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ORIGINAL CONTRIBUTION

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Possible role of interleukin-17 and macrophage migration inhibitory factor in cutaneous warts

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Summary

Background/Objectives: Cutaneous warts (CW), or verrucae, are benign proliferation of skin that result from infection with human papilloma viruses. Cellular immune reactivity plays a significant role in wart regression. The aim of this study was to elucidate the cellular immune status of patients with CW through measurements of their serum levels of interleukin-17 (IL-17) and macrophage migration inhibitory factor (MIF,) and, identify the possible role of IL-17 and MIF in CW. We assessed serum IL-17 and MIF levels in patients with different forms of CW and compare the results with controls.

Patient and methods: Serum levels of IL-17 and MIF were measured using commercially available ELISA assay kits in 60 patients with CW and 20 healthy controls.

Results: Serum levels of IL-17 and MIF were significantly lower in patients with CW when compared with the controls (*P*-value <.01, <.05, respectively). There was nonsignificant correlation between IL-17 and MIF.

Conclusion: Low IL-17 and MIF levels may have a contributory role in occurrence, maintenance, severity, and recurrence of different types of CW which depend mainly on the defect of cell-mediated immunity. This may shed new light on nontraditional strategies for the future medical treatments of CW through regulation of IL-17 and MIF.

KEYWORDS
cutaneous warts, interleukin-17, macrophage migration inhibitory factor

1 | INTRODUCTION

Cutaneous warts (CW), or verrucae, are benign proliferation of skin that result from infection with human papilloma virus (HPV). While humoral immunity may contribute to resistance to infection, most evidence suggests that cellular immune reactivity plays a significant role in wart regression.[1] The incidence of warts has also been reported to increase in immunosuppressed allograft recipients as well as in patients with some immunodeficiency syndrome, especially a defective cell-mediated immune response.[2] Host defense against HPV relies on intact and functioning cellular immunity including T-cell and natural killer cell cytotoxicity. Therefore, in patients in whom warts are severe or recalcitrant, concern for immune defects is raised.[3]

Interleukin-17 (IL-17) families are an important subclass of cytokines.[4] IL-17 A (hereafter referred to as IL-17) is the most intensively studied. IL-17–producing T cells arise as a specific population of CD4-positive T cells, called T helper 17 (Th17) cells, which are distinct from the classic Th1 and Th2 cells.[5,6]

Macrophage migration inhibitory factor (MIF) is a critical immunoregulatory cytokine, playing a role in the regulation of macrophage function in host defense by regulation of a number of proinflammatory cytokines including tumor necrosis factor (TNF) and interleukin-1 (IL-1). MIF exists in human epidermis, monocytes/

macrophages, T cells, B cells, endocrine, and epithelial cells. MIF is believed to be a criminal agent in many diseases such as allergic and irritant contact dermatitis, atopic dermatitis, psoriasis, vitiligo, alopecia areata, pemphigus vulgaris, and bullous pemphigoid.[7]

This study is an original study, evaluating the cytokine profile, in the form of IL-17 and MIF serum levels, in patients with CW to provide more insight into their contributory role, as indicators of the cellular immune reactivity, in CW.

2 | PATIENTS AND METHODS

2.1 | Study design and setting

A cross-sectional case-control study was carried out on 60 patients with CW, 32 males and 28 females. They were recruited from the outpatient clinic of the Dermatology and Venereology department, Hurghada general hospital, Egypt, after approval of Sohag university hospital ethical committee. In addition, 20 healthy age- and sex-matched subjects were selected as the control group. Prior to initiation of the study, every subject was informed about the aim of the study and gave a written consent. The study was carried out during the period from January 2015 to January 2016. Pregnant and lactating females, concomitant treatment of warts, concomitant intake of immunosuppressive drugs (cyclosporine, azathioprine, and methotrexate), and systemic diseases (diabetes, hypertension, and renal or heart diseases) were excluded from the study.

2.2 | Data collections

All the patients were subjected to complete general and local examination (number of warts, types of warts, onset, course, duration of the warts, family history of warts, history of recurrence of warts, medical history). The diagnosis of CW was confirmed in all patients by 2 dermatological residents based on established clinical diagnosis of the CW.

2.3 | Laboratory workup

Patient blood samples (5 cc) were taken from an antecubital vein. Serum separator tubes are used, and samples were allowed to be clotted for 30 minutes before centrifugation for 15 minutes at 1000 × g. Serum of each sample was transferred and divided into three aliquots using 1-mL cryotubes and stored at −80°C till time of analysis. All samples were measured in a single assay to avoid repeated freeze-thaw cycles. Commercially available enzyme-linked immunosorbent assay (ELISA) kits (using ELISA Multiskan EX microplate photometer, Thermo Scientific, STAT FAX-2100, USA) were used according to manufacturer's protocol for measurements of:

Plasma IL-17 (supplied by Boster Biological Technology, Ltd, USA, Catalog No:EK0430).

Plasma MIF (supplied by Wuhan ELAAB science.com, Ltd, China, Catalog No: E0698H).

2.4 | Statistical analysis

Quantitative data were represented as mean, standard deviation, median, and range. As the data were not normally distributed, Kruskal-Wallis rank test was used for comparison of three or more groups and Mann-Whitney test was used to compare 2 groups. Qualitative data were presented as number and percentage and compared using chi-square test. Spearman's correlation analysis also was used to determine the correlation between 2 continuous variables. *P*-value was considered significant if it was <.05. All statistical procedures were carried out using SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

This study included 60 patients with CW, 32 males (53.3%) and 28 females (46.7%). The mean age of the studied patients was 21.4 ± 9.1 years with age range from 0.17 to 17 years. In addition, 20 healthy control participants were included, 11 males (55%) and 9 females (45%) with their mean age 20.8 ± 9 with nonsignificant difference between the patients and controls regarding their age and sex.

The clinical data of the studied patients were presented in Table 1, as regards the type, number, recurrence, and duration of warts.

TABLE 1 The clinical data of the studied patients as regards cutaneous warts

Variable	No (%)
Type of warts	
Common	27 (45.00)
Planter	20 (33.33)
Anogenital warts	7 (11.67)
Plane	4 (6.67)
Plane + common	1 (1.67)
Planter + common	1 (1.67)
Number of warts	
1	33 (55.00)
2	10 (16.67)
3	8 (13.33)
4	1 (1.67)
5	3 (5.00)
6	2 (3.33)
7	2 (3.33)
8	1 (1.67)
Recurrence	
Primary	42 (70.00)
Secondary	18 (30.00)
Duration/days	
Mean (SD[a])	48.00 (57.89)
Median (range)	30 (10-360)

[a]SD: standard deviation.

Regarding the mean serum level of IL-17 in patients with CW, it was 89.4 pg/L, while in the control group, it was 123.44 pg/L with significant difference (*P*-value <.01). The mean serum level of MIF in patients with CW was 4.13 ng/mL, while in the control group, it was 5.1 ng/mL with significant difference (*P*-value <.05), Table 2.

There were nonsignificant differences in the mean serum levels of IL-17 and MIF in the patients with CW as regards age, sex, smoking status, number, types of warts, recurrence status, duration of disease, and family history; also, there was nonsignificant correlation between the mean serum level of IL-17 and MIF ($P > .05$).

4 | DISCUSSION

Cell-mediated immunity (CMI) plays a significant role in wart regression. The association between cellular immune defects and HPV infection and related morbidities comes from persons with human immunodeficiency virus (HIV) infection. Such individuals show an increased prevalence of anogenital HPV infection as well as longer periods of HPV persistence[8]; hence in the present study, we evaluated the cell-mediated immunity in patients with CW and not known to have any apparent cause of immune incompetence to confirm the isolated incriminating role of the impaired cell-mediated immunity in CW.

IL-17 deficiency models have increased risk of bacterial infection with increased bacterial load and dissemination, delayed neutrophil recruitment and clearance of bacteria, and more severe infections. Risk of fungal and viral infections is also increased in IL-17 deficiency states.[9] It has been found that serum levels of IL-17 significantly decreased in patients with leprosy. The lowest serum levels of IL-17 were found in lepromatous leprosy. It seems that defective secretion of IL-17 has a role in leprosy progression which depends mainly on cell-mediated immunity defect.[10] Korkmaz and Urer[11] reported high prevalence of CW in patients with lupus erythematosus and contribute this finding to the defects in some immune mechanisms, independently of immunosuppressive drugs.

MIF is considered to play an important role in cell-mediated immunity and is ubiquitously expressed in various tissues, including the skin.[12] MIF is known to play an important role in the skin with regard to inflammation, the immune response, cutaneous wound healing and skin disease.[13] However, little is known about the contribution of MIF to CW.

To the best of our knowledge, no previous studies could be traced in literature regarding the assessments of IL-17 and MIF in CW in the research field highlighting the link between the immunity and the various dermatological disorders and the present work is the first case-control study regarding this issue. The present study revealed significantly lower serum levels of IL-17 and MIF among patients with CW when compared with the control group; this low serum levels of IL-17 and MIF could be considered as an important contributing immunological factors for increasing the risk of HPV infections and development in different cutaneous warts; however, this needs further verification on more comprehensive large-scale studies and to be more confirmed by further assessment of the lesional and nonlesional tissue expression of IL-17 and MIF. Also, future researches upon the possibility of using local or systemic administration of IL-17 and/or MIF as medical treatment for CW are recommended. Further studies are required to investigate genetic polymorphism of MIF and IL-17 genes.

TABLE 2 The mean ± SD serum levels of IL-17 and MIF in patients with cutaneous warts in comparison with the control group

Variable[a]	Patients	Controls	*P-value
IL-17			
Mean (SD) (Pg/L)	89.4 (39.1)	123.44 (66.5)	<.01
MIF (ng/mL)			
Mean (SD)	4.13 (3.15)	5.1 (1.65)	<.05

[a]IL-17: interleukin-17, MIF: macrophage migration inhibitory factor, SD: standard deviation.
*P-value <.05 considered significant.

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