A case series of young women with spontaneous regression of vulval intraepithelial neoplasia: demographics and associated HPV genotypes.

Short title: Spontaneous regression of VIN

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ABSTRACT

Objective: To review the clinical features, demography and human papillomavirus (HPV) type in a group of young women with usual type vulval intraepithelial neoplasia (VIN) whose lesions regressed spontaneously.

Materials and Methods: A retrospective case note review was made of the records of women with a diagnosis of usual type VIN whose lesions resolved spontaneously. The clinical features, demography, associated conditions, time to regression, and follow-up data were extracted. Stored paraffin embedded biopsy tissue was tested for the presence and type of HPV.
**Results:** Fifty-four women were identified. The median age at diagnosis was 19 years. Forty-four women (81%) were of non-European ethnicity. The median time to regression was nine months. In 44 (81%) cases the lesion was an incidental finding during clinical examination. The majority of lesions were multifocal and pigmented (44 (81%) and 48 (89%) respectively). HPV was detected in 40 (87%) of the 46 available biopsy samples and HPV genotype 16 was identified in 33 (82.5%). Recurrences of usual type VIN occurred in three women and these all resolved spontaneously.

**Conclusion:** Women diagnosed with usual type VIN which resolves spontaneously are very young, mainly non-European, and usually present with multiple, asymptomatic pigmented lesions. HPV genotypes and their frequencies are similar to those detected in older women with usual type VIN. This clinically defined group of women may be managed by observation alone if follow-up is assured.

**INTRODUCTION**

The natural history of usual type VIN has been the subject of considerable debate. There are three possible outcomes: progression to invasive cancer, indefinite persistence or spontaneous regression. Clinical, pathological, epidemiological and molecular studies all support the malignant potential of usual type VIN. Natural history data are limited, but in a large meta-analysis progression to cancer occurred in 9% of women with VIN and the time from diagnosis of VIN to development of cancer in untreated patients was between one and eight years. There are no reports of the indefinite persistence of the lesion. Evidence for spontaneous regression is based largely on case reports, a small number of poorly documented cases in older published series and two recent small case series. It has primarily been documented in young non-European women, sometimes following pregnancy. While high-risk HPV genotypes are associated with usual type VIN and related lower genital tract cancers, HPV genotype has not been studied in cases that have regressed.

We report a group of 54 women with usual type VIN whose lesions resolved spontaneously. Stored paraffin embedded biopsy tissue from these women was tested for the presence and genotype of HPV.
MATERIALS AND METHODS

Women aged 30 years and under attending the Auckland Regional Vulval Clinic between 1993 and 2010, and the Regional Sexual Health Service between 2002 and 2010 who had a diagnostic code of VIN 2/3 were identified. A report was run using a query designed to identify all women seen during the above time period with a diagnostic code of VIN 2/3, then refined to include only those aged 30 and under. Only those women whose lesions regressed without any treatment were included in the study, as our study aim was to describe this particular group in detail, including demographic information and associated HPV types. Usual type VIN is defined according to the histological grading of WHO (2003) and the terminology of the International Society for the Study of Vulvovaginal Disease (ISSVD) as VIN 2/3. The current management protocol in Auckland recommends treatment of usual type VIN in women over the age of 30 due to the increased likelihood of progression to cancer. On the basis of past experience indicating a high likelihood of spontaneous regression, women 30 years and under with pigmented, multifocal papular lesions are managed by observation alone every three months for one year. Treatment is instituted if the lesion persists beyond 12 months or if there is clinical concern, such as the development of symptoms or changes in the morphology of the lesions. Complete resolution is established by vulvoscopy. Women are followed annually for five years.

Case notes of the identified women were reviewed and demographic data, clinical features, date of diagnosis, time to regression and follow-up were recorded. Histology reports were obtained from the case records. Archival formalin fixed paraffin embedded biopsy blocks were retrieved, sectioned, de-paraffinised and tested for HPV by PapType (Genera Biosystems, Melbourne Australia) as described previously. Any tissue sample that was negative on the PapType test for both internal control and HPV was tested for the presence of human beta globin gene and those positive for this smaller internal control region were further tested on the INNO-LiPA HPV genotyping test V2.0 (INNOGENETICS, Ghent, Belgium) which amplifies a 65 bp region of the open reading frame of the L1 consensus
region of the HPV genome using reverse line blot hybridization. Samples were marked as unassessable (UNA) if they were beta globin and HPV negative.

Ethics approval was granted by the Northern X Regional Ethics Committee, Department of Health, New Zealand (NTX/10/EXP/235).

RESULTS

We identified 54 women (27 from each service) aged 30 years or under with a histological diagnosis of usual type VIN whose lesions resolved spontaneously. The median age at diagnosis was 19 years (range 15-30 years). Forty-four (81%) women were of non-European ethnicity; twenty-four (44.5%) women identified as Maori, ten (18.5%) as Pacific Islanders, eight (14.8%) as Asian and two (3.7%) as “other” non-European. None of the women reported pregnancy in relation to the lesion. Forty-four (81%) women had no symptoms related to VIN; twenty-six women were either asymptomatic or had unrelated genital symptoms, and 18 presented with genital lumps identified as genital warts and had co-existent atypical lesions (e.g. hyperpigmented, erythematous, variable pigmentation or leukoplakic) noted on examination, which were confirmed as VIN on biopsy. Of the remaining ten patients, nine (17%) presented with genital lumps and one (2%) woman presented with localized irritation. Forty-eight (89%) women gave a history of “any” STI, of whom 40 (83.3%) had a current or past history of genital warts. Twenty-five (46%) women gave a history of CIN, and 37 (69%) women were smokers at the time of initial diagnosis of VIN. The majority of lesions were multifocal and pigmented (44 (81%) and 48 (89%) respectively). The median duration of lesions was nine months (range 1-40 months).

Repeat biopsies were performed on seven women with new lesions noted during follow-up, two of whom were found to have recurrent usual type VIN. These lesions appeared 14 and 55 months following resolution of the original lesions. One woman had a clinical recurrence of VIN, which resolved before being biopsied. All recurrent VIN lesions resolved during follow-up. Women were followed for up to five years after complete regression of the lesions. Thirty-six (67%) women were followed for three to five years and 43 (80%) for at least two years. Six (10%) women did not attend for follow-up after resolution of lesions.
Archived biopsy material was available for HPV typing in 46 (85%) of the 54 women. HPV was detected in 40 (87%) of the 46 samples and high-risk HPV genotypes were identified in 37 (92.5%). HPV 16 was detected in 33 (82.5%) samples; as the only genotype in 29 (72.5%) and with genotype 6, 66, 52 and 58 respectively in four (10%) samples. Other high risk genotypes were detected in four samples; 31, 51, 51 and 31, and 56 respectively. Low risk genotypes only were detected in two samples; 11 in one and 6, 43 and 40 in the other. Six samples were HPV DNA negative and one sample showed low level reactivity but could not be amplified enough to identify the HPV genotype.

DISCUSSION

We report a large case series of women with documented regression of usual type VIN. Collection of such numbers was facilitated by close co-operation between the sexual health and gynaecology services, and the introduction of a one-year observational policy for asymptomatic women under 30 years of age who presented with multifocal pigmented usual type VIN. An earlier study from our unit reported regression in 47 of 109 (43%) women under 30 years (mean 24.6 years). This suggests that regression is a clinically important event in young women with VIN 2/3. Striking features of this group include the predominance of non-European women, the clinical appearance and transient nature of the lesions, and the rarity of recurrence. The median age of 19 years is half that of women with VIN attending the Regional Vulval Clinic. The young women were typically non-European (81%), which is a finding consistent with previous reports on spontaneous regression but in marked contrast to the general population of the region (39%, (2006 Census)) and the ethnic mix of women with VIN or vulval cancer attending the Regional Vulval Clinic (33%). The majority of women were asymptomatic (81%), in contrast to other reports of usual type VIN, which document a strong association with pruritus. In addition, the majority of lesions were multifocal (81%) and pigmented (89%) in contrast to those seen at the Regional Vulval Clinic (44% and 27% respectively). Recurrence rates of 30-50% are reported following treatment of usual type VIN, however in this study recurrence was an uncommon feature (5.5%) and when this occurred regression was
documented on a second occasion. Regression following pregnancy was not recorded in this study although it has been reported by others. Despite their morphology and histology the VIN lesions in these women behaved in a similar fashion to a self-limited genital wart infection. We postulated this clinical variant of usual type VIN may have resulted from infection with unusual HPV genotypes, or the genotypes associated with benign genital wart infection i.e. 6 and 11. However the predominance of high-risk HPV genotypes (95%) was consistent with other studies of usual type VIN. Since HPV genotypes are similar in both the cases that regress and those that progress, host factors must influence the outcome of infection. Integration of HPV DNA into the host chromosome is considered a critical step for progression of lesions to invasion. If strong T lymphocyte responses to HPV occur before integration, spontaneous regression of VIN may occur. A local T lymphocyte response was demonstrated in a 24-year-old woman with VIN whose disease regressed, but in none of five 39-50 year old women whose disease persisted or progressed. These findings may explain the very low median age observed in our study group.

The natural history of VIN remains controversial. However we believe regression is more common than previously thought; is frequently unrecognized as a result of cursory inspection of the vulva in asymptomatic women and the transient nature of the lesions. Our conclusions are limited by the retrospective design of the study and the lack of a comparison group. However, these findings support our management policy of observation in young women with asymptomatic VIN lesions, providing close follow-up strategies are available.

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