

The Immunotherapy of Anal Condyloma Acuminatum*

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CONDYLOMA ACUMINATUM is a common lesion of the anorectal and urogenital regions. Various methods have been utilized for treatment of anal condyloma acuminatum, but none has been uniformly and consistently curative; therefore, the recurrence rate is extremely high. This report describes the use of immunotherapy in the treatment of anal condyloma acuminatum with excellent results and a low recurrence rate.

Material and Method

During a two-year period, immunotherapy was used in the treatment of 39 consecutive patients who had extensive anal condyloma acuminatum. There were 36 men and three women in this group. Most patients were in the third and fourth decades of life, with an average age of 27 years. All but three of the men were either overt homosexuals or had histories of occasional anal intercourse. There was no such previous history in any of the cases of the female patients.

Durations of the disease ranged from four weeks to ten years, with an average of 6.8 months. Eight of the patients either had warts on other body sites at the time

of initial examination or had histories of having had facial, truncal or extremity warts that had either spontaneously disappeared or been removed by chemical or surgical means. Twenty-four patients had had no previous therapy for their condylomas, and 15 patients had had a total of 36 sessions of treatment by chemicals, fulguration or formal surgical removal of the condylomas, with prompt recurrence and persistence of their disease. Some of the patients had had various combinations of treatment or had been treated more than once by the same method (Table 1). There were histories of syphilis in one case, gonococcal proctitis in four, and gonococcal urethritis in eight. One of the women, who also had severe vulvovaginal condylomas, had a history of pelvic inflammatory disease.

Most of the patients (37 of 39) complained of appearance or recurrence of warts in the perianal region. Pruritus ani and bleeding secondary to trauma were seen frequently; however, severe anal pain was rare even in the presence of extensive disease. Symptoms are summarized in Table 2.

Anorectal examination revealed condylomata acuminata in a variety of sizes and shapes, from small, single-pointed vegetation to fist-sized cauliflower-like masses. All patients in this group had extensive disease as manifested by circumferential anal and/or perianal involvement (Fig. 1).

Associated clinical findings are listed in Table 3. Proctosigmoidoscopy was routinely performed preoperatively, and be-

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TABLE 1. *Prior Therapy of Anal Condyloma Acuminatum Treated by Immunotherapy*

Patients with no previous treatment	24
Patients previously treated (recurrent disease)	15
Podophyllin	18
Fulguration	8
Surgical excision	8
Acid compounds	2
Total prior therapeutic sessions	36

TABLE 2. *Distribution of Symptoms*

	Number of Patients
Visible perianal warts	37
Pruritus ani	24
Bleeding	17
Anal discomfort, and wetness	7
Protrusion	2
Vaginal discharge	2
Perineal pain and drainage	1

TABLE 3. *Clinical Findings*

	Number of Patients
Condyloma acuminatum	39
Anal and perineal	35
Anal canal only	2
Perianal only	2
Internal hemorrhoids	5
Severe perianal dermatitis	2
Anal fissure	1
Perianal hidradenitis suppurativa	1
Vulvovaginal condylomas	1

nign adenomatous polyps were found in two patients. These were treated by excision biopsy and fulguration.

Collection of Condyloma Tissue for Vaccine Preparation: The majority of patients (31 of 39) were admitted to the hospital and given general or spinal anesthesia. Large and exophytic warts were then excised and collected in sterile virus-

holding medium. All these patients had uneventful recoveries and were discharged from the hospital on the second or third postoperative days.

Of the remaining eight patients, three had a few large easily accessible perianal condylomas, and five others refused to be admitted to the hospital. These patients were given local anesthesia in the office and some of the perianal condylomas were excised and collected in virus-holding medium.

Microscopic slides were prepared in all cases for histologic confirmation of the diagnosis. In both groups of patients, an attempt was made to submit at least 5 g of condyloma tissue for the preparation of vaccine and cell cultures.

Preparation of Cell Cultures: Fresh condyloma tissue collected in virus-holding medium was cut into 1-mm² pieces and washed twice in Hank's basic salt solution. The pieces were immersed in chicken plasma and placed in clean tissue-culture bottles and tubes. The tissue was left at room temperature for 20 to 30 minutes for the plasma to gel. Nutrient medium containing Medium 199 supplemented with penicillin and streptomycin, 100 μ /ml, with 10 per cent inactivated calf serum was added. The medium was changed once a week until growth of cells was observed (Fig. 2); then it was changed twice a week. Cells developed after two to three weeks of incubation (Fig. 3). The cells were stained for viral inclusion bodies and antigens, but were found to be negative for both.

Preparation of Vaccine: Condyloma tissue was collected in virus-holding medium that contained basic salt solution, albumin and antibiotics. The tissue was kept frozen until prepared. After thawing, the tissue was washed twice in Hank's basic salt solution, cut into small pieces, and 10 per cent suspension, by weight, was prepared in Medium 199 supplemented with penicillin

and streptomycin, 100 μ /ml. The suspension was homogenized in a Sorvall electric Omni-mixer and the homogenate was frozen in a dry-ice alcohol bath and thawed four times. The homogenate was then centrifuged at 5,000 rpm for 10 minutes in an IEC refrigerated centrifuge and the supernatant was collected and heated for 60 minutes at 56 C. After this inactivation process, the homogenate was centrifuged again at 10,000 rpm for 10 minutes in a refrigerated Sorvall centrifuge and the supernatant was collected into a Vacutainer tube to be used as the vaccination material. The vaccine was then tested for bacterial sterility.

Vaccination of Patients: The vaccine is kept frozen until bacterial sterility is proven. Then 0.5 ml of the vaccine is injected subcutaneously in the deltoid area, once a week for six consecutive weeks. In the interim the vaccine is stored in a frozen state. No adverse reaction has been observed in any patient receiving the vaccine.

Results

All patients were examined by anoscope biweekly during and immediately after termination of vaccination. Subsequently, they were examined at 4-12 week intervals.

Of the 39 patients, three were lost to follow-up either during or right after immunotherapy. These patients are excluded from the study. The follow-up periods for the remaining 36 patients ranged from 5 to 26 months, with an average of 15 months.

Thirty-three patients (91.7 per cent) had favorable results following immunotherapy. Thirty patients (83.3 per cent) had had no recurrence at the time of completion of immunotherapy and have remained free of disease during the follow-up periods (Fig. 4). Three patients (8.3 per cent) had only one or two clusters of condylomas seen after completion of immunotherapy. These were fulgurated once with

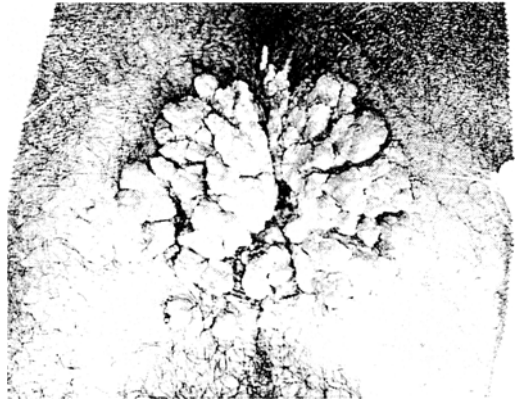


FIG. 1. Extensive anal and perianal condyloma acuminatum in a young black man.

the electrocoagulation unit at the office, and the patients have remained free of disease since.

Three patients (8.3 per cent) manifested recurrent condylomas as early as two weeks postoperatively and before immunotherapy could be instituted. Two of these three patients needed as many as six sessions of either fulguration or application of 25 per cent podophyllin in tincture of benzoin to control recurrence after completion of immunotherapy. The condyloma of one patient has remained resistant to all treatments, including three previous surgical excisions performed elsewhere. This patient has had a repeat surgical excision of his condyloma and is awaiting a second course of immunotherapy. The results of immunotherapy are summarized in Table 4.

Discussion

Condyloma acuminatum is currently believed to be of viral etiology. Transmission by cell-free filtrate was first reported by Ciuffo in 1907.⁴ Lewis and Wheeler¹⁰ cited the autoinoculability of warts, and the inoculation of ground suspension of warts to volunteers has resulted in the transmission of the disease. Strauss *et al.*²² identified intranuclear inclusion in 1949.



FIG. 2. Photomicrograph showing growth of condyloma cells in tissue culture. Dark area at left is the original excised condyloma tissue. $\times 40$.

Electron microscopic studies of epithelial cells from condylomas has shown indirect evidence of viral agents.^{14, 21} Walter *et al.*,²⁴ using fluorescein-tagged anti-human wart antiserum, demonstrated the presence of viral antigen in the nuclear areas of the granular layer of dermal papillomas in man. Oriel and Almeida,¹⁹ using the electron microscopic technique of negative staining, demonstrated intranuclear virus particles in specimens from 13 of 25 patients who had anal and genital warts. In morphology and distribution, these particles resemble those previously found in human cutaneous warts.

The virus is probably transmitted by sexual contact as venereal disease. Thus,

condyloma acuminatum is commonly referred to as "venereal warts." The anorectal and urogenital areas offer a warm, moist environment, which is necessary for the growth of the virus. There is a high incidence of anal condyloma acuminatum in male homosexuals. Marino¹² reported that 25 per cent of anorectal lesions found in male homosexuals were condyloma acuminatum.

In this series, 91 per cent of the men were either homosexuals or had histories of anal intercourse. This incidence was reported as 46 per cent by Swerdlow and Salvati²³ and 81.8 per cent by Waugh.²⁵ In Oriel's series,¹⁷ 83 per cent of the men and 62 per cent of women with anal con-

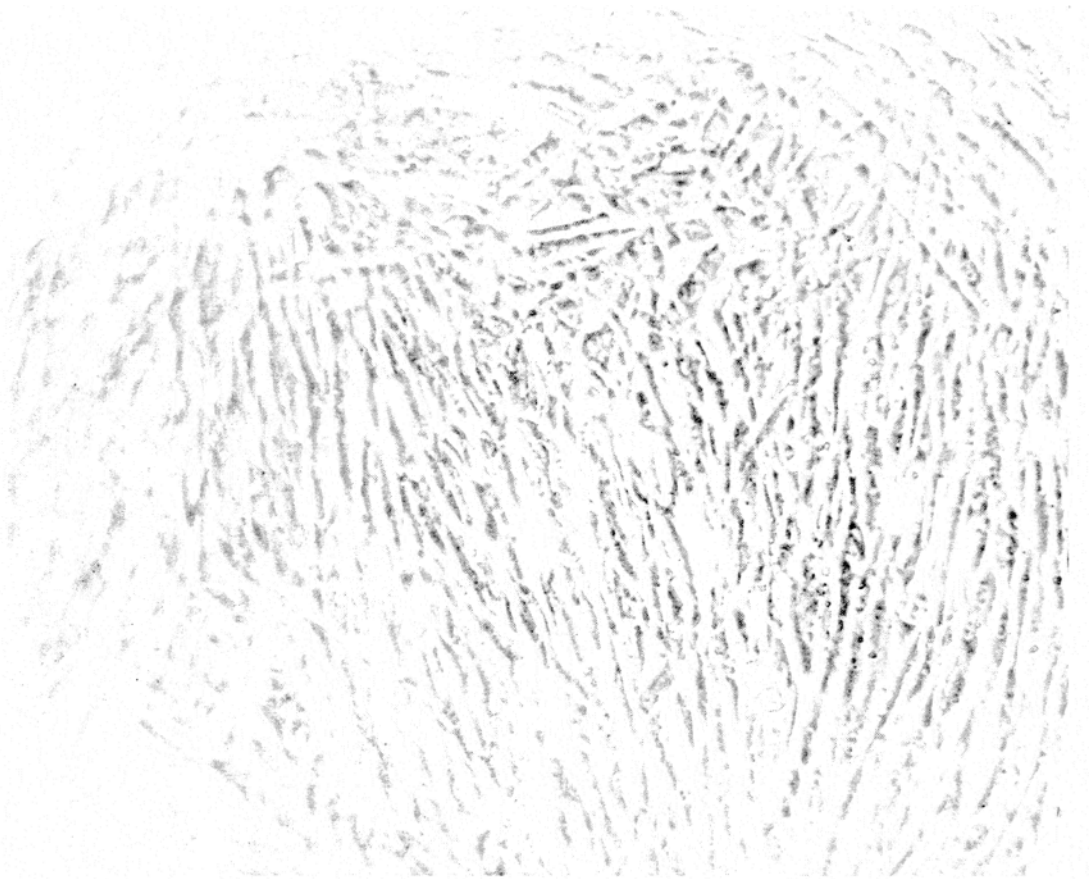


FIG. 3. Photomicrograph taken three weeks after incubation of condyloma tissue in tissue culture medium, demonstrating cellular proliferation. $\times 100$.

dyloma acuminatum had histories of anal intercourse. To prove the venereal transmission of anal condyloma acuminatum, Oriol¹⁷ attempted to examine all sexual contacts or partners of the patients before and after appearance of anal warts. None of the examined contacts, however, had penile warts.

It must be noted also that not all patients who have anal warts have had anal coitus. The presence of cutaneous warts has been implicated as an etiologic factor in such cases. About 25 per cent of our patients had had cutaneous warts previously or had them at the time of examination. This incidence was reported as 15 per cent by Oriol,¹⁸ but he also found that cutaneous

warts were common in a control group. Young²⁶ has suggested that the wart virus may be a normal inhabitant of the anorectum in some people, and that anal coitus may allow its entry into the anoderm because of repeated trauma. However, if one accepts this theory, one would expect to see anal warts as a complication of chronic anal disorders such as anal fissure. Therefore, although the venereal etiology of anal condyloma acuminatum is quite probable, the lack of culture techniques for condyloma virus precludes an unequivocal conclusion.

Numerous methods have been used for the treatment of condyloma acuminatum (Table 5), but none has been universally



FIG. 4. Same patient as in Figure 1, six weeks after completion of immunotherapy. Note the normal anal appearance except for a right posterior skin tag. No condyloma tissue is present.

successful. Forty consecutive patients treated by us prior to utilization of immunotherapy were studied retrospectively. The major methods of therapy used were podophyllin, bichloroacetic acid, excision, and fulguration. In 18 cases only one modality of treatment was used; however, in 22 others combinations of these methods were utilized. In only 10 cases (25 per cent) were these treatments successful in eliminating all condylomas in one or two sessions. In 30 others (75 per cent) the patients needed periodic application of one or more methods of treatment for prolonged periods, ranging from four months to more than two years. In a similar series of patients there were 11 failures in 48 cases.²³ Even when the treatment is eventually successful, it is difficult to predict how many sessions of treatment will be necessary to eradicate the condyloma.

The possible reasons for the high recurrence rate are: 1) The disease is probably the result of sexual contact, and many patients resume sexual activity before completion of their treatment. 2) The incubation period of the virus is unknown, and if this period were many months, a new

condyloma might appear after the completion of an apparently successful course of therapy; by reinfesting the sexual partners of the patient it could easily start a new cycle. 3) The treated patients may change sexual partners and acquire new infections (same or different strains of virus?).

The use of immunotherapy, therefore, becomes quite attractive in the treatment of extensive or recurrent condyloma acuminatum. In 1944, Biberstein² published a lengthy report, "Immunization Therapy of Warts." He used a vaccine on a variety of warts, and also reported that beneficial results were seen in 90 per cent of the patients who had condyloma acuminatum. However, until the recent report of Powell *et al.*²⁰ in 1970, immunotherapy had apparently fallen into disuse. In this study, 24 patients who had persistent or recurrent

TABLE 4. Results of Immunotherapy

Total number of patients	39
Lost to follow-up	3
Total number of patients available for follow-up	36
Excellent results	30 (83.3 per cent)
Good results	3 (8.3 per cent)
Poor results	3 (8.3 per cent)

TABLE 5. Methods of Treating Condyloma Acuminatum

Surgical excision
Electrodesiccation ¹¹
Podophyllin ⁵
Bichloroacetic acid ²³
Cryotherapy
Carbon dioxide snows. ^{8, 11}
Liquid air ⁷
Liquid nitrogen ^{11, 15}
Antitumor preparations
Thiotepa ^{3, 9}
5-Fluorouracil ^{6, 16}
Bleomycin ¹³
Immunotherapy ^{16, 20}

anorectal or urogenital condylomas were treated with autogenous vaccine, with excellent results in 20, good results in three, and poor results in one. Nel and Fourie¹⁶ reported 70 per cent complete regression, 10 per cent partial regression, and 20 per cent no regression in 10 cases in which condylomas were treated by immunotherapy. They also suggest the initial topical application of 5 per cent 5-fluorouracil ointment to decrease the size of giant condylomas prior to immunotherapy to achieve better results. Ablin and Curtis¹ also reported excellent results and no recurrence following the immunotherapy of a patient with large genital warts. In our series, 91.7 per cent of the patients had excellent or good results, and 8.3 per cent showed early recurrence with no regression despite immunotherapy. Immunotherapy had no adverse systemic effect and did not alter the course of the disease unfavorably.

The mechanism by which immunotherapy causes regression of condylomas remains speculative. It has been suggested²⁰ that the relative isolation of potential antigen (virus?) in the superficial layers of condyloma precludes its contact with the circulating lymphocytes. Injection of autogenous vaccine subcutaneously may provide more direct exposure of the antigen to the antibody-forming cells, thereby augmenting the immune mechanisms of the host. However, Nel and Fourie¹⁶ believe that regression probably depends on "killer lymphocytes" destroying "foreign tumor cells" rather than on antiviral antibodies. They also attribute the concomitant increase in antiviral antibodies to the destruction of tumor cells and the liberation of intracellular viral antigens. Failure of immunotherapy is also attributed to the presence of preformed circulating antibodies, which could conceivably have a blocking effect and thus prevent contact with the "killer lymphocytes," and perhaps even result in enhancement.

In an attempt to answer some of these questions, we are presently studying the cellular and humoral responses of patients with condyloma acuminatum before and after immunotherapy.

Conclusion

The immunotherapy of condyloma acuminatum offers a high success rate. Specific indications for immunotherapy are: 1) extensive anal and perianal condyloma acuminatum; 2) resistance to other conventional methods of therapy; 3) recurrence following other forms of treatment.

References

1. Ablin RJ, Curtis WW: Immunotherapeutic treatment of condyloma acuminata. *Gynecol Oncol* 2: 446, 1974
2. Biberstein H: Immunization therapy of warts. *Arch Dermatol* 50: 12, 1944
3. Cheng SF, Veenema RJ: Topical application of thio-tepa to penile and urethral tumors. *J Urol* 94: 259, 1965
4. Ciuffo G: Inesto positivo con filtrato di verruca volgare. *Gior Ital Mal Ven Pelle* 48: 12, 1907
5. Culp OS, Kaplan IW: Condylomata acuminata: Two hundred cases treated with podophyllin. *Ann Surg* 120: 251, 1944
6. Farber S, McMillan L: Treatment of condyloma acuminata (letter to editor). *S Afr Med J* 46: 522, 1972
7. Gold JD: Liquid air and carbonic acid snow: Therapeutic results obtained by the dermatologist. *NY Med J* 92: 1276, 1910
8. Hall AF: Advantages and limitations of liquid nitrogen in the therapy of skin lesions. *Arch Dermatol* 82: 9, 1960
9. Halverstadt DB, Parry WL: Thiotepa in the management of intraurethral condylomata acuminata. *J Urol* 101: 729, 1969
10. Lewis GM, Wheeler CE Jr: *Practical Dermatology*. Third edition. Philadelphia, W. B. Saunders, 1967, 679 pp
11. Lyell A: Management of warts. *Br Med J* 2: 1576, 1966
12. Marino AW Jr: Proctologic lesions observed in male homosexuals. *Dis Colon Rectum* 7: 121, 1964
13. Mishima Y, Masahiro M: Effect of bleomycin on benign and malignant cutaneous tumours. *Acta Derma Venereol* 52: 211, 1972
14. Morgan HR, Balduzzi PC: Propagation of an intranuclear inclusion-forming agent from human condyloma acuminatum. *Proc Natl Acad Sci USA* 52: 1561, 1964

15. Nahra KS, Moschella SL, Swinton NW Sr: Condyloma acuminatum treated with liquid nitrogen: Report of five cases. *Dis Colon Rectum* 12: 125, 1969
16. Nels WS, Fourie ED: Immunotherapy and 5 per cent topical 5-fluoro-uracil ointment in the treatment of condylomata acuminata. *S Afr Med J* 47: 45, 1973
17. Oriol JD: Anal warts and anal coitus. *Br J Vener Dis* 47: 373, 1971
18. Oriol JD: Natural history of genital warts. *Br J Vener Dis* 47: 1, 1971
19. Oriol JD, Almeida JD: Demonstration of virus particles in human genital warts. *Br J Vener Dis* 46: 37, 1970
20. Powell LC Jr, Pollard M, Jinkins JL Sr: Treatment of condyloma acuminata by autogenous vaccine. *South Med J* 63: 202, 1970
21. Smith KO, Dougherty E, Melnick JL, et al: Fine structure of unassembled viral subunits from human warts. *J Bacteriol* 90: 278, 1965
22. Strauss MJ, Shaw EW, Bunting H, et al: "Crystalline" virus-like particles from skin papillomas characterized by intranuclear inclusion bodies. *Proc Soc Exp Biol Med* 72: 46, 1949
23. Swerdlow DB, Salvati EP: Condyloma acuminatum. *Dis Colon Rectum* 14: 226, 1971
24. Walter EL Jr, Walker DL, Cooper GA: Localization of specific antigen in human warts. *Arch Pathol* 79: 419, 1965
25. Waugh M: Condyloma acuminata. *Br Med J* 2: 527, 1972
26. Young HM: Viral warts in the anorectum possibly precluding rectal cancer. *Surgery* 55: 367, 1964

Memoir

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