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Evaluation of Serum Level of IgE (Total) and TNFα in Warts Resistant to Cryotherapy

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ABSTRACT

Background: Warts are common benign epidermal lesions caused by human papillomavirus (HPV) infection. IgE is the classic anaphylactic antibody that mediates the most immediate allergic and anaphylactic reactions and works to produce immunity against parasites and intracellular pathogens like viruses. Tumor necrosis factor α (TNFα) is considered as a pro-inflammatory cytokine, which is responsible for many functions like causing of cytolysis of specific tumor cell lines.

Objective: To study the level of the immunoglobulin E (IgE) and TNFα in the sera of patients suffering from warts resistant to cryotherapy.

Patients and Methods: This study was a case control study that included 90 subjects divided into 2 groups, case group that included 45 patients with warts and control group that included 45 age and sex matched healthy controls. This study included patients suffering from warts after 2 weeks of the last session of cryotherapy after receiving 2 sessions at least. Laboratory tests included measurement of serum IgE and serum TNFα.

Results: About half of the patients had plantar warts, 42.2% had common warts, and 6.7% had genital warts. Median TNFα and IgE serum levels in this study were significantly higher among cases in comparison with controls. No significant relation was reported between TNFα and IgE serum levels and number of warts, type of warts, site of warts or number of sessions.

Conclusion: Serum levels of TNFα and IgE were significantly elevated in patients suffering from warts resistant to cryotherapy in comparison with healthy individuals.

Keywords: Warts, Cryotherapy, Immunoglobulin-E, Human Papillomavirus, TNFα.

INTRODUCTION

Warts are benign epithelial keratinocytes growth produced by HPV infection, characterized by well-defined hyperkeratotic protrusions which may affect both skin and mucous membranes**.** Warts are classically small, rough and solid growths which are similar in color to the normal skin. In general, they are asymptomatic, but they may be painful if present on the soles, when fissured or when growing beneath the nail plate. In addition, they may be associated with conjunctivitis or keratitis if present on the eyelids [1].

HPV is a large group of viruses (to date, over 226 types have been recognized). They are non – enveloped, approximately 50 – 55 nm (relatively small). They have circular double - stranded DNA genome associated with histones. Different HPV types have markedly different oncogenic potentials**.** Mode of infection: Direct: skin to skin contact and Indirect: through contaminated objects and surfaces [2]**.** The principal immunological mechanism against HPV infection (e.g. rejection of warts) is mediated via the cell mediated immune system including natural killer (NK) and cytotoxic T cells. It has been explained that T helper 1 cytokines: (IL2, INF gamma and TNFα) and IL17 are comprised in HPV clearance [3]**.**

Impaired cell mediated immunity or the disproportion between T helper 1 and T helper 2 could be associated with recurrent warts. In addition, HPV can promote immune evasion in infected cells, allowing the virus to remain undetected for extended periods of time. One of the most important processes for cervical lesions is the formation of immunological tolerance in the host's immune system by recurrent HPV infection. HPV persists in therapy-resistant warts may be due to impaired memory T-cell population, failure of HPV-specific lymphocytes to clonally expand, traffic to infected areas, or the degree of a powerful immune response [4]**.**

Immunoglobulin E (IgE) is the classic anaphylactic antibody that mediates the most immediate allergic and anaphylactic reactions (Type 1 hypersensitivity reaction). As well as work to produce immunity against parasites and intracellular pathogens like viruses. Mast cells and basophils express high-density affinity receptors for the Fc portion of IgE. Activation of these receptors induces the release of mediators which include histamine, serotonin, leukotrienes and prostaglandins (resulting in urticaria and anaphylaxis). IgE is produced by plasma cells. Changes in the upper limits of normal total IgE are recorded: they can range from 150 to 1000 UI/ml; but the usual accepted upper limit is between 150 and 300 UI/ml. Elevated serum IgE could be triggered by allergic conditions, infections like HIV infection and chronic hepatitis and immune situations such as hyper IgE syndrome and SLE [5,6].

In addition, TNFα is considered as a pro-inflammatory cytokine that is responsible for several functions such as induction of cytolysis of specific tumor cell lines. The activation of macrophage, NK cells, T and B lymphocytes, astrocytes, endothelial cells, certain tumor cells and epithelial cells result in the formation of TNFα. TNFα has an essential role with regard to the control and suppression of intracellular microbes, it induces employment of inflammatory cells

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to infection area, as well as induces the creation and the protection of granulomas to control the infection. In addition, TNFα immediately trigger macrophages, and next phagocytose with pathogens killing [7].

This work was made to study the level of the immunoglobulin E (IgE) and TNFα in the sera of patients suffering from warts resistant to cryotherapy and to assess the validity of utilization of them as biomarkers of immune response against HPV infection.

PATIENTS AND METHODS

This was a case control study included nighty (90) subjects. They were chosen from the outpatient clinic of Dermatology, Andrology and STDs Department, Mansoura University Hospitals (MUH) within duration of one year from January 2022 to January 2023. They were divided into 2 groups, case group that included 45 patients with warts and control group that included 45 age and sex matched healthy controls. This study included patients aged from 6 to 70 years suffering from warts after 2 weeks of the last session of cryotherapy after receiving 2 sessions at least. But excluded patients with immunological diseases (psoriasis, vitiligo, rheumatoid arthritis and autoimmune connective tissue diseases), which can affect the serum level of the studied markers.

Methods

All participants in the study were subjected to full history taking including personal history (age, gender, occupation, marital status, special habits, pregnancy and lactation), complaint analysis (duration of warts, number of received sessions of cryotherapy), medical history, history of previous infection with HPV viruses, and family history of warts.

A complete general examination was done to exclude any immunological disease. Full dermatological examination included skin, hair, nail, oral and genital mucosa to evaluate disease distribution and severity and to describe wart site, size, number and clinical type.

Laboratory tests included measurement of serum IgE and serum TNFα. A five milliliters sample (5 ml) of peripheral blood was drawn from all subjects by clean venipuncture using disposable syringe and placed on plain tube for serum separation. The tube was left at 22°C for half an hour till coagulation and then centrifuged. The resultant serum was collected and aliquoted and stored at -20°C for further testing. The duration of time between serum sampling and their analysis was ≤ 2 months to avoid loss of bioactivity and contamination. Serum levels of total IgE and TNF-α were determined using commercial kits (Human IgE ELIZA kit) and (Human TNF-α ELIZA kit) using antibodies specific for human IgE and TNF-α coated on wells.

Ethical Consideration

The Mansoura Faculty of Medicine's IRB accepted the current study design. Approval of the managers of the healthcare facilities where the study was conducted was obtained. An informed consent was obtained from all the studied adult subjects and from the caregiver of the participants < 18-years old. Every care was taken to protect the data's privacy. All data were utilized only for scientific aims. The Helsinki Declaration was adhered to at every stage of the investigation.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS Corp., released 2013, version 22.0. Armonk, NY, USA. Qualitative data were defined by utilizing number and percent and were compared by Chi-Square test or Monte Carlo test. Quantitative data were defined by utilizing median and range for non-normally distributed data and mean±SD for normally distributed data following assessing normality using Kolmogrov-Smirnov test.

Normally distributed quantitative data were compared by Student t-test to compare 2 independent groups and by one-way ANOVA test to compare more than 2 independent groups with post hoc Tukey test to detect pair-wise comparison. Non-normally distributed quantitative data were compared by Mann-Whitney U test to compare 2 independent groups and by Kruskal Wallis test to compare at least three independent groups with Mann Whitney U test to detect pair-wise comparison. Validity was detected from the ROC curve. Concerning all the previously utilized test, p was considered significant when its value was less than 0.5.

RESULTS

Table **(1)** shows that there was no statistically significant difference between cases and control group as regard age, sex, occupation and residence. Median TNFα and median IgE were statistically significantly higher among cases than control group.

Table (1): Comparison of sociodemographic characteristics and TNFα and IgE of the studied groups.

	Cases group (n=45)	**Control group (n=45)**	**Test of significance**
Age/years			t=0.074
mean±SD	29.91±14.33	29.69±14.33	p=0.942
Sex			
male	17(37.8%)	17(37.8%)	χ^2=0.0
female	28(62.2%)	28(62.2%)	p=1.0
Occupation			
Office worker	26(57.8%)	30(66.7%)	
Outside worker	5(11.1%)	8(17.8%)	MC=3.31
House wife	14(31.1%)	7(15.6%)	P=0.191
Residence			
Urban	16(35.6%)	20(44.4%)	χ^2=0.741
Rural	29(64.4%)	25(55.6%)	p=0.389
TNFα (pg/ml)			Z=7.84
median (min-max)	47(22.05-114.50)	16.94(0.96-43.63)	P<0.001*
IgE (IU/ml)			Z=7.15
median (min-max)	58.77(22.61-189.4)	19.72(1.8-53.52)	P<0.001*

Median and range: nonparametric test.
t: Student t test, χ^2: Chi-Square test, MC: Monte Carlo test, Z: Mann Whitney U test, *: Statistically significant

Table **(2)** displays that the most common number of warts was from 1 to 2 warts. Of the studied cases, 51.1% had plantar warts. The most common site of warts was in the lower limb. Of the studied cases, 55.6% had treatment sessions from 2 to 3.

Table (2): Wart characteristics and distribution among studied cases

	n=45	**%**
Number of warts		
1-2	14	31.1
3-4	12	26.7
5-9	10	22.2
≥10	9	20.0
Type of warts		
Genital	3	6.7
Plantar	23	51.1
Common	19	42.2
Site of warts		
Upper limb	19	42.2
Lower limb	23	51.1
Genital area	3	6.7
Number of sessions		
2-3	25	55.6
4-9	12	26.7
≥10	8	17.8

Table **(3)** displays that there was no significant relationship between TNFα and number of warts, type of warts, site of warts and number of sessions. Higher TNFα was detected among cases with lower number of warts, higher number of sessions, plantar than genital and common warts.

Table (3): Relation between TNFα and wart characteristics among studied cases.

	TNFα (pg/ml) median (min-max)	**Test of significance**
Number of warts		
1-2	53.20(24.77-114.5)	KW
3-4	50.82(28.52-71.56)	P=0.510
5-9	45.18(27.88-84.77)	
≥10	38.37(22.05-79.84)	
Type of warts		
Genital	49.44(28.52-72.9)	KW=-0.153
Plantar	50.49(22.05-114.5)	P=0.927
Common	44.21(27.88-79.84)	
Site of warts		
Upper limb	44.64(27.88-79.84)	KW=0.008
Lower limb	49.72(22.05-114.5)	P=0.996
Genital area	49.44(28.52-72.9)	
Number of sessions		
2-3	45.53(22.05-84.77)	KW=1.28
4-9	42.52(30.27-68.62)	P=0.528
≥10	51.25(27.66-114.5)	

KW: Kruskal Wallis test

Table **(4)** shows that there was no significant relationship between IgE and number of warts, type of warts, site of warts and number of sessions. Higher IgE was detected among cases with lower number of warts, higher number of sessions, plantar than common and genital warts.

Table (4): Relation between IgE and wart characteristics among studied cases.

	IgE (IU/ml) median (min-max)	**Test of significance**
Number of warts		
1-2	62.68(25.31-126.44)	KW
3-4	62.47(29.74-189.4)	P=0.188
5-9	58.41(27.82-111.69)	
≥10	38.66(22.61-137.61)	
Type of warts		
Genital	33.20(29.74-79.84)	KW=1.58
Plantar	61.37(22.61-189.4)	P=0.454
Common	48.80(27.82-137.61)	
Site of warts		
Upper limb	56.66(27.82-137.61)	KW=1.20
Lower limb	61.37(22.61-189.4)	P=0.548
Genital area	33.20(29.74-79.84)	
Number of sessions		
2-3	60.66(22.61-137.61)	KW=1.09
4-9	55.65(31.71-111.69)	P=0.581
≥10	63.06(28.62-189.4)	

KW: Kruskal Wallis test

Table **(5)** displays that area under ROC curve for TNFα and IgE in differentiating between cases and controls (0.980 and 0.938, respectively). The best detected cut off point for TNFα and IgE were 24.53 and 27.71, respectively.

Table (5): Validity of TNFα and IgE in differentiating cases from controls

	AUC (95% CI)	**P value**	**cut off points**	**Sensitivity%**	**Specificity%**	**PPV%**	**NPV%**	**Accuracy %**
TNFα (pg/ml)	0.980 (0.958-1.0)	<0.001*	24.53	97.8	88.9	89.8	97.6	93.3
IgE (IU/ml)	0.938 (0.893-0.982)	<0.001*	27.71	95.6	73.3	78.2	94.3	84.4

Table **(6)** demonstrates that there was no statistically significant relation between number of sessions and sociodemographic characteristics of the studied cases for age, sex, occupation and residence. There was no statistically significant relation between number of sessions and the number of warts, type of warts and site of warts.

Table (6): Relationship between sociodemographic and warts characteristics with number of sessions

	Number of sessions			**Test of significance**
	2-3	4-9	≥10	
Sociodemographic				
Age/years mean±SD	28.0±14.75	30.50±14.03	35.0±13.88	F=0.728 P=0.489
Sex				
male	10(40)	4(33.3)	3(37.5)	MC=0.154
female	15(60)	8(66.7)	5(62.5)	P=0.926
Occupation				
Office worker	15(60)	6(50)	5(62.5)	MC=0.896
Outside worker	3(12)	1(8.3)	1(12.5)	P=0.925
House wife	7(28)	5(41.7)	2(25)	
Residence				
Urban	7(28)	7(58.6)	2(25)	χ^2=3.73
Rural	18(72)	5(41.7)	6(75)	P=0.155
Warts' characteristics				
Number of warts				
1-2	8(32.0)	4(33.3)	2(25)	MC=7.53
3-4	5(20.0)	3(25)	4(50)	P=0.275
5-9	4(16.0)	4(333)	2(25)	
≥10	8(32.0)	1(8.3)	0	
Type of warts				
Genital	3(12)	0	0	MC=7.36
Plantar	11(44)	5(41.7)	7(87.5)	P=0.118
Common	11(44)	7(58.3)	1(12.5)	
Site of warts				
Upper limb	11(44)	6(50)	2(25)	MC=4.29
Lower limb	11(44)	6(50)	6(75)	P=0.367
Genital area	3(12)	0	0	

F: One-way ANOVA test, χ^2=Chi-Square test, MC: Monte Carlo test

Table **(7)** demonstrates that there was no significant relationship between TNFα and IgE and number of sessions.

Table (7): Relation between TNFα and IgE and number of sessions

	Number of sessions			**test of significance**
	2-3	4-9	≥10	
TNFα	45.53 (22.05-84.77)	42.52 (30.27-68.62)	51.25 (27.66-114.5)	KW=1.28 P=0.528
IgE	60.66 (22.61-137.61)	55.65 (31.71-111.69)	63.06 (28.62-189.4)	KW=1.09 P=0.581

KW: Kruskal Wallis test. Parameters are described as median (min-max)

DISCUSSION

Warts are benign cutaneous lesions in which HPV plays an essential role in their pathogenesis. Common and plantar warts have been considered the commonest forms [8]. The virus has approximately 200 strains spread across five genera; 49 of these strains are identified by their DNA sequences [9].

In the context of malignant tumor treatment, cryotherapy, although primarily a cyto-destructive process, does induce an immune response against treated tissues, as revealed by its anti-tumoral action [10]. The persistence of HPV in therapy-resistant warts might be owing to failed HPV-specific lymphocytes to clonally expand, traffic to infected regions [11].

Immunoglobulin E (IgE) has a crucial function in immediate allergic reactions and could provide immunity against certain parasitic and viral infections, along with adjusting the homeostasis of mast cells [12]. TNFα has been regarded as a pro-inflammatory cytokine that plays essential roles such as the induction of cytolysis of certain tumor cell lines. The stimulation of macrophages, NK cells, lymphocytes, astrocytes, endothelial cells, some tumor cells, and epithelial cells leading to the formation of TNFα [13].

Thus, the aim of the current study was to study the levels of the immunological markers: immunoglobulin E (IgE) and TNFα in the sera of patients suffering from warts resistant to cryotherapy. To obtain this aim, 45 cases with warts resistant to cryotherapy were included and compared with 45 matched healthy subjects as a control group. As far as we reviewed in the literature there is scarce in studies investigated serum levels of IgE and TNFα in the sera of patients suffering from warts resistant to cryotherapy. The only previously published study about this topic was carried out by **Radi *et al.*** [14] on cases with genital warts in Iraq.

Of the 45 studied cases in the present study; 55.6% received from 2 to 3 treatment sessions, 26.7% received from 4 to 9 treatment sessions and 17.8% received 10 or more sessions. In **Kaimal *et al.*** [11] study, 28 patients with recalcitrant warts were included with a definition of less than fifty percent reduction in the mean percentage resolution in size of the wart following three or more successive sessions of cryotherapy.

Our study demonstrated that; 31.1% of the studied cases had from 1 to 2 warts, 26.7% of patients had from 3 to 4 warts, 22.2% of patients had 5 to 9 warts and 20% of patients had 10 or more warts. Similarly, **Kaimal *et al.*** [11] found that most of patients (71.4%) had multiple warts (a mean of 9.5), while only 28.6% of patients had single wart.

According to the current study, plantar warts were the most reported type in 51.1% of patients, followed by common warts in 42.2% of patients, while 6.7% of patients had genital warts. Warts distributed at lower limb were reported in 51.1% of cases, 42.2% of cases had upper limb warts while 6.7% of cases had genital warts. In line with our study, **Kaimal *et al.*** [11] reported palmoplantar warts in 75% of patients, common warts 32.1% of patients, and periungual warts in 50% of patients. Moreover, **Raghukumar *et al.*** [15] reported that 48% of cases had palmoplantar warts, 45% of cases had common warts, 3% of cases had periungual warts.

Median TNFα serum levels in our study were significantly higher among cases in comparison with controls (47 pg/ml versus 16.94 pg/ml; P<0.05). In accordance with the present study, **Radi *et al.*** [14] compared serum levels of IgE and TNFα in 33 females suffering from genital warts with 33 healthy persons as control group. They reported a significant increase in TNFα serum levels among patients compared to controls (68.18±1.7 pg/ml versus 46.68±1.1 pg/ml].

In terms of immunocompetent individuals, viral clearance and control of the progression of virus-induced warts are mediated via immune response activity. The cell-mediated immune response is particularly crucial in the management of HPV [16]. Throughout this process, cytokines released by T cells and accessory cells play critical roles in regulating and controlling cellular immunity. Cytokines, such as interferon-γ, aid in controlling HPV infection by increasing MHC expression in tumor cells and inhibiting angiogenesis [17], and TNF-α, that suppress anti-tumor properties and suppresses the growth of certain cell lineages transformed by HPV [18].

According to the present study, median IgE serum levels were significantly higher among cases in comparison with controls (58.77 versus 19.72 pg/ml; P<0.001). Likewise, **Radi *et al.*** [14] have displayed a significant increase in IgE serum levels among patients in comparison with controls (Mean ± S.D: 202.36 ±10.16 vs 24.12± 1.68 IU/ML). Moreover, they suggested that IgE has an indistinct role in HPV but could relate to alteration in TNFα.

In their case report, **Zare *et al.*** [19] reported the presence of HPV warts and Netherton syndrome with high expression of IgE and high total leucocytic count. They suggested Intravenous immunoglobulin (IVIG) (0.4 g/kg) and anti-TNFα antibodies, that showed potent efficacy. The cause of significant elevation of serum level of IgE and TNFα in the current study needs more investigation to detect its cause and mechanism as it is most probably related to the disease itself (warts) and to its resistant nature to cryotherapy.

Our study reported no significant relation between TNFα serum level and number of received cryotherapy sessions. Higher TNFα serum levels were detected among cases with higher number of sessions. Yet, the differences were not significant. Also, we found no significant relation between TNFα and number of sessions (P=0.528). In line with our study, **Guillot *et al.*** [20] demonstrated sub-chronic exposure to local cryotherapy for treatment of adjuvant-induced arthritis. They noticed that cryotherapy significantly decreased plasma IL-17A and IL-6 protein levels. On the other

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hand, they observed that cryotherapy had no effects on TNFα pathway.

No significant relation was detected in the present study between IgE and number of received cryotherapy sessions. Higher IgE is detected among patients who received higher number of sessions. Yet, the differences were not significant. Of note, the effect of cryotherapy on serum level of IgE was not previously studied [21].

In the current study, higher levels of TNFα and IgE serum levels were detected among cases with lower number of warts. Till now, the differences weren't significant (P=0.510 and 0.188 respectively). Under normal physiological conditions, HPV infections could be managed by an intact cell-mediated as well as by humoral immunity. So, cases with immunodeficiency are at a higher possibility of acquiring severe and recurring warts. In the same line, a greater number of warts may denote deficient immune response against warts [21].

No significant relation was found in our study between number of sessions with age of the studied cases (P=0.489). Similarly, in **Kim *et al.*** [22] study on 89 patients receiving cryotherapy for foot warts, reported no significant differences in therapeutic response based on age of patient. Moreover, **Khozeimeh *et al.*** [23] have displayed that, there was no significant association between age of cases and the therapeutic response in the cryotherapy group.

No significant relation was found in the current study between number of sessions with sex, occupation or residence of the studied cases (P=0.926, 0.925 and 0.155 respectively). Similarly, **Johnson *et al.*** [24] recorded no difference in gender between responders and non-responders among patients who received cryotherapy treatment.

In the current study, no significant relation was reported between number of received sessions and site of warts (P= 0.367). In line with our study, **Kim *et al.*** [22] reported no significant differences in therapeutic response based on wart site. In the current study, no significant relation was reported between number of received sessions with number, or type of warts (P=0.275, and 0.118 respectively). In disagreement with our study, **Kim *et al.*** [22] reported that a greater number of lesions was significantly accompanied by minimal therapeutic response (p=0.007). The difference can be attributed to larger sample size (89 patients) and inclusion of only foot warts in their study.

Non-inherited causes of immunodeficiency, such as malignant tumors, chemotherapeutic agents, biologic therapies, and immunosuppressive agents, may be accompanied by non-manifested HPV infections through affection of numerous immune components [25]. In the same line, alteration of immune functions in diseases is accompanied by increased HPV risk [26].

Many iatrogenic forms of immunosuppression increase HPV risk, comprising in cases receiving immunosuppression for solid organ transplants and cases receiving TNFα inhibitors [26,27]. The increase in risk of HPV attributable to TNFα inhibitors could recommend a certain role for TNFα in HPV clearance, confirmed by the capacity of TNFα to stimulate E6 and E7 proteins in HPV-immortalized keratinocytes [28].

CONCLUSION

Based on our findings, we can conclude that serum levels of TNFα and IgE were significantly elevated in patients suffering from warts resistant to cryotherapy in comparison with healthy individuals. Moreover, TNFα and IgE were found to have significant discriminative ability to differentiate between patients suffering from resistant warts and healthy individuals. However, no significant association was reported between serum levels of TNFα and IgE with type or number of warts. Also, no significant association was reported between serum levels of TNFα and IgE with number of received cryotherapy sessions.

RECOMMENDATIONS

More prospective studies on larger scales are needed to study the levels of IgE and TNFα in the sera of patients suffering from warts resistant to cryotherapy. More prospective studies on larger scales are needed to study the relation between IgE and TNFα with different types and sites of warts.

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