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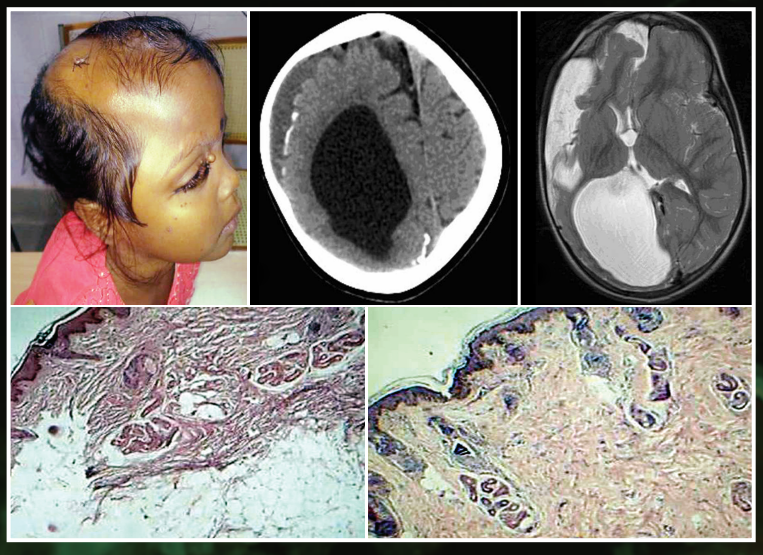

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Skin Tags: A Link Between Lesional Mast Cell Count/Tryptase Expression and Obesity and Dyslipidemia

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Abstract

Background: The etiology of skin tags (STs) is not fully understood. A relation to diabetes mellitus and obesity was suggested. Few studies of possible mast cells (MCs) involvement were reported. Tyrptase is a mast cell mediator and a potent fibroblast growth factor. It may provide a molecular link between mast cell activation and fibrosis. **Aims:** The aim was to assess clinical and laboratory findings in patients with STs, and the possible link between obesity, dyslipidemia, and lesional MC count/tryptase expression. **Materials and Methods:** A total of 20 patients with STs were subjected to clinical examination, estimation of body mass index (BMI), fasting blood glucose (FBG), postprandial blood glucose (PPBG), serum cholesterol and triglycerides, abdominal ultrasound for fatty liver assessment, in addition to study of MCs through staining for MC tryptase in two skin biopsies; lesional and nonlesional (control). **Results:** All patients showed abnormally high BMI and hypertriglyceridemia, with abnormal sonographic pattern in 15 patients (75%). STs number positively correlated with the age of patients. STs showed significantly higher MC counts and tryptase expression, compared with control skin ($P < 0.001$), with no correlation of the STs number or MC count with BMI, FBG, PPBG or serum cholesterol. Obese patients showed a significantly higher MC count than overweight and there was a positive correlation between MC count and serum triglycerides. Axilla and under breast STs showed a higher MC count compared with other sites. **Conclusions:** STs seem to be related to obesity and hypertriglyceridemia. MCs with their tryptase are possibly involved in pathogenesis of STs. MC count is related to the associated factors; obesity and serum triglycerides. MC tryptase expression is a reliable method for accurate tissue MC counting.

Key Words: *Dyslipidemia, mast cell, obesity, skin tag, tryptase*

What was known?
1. STs are suggested to be related to obesity and diabetes.
2. Possible involvement of mast cells in STs pathogenesis was reported.

Introduction

Skin tags (STs) are common benign neoplasms of middle-aged and elderly subjects located predominantly in intertriginous skin.[1] They usually occur as small, soft, pigmented or skin-colored, filiform, often pedunculated lesions which consist of loose fibrous tissue.[2]

The etiology of STs is not fully understood. A relation to diabetes mellitus (DM), obesity, friction, acromegaly, colonic polyps, and human papilloma virus (HPV) has been suggested. However, fibroblast proliferation and epidermal hyperplasia are the main pathologic abnormalities seen in STs. Mast cells (MCs) were found to increase in all examined STs regardless of the presence of DM or obesity and it can probably induce STs through interaction with fibroblasts and keratinocytes.[1]

MCs contain many granules rich in biological mediators. When activated, a MC rapidly releases its characteristic mediators into the interstitium.[3] One of these mediators is tyrptase; the most abundant mediator stored in MC granules.[4] MC tryptase is a potent fibroblast growth factor and may provide a molecular link between MC activation and fibrosis.[5] The aim of this study was to assess the clinical and laboratory findings in patients with STs, and the possible relation between obesity, dyslipidemia, and lesional mast cell count/tryptase expression using immunohistochemistry (IHC).

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Materials and Methods

A cross-sectional study was implemented, in which 20 patients with STs were recruited from Dermatology Outpatient Clinic, Ain Shams University Hospital after obtaining an informed written consent. The study was conducted according to the Declaration of Helsinki Principles, and was approved by the medical ethical committee of Ain Shams University. All patients were subjected to the following:

1. Thorough dermatological examination including the number, site, color, shape, clinical types and consistency of STs, and association with acanthosis nigricans (AN).
2. Body mass index (BMI) calculation: According to National Institutes of Health, a BMI of 18.5-24.9 indicated normal weight, 25-29.9; overweight, 30-34.9; class I obesity, 35-39.9; class II obesity, and >40; extreme obesity.[6]
3. Fasting blood glucose (FBG), and postprandial blood glucose (PPBG) estimation: A patient was considered diabetic (according to American Diabetes Association

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1997 criteria),[7] if FBG was ≥ 126 mg/dL or 2 hours PPBG concentration ≥ 200 mg/dL, or regardless of preceding meal, blood glucose concentration ≥ 200 mg/dL besides symptoms of DM. Normal level was considered when FBG was <100 and PPBS < 140 mg/dL. Prediabetes was defined as blood glucose levels higher than normal but not high enough for a diagnosis of DM.[8]

4. Lipid profile assessment: Total cholesterol level was considered to be elevated if >240 mg/dL. Triglycerides level was considered normal if less than 150 mg/dL.[9]

Abdomenal ultrasound was done to check for fatty liver. Following not less than 8 hours fasting, ultrasound was done by a single sonographer using an FFsonic UF-4100. Liver echo pattern was graded according to the degree of hepatic steatosis as follows:[10]

Grade I (mild): A slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders.

Grade II (moderate): A moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm.

Grade III (marked): A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm, and posterior portion of the right lobe of the liver.

Patients on any kind of treatment likely to alter the results of the study were excluded, such as antihistaminics, mast cell stabilizers, lipid lowering medicines, and oral hypoglycemics.

Two biopsies: One from a ST, and the other from normal skin (as a control). The STs were grasped with forceps and cut at the base with sharp scissors. Normal skin biopsy specimens were taken from inner side of the arm with a punch biopsy instrument.

Biopsies were fixed in a 10% formalin solution for 24 hours. All biopsies were processed by the routine paraffin technique. Sections of approximately 4 μm thickness were cut as near the middle of the biopsy as possible and perpendicular to the skin surface and subjected to routine hemtoxylin and eosin (H and E) staining and IHC with MC tryptase primary antibody. A monoclonal mouse antibody MC tryptase [MC tryptase Ab-2 (clone AAI), USA, 1/1/1997, MS-1216-R1 (ready to use for IHC staining) Cat. Thermo Scientific, MA, USA] was used for staining of paraffin-embedded tissue sections. The secondary antibody (Universal Kit) is a supersensitive immuno-detection system (Ultravision, Invitrogen, REF 95-9943B-Lot 546894A, MA, USA] which contains biotinylated goat antimouse secondary antibody. The substrate chromogen: Di-amino benzidine (DAB) mixture was prepared immediately before use. Counterstaining with Harris hematoxylin was done.

MC counting was done using Olympus Soft Pro software (Tokyo, Japan). In normal nonlesional skin and STs, the numbers of immunostained cells per field in at least five randomly selected fields at ×200 magnifications were counted manually. This covered an area of about 1276 × 956 μm^2 in each of the three sections per biopsy. The average of the three readings was used for statistical analysis.

Data were analyzed using the statistical package for the social science (SPSS) (version 15). The Mann-Whitney test and Kruskal-Wallis test were used for comparisons, as data were nonparametric. Correlation between MC and other parameters was performed using Spearman's correlation test. The probability (*P*) was considered significant when <0.05 and highly significant when <0.001.

Results

Two males and 18 females with STs were included in this study; age ranged from 25 to 50 years, with median (interquartile range; IQR); 35.5 (31.25 to 40) years. The ST number ranged from 1 to 6, median (IQR); 3 (3-5). Sites of presentation were as follows: The neck [Figure 1a] (12 cases, 60%), axilla [Figure 1b] (4 cases, 20%), under the breast [Figure 1c] (3 cases, 15%), and the back (1 case; 5%). The size of STs ranged from 4 mm to 5 mm. AN was detected in five cases. History of pruritus was negative in all cases. Family history of similar lesions was positive in 18 cases.

BMI ranged from 25 to 45, median = 30 [12 patients (60%) were overweight, 7 (35%) were obese and 1 (5%) had morbid obesity]. FBG ranged from 70 to 200 mg/dl, median (IQR); 122 (94.75-143.75). PPBG ranged from 90 mg/dl to 240 mg/dl, median (IQR); 170 (112.50-197.50) [8 cases (40%) were prediabetics, 5 (25%) were diabetics, and 7 (35%) were normal]. Cholesterol ranged from 140 mg/dl to 270 mg/dl, median (IQR); 250 (218.75-258.75) (elevated in 15 cases; 75%). Triglycerides ranged from 210 mg/dl to 340 mg/dl, median (IQR); 245 (230-297.5) (elevated in all cases). The abnormal sonographic findings were echogenic liver in 15 patients (75%): 7 patients (35%) showed grade I echogenicity, 5 patients (25%) grade II echogenicity, and 3 patients (15%) grade III echogenicity.

MC tryptase expression was increased in STs and MC count ranged from 17 to 29, median (IQR); 23 (18-26), while in normal skin tryptase expression was less and MC count ranged from 1 to 3, median (IQR); 3 (2-3). Data of the study group are shown in Tables 1 and 2.

The median MC count (IQR) was 18 (17.00-24.50) in overweight patients, 26 (23-28) in obese, and 23 in morbid obesity. The median (IQR) MC count in axilla was 27 (23.5-29), under the breast was 28 (26-29), and in the neck was 18 (17-23). The median (IQR) MC count in both positive and negative cases for AN was 23 (17-24 and 18-28 respectively). The median (IQR) MC count in cases

Figure 1: STs on (a) the neck (b) axilla and (c) under the breast

Table 1: Characteristics of the study group as regards all numerical parameters

Parameter	Median	IQR	Minimum	Maximum
Age	35.5	31.25-40	25	50
Number of STs	3	3-5	1	6
BMI	30	27.25-35	25	45
FBG	122	94.75-143.75	70	200
PPBG	170	112.5-197.5	90	240
Cholesterol	250	218.75-258.75	140	270
Triglyceride level	245	230-297.5	210	340
MC count in STs	23	18-26	17	29
MC count in control	3	2-3	1	3

BMI: Body mass index, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, STs: Skin tags, MC: Mast cell, IQR: Interquartile range

Table 2: Distribution of patients according to different studied parameters

Parameter	Subgroup	Number	%
Gender	Male	2	10
	Female	18	90
Site of skin tags	Axilla	4	20
	Back	1	5
	Neck	12	60
	Under the breast	3	15
Associated acanthosis nigricans	Negative	15	75
	Positive	5	25
History of pruritus	Negative	20	100
	Positive	-	-
Family history	Negative	2	10
	Positive	18	90
Body mass Index	Overweight	12	60
	Obesity	7	35
	Morbid obesity	1	5
Diabetes	Normoglycemics	7	35
	Prediabetics	8	40
	Diabetics	5	25
Cholesterol	Normal	5	25
	Elevated	15	75
Sonographic echogenecity	Grade I	7	35
	Grade II	5	25
	Grade III	3	15

with negative or positive history of similar lesions in family members was 23.5 (18-26) and 23 (17.8-26) respectively. In normoglycemics, the median (IQR) MC count was 18 (17-028), in prediabetics; 23 (17.25-26.75); and in diabetics; 25 (20.5-25.5). The median (IQR) MC count in both cases with normal and with elevated cholesterol was 23 (20-27 and 18-26 respectively).

Sections stained with H and E revealed that STs had hyperplastic epidermis, papillomatosis, hyperkeratosis, and acanthosis, with upper dermal inflammatory infiltrate. There were no MCs detected [Figure 2a and b]. IHC staining revealed tryptase-positive MCs in upper dermis. Some sections showed many MCs with increased tryptase expression; positively stained cytoplasmic granules by higher magnification [Figure 2c and d]. In contrast, adjacent normal skin revealed scarce tryptase-positive MCs in the upper dermis [Figure 2e and f]. Evidence of extracellular tryptase granules was observed in few STs sections.

As regards the number of STs, it showed no significant correlation with any of BMI, FBS, PPBS, cholesterol, or triglycerides (r_s = 0.14, −0.03, −0.17, −0.15, −0.08 respectively, $P > 0.05$). However, a highly significant positive correlation was found between the number of STs and the age of the patients (strong association) (r_s = 0.71, $P < 0.0001$).

STs showed a highly significant elevation of the median MC count (IQR) [23 (18-26)] compared with control skin [23 (2-3)] ($P < 0.0001$). The MC count showed no significant correlation with the age of the patients, number of STs, BMI, FBS, PPBS, or cholesterol (r_s = 0.09, 0.002, −0.05, −0.01, −0.03, −0.05 respectively, $P > 0.05$). However, there was a significant positive correlation between MC counts and triglycerides (moderate association) (r_s = 0.51, $P < 0.05$).

Comparing MC count in STs with regard to different studied variables [Table 3] revealed the presence of a statistically significant difference in MC count in lesions taken from different sites (P = 0.006); with MC counts in STs in the axilla and under the breast lesions showed no significant difference (P = 0.1), but showed increased counts when compared with neck lesions (P = 0.009 and 0.008 respectively) (data not shown). Obese patients showed significantly higher MC counts when compared to overweight (P = 0.004). There was no statistically significant difference between MC counts in patients with

or without associated AN, with or without positive family history, normoglycemic patients, prediabetics, or diabetics, or patients with normal or elevated cholesterol ($P > 0.05$).

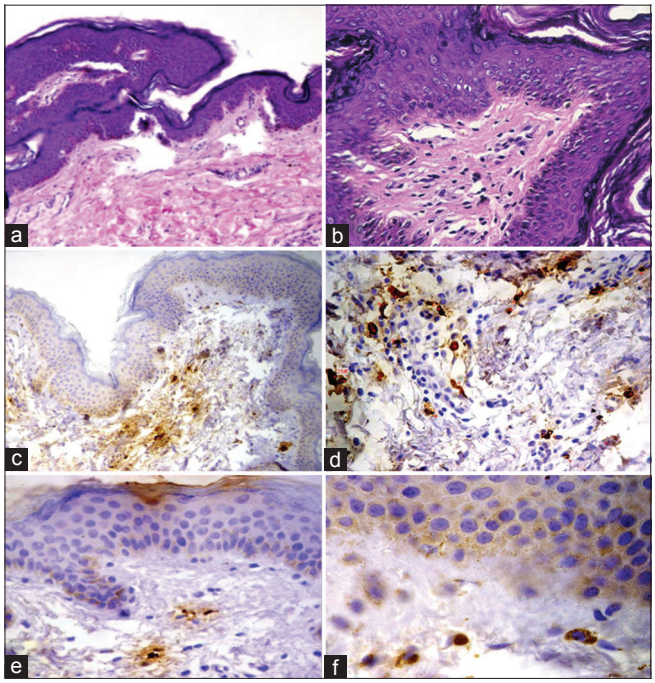

Figure 2: (a) Skin tag with adjacent normal skin (H and E, ×100), (b) Higher magnification showing hyperplastic epidermis and upper dermal chronic inflammatory cellular infiltrate (H and E, ×400), (c) Skin tag with hyperplastic epidermal covering, and many upper dermal mast cells positively stained for tryptase (IHC, ×200), (d) Many mast cells with positively stained cytoplasmic granules (IHC, ×400), (e) Nonlesional normal skin showing: Scarce mast cells in the upper dermis (IHC, ×400), (f) Higher magnification of mast cells showing positively stained cytoplasmic granules (IHC, ×1000)

Discussion

MC cytokines directly or indirectly stimulate fibroblast growth, differentiation, and collagen deposition.[11] In addition, MCs stimulate keratinocyte proliferation and epidermal acanthosis.[12] MC tryptase staining is specific for these cells and allow them to be seen even if they have degranulated. It may also stain tryptase that has been released into the tissues.[13] MC tryptase is a potent fibroblast growth factor that may provide a molecular link between MC activation and fibrosis.[5] Thus, we chose to study the MC count and activity in STs using IHC for tryptase.

The significant positive correlation of STs number with age agrees with the literature showing progressive increased frequency of STs up to the fifth decade.[14] This could be attributed to monocyte chemoattractant protein-1; a chemoattractant for MCs, found to increase with age.[15] However, no correlation was found between the number of STs and PPBG, FBG, BMI, triglycerides, or cholesterol in our study. The sites of presentation of STs ordered descendingly in terms of frequency were the neck, axilla, under the breast, and lastly the back. This frequency is in accordance with the literature reporting that STs are most often found in intertriginous areas (e.g., axillae, neck, eyelids), trunk, groin, abdomen, and then back, due to more liability of skin to skin or skin to clothes friction in intertiginous sites.[16] Particularly the neck is subjected to more often skin to skin and skin to clothes friction by collars, necklaces, etc., in addition to more likely presentation with neck lesions for cosmetic reasons. El Safoury, *et al.*[17] stated that friction of the skin may stimulate an increase in the number of MCs in the dermis, which then

Table 3: Comparison between mast cell counts with regard to different studied variables

Parameter	Subgroups	Mast cell counts		Test value	*P*
		Median	Interquartile range		
Gender	Male (2)	22	18-0.25	0.13	0.90†
	Female (18)	23	17.75-26.5		
Site	Axilla (4)	27	23.5-29	12.44	0.006*
	Back (1)	26	-		
	Neck (12)	18	17-23		
	Under the breast (3)	28	26-29		
Associated acanthosis nigricans	Negative (15)	23	18-28	1.15	0.25†
	Positive (5)	23	17-24		
Family history	Negative (2)	23.5	18-26	0.64	0.52†
	Positive (18)	23	17.8-26		
Body mass index	Overweight (12)	18	17-24.5	2.09	0.004†
	Obesity (7)	26	23-28		
	Morbid obesity (1)	23	-		
Diabetes mellitus	Normal (7)	18	17-28	0.38	0.82*
	Prediabetics (8)	23	17.25-26.75		
	Diabetics (5)	25	20.5-25.5		
Cholesterol	Normal	23	20-27	0.35	0.72†
	Elevated	23	18-26		

*Kruskal-Wallis test, †Mann-Whitney test

release preformed or newly synthesized TNF-α as well as other mediators, inducing several of the histopathological changes found in STs. However, Zaher, *et al*.[1] raised the question that if friction (regardless hyperinsulinemia) is the precipitating factor of STs, why the STs do not affect the whole axilla? They suggested that areas with high count of MCs can only initiate STs formation, whether stimulated by friction or viral infections as HPV in the presence or absence of hyperinsulinemia. Thus, our finding of a higher MC count in the axilla and under the breast than in the neck cannot be explained by these sites being more subjected to friction, for further research.

Although it was formerly reported that STs are often found in and around the affected areas of AN,[18] particularly lesions in axillae and groin,[19] AN was detected in only 25% of our cases with neck lesions. Furthermore, the MC count did not show a significant difference in STs of patients with and without AN.

DM was found in 25% and prediabetes in 40% of our patients. These rates are less than those reported in other studies; 62% in the Thappa (1995) study,[20] and 75% in the Demir and Demir (2002) study.[21] Moreover, we found no correlation between MC counts and PPBS or FBS. Despite these findings, DM and obesity could still contribute to ST development through hyperinsulinemia which may favor upregulated tissue growth leading to many disorders including STs.[22] Hyperinsulinemia may induce both epidermal and fibroblasts proliferation in STs via activation of insulin-like growth factor-I (IGF-I) receptors on their surfaces.[23]

As regards BMI, our entire patients showed abnormal BMI with 60% of patients being overweight, 35% showing obesity, and 5% having morbid obesity. Obesity is strictly related to the development of fatty liver. In the present study, 75% of obese/overweight patients had ultrasound-detected fatty liver which is lower than El-Koofy and colleagues[24] who found it in 96.9% of their studied population. However, only 45% of their obese/overweight patients had biopsy-proven fatty liver.

STs could develop more commonly in overweight or obese people because of increased friction.[25] The higher MC count in our obese patients compared with overweight could thus be due to the presence of more frictional forces in such patients. However, El Safoury, *et al*.[17] found no correlation between MC count and their patient's BMI.

The dyslipidemic profile referring to serum triglyceride level >150 mg/dl and cholesterol level >240 mg/dl[9] was found in 75% of our patients, while the remaining 25% of the patients showed sole hypertriglyceridemia. The significant positive correlation between MC counts and triglycerides could point to an important contribution of MCs to ST formation in obese patients, or generally in patients with dyslipidemia. These results could not be compared with others due to absent previous reports with this regard. However, this finding together with the previously reported association of carotid plaque MCs with atherogenic serum lipids;[26] the involvement of interleukin-4 secreted by MCs in lipoprotein modification and macrophage metabolism of modified lipoproteins;[27] and the intimate relation of lipid metabolism to the formation of MC mediators,[28] all point to a definite relation between MC recruitment in STs and dyslipidemic profile of patients, warranting further investigations.

The significantly higher number of MCs expressing tryptase in our patients' ST, compared with nonlesional skin points to a possible role of MCs in the pathogenesis of STs, by stimulating fibroblast proliferation and collagen synthesis through some mediators such as tryptase.[29] MC mediators are also capable of inducing epidermal hyperplasia, contributing to the main pathologic abnormalities observed in STs.[1] Thus, we can postulate that tryptase contributes to the role of MCs in fibrosis in patients with STs, particularly that we observed some interstitial tryptase granules in few ST sections.

Two previous studies were performed to detect the possible role of MCs in STs development. In the first study by Zaher, *et al.*,[1] 30 participants with STs were divided into 15 nondiabetics and 15 diabetics. Three biopsies were obtained from each participant: A large ST, a small ST, and adjacent normal skin. The MC count in ST lesions was significantly higher than that in normal adjacent skin in both groups with no statistically significant difference, suggesting an important role of MCs in the pathogenesis of STs.[1] Similarly, we found a significantly higher level of MC count in STs, compared to control skin taken from diabetics, prediabetics or normoglycemic patients. However, the median count of MC in STs in our study was higher than that in the Zaher, *et al*. study. This finding proves a more beneficial value of using staining for tryptase rather than toluidine blue stain for MC identification, in addition to confirming the importance of MC involvement in the pathogenesis of STs. Another study by El Safoury *et al*.[30] was conducted to perform quantitation of MCs and collagen fibers in STs and normal skin in 15 diabetics and 15 nondiabetics. Three biopsies were obtained from one anatomical site: A large ST, a small ST, and adjacent normal skin. Each section was stained with Bismarck brown stain for MCs and Masson's trichrome stain for collagen fibers. In contrast to our results, they found the MC count to be higher in diabetic than nondiabetic participants (except in large STs of the nondiabetic group).[30] This difference may be due to use of different stains which affect MC counts.

Antihistamines are proven to have a role in symptom relief in some fibrotic disorders as porphyria cutanea tarda,[31] scleroderma and keloids.[32] In addition, cromolyn sodium, a mast cell stabilizer, is the only FDA approved medicine for treatment of mastocytosis.[33] Thus, antihistamines and MC stabilizers may be beneficial in treatment and/or prevention of STs, associated with large number of MCs, for future clinical trials.

In conclusion, STs seem to be related to obesity as all our cases showed abnormally increased BMI and hypertriglyceridemia. The presence of MCs in all examined STs, regardless of DM, or hypercholesterolemia, points to the possible crucial role of MCs in the etiogenesis of STs probably by its interaction with fibroblasts and keratinocytes through its mediators (particularly MC tryptase). MC tryptase expression is a reliable method for accurate MC counting in tissue sections, and its increase in STs further supports its contribution to the disease pathogenesis. MC counts in STs correlate with the main associated factors of the condition; obesity represented by BMI and hypertriglyceridemia.

What is new?

1. STs are related to obesity as evidenced by high BMI and hypertriglyceridemia.
2. MCs have a crucial role in ST pathogenesis, via in-part - tryptase expression.
3. MC count in STs correlates with BMI and triglycerides.

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