically; Mr Frank Noyce in Cincinnati, Ohio who uses host tissue to reconstruct knee ligaments; and the Hughston Clinic which favours the use of manmade artificial ligaments.

He also hopes to visit research and development departments which have pioneered stabilising knee braces, and factories where braces and artificial ligaments are manufactured.

W/Cdr Holloway is very interested in the prevention and management of sports injuries and is a member of the sports injuries committee of the RAF Sports Board.

The Smith & Nephew Foundation was established in 1974 by Smith & Nephew Associated Companies plc headquartered in London. The Foundation supports international training and research fellowships for doctors and surgeons from the UK and overseas as well as study scholarships for British nurses.