International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2023; 6(1): 07-12
Received: 06-10-2022
Accepted: 13-11-2022

Ghada Saad Abd El-Aziz
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Tanta, Egypt

Safinaz Hamdy El-Shorbagy
Department of Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt

Abeer Abd El-Hakam Hodeib
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Tanta, Egypt

Amany Mohammad Abdel-Latif
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Tanta, Egypt

Corresponding Author:
Ghada Saad Abd El-Aziz
Department of Dermatology and Venereology, Faculty of Medicine, Tanta University, Tanta, Egypt

Immunohistochemical expression of connective tissue growth factor in skin tags

Ghada Saad Abd El-Aziz, Safinaz Hamdy El-Shorbagy, Abeer Abd El-Hakam Hodeib and Amany Mohammad Abdel-Latif

DOI: https://doi.org/10.33545/26649411.2023.v6.i1a.123

Abstract
Background: Skin tags (STs), also known as acrochordons, are the most common fibro epithelial skin tumours. Connective tissue growth factor (CTGF) is a novel peptide that exhibits platelet-derived growth factor-like activities and is produced by skin fibroblasts after activation with transforming growth factor-beta (TGF-β). The aim of this research was to evaluate the immunohistochemical expression of connective tissue growth factor in skin tags to provide an insight about its role in the pathogenesis of the disease.
Methods: This prospective case-control research was carried out on 20 skin tags' cases clinically and histopathologically diagnosed, and 10 healthy individuals of matched age and sex, served as control group. All cases were subjected to dermatological examination, skin biopsy and immunohistochemical staining.
Results: There was significant difference between the cases and controls regarding epidermal (Acanthosis, hyperkeratosis, papillomatosis) and dermal changes (perivascular inflammatory infiltrate, fibroblasts, collagen arrangement) (P value <0.05). There was a statistically significant difference in CTGF staining pattern between STs and normal skin (P. value <0.001). There were insignificant relationship between CTGF immunoexpression score (IRIDI score) and each of gender, age or BMI of cases with STs. Insignificant relation was found between site of STs and intensity of CTGF immunoexpression score (IRIDI score).
Conclusions: CTGF immunohistochemical expression was increased in STs which could be incriminated in its pathogenesis through its role in fibroblast proliferation, angiogenesis and collagen synthesis and deposition.

Keywords: Immunohistochemical expression, connective tissue growth factor, skin tags

Introduction
The most prevalent Fibroe Pithelial skin tumours are skin tags (STs), also known as acrochordons. They are developed benign polyps in the eyelids, Intergluteal folds, neck, axillae, inguinal region, thigh, perineal region, and inframammary region. Most of them are soft, pedunculated papules that stick out from the skin. They can appear as single or numerous lesions, and their sizes can range from 2 to 10 mm. They typically increase in size gradually and do not involute on their own. They can either be hyper chromic or normochromic [1-3]. They are histologically made up of dilated capillaries and loose collagen fibres [4].

After being activated by transforming growth factor-beta (TGF-), skin fibroblasts create connective tissue growth factor (CTGF), a new peptide with platelet-derived growth factor-like properties. The simultaneous production of TGF- and CTGF during wound healing raises the possibility of a cascade process controlling tissue regeneration [5]. It has been shown that a wide range of cell types, including fibroblasts, epithelial cells, endothelial cells, and vascular smooth muscle cells, express CTGF [6]. On fibroblasts, CTGF was found to exert mitogenic and chemotactic effects [7]. It has been demonstrated that CTGF is expressed in fibroblasts as a cell-associated, glycosylated 38-kDa form as well as a smaller, secreted 10- to 12-kDa product that nonetheless has biological activity and triggers a series of events [8]. In various fibrotic illnesses of the skin, kidney, liver, and heart [9, 10] involving inflammation and connective tissue build-up, CTGF expression has been observed to be synchronously increased together with TGF- [11].

The aim of this research was to evaluate the immunohistochemical expression of connective tissue growth factor in skin tags to provide an insight about its role in the pathogenesis of the disease.

Cases and Methods

This prospective case-control research was carried out on 30 subjects. They included 20 cases clinically and histopathologically diagnosed cases of STs and 10 healthy individuals of matched age and sex, served as control group at the Outpatient Clinics of Dermatology and Venereology Department and Plastic Surgery Department, Tanta University Hospitals, Egypt. The research was done after approval from the Ethical Committee Tanta University Hospitals. A written consent was obtained from all participants before starting the research.

Exclusion criteria were taking any drug that affect glucose metabolism (insulin, glucocorticoids, oestrogens, glucosamine, catecholamines, thyroid hormones, androgen and adrenergic agonists), metabolic syndrome and unsteady weight in the past three months.

All cases were subjected to complete history taking, complete general examination, dermatological examination for exclusion of any associated skin disease and determination of number, colour, texture and clinical types of the lesions (type I, type II or type III).

Skin biopsy

Excisional skin biopsy were taken under local anesthesia. All biopsy were fixed in 10% neutral buffered formalin for routine processing in Pathology Department, Faculty of Medicine, Tanta University. All the biopsy were transferred to ascending grades of alcohol, put in xylene to clarify the tissues and lastly embedded in paraffin to form the blocks. All paraffin blocks were cut by ordinary microtome to usual histologic sections 3-5 micron in thickness and mounted on glass slides. Histopathological examination by ordinary H&E staining for routine pathological diagnosis. Immunohistochemical staining was performed on 10% formalin fixed, paraffin embedded tissue blocks by using CTGF (Protein A purified), Rabbit Polyclonal Antibody, Concentrated diluted 1:50 for immunohistochemical staining, Cat no. YPA 1963, Biospes (China). In each staining session a section of normal skin was used as a positive control in which CTGF is expressed nuclear. As a negative control, sections of skin tags were processed but PBS was used instead of primary antibody (CTGF).

Staining procedure [12]

Deparaffinization and rehydration of sections, blocking endogenous peroxidase, antigen retrieval, blocking nonspecific staining, exposure to primary antibody, exposure to biotinylated secondary antibody, exposure to streptavidin-biotin complex, then preparation of the researching colour reagent by application for 15 minutes then the sections were rinsed well with distilled water.

In each staining session a section of normal skin was used as a positive control in which CTGF is expressed nuclear. As a negative control, sections of skin tags were processed but PBS was used instead of primary antibody (CTGF)

Interpretation of the immunostaining

Microscopic examination of the slides was performed to determine the expression status of the markers as follow: For CTGF, the immunopositive status was indicated by brown colour of the nucleus of the fibroblast of STs cells. Any stain in the epidermis was neglected. The degree of immunoexpression of the samples was assessed semi-quantitatively using a scale [13] (0 = absence of immunoexpression, 1 = weak (<25% immunoreactive cells), 2 = moderate (25-50% of immunoreactive cells), 3 = strong (>50% of immunoreactive cell)). The intensity of immunostaining of the samples was assessed using a scale (131) (0 = absent staining, 1 = weak staining intensity, 2 = moderate staining intensity, 3 = strong staining intensity). The score of the proportion of stained cells was multiplied by the score of the staining intensity to provide Immunoreactivity intensity distribution index (IRIDI) score [14] ((1-3) = low score, (4-6) = moderate score, (7-9) = high score).

Statistical analysis

Statistical analysis was done by SPSS v16 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as range, mean and standard deviation (SD). Chi-square was used as a test of significance and when expected variables were too small (< 5), Fisher exact test was used qualitative variables were presented as frequency and percentage (%). A two tailed P value < 0.05 was considered significant [15].

Results

Regarding the demographic data and body mass index, there was insignificant difference between cases and controls (Table 1).

Table 2 shows distribution of the studied cases according to family history of skin tags, complaints, affected sites, possible precipitating factors, associated conditions and different parameters.

There was significant difference between the cases and controls regarding epidermal (acanthosis, hyperkeratosis, papillomatosis) and dermal changes (perivascular inflammatory infiltrate, fibroblasts, collagen arrangement) (P value <0.05). Insignificant difference was found between cases and controls regarding horn cyst formation and proliferated capillaries. There was a statistically significant difference in CTGF staining pattern between STs and normal skin (P. value <0.001) (Table 3).

There were insignificant relationship between CTGF immunoexpression score (IRIDI score) and each of gender, age or BMI of cases with STs. Insignificant relation was found between site of STs and intensity of CTGF immunoexpression score (IRIDI score) (Table 4).

Discussion

Skin tags are very frequent benign dermal connective tissue neoplasms made of loose fibrous tissue, often known as soft fibromas, achrocordons, or fibroepithelial polyps [16]. About 25% of humans have acrochordons by the second decade, and this frequency gradually rises until the fifth decade [17]. Acrochordons are equally common in males and females. Sometimes there is an acrochordon family history. They are typically asymptomatic and don't hurt unless they are inflamed or irritated [18].

In the current research, women were more negatively impacted than men. This might be explained by female cases' requests for medical guidance having beauty concerns. According to Hassan *et al.* findings [19]. 's STs predominate in women and have two peaks: one during

pregnancy, which typically regresses during puberty, and the other peak during menopause. This draws attention to the role that hormones play in the development of these diseases. Maluki and Abdullah [20], on the other hand, claimed that STs are equally prevalent in male and female populations.

Seventy percent of cases in the current research reported having a positive family history. Similar to this, Erkek *et al*. [21] revealed that 65.5% of their cases had a positive family history.

Regarding the localization of STs in the studied cases, the commonest sites of STs were axillae (65%) and neck (55%). El Safoury *et al*., [22] reported that STs were most commonly seen on the neck, axillae and groin.

Regarding the precipitating factors of the cases, the most reported factors were obesity, DM, and hypertension. According to El Safoury *et al*. [22], STs have been linked to a variety of illnesses, including DM and obesity. They added that STs might act as a DM marker.

However, compared to the general population, Kahana *et al*. [23] reported that STs were not associated with an increased incidence of obesity. Instead, they reported that cases with STs had a greater impairment of carbohydrate metabolism, and ST detection may serve as a cutaneous marker for identifying cases at increased risk of developing diabetes mellitus (DM). Conversely Sari *et al*. [20] did not find a relationship between DM and STs.

In a correlation between STs number and BMI in this research, it was noticed that there was no relation between them. Sari *et al*. [24] reported absent correlation between number of STs and BMI. In a research of Garcia-Hidalgo *et al*. [25] done on 156 obese cases, the percentage of those with STs increased with increased BMI.

Among the associated dermatological diseases, acanthosis nigricans had the highest percentage. Similar findings were also reported in a research on STs done by Garcia-Hidalgo *et al*. [25] in 156 obese adults to detect cutaneous findings with obesity. However, El Safoury *et al*. [26] showed no significance between cases with STs with or without acanthosis nigricans.

In the present research, CTGF immunohistochemical expression was significantly increased in STs. It could be incriminated in the pathogenesis of STs through its role in fibroblast proliferation, angiogenesis, collagen synthesis and deposition. This was in line with the findings of Ramazani *et al*. [27], who claimed that CTGF plays a role in the regulation of numerous diseases, including the growth of tumours and tissue fibrosis, as well as biological processes such cell proliferation, differentiation, adhesion, and angiogenesis. However, according to Vasilieva *et al*. [28], CTGF causes a decline in fibroblast proliferation and a reduction in their overall number. Additionally, he noted a negative association between the changes in the quantity of vessels and the percentage of vessels in the dermis that were stained positively for CTGF., so he suggested a negative effect of CTGF on angiogenesis in the dermis. On the other hand, Chen and Lau [29] reported that CTGF has both stimulatory and inhibitory actions on fibroblast proliferation and angiogenesis. They underscored its ability to promote either cell death or survival as cell adhesion molecules.

In the present research, CTGF dermal nuclear immunoexpression scoring (IRIDI score) was low (+1) in 4 cases (20%), moderate (+2) in 10 cases (50%) and high (+3) in 6 cases (30%) compared to normal skin where it was low in all samples (100%) (P. value <0.001).

However, in the present research, there was insignificant relation between CTGF immunoexpression score (IRIDI score) and each of sex or age of cases with STs. These results were supported by Ying *et al*. [30] who reported that there is insignificant relationship was found between the level of CTGF expression and the age and sex of the cases with gastric carcinoma.

Moreover, CTGF immunostaining revealed insignificant relation with BMI in the current research. While in a research done by Tan *et al*. [31] He demonstrated that CTGF is down regulated during the development of adipocytes. Exogenous CTGF protein was efficient in preventing adipocyte differentiation when administered either before commitment or during differentiation. The essential transcription factors involved in the programme for adipogenesis were also suppressed by CTGF. These studies set the stage for further research into the roles of CTGF in fat tissue because the higher levels of CTGF expression observed in the central fat depots suggested that CTGF may affect the degree of adipocyte differentiation *in vivo* and consequently the development of insulin-resistant adipocytes.

Table 1: Demographic data and body mass index of the studied groups

		Patients (No.= 20)	**Control (No. = 10)**	**p-value**
		No (%)	**No (%)**	
Sex	Male	8 (40%)	7 (70%)	0.121
	Female	12 (60%)	3 (30%)	
Age (years)	Group 1 (21 – 30)	4 (20%)	_	0.322
	Group 2 (>30 – 45)	7 (35%)	6 (60%)	
	Group 3 (> 45 – 60)	9 (45%)	4 (40%)	
	Mean ± SD	41.40±12.30	44.80±3.29	0.259
BMI	Normal	7 (35%)	3 (30%)	1.000
	Obese	6 (30%)	4 (40%)	
	Overweight	7 (35%)	3 (30%)	--

Data are presented as mean ± SD or frequency (%).

Table 2: Distribution of the studied patients according to family history of skin tags, complaints, affected sites, possible precipitating factors, associated conditions and different parameters (N=20)

		No = 20 (%)
Family history	Positive	14 (70%)
	Negative	6 (30%)
Complaints	Disfigurement	18 (90%)
	Itching	9 (45%)
	Pain	1 (5%)
Site	Axillae	13 (65%)
	Neck	11 (55%)
	Chest	4 (20%)

	Inframammary	3 (15%)
	Thigh	1 (5%)
	Eyelid	1 (5%)
	Back	1 (5%)
Precipitating factors and associated conditions		
Free		9 (45%)
Precipitating factors and associated conditions	Obesity	6 (30%)
	Diabetes mellitus	4 (20%)
	Hypertension	5 (25%)
	Colitis	2 (10%)
Associated dermatological conditions	Acanthosis Nigricans	3 (15%)
	Androgen etic alopecia	1 (5%)
Number	Single	9 (45%)
	Multiple	11 (55%)
Colour	Flesh	13 (65%)
	Hyper pigmented	3 (15%)
	Mixed	4 (20%)
Surface	Smooth	11 (55%)
	Irregular	4 (20%)
	Mixed	5 (25%)
Clinical types	Small papules	8 (40%)
	Filiform lesions	11 (55%)
	Pedunculated tumours	1 (5%)

Data are presented as frequency (%).

Table 3: Histopathological changes (H&E) in both studied groups

		Patients (n = 20)	Control (n = 10)	P- value
Epidermal changes				
Acanthosis		15 (75%)	0 (0%)	<0.001*
Hyperkeratosis		15 (75%)	0 (0%)	<0.001*
Papillomatosis		17 (85%)	0 (0%)	<0.001*
Horn cyst formation		3 (15%)	0 (0%)	0.532
Dermal changes (H&E)				
Perivascular inflammatory infiltrate		17 (85%)	0 (0%)	<0.001*
Fibroblasts	Scattered	4 (20%)	10 (100%)	<0.001*
	Dense	16 (80%)	0 (0%)	
Collagen arrangement	Loose	8 (40%)	10 (100%)	0.002*
	Dense haphazard	12 (60%)	0 (0%)	
Proliferated capillaries		16 (80%)	10 (100%)	0.272
Dermal changes (Immunohistochemical expression of CTGF)				
Dermal immunoexpression	Absent	0 (0%)	0 (0%)	<0.001*
	Weak	4 (20%)	10 (100%)	
	Moderate	10 (50%)	0 (0%)	
	Strong	6 (30%)	0 (0%)	
Intensity of the stain	Weak	1 (5%)	6 (60%)	<0.001*
	Moderate	4 (20%)	4 (40%)	
	Intense	15 (75%)	0 (0%)	
IRIDI score	Low	4 (20%)	10 (100%)	<0.001*
	Moderate	10 (50%)	0 (0%)	
	High	6 (30%)	0 (0%)	

Data are presented as frequency (%).

Table 4: Relation between dermal connective tissue growth factor immunostaining score (IRIDI score) and each of gender, age and Body Mass Index and Relation between of dermal connective tissue growth factor immunostaining score (IRIDI score) and site of skin tags in patients' group

Dermal immunostaining score (IRIDI score)					
		Low (No = 4)	**Moderate (No = 10)**	**High (No = 6)**	**P- value**
Gender	Male	2 (50%)	5 (50%)	1 (16.7%)	0.474
	Female	2 (50%)	5 (50%)	5 (83.3%)	
Age (years)	(17 – 30)	0 (0%)	3 (30%)	1 (16.7%)	0.700
	(>30 – 45)	2 (50%)	2 (20%)	3 (50%)	
	(>45 – 65)	2 (50%)	5 (50%)	2 (33.3%)	
	Mean ± SD	48±13.64	40.0±12.84	39.33±11.09	0.509
BMI	Normal	2 (50%)	4 (40%)	1 (16.7%)	0.903
	Obese	1 (25%)	3 (30%)	2 (33.3%)	
	Overweight	1 (25%)	3 (30%)	3 (50%)	
Dermal intensity					

Site	Low (No. = 4)	Moderate (No. = 10)	High (No. = 6)	P- value
Neck	2 (50%)	6 (60%)	3 (50%)	1.000
Axillae	2 (50%)	6 (60%)	5 (83.3%)	0.564
Chest	1 (25%)	3 (30%)	0 (0%)	0.366
Thigh	0 (0%)	1 (10%)	0 (0%)	1.000
Inframammary	1 (25%)	0 (0%)	2 (33.3%)	0.154
Eye lid	0 (0%)	1 (10%)	0 (0%)	1.000
Back	0 (0%)	1 (10%)	0 (0%)	1.000

Data are presented as frequency (%)

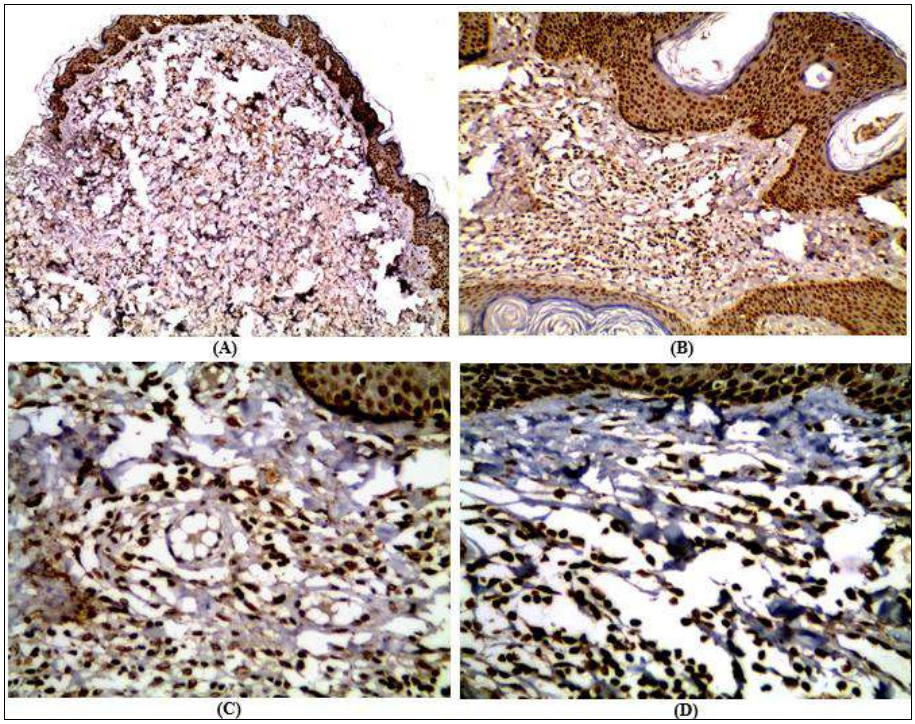

Fig 1: (A) A case of normal skin (control group) showing weak (+1) nuclear CTGF immunoexpression in dermis, moderate staining intensity (+2) and low IRIDI score (IHC X 200), (B) A case of skin tag showing strong positive (+3) nuclear immunoexpression of CTGF, strong staining intensity (+3) and high IRIDI score (IHC X200), (C) High power view of the previous section (B) showing strong positive (+3) nuclear immunoexpression of CTGF of stromal fibroblasts, strong staining intensity (+3) and high IRIDI score (IHC X400), (D) A high power view showing strong positive (+3) nuclear immunoexpression of CTGF in fibroblasts (arrows) and some inflammatory cells, strong staining intensity (+3) and high IRIDI score (IHC X400)

Conclusions

CTGF immunohistochemical expression was increased in STs which could be incriminated in the pathogenesis of STs through its role in fibroblast proliferation, angiogenesis and collagen synthesis and deposition

Acknowledgement

Not available

Author's Contribution

Not available

Conflict of Interest

Not available

Financial Support

Not available

References

1. Rasi A, Soltani-Arabshahi R, Shahbazi N. Skin tag as a cutaneous marker for impaired carbohydrate metabolism: a case-control study. Int J Dermatol. 2007;46:1155-9.
2. Pariser RJ. Benign neoplasms of the skin. Med Clin North Am. 1998;82:1285-307.
3. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. Dermatologica. 1987;174:180-3.
4. Canalizo-Almeida S, Mercadillo-Pérez P, Tirado-Sánchez A. Giant skin tags: report of two cases. Dermatol Online J. 2007;13:30-9.
5. Igarashi A, Nashiro K, Kikuchi K, Sato S, Ihn H, Fujimoto M, *et al*. Connective tissue growth factor gene expression in tissue sections from localized scleroderma, keloid, and other fibrotic skin disorders. J Invest Dermatol. 1996;106:729-33.
6. Moussad EE, Brigstock DR. Connective tissue growth factor: what's in a name? Mol Genet Metab. 2000;71:276-92.
7. Bradham DM, Igarashi A, Potter RL, Grotendorst GR. Connective tissue growth factor: a cysteine-rich mitogen secreted by human vascular endothelial cells is related to the SRC-induced immediate early gene product CEF-10. J Cell Biol. 1991;114:1285-94.
8. Steffen CL, Ball-Mirth DK, Harding PA, Bhattacharyya N, Pillai S, Brigstock DR. Characterization of cell-associated and soluble forms of connective tissue growth factor (CTGF) produced by fibroblast cells *in*

vitro. Growth Factors. 1998;15:199-213.
9. Paradis V, Dargere D, Vidaud M, De Gouville AC, Huet S, Martinez V, *et al*. Expression of connective tissue growth factor in experimental rat and human liver fibrosis. Hepatology. 1999;30:968-76.
10. Chen MM, Lam A, Abraham JA, Schreiner GF, Joly AH. CTGF expression is induced by TGF- beta in cardiac fibroblasts and cardiac myocytes: a potential role in heart fibrosis. J Mol Cell Cardiol. 2000;32:1805-19.
11. Frazier K, Williams S, Kothapalli D, Klapper H, Grotendorst GR. Stimulation of fibroblast cell growth, matrix production, and granulation tissue formation by connective tissue growth factor. J Invest Dermatol. 1996;107:404-11.
12. Buchwalow IB, Bocker W. Immunostaining enhancement. Immunohistochemistry: Basics and Methods. Springer-VerlagBerlin Heidelberg 2010;206(3):624-35.
13. Wang G, Zhang W, Meng W, Liu J, Wang P, Lin S, *et al*. Expression and clinical significance of connective tissue growth factor in thyroid carcinomas. J Int Med Res. 2013;41(4):1214-20.
14. Bayramgurler D, Ozkara SK, Apaydin R, Ercin C, Bilen N. Heat shock proteins 60 and 70 expression of cutaneous lichen planus: comparison with normal skin and psoriasis vulgaris. J Cutan Pathol. 2004;31(9):586-94.
15. Petrie A, Sabin C. Medical statistics of a Glance. Blackwell. 2005; R (853): s(7): 476.
16. Weedon D. Tumors and tumor-like proliferations of fibrous and related tissues. In: Weedon D, editor. Weedon's Skin Pathology 7. 3rd ed. London: Churchill Livingstone Elsevier; 2010. p. 809-44.
17. Thakur JS, Thakur A, Chauhan CG, Diwana VK, Chauhan DC. Giant pedunculated seborrheic keratosis of penis. Indian J Dermatol. 2008;53:37-8.
18. Emir L, Ak H, Karabulut A, Ozer E, Erol D. A huge unusual mass on the penile skin: acrochordon. Int Urol Nephrol. 2004;36:563-5.
19. Hassan AM, Mohammad LM, Nassar AM, Abd-Elazeem MA, Abaza MM. Immunohistochemical study of estrogen and androgen receptors in skin tags. J Microsc Ultrastruct. 2013;1:76-83.
20. Maluki A, Abdullah A. Metabolic Associations with Skin Tags. Int J Dermatol Clin Res. 2016;2:3-11.
21. Erkek E, Kisa U, Bagci Y, Sezikli H. Leptin resistance and genetic predisposition as potential mechanism in the development of Skin tag. Hong Kong J Dermatol Venerol. 2011;19:108-14.
22. El Safoury OS, Fawzy MM, Hay RM, Hassan AS, El Maadawi ZM, Rashed LA. The possible role of trauma in skin tags through the release of mast cell mediators. Indian J Dermatol. 2011;56:641-6.
23. Kahana M, Grossman E, Feinstein A, Ronnen M, Cohen M, Millet MS. Skin tags: a cutaneous marker for diabetes mellitus. Acta Derm Venereol. 1987;67:175-7.
24. Sari R, Akman A, Alpsoy E, Balci MK. The metabolic profile in patients with skin tags. Clin Exp Med. 2010;10:193-7.
25. García-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J, Villa AR, Dalman JJ, Ortiz-Pedroza G. Dermatoses in 156 obese adults. Obes Res. 1999;7:299-302.
26. El Safoury O, Rashid L, Ibrahim M. A study of androgen and estrogen receptors alpha, beta in skin tags. Indian J Dermatol. 2010;55:20-4.
27. Ramazani Y, Knops N, Elmonem MA, Nguyen TQ, Arcolino FO, van den Heuvel L, *et al*. Connective tissue growth factor (CTGF) from basics to clinics. Matrix Biol. 2018;69:44-66.
28. Vasilieva O, Golubtzova N, Filippov F, Gunin A. Connective tissue growth factor (CTGF) in the human dermis through ontogenesis. Russ J Dev Biol. 2016;47:63-8.
29. Chen CC, Lau LF. Functions and mechanisms of action of CCN matricellular proteins. Int J Biochem Cell Biol. 2009;41:771-83.
30. Liu L-Y, Han Y-C, Wu S-H, Lv ZH. Expression of connective tissue growth factor in tumor tissues is an independent predictor of poor prognosis in patients with gastric cancer. World J Gastroenterol. 2008;14:2110-32.
31. Tan JT, McLennan SV, Song WW, Lo LW, Bonner JG, Williams PF, *et al*. Connective tissue growth factor inhibits adipocyte differentiation. Am J Physiol Cell Physiol. 2008;295:740-51

How to Cite This Article
Abd El-Aziz GS, El-Shorbagy SH, Hodeib AAE, Abdel-Latif AM. Immunohistochemical expression of connective tissue growth factor in skin tags. International Journal of Dermatology, Venereology and Leprosy Sciences. 2023; 6(1): 07-12.

Creative Commons (CC) License
This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.