Recalcitrant vulvodynia

A clinicopathological study

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Abstract **This study is an analysis of 26 women with burning vulva syndrome. They seldom had frankly abnormal physical findings, and application of acetic acid and colposcopically directed biopsy are therefore mandatory. Histopathological study showed characteristic features of human papillomavirus (HPV) in 20 patients (77%). HPV has been shown to be a cause of vulvar vestibulitis syndrome and was an associated problem in 3 of the 5 patients who had essential or dysaesthetic vulvodynia. The latter is similar to causalgia, with a poor prognosis for resolution. Single patients had the following specific conditions: lichen planus, lichen sclerosus, mature neuroma and chronic candidiasis. The study shows that vulvodynia is a multifactorial problem for which management strategies have evolved over the course of time. Although interferon-α-2b offers much promise for the treatment of vulvodynia caused by subclinical HPV infection, the complete cure rate was only 58%. Overall 38% of patients still experience their problem, which indicates that they should be discouraged from going from physician to physician in the hopes of finding a 'cure'.**

S Afr Med J 1993; **83**: 730-733.

A syndrome characterised by burning vulvar discomfort and introital dyspareunia but associated with essentially normal physical findings was first described in 1889.[1] At that time it was referred to as hyperaesthesia of the vulva. Inexplicably this problem virtually disappeared after the turn of the century, and it was not until the mid-1970s that a concerted effort was made to elucidate its causes. At the 1975 meeting of the International Society for the Study of Vulvar Diseases (ISSVD), Weisfogel coined the term 'burning vulva'. The word vulvodynia (based on the Greek *odynia* (pain)) was suggested for this condition by Tovell and Young[2] in 1978. In 1983, the ISSVD formed a task force under the direction of McKay to study this entity and definitive terminology was published in 1984.[3] Vulvodynia is defined as chronic vulvar discomfort, especially that characterised by the patient's complaint of burning and sometimes stinging, irritation or rawness. Burning vulva syndrome refers to vulvodynia for which no physical cause can be found or that persists despite appropriate treatment for associated physical findings.[3]

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Accepted 2 Nov 1992.

The cause of the syndrome remains contentious. In 1983 both Woodruff and Parmley[4] and Friedrich[5] reported pathological findings of infection of the minor vestibular glands. Subsequently Friedrich[6] described a triad of presenting features which he named the vulvar vestibulitis syndrome (VVS). These were: (*i*) severe pain on vestibular touch or attempted vaginal entry; (*ii*) tenderness to pressure localised within the vulvar vestibule; and (*iii*) physical findings confined to vestibular erythema of variable degree. Pyka *et al.*[7] detailed the histopathological characteristics of vulvar vestibulitis. Nonspecific chronic inflammation in the stroma surrounding the region of the minor vestibular glands was present in all patients, but the glandular epithelium and lumina were not involved. Minor vestibular glands were noted in 66%. In these cases there was squamous metaplasia of the acini and ducts with development of so-called 'vestibular clefts'. Koilocytosis was present in 27%.

There has been much speculation as to the cause of vulvar vestibulitis, ranging from various infective agents to sexual activity. Hypersensitivity to *Candida* or to several treatment vehicles was also postulated, but this was disproved by Marinoff and Turner.[8] Many physicians have attributed the symptoms solely to psychogenic factors.[3] Recently histopathological studies and viral DNA detection have shown that in a subset of patients with vestibulitis the aetiological agent is human papillomavirus (HPV).[9,10]

Apart from the categories of vulvar vestibulitis and HPV infection (papillomatosis) there are other causes of vulvodynia or burning vulva syndrome, which can be classified as follows:[11] (*i*) vulvar dermatoses; (*ii*) essential or dysaesthetic vulvodynia; (*iii*) cyclic vulvitis; and (*iv*) diverse entities such as neuroma,[12] which we suggest are included in a miscellaneous category. Benrubi[13] has shown that patients may have concurrent or overlapping causes for their vulvodynia.

Unrealistic expectations and unrewarding medical experiences contribute to the resentment, frustration and anger so often expressed by these patients.[11]

The present study of women referred to the senior author because of his interest in vulvodynia and burning vulva syndrome delineates the causes of the condition and evaluates treatment methods.

Subjects and methods

During the past 8 years, 26 white patients between the ages of 12 and 75 years were referred by gynaecologists because of recalcitrant symptoms of vulvar burning and pain. Women with a history of vulvar warts or previous treatment for condyloma acuminata were excluded. All had experienced vulvodynia for at least 6 months, ranging from 6 to 120 months (mean 33, median 24). In those with consorts, the most prominent symptom was unbearable vulvar pain at the time of penile penetration.

All patients underwent detailed vulvovaginal assessment. Routine saline wet mount cytological examination was performed and microbiological samples were taken for culture. A cytological smear was taken from the cervix, or the vagina in hysterectomised women. Evidence

of erythema at the vulvar vestibule was carefully looked for and point tenderness sought by palpation of the minor vestibular gland orifices with a cotton-tipped applicator. Colposcopic examination of the entire lower genital tract was performed after application of 3% acetic acid solution to the vulva for 3 - 5 minutes. Each patient had a vulval biopsy specimen taken from an area of maximum tenderness showing acetowhite changes. These specimens were examined histopatho-logically.

Sensory testing of the cutaneous surfaces of the labia majora and minora, clitoris, urethral meatus, vulvar vestibule, anus, perineum and peri-anal skin was performed with a cotton wisp and sharp pin. Patients in whom the abnormal sensory responses of allodynia, hyperalgesia, hyperpathia and hypo-aesthesia were elicited in varying permutations within the areas innervated by the pudendal nerve were considered to have essential or dysaesthetic vulvodynia. They underwent radiographic studies of the lumbosacral spine to exclude associated disc problems, arthritis, or space-occupying lesions.

A diagnosis of HPV was made when acetowhitening was present and histopathological examination showed evidence of koilocytotic atypia with basal cell hyperplasia; associated features included mitoses, multinucleation, dyskeratosis, parakeratosis and acanthosis (Fig. 1). Women with evidence of koilocytotic changes were treated conservatively with steroid creams, by topical application of 5-fluoro-uracil cream, by CO_2 laser vaporisation, or by injection 3 times a week of 1 000 000 interferon-α-2b intradermally through a 28-gauge (0,36 mm), 12 mm needle fitted to an insulin syringe. A total of 12 injections was given, utilising the circumferential technique as described by Horowitz.[14]

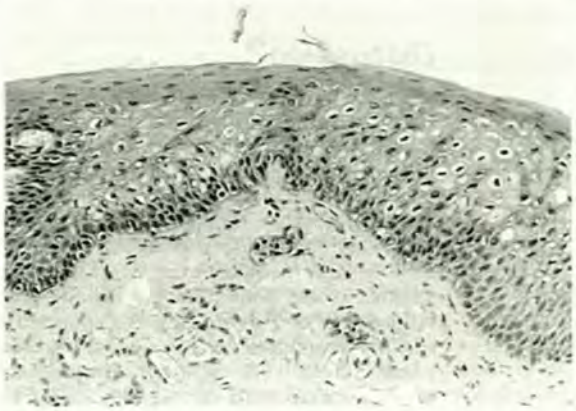

FIG. 1.
Histological section of vulval biopsy specimen showing basal cell hyperplasia, koilocytotic atypia and parakeratosis, diagnostic of HPV infection (H and E × 400).

Patients with features consistent with vulvar dysaesthesia and associated HPV were included as a subset within the category of essential or dysaesthetic vulvodynia. They received treatment for the HPV and a combination of several modalities for the dysaesthesia. A tricyclic antidepressant, amitriptyline or clomipramine, at a dose of 10 - 75 mg at night was prescribed. The anticonvulsant, carbamazepine, used successfully in postherpes zoster neuralgia,[15] was prescribed in 2 cases starting at a dose of 100 mg and increasing by increments of 100 mg every 2 days until a daily dose of 600 mg was reached. Appropriate orthopaedic surgery was performed where indicated. One patient also received intensive psychotherapy, and flupenthixol 1 mg daily was added by the psychiatrist to the carbamazepine, clomipramine and hydroxyzine.

Disorders in the category of vulvar dermatoses were diagnosed utilising histopathological criteria for specific disease entities. When indicated, immunofluorescence and immunohistochemical studies were used to confirm the diagnosis. Specific dermatoses were treated utilising standard dermatological regimens.

Results

Colposcopic examination of the vulva after application of 3% acetic acid and subsequent correlation with histopathological features of HPV changes permitted identification of distinct types of subclinical papillomavirus infection. The most frequent manifestation was flat acetowhite epithelium involving the posterior fourchette, extending in a horseshoe distribution on the inner aspects of the labia minora and adjoining perineum. Micropapilliferous lesions were characterised by multipapillary and villiform projections largely confined to introital mucous membranes. The papillary fronds resemble the individual asperites of a clinical exophytic condyloma. Individual fronds that had merged together appeared as fused papillae, giving the vulval skin a granular appearance. The lesions often revealed an associated punctate vascular pattern and occasionally mosaicism or capillaries extending into individual papillae. It is crucial to recognise that similar micropapilliferous changes without mosaicism or punctation may be seen as a normal introital anatomical variant.[16] Associated acetowhite plaques and/or scattered islands were often present on the anogenital skin and lateral aspects of the labia minora, interlabial grooves or labia majora, and many patients had combinations of flat acetowhite lesions, fissures, micropapillae and scattered islands. One patient had a colposcopically visible papular lesion, which histopathological examination proved to be vulvar intra-epithelial neoplasia, grade III (carcinoma *in situ*), associated with sub-clinical HPV.

It must be emphasised that flat acetowhite change may be ubiquitous, and thus merely helps to identify the areas to be biopsied.

In 5 patients tender erythematous foci surrounding the hymenal ring were sufficiently red to be visible to the unaided eye; all were found to have prominent flat acetowhitening at colposcopy. Histopathological examination in 3 of these cases confirmed the presence of HPV changes with associated chronic inflammatory infiltrate, mainly in the dermis (Fig. 2), and in 1 case revealed a lymphoplasmocytic infiltrate in a predominantly perivascular and periglandular distribution, without adenitis of the minor vestibular glands (Fig. 3); the remaining patient, who had chronic vulvar candidiasis, was found to have histopathological features of nonspecific chronic inflammation.

Table I summarises the final diagnoses made on the basis of the clinical and histological features and shows that subclinical HPV infection alone was the cause of vulvodynia in 14 (54%) of the 26 patients. It was also present in 2 of 3 patients with erythematous VVS and in 4 of 5 with vulval dysaesthesia. HPV was therefore an associated problem in 77% of the patients overall. It is clear that patients may have concurrent and overlapping causes for their vulvodynia. Koilocytosis was detected on cytological examination of cervical or vaginal smears in 10 of 20 patients with vulvar HPV. The treatment methods and results are summarised in Table II. Despite the fact that intralesional interferon-α-2b was clinically the most effective modality, Fisher's exact probability analysis using the two-tailed test showed no significant difference between CO_2 laser and interferon-α. The numbers, however, are too small to exclude an important statistical difference.

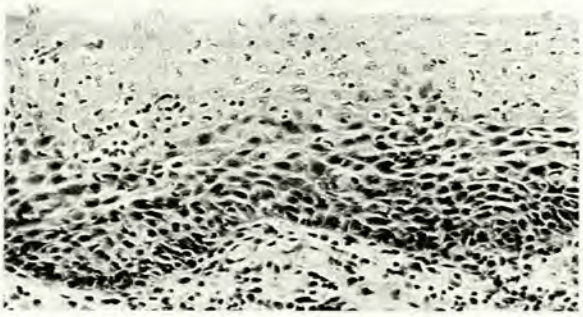

FIG. 2.
Histopathological features of HPV infection associated with a florid chronic inflammatory cell infiltrate in the underlying stroma with exocytosis into the overlying epithelium (H and E × 600).

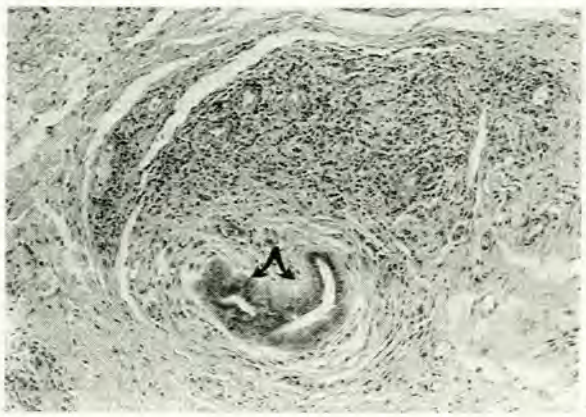

FIG. 3.
Histopathological findings in a patient with VVS. Note the periglandular chronic inflammatory cell infiltrate with sparing of the minor vestibular gland (arrows) **(H and E × 250).**

TABLE I.
Clinicopathological final diagnoses classified into categories

Subclinical HPV only	
Flat acetowhite lesions	6
Micropapilliferous	1
Flat acetowhite with associated VIN III	1
Combined lesions (flat acetowhite, micropapillary, fissures, islands)	6
VVS	
Chronic inflammation only	1
Concurrent HPV changes	2
Vulvar dysaesthesia	
Pudendal neuralgia only	1
Concurrent HPV lesion	3
Concurrent HPV and vestibulitis	1
Dermatoses	
Lichen sclerosus	1
Lichen planus	1
Cyclic vulvitis	
Candidiasis	1
Miscellaneous	
Mature neuroma	1

VIN III - vulvar intra-epithelial neoplasia grade III.

The 5 patients with dysaesthetic vulvodynia were all postmenopausal, depressed and complained of diffuse unremitting genital burning exacerbated by coitus. Their ages ranged from 49 years to 75 years (mean 61 years). Introital tenderness extended laterally around the labia majora and sensory testing revealed abnormal responses. One patient described radiation of discomfort to the thighs and 1 to the groin; because this suggested pudendal neuralgia, the pudendal nerves were infiltrated by local anaesthetic without anticipated temporary relief. Although McKay[11] reported that tricyclic antidepressant therapy was often successful, it proved ineffectual in our patients. CO_2 laser vaporisation for associated HPV lesions in 3 patients was unhelpful. Two in the latter subset also had lumbar abnormalities for which orthopaedic treatment was unsuccessful. Systemic acyclovir in 1 patient who had high antibody titres for herpes simplex was unsuccessful. Only 1 of 5 patients (20%) has improved partially.

One patient had a mature traumatic neuroma which was successfully treated by partial vulvectomy.[12] The patient with lichen planus improved only partially despite oral methylprednisolone, dapsone, azathioprine, isotretinoin and topical application of cyclosporin A solution. The woman with lichen sclerosus experienced symptomatic relief after regular twice-weekly application of clobetasol proprionate 0,05% cream, a potent topical steroid, for 3 months. Although *Candida* strains were cultured in 7 patients (27%) and treated appropriately, only in the youngest patient in the series, aged 12 years, was *Candida* considered to have caused the patient's symptom complex. Her problem of cyclic vulvitis resolved on long-term daily oral ketoconazole and topical terconazole cream.

Discussion

This study shows that vulvodynia has many causes but three main categories: subclinical HPV, VVS, and dysaesthesia. Consistent with Benrubi's[13] findings, some patients had concurrent and overlapping causes. All the patients in our series were white. Furlonge *et al.*[17] noted a similar absence of black patients in the UK, as did Reid *et al.*[18] in the USA. Both these groups reported that 92% of their patients were white. It is not yet known whether white women have a genetic predisposition to vulvodynia or this finding is explained by a marked sociocultural difference in response to disease manifestations. There were two demographic subsets in our series. Patients with vulvodynia caused by HPV had a median age of 30 years, whereas the median age of those with dysaesthesia was 58 years. In the latter, tricyclic antidepressants and appropriate orthopaedic treatment failed, raising the possibility of an inflammatory neuritis which causes decreased A-fibre activity leading to impairment of touch and proprioception.[13]

Colposcopically directed biopsies are mandatory in order to obtain appropriate specimens for histopathological studies, which form the basis for therapeutic decisions. Acetowhite reactions often affect not only the vestibular mucosa but also the adjacent vulvar skin. The presence of vulvar intra-epithelial neoplasia grade III against a background of subclinical HPV in 1 of our patients is consistent with the recognition that genital neoplasia may begin with HPV infection.[19] The fact that 77% of the patients in our series had histopathological evidence of HPV parallels the alarming increase in the number of cases seen in the USA.[10,19]

The subepithelial chronic inflammatory infiltrate seen in most patients with HPV may not only be associated with an immune response to the virus but causally related to the tenderness experienced by the patient.

TABLE II.
Results of treatment for vulvar HPV

Treatment	No.	Result					
		CR		PR		NR	
		No.	%	No.	%	No.	%
Conservative	4	2	50	1	25	1	25
5-fluoro-uracil cream	2	1	50	1	50	–	
CO_2 laser vaporisation	7	2	29	2	28	3	43
Intralesional interferon-α	7	4	58	3	42	–	
Total	20						

CR = complete response; PR = partial response; NR = no response.

Published methods of HPV treatment were utilised. The small numbers in each therapeutic group (Table II) and absence of uniform protocols, placebo controls and non-blind evaluation render valid conclusions impossible. However, our results and experience reported by others permit guidelines. As 2 of 4 cases resolved with further observation and application of steroid creams, an initial period of conservative management is indicated. In 1987 Campion[20] concluded that a period of observation was justified, and in 1992 Coppleson and Pixley[21] concurred with the opinion that a conservative approach is recommended where possible. Although topical application of 5% 5-fluoro-uracil cream as advocated by Reid *et al.*[18] proved helpful in 2 patients, this treatment was abandoned because of accompanying incapacitating pain during desquamation. Ablation of the affected epithelium to the first surgical plane using a partially defocused beam from a CO_2 laser, the method of treatment preferred by Reid,[22] yielded poor results, consistent with the experience of others.[23]

In an effort to find a less invasive form of therapy, intralesional injection of interferon-α-2b was utilised in 7 patients, with complete response in 58%, compared with 88% reported by Horowitz.[14] Enthusiasm should be guarded, since Kent and Wisniewski[24] reported a 63% complete response rate and Marinoff and Turner[25] only 45%. Patients who do not respond can undergo surgical or laser ablation. The mechanism of the effect of interferon is still unclear. It appears to stimulate natural killer cells, which destroy infected cells,[14] and binds to cell surface membrane receptors where it induces enzymes which prevent viral replication in virus-infected cells.[24] In addition, it enhances phagocytic activity of macrophages and augments cytotoxicity of lymphocytes.[24]

It is currently accepted that HPV is one of the causes of the VVS.[9,10,21,25,26] Accordingly, it is not surprising that in our series 2 of the patients with VVS had HPV and 1 patient with dysaesthetic vulvodynia had HPV and VVS. Only 1 patient had the histopathological criteria for VVS described by Pyka *et al.*[7] The patient with so-called cyclic vulvitis[11] caused by chronic candidiasis had clinical features of VVS. Our histopathological findings are in keeping with those of Furlonge *et al.*[17] who reported nonspecific chronic inflammation in 46% and HPV in 38% of patients with VVS. Peckham *et al.*[27] reported that histopathological study in their patients with VVS failed to show a characteristic pattern of inflammation or an association with the minor vestibular glands. They cautioned that the operation of vestibulectomy and vaginal advancement, while promising, should only be performed in recalcitrant cases. Reid *et al.*[18] reported that their experience with vestibulectomy was unsatisfactory. Reports of success with the CO_2 laser are also variable.[23] The exact causes and preferred treatment of VVS remain unresolved.

Despite intensive therapy, at the time of last contact 10 of the 26 patients (38%) still had troublesome vulvodynia, indicating that it remains a potentially insoluble problem and that neither the patient nor the physician should expect its rapid resolution.

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