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Original Article

Interferon Gamma and Secretory Immunoglobulin A Levels Decrease in Persistent Anal Condyloma Acuminatum Infection

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ABSTRACT

Background: Condyloma acuminatum (CA) is a common sexually transmitted disease caused by human papillomavirus (HPV). In recent years, research on anal CA has primarily focused on treatment rather than underlying mechanisms. The mechanism of HPV persistence and recurrence in CA require further exploration. It needs multiple researches in mechanisms to focalize treatment targets.
Objective: To investigate the relationship between intestinal mucosal immunity and the relapse of anal CA and persistent infection.
Methods: Levels of interferon gamma (IFN-γ) and secretory immunoglobulin A (sIgA) were measured using enzyme-linked immunosorbnent assay in anal mucosal cells obtained from patients treated at Tianjin Union Medical Center from September 2022 to December 2024. All the participants signed Informed Consent and the whole plan was approved by Institutional Review Board in Tianjin Union Medical Center (No. B155).
Results: The levels of IFN-γ and sIgA significantly decreased after infection, and persistent infection exhibited even lower levels. These two factors increased following treatment, reaching peak concentrations at 4 weeks before decreasing again.
Conclusion: These findings demonstrate a significant association between persistent anal CA infection and dysregulation of intestinal mucosal immunity.

Keywords: Condylomata acuminata; Anal canal; Intestinal mucosa; Immunoglobulin A, Immunology; Interferon-gamma; Secretory

INTRODUCTION

Condyloma acuminatum (CA) is a common sexually transmitted disease caused by human papillomavirus (HPV). The incidence of CA in the anal canal is increasing due to anal sexual behaviors. HPV proliferates rapidly in the warm and moist environment of the anal canal, and infections in this area often go undetected until big sizes[1]. This poses a significant challenge for treatment due to the deep-seated nature of the infection, the presence of numerous warts and folds in the anal canal, and the resulting substantial burden on patients[2]. Consequently, the recurrent rate in the anal tract is higher than in other affected sites. In recent years, research on anal CA has primarily focused on treatment rather than underlying mechanisms. Immune evasion is considered the primary mechanism behind HPV persistence and recurrence[3], although the exact mechanisms require further exploration.

Mucosal immunity plays an important role in anal virus infection. Secretory immunoglobulin A (sIgA) and interferon gamma

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(IFN-γ) are key molecules in the process of barrier integrity, signaling conduction and virus elimination[4]. sIgA can recognize invasive virus and protect anal mucosa from it through adhesion and neutralization. IFN-γ inhibits viral replication directly. It also activates macrophages which inducing targets epithelial cell apoptosis to promote anti-virus effects. Experts reveal that cervical HPV infection is closely related to mucosal immunity[5]. But the relationship between CA and mucosal immunity remains unknown. It needs multiple researches in mechanisms to focalize treatment targets.

This study aims to investigate the relationship between persistent HPV infection and mucosal immunity in the anal canal by examining changes in the level of IFN-γ and sIgA during different stages of infection.

MATERIALS AND METHODS

Research participants

All patients who visited and received treatment at the Dermatology and Venereology Department of Tianjin Union Medical Center outpatient service from September 2022 to December 2024 were included in this study. Inclusion criteria comprised four conditions: 1) Patients diagnosed with CA by doctors, with or without pathological biopsy confirmation, involving the anal canal as a pathogenic site. Patients in control groups screened to exclude HPV infection in the anal canal. 2) Patients who had not received any topical medications or physical therapy. 3) Involvement of HPV types 6, 11, 16 and 18 by HPV-polymerase chain reaction (PCR) test. 4) Exclusion of other infectious diseases. Exclusion criteria comprised five conditions: 1) Patients taking glucocorticoids or immunosuppressants. 2) Patients who had syphilis or acquired immune deficiency syndrome. 3) Patients who were pregnant or lactating. 4) Patients who had previously received treatment for CA. 5) Patients planning to use interferon in treatment. The controls groups were involved without HPV infection by PCR test in the same period and similar ages compared to experimental groups.

Groups and detection time

We collected the specimens before treatment and in the following 2 weeks, 4 weeks, 6 weeks and 3 months follow-up with or without warts. The specimens in control groups were only collected in first visitation if the HPV was negative (**Table 1**).

Persistent infection

Persistent infection[6] was defined as the recurrence of warts or a positive acetowhite test result after 3 months of treatment at the onset sites.

Specimen collection

For patients with warts, shed cells were obtained by swabbing the surface of the warts. For patients without warts, shed cells were collected by swabbing the area where the acetowhite test was positive. For patients in the control groups, shed cells were collected from any area in the anal canal. One of the two copied specimens was tested for HPV-PCR test and one was stored in phosphate buffer saline and standardized by cells counting.

Therapy method

CA patients were treated with CO_2 laser therapy.

Detection index

Protein quantification was performed using the BCA method.

Table 1. Groups and cases

Variables	Testing time					
	Before treatment (initial infection)	2 wk after treatment	4 wk after treatment	6 wk after treatment	3 mo after treatment	Total
HPV 6/11						
Group name	Group 1	Group 4	Group 6	Group 8	Group 10	-
Involved cases	15	7	7	9	12	50
Cases without warts	0	3	3	4	2	12
Cases with warts	15	4	4	5	10	38
HPV 16/18						
Group name	Group 2	Group 5	Group 7	Group 9	Group 11	-
Involved cases	13	4	4	5	15	41
Cases without warts	0	1	1	2	0	4
Cases with warts	13	3	3	3	15	37
Control						
Group name	Group 3			No detection		
Involved cases	45					
Cases without warts	45					
Cases with warts	0					

HPV: human papillomavirus.

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sIgA and IFN-γ levels in supernatant were detected using enzyme-linked immunosorbnent assay.

Statistical methods

A *p*-value less than 0.05 was considered statistically significant by SPSS. T-test was applied in 2 samples comparison, while analysis of variance (ANOVA) test was applied over 3 samples.

Ethics statement

All the participants signed Informed Consent and the whole plan was approved by Institutional Review Board in Tianjin Union Medical Center (No. B155).

RESULTS

Groups and specimen collection

A total of 136 patients were divided into groups, including 125 males, with ages ranging from 16 to 63 years. Among them, 50 were infected by HPV6/11, and 41 were infected by HPV16/18. Additionally, 45 patients were assigned to the control group. We recorded if the specimen was collected from warts or not. Number of cases involved in each group was showed in **Table 1**.

IFN-γ and sIgA levels significantly decreased initial and persistent infection in CA

The levels of IFN-γ decreased to 752±482 pg/mg in CA patients before treatment and to 567±338 pg/mg in persistent infection compared to 2,518±1,325 pg/mg in control group (**Fig. 1**, **Table 2**). Similarly, the levels of sIgA decreased to 34±20 μg/mg during initial infection and to 27±18 μg/mg in persistent infection compared to 116±86 μg/mg in control group (**Fig. 2**, **Table 2**). Both IFN-γ and sIgA exhibited a statistically significant decrease after HPV initial infection in CA and persistent infection. However, no difference was observed between different types of HPV.

IFN-γ and sIgA exhibited a peak trend over time after treatment, reaching their highest levels at 4 weeks

The IFN-γ levels were 757±422 pg/mg in HPV 6/11 infected group before treatment, then rose to 1,205±535 pg/mg at 2 weeks and 2,114±775 pg/mg at 4 weeks after treatment, following with a decrease to 1,413±804 pg/mg at 6 weeks. The IFN-γ levels were 747±541 pg/mg in HPV 16/18 infected group before treatment, then rose to 841±551 pg/mg at 2 weeks and 1,304±583 pg/mg at 4 weeks after treatment, following with a decrease to 951±775 pg/mg at 6 weeks (**Fig. 3**, **Table 2**). Similarly, sIgA were 39±23 μg/mg in HPV

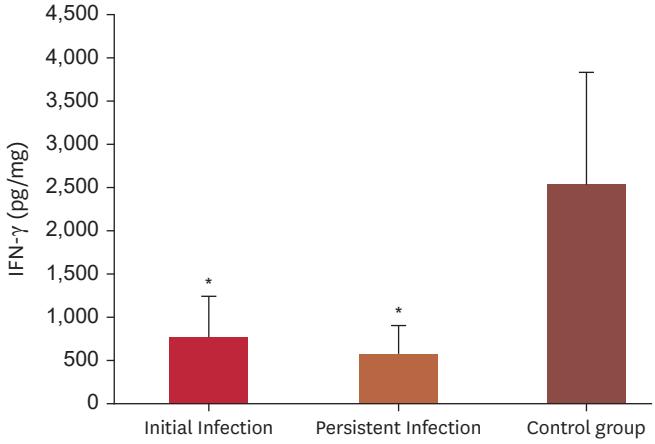

Fig. 1. IFN-γ level of initial infection and persistent infection compared with control (*p<0.05 compared with control group by t-test; p=0.000). "Initial Infection" group include Group 1 and Group 2. "Persistent Infection" group include Group 10 and Group 11.
IFN: interferon.

Table 2. Average values and standard deviation of IFN-γ and sIgA over time after treatment

Variables	Testing time					
	Before treatment (initial infection)	2 wk after treatment	4 wk after treatment	6 wk after treatment	3 mo after treatment	Control group
IFN-γ (pg/mg)						
According to HPV type						
HPV6/11	757±422	1,205±535	2,114±775	1,413±804	662±399	-
HPV16/18	747±541	841±551	1,304±583	951±745	472±278	-
Average	752±482	-	-	-	567±338	-
According to warts after treatment						
No warts	-	1,740±90	2,639±691	2,003±463	1,461±279	2,518±1,325
Warts	752±482	691±151	1,351±392	681±381	484±226	-
sIgA (μg/mg)						
According to HPV type						
HPV6/11	39±23	68±31	106±33	62±25	32±24	-
HPV16/18	28±18	44±23	70±25	51±41	23±12	-
Average	34±20	-	-	-	27±18	-
According to warts after treatment						
No warts	-	89±30	125±29	78±17	72±25	116±86
Warts	34±20	42±10	74±22	43±31	23±13	-

IFN: interferon, sIgA: secretory immunoglobulin A, HPV: human papillomavirus.

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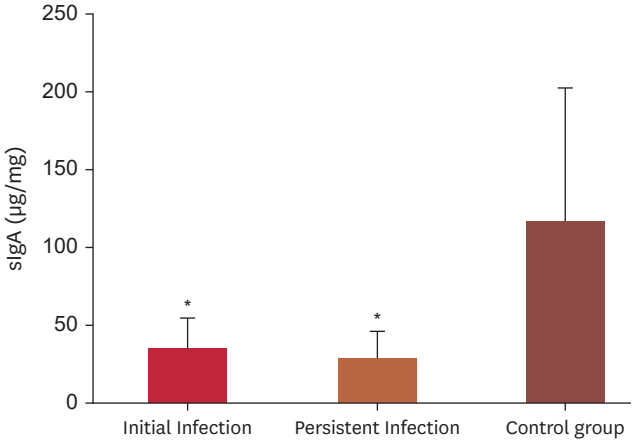

Fig. 2. sIgA level of initial infection and persistent infection compared with control (*p<0.05 compared with control group by t-test; p=0.000). "Initial Infection" group include Group 1 and Group 2. "Persistent Infection" group include Group 10 and Group 11.
sIgA: secretory immunoglobulin A.

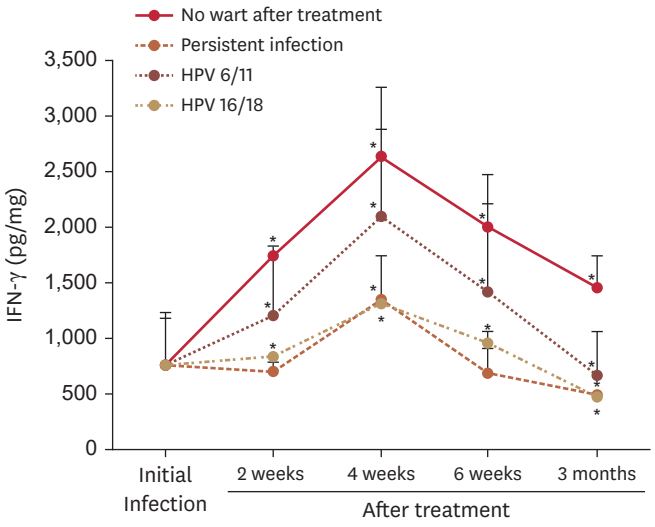

Fig. 3. IFN-γ level according to different HPV infective type and resolved or persistent infection after treatment over time (*p<0.05 compared with "Initial Infection" group. The difference between different types was statistically significant by ANOVA. The difference between resolved and persistent infection was statistically significant by ANOVA).
IFN: interferon, HPV: human papillomavirus, ANOVA: analysis of variance.

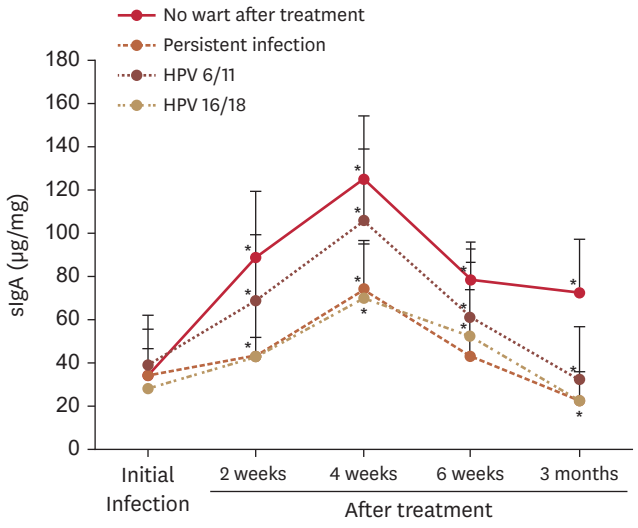

Fig. 4. sIgA level according to different HPV infective type and resolved or persistent infection after treatment over time (*p<0.05 compared with "Initial Infection" group. The difference between different types was statistically significant by ANOVA. The difference between resolved and persistent infection was statistically significant by ANOVA).
sIgA: secretory immunoglobulin A, HPV: human papillomavirus, ANOVA: analysis of variance.

6/11 infected group before treatment, then rose to 68±31 μg/mg at 2 weeks and 106±33 μg/mg at 4 weeks after treatment, following with a decrease to 62±25 μg/mg at 6 weeks. sIgA were 28±18 μg/mg in HPV 16/18 infected group before treatment, then rose to 44±23 μg/mg at 2 weeks and 70±25 μg/mg at 4 weeks after treatment, following with a decrease to 51±41 μg/mg at 6 weeks (**Fig. 4**, **Table 2**). Following HPV infection and repeated treatment, IFN-γ and sIgA levels gradually increased, following a peak trend. They reached their highest level at 4 weeks before decreasing. However, the HPV 16/18 groups showed lower levels compared to the HPV 6/11 groups.

IFN-γ and sIgA remained a relative lower level in persistent infection than those resolved after treatment

After treatment, IFN-γ in groups without warts increased to 1,740±90 pg/mg at 2nd week, 2,639±619 pg/mg at 4th week, 2,003±463 pg/mg at 6th week and 1,461±279 pg/mg at 3rd month compared to 752±472 pg/mg before treatment. While IFN-γ in groups with warts after treatment increased to 691±151 pg/mg at 2nd week, 1,451±392 pg/mg at 4th week, 681±381 pg/mg at 6th week and 484±226 at 3rd month (**Fig. 3**, **Table 2**). It showed a relative lower level in persistent infection than those without warts after treatment. The same condition occured in sIgA. After treatment, sIgA in groups without warts increased to 89±30 μg/mg at 2nd week, 125±29 μg/mg at 4th week, 78±17 μg/mg at 6th week and 72±25 μg/mg at 3rd month compared to 34±21 μg/mg before treatment. sIgA in groups with warts after treatment increased to 42±10 μg/mg at 2nd week, 74±22 μg/mg at 4th week, 43±31 μg/mg at 6th week and 23±13 at 3rd month (**Fig. 4**, **Table 2**).

DISCUSSION

The intestinal mucosa serves as a crucial barrier within the immune system, protecting the body against numerous pathogens. In this defense mechanism, intraepithelial lymphocytes, lamina propria

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lymphocytes, and Peyer's lymph nodes play vital roles in combating invasion and infection[7]. sIgA emerges as a significant molecule in the intestinal mucosal immune barrier, secreted by mucosal lamina propria and plasmocytes. Its role involves preventing pathogens from adhering to epithelial cells and maintaining mucosal integrity. The immune function of sIgA encompasses two essential aspects[8]. First, with its four antigen-binding sites, sIgA acts as an agglutinin, binding to pathogens. Second, the resultant combination complex stimulates Goblet cells in the mucosa to secrete mucus, facilitating the removal of adherent pathogens from epithelial cells. Decreased secretion of sIgA can lead to intestinal immune dysfunction[9]. Furthermore, intestinal intraepithelial lymphocytes (iIEL) participate in intestinal immune surveillance and immune defense. These cells secrete Th1 and Th2-related cytokines in response to exogenous signals, including IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IFN-γ, and TNF-α. iIELs play a crucial role in antibacterial, antiviral, and antitumor functions within the intestinal environment[10].

Current research on HPV and mucosal immunity primarily focuses on cervical infection. Studies have shown that sIgA levels are significantly lower in patients with cervical lesions compared to those without cervical lesions. The local immune function within the cervix plays a crucial role in the development of cervical lesions[11]. Furthermore, the recovery process following treatment for HPV infection is time-dependent. Patients with CIN typically begin to experience immune system recovery in the 6th month after treatment. By the 12th month post-treatment, the immune system generally returns to a normal state. Monitoring the levels of local immune factors in the vagina can be valuable in assessing the progression and prognosis of cervical lesions in patients[12].

This research represents the first exploration into the changes in immune function following HPV infection in CA and treatment, focusing on IFN-γ and sIgA. The observed decrease in IFN-γ and sIgA levels during initial treatment suggests that mucosal immune dysfunction may be a contributing mechanism in CA. Following 2–4 weeks of treatment, IFN-γ and sIgA levels gradually increased compared to the initial state, indicating activation of the mucosal immune system and the release of molecules and cytokines for viral defense. After 4 weeks of treatment, IFN-γ and sIgA levels reached their peak, possibly due to some patients experiencing recurrent infections. After 6 weeks of treatment, IFN-γ and sIgA levels began to gradually decrease from their peak values, particularly in the persistent infection groups. While most patients showed clinical improvement by 6 weeks, some still tested positive on the acetowhite test, suggesting the presence of latent viruses that may be inhibited by immune reactions. After 3 months of treatment, IFN-γ and sIgA levels were further decreased and were lower than their initial states. Patients with persistent infection patients in our study groups continued to experience recurrent warts even after 6 months of treatment. This suggests that the mucosal immune function in these patients may have been initially inactivated or inhibited during progression, leading to persistent infection. Further exploration is required to elucidate the exact mechanisms involved. Additionally, the HPV 16/18 groups showed a lower peak compared to the HPV 6/11 groups. This discrepancy may be attributed to high-risk HPV types having a stronger inhibitory effect on mucosal immune function, potentially contributing to their higher recurrence rates.

These results underscore a significant correlation between persistent infection in anal CA and the dysregulation of intestinal mucosal immunity, as evidenced by changes in IFN-γ and sIgA levels. However, it still has a limitation. This research investigates the primary mechanisms in recurrence and persistent infection. The precise mechanisms underlying this relationship require further exploration.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

All data is available for open access.

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