

Condylomata acuminata in Women: The Effect of Concomitant Genital Infection on Response to Treatment

C. COOPER and H. S. K. SINGHA

Department of Genito-urinary Medicine, The Royal South Hants Hospital, Southampton, England

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316 women with genital warts were studied to relate treatment response to concomitant genital infection at presentation. There was a highly significant difference between the response patterns of those patients who presented with warts alone, and those presenting with other infections (most commonly candidiasis and non-specific vaginitis). The diagnosis and treatment of associated infections hastens the response of warts to cytotoxic therapy, but there appears to be a subgroup amongst women presenting with warts alone, who require a considerably longer course of treatment. The relevance of these findings to the pathogenesis and management of genital warts is discussed. *Key words: Genital warts; Management.* (Received August 28, 1984.)

C. Cooper, Department of Genito-urinary Medicine, Royal South Hants Hospital, Graham Road, Southampton, Hampshire, England.

The management of patients with genital warts represents a considerable burden upon clinicians in genito-urinary medicine. The disease appears to be increasing in frequency—between 1974 and 1981, the number of women with wart infections presenting to Genito-urinary Clinics in England rose by 70% (1). The genital wart virus, a papovavirus, has been shown to be sexually transmitted, with an incubation period of 3 weeks to 8 months (2). In hospital practice, approximately 50-60% of patients with warts have other genital infections (3, 4, 5). It has been postulated that these accompanying infections are of special importance in creating a suitable environment (both through warmth, and moisture) for the wart virus to proliferate. Thus, any infection which increases genital secretion would predispose to warts, and persistence of the additional moisture would increase the difficulty in eradicating warts, prolonging treatment duration.

The treatment of genital warts is notoriously unsatisfactory, and recurrences are common, although the reasons for this are not clear. The most commonly used therapeutic measure is the application of podophyllin, a cytotoxic agent which acts against rapidly growing, virus-transformed cells (6).

The aim of this study was to document the pattern of response to treatment in 316 women presenting consecutively with genital warts, and to relate this to the presence or absence of any concomitant genital infection at presentation.

PATIENTS AND METHODS

432 women presented consecutively with genital warts over a 3 year period. The study group of 316 women was chosen by exclusion of those: (a) were pregnant or post-partum, (b) had previously suffered from genital warts and presented with recurrences during the study period, or became lost to follow-up, (c) presented with warts which did not morphologically resemble condylomata acuminata, and (d) had any treatment other than podophyllin (such as cryotherapy or surgery) at any stage in their management, for warts.

Each patient was routinely examined at the outset, for associated genital infections; specimens were taken from the urethra and cervix for gram stain, non-specific culture, and inoculation onto

selective gonococcal culture medium, and from the vaginal vault for wet film phase contrast microscopy, gram stain and culture. Diagnostic criteria were as follows:

- (i) gonorrhoea—positive microscopic findings confirmed by culture,
- (ii) trichomoniasis—identification of the parasite on wet film preparations.
- (iii) candidiasis—presence of hyphae, pseudo-hyphae, or spores on microscopy, with positive culture.
- (iv) non-specific vaginitis—malodorous thin discharge, presence of clue cells on wet film preparations, and gram variable coccobacilli on gram stained smears.

Treatment of condylomata acuminata adhered to a protocol of twice weekly applications of 25% podophyllin in mineral oil, with weekly clinical review. Treatment of associated genital infections followed the protocol laid down for the Department of Genito-urinary Medicine, Southampton, and response was verified by microscopy and culture in all cases. Women with non-specific vaginitis were treated with metronidazole, and response was verified clinically and microscopically.

The case notes were then retrospectively analysed to document the duration of treatment from presentation to resolution of warts, and the presence of associated infections.

RESULTS

Of the 316 women presenting with genital warts during the study period, 151 (48%) had associated genital infections, the commonest being candidiasis—73 patients (23%), and non-specific vaginitis—60 patients (19%). Other infections encountered included trichomoniasis (12 patients), and gonorrhoea (6 patients).

The number of treatments with podophyllin required for remission of warts in these groups of patients are expressed in Table I, and the warts survival curve showing response to treatment in each of the three major groups—women presenting with warts only, with warts and candidiasis, or warts and non-specific vaginitis—is shown in Fig. 1.

The median value for the number of treatments required for resolution of warts in each of the three groups shown, is as follows: (i) warts only: 8 treatments, (ii) warts with candidiasis: 4 treatments, and (iii) warts with non-specific vaginitis: 4 treatments. Grouping the duration of treatment as two, four, and greater than or equal to six weeks, gave a $\chi^2=32.63$, $df=4$, $p<0.001$, suggesting a highly significant excess of treatment required for patients presenting with warts only.

It is noteworthy that in the 18 patients whose accompanying infection included trichomoniasis and gonorrhoea, 12 (67%) showed resolution of warts within four applications of podophyllin (two weeks).

Table I. Duration of treatment with podophyllin in women with genital warts, classified according to accompanying genital infection

Duration of treatment (weeks)	Number of applications of podophyllin	Diagnosis at presentation								Warts and gonorrhoea	
		Warts only		Warts and candida		Warts and non-specific vaginitis		Warts and trichomonas vaginalis			
		No.	%	No.	%	No.	%	No.	%	No.	%
2	4	74	45	49	67	45	75	6	50	6	100
4	8	39	24	21	29	11	18	1	8.3	—	—
6	12	23	14	2	3	4	7	3	25	—	—
8	16	9	5	1	1	—	—	1	8.3	—	—
10	20	12	7	—	—	—	—	1	8.3	—	—
12	24	5	3	—	—	—	—	—	—	—	—
14	28	3	2	—	—	—	—	—	—	—	—
Total		165	100	73	100	60	100	12	100	6	100

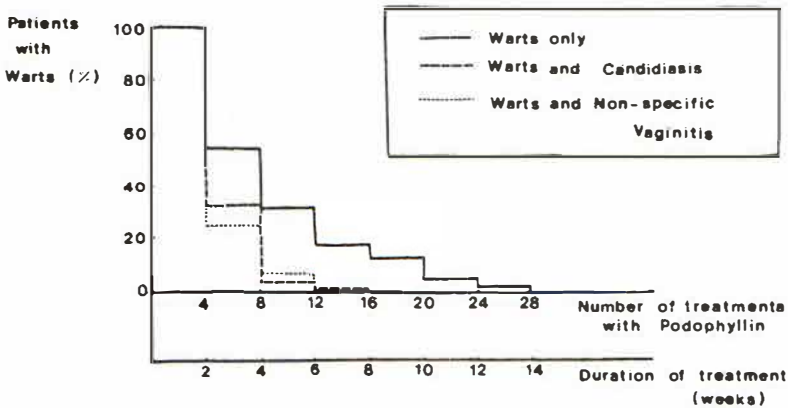


Fig. 1. Response pattern of warts to treatment (warts "survival" curve) in women presenting with warts alone, warts with candidiasis, and warts with nonspecific vaginitis.

DISCUSSION

Our results are in accord with those of previous studies in demonstrating a high incidence of concomitant genital infections in women presenting with warts (3, 4, 5); these comprised mainly candidiasis and non-specific vaginitis.

They further show that the natural history of genital warts, in terms of response to treatment with podophyllin, is markedly different in women who present with warts only, as compared to those who present with warts accompanied by some other genital infection. It is those women who have a concomitant infection diagnosed at presentation, who respond better to treatment of their warts with podophyllin, as measured by the number of applications of podophyllin required for remission of the warts. There is at present considerable debate over the aetiology, clinical relevance, and treatment of non-specific vaginitis. Whether a heterogeneous entity or not, the importance of the diagnosis in our study lies in the fact that it represents a concomitant infection in those women presenting with warts. The similarity in response pattern of patients presenting with warts and candidiasis, to those presenting with warts and non-specific vaginitis, further supports the hypothesis that diagnosis and treatment of concomitant infection hastens the response of warts to podophyllin; it is not the nature of the infection, but its presence, which appears to influence the pattern of response. The number of patients who had concomitant gonococcal and trichomonal infections were not large enough to attain statistical significance, but also generally conformed to this pattern, with relatively rapid response of warts to podophyllin.

In patients presenting with warts alone, the majority had responded within eight applications of podophyllin, but a separate subgroup of approximately 25% required considerably longer treatment regimens (up to 13 weeks of podophyllin). These patients, nonetheless, went into remission without alteration in the mode of treatment. The reason for the presence of this refractory subgroup amongst women presenting with warts alone, is unclear. It is unlikely to be related to the efficacy of podophyllin as a therapeutic agent, or to individual differences in treatment regimens (such as application of insufficient quantities of cytotoxic, or failure to treat certain lesions), as one would then have expected such a refractory subgroup in each of the other categories of patients, presenting with concomitant infections.

Two other explanations seem more likely. Firstly, screening for concomitant infections was only carried out at presentation. It is conceivable that in the refractory subgroup, these infections develop during the course of the disease, being undetectable at presentation, and delay the response of warts to podophyllin in their hosts. This hypothesis could

be tested by repeated screening of all patients, at, say, two weekly intervals, for concomitant infections.

Secondly, it is plausible that complete response of genital warts to cytotoxic therapy is dependent upon the immunological status of the host. Both cell-mediated and humoral responses to human papilloma virus are detectable in patients suffering from warts (7, 8, 9). Cell-mediated immunity, measured by lymphocyte transformation responses to several standard mitogens, has been shown to be reduced in patients with genital warts (8). It is possible that the group of women presenting with warts only, who are refractory to cytotoxic treatment, are unable to mount satisfactory immunological responses to the wart virus.

Treatment regimens for genital warts are difficult to assess. There is considerable variation, both in the types of treatment used, and in the severity of disease at presentation, making retrospective comparison difficult. It is of note, however, that during the period of our study, the department adhered to a well-defined protocol for the treatment of warts, with podophyllin as a single agent (only 16 patients were excluded from the study due to the use of alternative forms of treatment, such as cryosurgery or cauterly); further, application of podophyllin is routinely carried out twice weekly, allowing relatively easy assessment of the duration of treatment before remission.

The screening of patients with genital warts at presentation, and effective treatment of any other infection present, does reduce the duration of treatment of the warts with cytotoxic agents. However, in women presenting with genital warts alone, there appears to be a separate subgroup who requires protracted courses of treatment, at considerable expense. The identification of such a group, we feel, is important, and further investigation of the pathogenesis and natural history of the condition in these patients might lead to a saving in resources, through more effective management protocols, and a greater understanding of the complex inter-relationship between man and the human papilloma virus.

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