ASSESSMENT OF THE SERUM AND TISSUE LEVELS OF ENDOCAN IN MYCOSIS FUNGOIDES PATIENTS

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ABSTRACT

Background: Although mycosis fungoides (MF) is considered to be the commonest form of primary cutaneous T-cell lymphomas (CTCL), categorized into stages based on clinical, pathological & visceral involvement. Endocan emerged in the past years as a reliable prognostic factor in several cancers, and was tied to the pathogenesis of cancers; hence endocan represents a promising therapeutic target for cancers in the future.Aim of the work: The aim of this work is to study MFpatient's serum endocan level, & tissue endocan level of different stages in comparison to controls, assessing the possibility of using endocan as a prognostic factor in M.F. Materials and Methods: Twenty five patients with MF and fifteen age and sex matched healthy controls were enrolled in the study. The tissue and serum expression of Endocan (ESM-1) were measured using enzyme-linked immunosorbent assay (ELISA) technique.Results: The mean tissue level of ESM-1 was significantly higher in patients (2907.8 ± 4575 pg/gm), than in controls (59.1 ± 15 pg/gm) (p < 0.001). A strong positive statistical correlation was detected between the tissue ESM-1 levels of MF patients and the stage of the disease (p <0.001, r=0.658), also with the extent of lesions in MF patients (p < 0.001, r=0.771). A statistically significant rise was detected in the tissue ESM-1 levels compared (mean value 2907.8 ± 4575) to the serum ESM-1 levels in MF patients (mean value19.9 ± 71.7, p < 0.001), with a positive statistical correlation (p= 0.024, r= 0.449). The mean serum ESM-1 level was not statistically significant in patients (19.9 ± 71.6 pg/ml), compared to controls (7 ± 2.8 pg/ml) (p = 0.086). No statistically significant correlation was detected between the serum ESM-1 levels and the stage of the disease (p= 0.218).Conclusion: These study findings prove that tissue endocan or ESM-1 levels are elevated in MF patients, and are positively correlated to the clinical stage of the disease and with the extent of lesions, suggesting its possible role as a prognostic factor in MF.

Key words: endocan (ESM-1), mycosis fungoides (MF), prognosis, enzyme-linked immunosorbent assay.

INTRODUCTION

Mycosis Fungoides (MF) is regarded as a primary cutaneous T-cell lymphoma *(1)* and it is considered the most common form of CTCL with an average of 60% of new cases. It accounts for 3% to 5% of non-Hodgkin's lymphoma *(2)*, with affection male/female ratio of 1.6-2/1, mostly affecting adults over 50 years of age *(3)*.

The cause of CTCL is unclear *(4)*. Several theories have been reported.MF most likely develops secondary to chronic antigenic stimulation *(5)* Bacterial super antigens *(6)* or some reported viruses *(7)*. Another theory is the failure of the Fas ligand expression which is partially responsible of the T-cell apoptosis *(8)*

Angiogenesis is an important step in the pathogenesis of MF, after the tumor cells have recruited inflammatory cells (macrophages, lymphocytes, mast cells) encouraging them to release their own angiogenic factors **(9)**. MF cells in plaque & nodular stages express the functional Th2 phenotype which acts as a potent growth factor on microvascular endothelial cells. *(10)*.

Angiopoietins are ligands for the endothelium-specific tyrosine kinase Tie2 receptor; categorized into 4 types (Ang1, Ang2, Ang3, Ang4) Ang-2 performs more important functions than Ang-1 in certain diseases with marked angiogenesis. Ang-2 is expressed in lesional skin of MF, while serum levels of Ang-2 were elevated only in patients with Sezary Syndrome (SS). *(11)*.

Angiogenin is another factor involved in the angiogenic process. Serum angiogenin levels in patients with CTCL were significantly higher compared to those of healthy controls, while serum angiogenin levels were elevated only in erythrodermic CTCL patients *(12)*.

Clinical diagnosis of MF is challenging, as it can present with many stages including patches, infiltrated plaques, and tumors *(2)*.The disease mimics clinically a wide range of dermatological conditions and other cutaneous lymphomas *(13)* while lymph node and visceral involvement, as well as large cell transformation, usually occurs in the late stages of the disease *(1)*.

Pathological diagnosis of MF depends on the stage, in the classic early patch stage MF, microscopic findings are usually unspecific and non-conclusive *(13)*.As lesions progress we can seedense sub-epidermal and band-like

lymphocytic infiltrate,epidermotropism is most prominent, Pautrier's abscesses are found in one-third of the cases atypical cells with irregular and cribriform nuclei are frequently found. There is a simultaneous decrease in the number of T-reactive lymphocytes and dendritic cells. In this phase, conversion into large T cell lymphoma CD30+ or CD30- may occur *(14).*Still remains the pathological diagnosis uncertain unless tumour markers are done, MF tumor cells show epidermotropic peripheral T lymphocytes whose phenotype is CD2+, CD3+, CD4+, CD5+, CD8- , CD45RO+, CD20- and CD30-, (Figures-20, 21) *(15).*

Staging of MF/SS into 4 clinical stages based on the TNMB (tumor–node–metastasis–blood), the classification which takes into consideration the extent of skin involvement based on the percentage of body surface area (BSA), the presence of lymph node or visceral disease and the finding of Sézary cells in the peripheral blood (Table-1) *(16)*

Endocan, previously called endothelial cell specific molecule-1(ESM-1), a soluble dermatan sulphate proteoglycan (DSPG), which is expressed by the vascular endothelium, has been interestingly found freely circulating in the blood stream of healthy subjects *(17)*.

Endocan plays a major role in the regulation of cell adhesion, inflammatory disorders and tumor progression *(18).* Endocan expression is controlled by a number of cytokines and growth factors *(19)*.

Endocan in a dose dependent manner inhibits the specific binding of soluble intercellular adhesion molecule 1 (ICAM-1) to lymphocytes through LFA-1 pathway suggesting that by doing so, endocan can inhibit the adhesion and/ or activation of leukocytes in tissues *(20).* The suppressed ICAM-1/LFA-1 interaction participates not only in acute inflammatory responses, but more interestingly in anti-tumor immunity *21)*

It was also proven that Endocan could bind and activate hepatocyte growth factor (HGF) *in vitro (22).* Following its activation, HGF plays major roles in many physio-pathological processes, including development, wound healing, tumor progression, angiogenesis and metastasis *(23).* Through its ability to promote HGF activity, Endocan may consequently be involved in some of these processes *in vivo (24).*

Moreover, it was also evidenced that in the presence of VEGF and FGF-2, endocan mRNA levels were up-regulated 4-fold in an *in vitro* model of angiogenesis *(25).* Furthermore, Endocan has been shown to promote the mitogenic and migratory activities of VEGF-A and -C *in vitro (26)* confirming its role in neo-angiogenesis.

Endocan was found to induce tumor formation and to be closely related to the conversion of dormant tumors into fast-growing angiogenic tumors *(27).* Recent studies demonstrated that, endocan is over-expressed at the mRNA and/or protein levels in several malignant tumors *(28).* In addition, endocan over-expression in cancer tissues and sera has been associated with tumor progression and poor outcomes *(29).*

In this study, the estimated M.F patients serum endocan level, & tissue endocan level of different stages were compared to those of controls, assessing the possibility of using endocan as a prognostic factor in M.F.

MATERIALS & METHODS

The study was conducted on 25 mycosis fungoides patients and 15 sex & age matched healthy controls recruited from Kasr El Aini Hospital, Dermatology outpatient clinic. Written informed consents were obtained from all participants.

1-patients group

25 MF patients, all over 18 years old, no sex predilection, not subjected to any treatment in the past 6 month, excluding any patient with

- Co-existing chronic inflammatory diseases as atopic dermatitis.
- History of co-existing or previously treated. cutaneous or internal malignancy
- Sepsis or infectious skin disease
- History of acute coronary syndrome and atherosclerosis.

Every participant was subjected to the following:

- Detailed history taking (Appendix1).
- *Clinical assessment:* type & extent of lesions (Appendix1). & Lymph nodes assessment.
- *Skin biopsy:* 4mm punch biopsy was taken from lesional skin of mycosis fungoides from each patient. The skin biopsy was divided in two halves, and one half was sent for histopathological confirmation of the diagnosis, While the other half of the skin biopsy was stored in an empty test tube at -80°C for measuring the tissue Endocan levels by ELISA technique.
- *Investigations:* Each patient performed chest X-Ray and abdominal ultrasound.

- *Staging:* The stage of the disease was determined for each patient according to the ISCL/EORTC revision for staging as shown in table (4).
- *Blood sample:* 5 ml venous blood was withdrawn from each patient after separation of serum samples, the sera were then stored at -80°C until analysis. Measurements of the serum Endocan (ESM-1) levels for each patient were done by an ELISA technique.

2- Control group:

The second group included 15 subjects, from whom skin biopsies were taken from excess skin of abdominoplasty operation in the operative theatre of the Surgical Department of Kasr El Aini Hospital, Cairo University. The controls were subjected to the following:

- *Detailed history taking:* to determine age & sex of the participant and to exclude history of chronic inflammatory skin diseases, co- existing tumors, Behest's disease, sepsis, acute coronary syndrome, or infectious skin diseases.
- *Blood sample*: as formerly described.
- *Skin biopsy:* as formerly described (from excess skin of abdominoplasty operation).

Statistics:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples when comparing 2 groups and Kruskal Wallis test when comparing more than 2 groups. Within group comparison of numerical variables was done using Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, Chi square (χ^2)

test was performed. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

RESULTS

The current study included 25 MF patients and 15 age and sex matched controls. Their demographic and clinical data are summarized in table (2).

The mean tissue level of ESM-1 was significantly higher in patientsthan in controls in a statistically significant manner (p < 0.001). Also, the mean serum ESM-1 level was higher in MF patients than in controls, however, this rise was not found to be statistically significant (p = 0.086) table (2)

- Tissue Endocan levels in MF patients was positively correlated to MF stage in a statistically significant manner (p=0.006), (Table 3).
  Therefore, tissue Endocan expression increases with the progression of the stage, and this rise is statistically significant as shown in table- 3.
  On comparing serum Endocan levels in MF patients to their stage of the disease, it was not found to be statistically insignificant (p=0.272), (Table 3).
- A strong positive statistical correlation was detected between the tissue ESM-1 levels of MF patients and the stage of the disease (p < 0.001), (r=0.658), also with the extent of lesions in MF patients (p < 0.001), (r=0.771), (Table 4).
- Also, a statistically moderate positive correlation was detected between the serum ESM-1 levels and the extent of lesions, however this correlation was not significant (p=0.007, r= 0.527), (Table 4).

Table (1): Staging of MF/SS into 4 clinical stages based on the TNMB (tumor–node–metastasis–blood)

T: Skin	
T1	Limited plaques, or patches covering <10% of skin surface
T2	Generalized plaques,or patches covering ≥10% of skin surface
T3	Cutaneous tumors
T4	Generalized erythroderma
N: Lymph Nodes	
N0	No palpable lymphadenopathy, lymph node pathology negative for CTCL
N1	Palpable lymphadenopathy; lymph node pathology negative for CTCL
N2	palpable lymphadenopathy, lymph node pathology positive for CTCL(Nodal architecture uneffaced)
N3	Palpable lymphadenopathy, lymph node pathology positive for CTCL(Nodal architecture partially effaced)
M: Viscera	
M0	No visceral organ involvement
M1	Visceral organ involvement, pathology present
B: Blood	
B0	Atypical circulating cells (sezary cells) not present (<5%)
B1	Atypical circulating cells present (≥5%)
B2	High blood tumor burden (>1000/ulsezary cell+ positive clone)

Table (2): Comparison between tissue and serum levels of Endocan in patients and controls

Clinical Variable	Patients	Controls	p value
Tissue Endocan (pg/gm) Range Mean ± SD Median	386.6 to 23871.8 2907.8 ± 4575 1865.4	34.6 to 85.3 59.1 ± 15 53.8	< 0.001*
Serum Endocan (pg/ml) Range Mean ± SD Median	0.55 to 363.6 19.9 ± 71.7 5.2	1.2 to 10.9 7.1 ± 2.8 7.3	0.086

- SD= standard deviation , p value* < 0.05 is significant

Table (3): Comparing tissue and serum ESM-1 levels in Mycosis Fungoides patients to the stage of the disease

Clinical Variable	Stage			p value
	IA	IB	IIB	
Tissue ESM-1 (pg/gm) Range Mean ± SD Median	386.6 to 848 576.5 ± 196.2 535.6	577.7 to 23871.8 3279.8 ± 4995.6 1939.4	4792.8	0.006*
Serum ESM-1 (pg/ml) Range Mean ± SD Median	0.6 to 5.2 3.4 ± 2.25 3.9	1.2 to 363.6 23.94 ± 80 5.7	5	0.272

SD = Standard Deviation   p * value < 0.05 is significant.

Table (4): Correlations between the serum and tissue levels of ESM-1 in Mycosis Fungoides patients and clinical variables

Clinical Variable	Serum ESM-1		Tissue ESM-1	
Stage	p= 0.218		p < 0.001*	r=0.658
Extent	P= 0.007*	r= 0.527	p < 0.001*	r=0.771
Age	p= 0.653		p = 0.574	

P * value < 0.05 is significant.

Appendix1: MF SHEET
Personal History:
Name: ………………………………………………………. Age: …….. Sex: …………………....
Address: ………………………………………………….. Tel: ……………………………………
Date: ……………….. Occupation: …………………………………. Skin type: …………………………
Present history:
Onset: Rapid☐ Gradual☐ Course: Progressive (Slow☐ rapid☐) in relapse☐
Duration: **……………………………………………………………………………**
Precipitating Factors:
Job (cement☐ chemicals☐)
Past History:
 Autoimmune disease☐ specify: **…………………………………………………**
Associated diseases: …………………………………………………………
Family history:
Skin dis. ☐ specify**…………………………………** others☐ specify**…………**
…………………………………………………………………………………………
Skin Examination:
Distribution: Generalized ☐ Localized☐
Anatomical:
Scalp / Face / Trunk (chest, back, breast) / Flexures (groin, inframammary, axillary)
UL (arm, forearm) / Hands / Palms / Hips /buttocks / LL (thigh, legs) / Feet / Sole / Nails
Type of Lesion:
Patches☐ V. thin plaques☐ Plaques ☐ Hyperp igmented ☐ Tumor ☐ Ulcer☐ poikilodermatous☐
palmoplantar hyperkeratosis ☐ semilunar ☐ Annular ☐scaly Erythematous ☐ Retiform ☐
PLC-like☐ Atrophic☐
**Extent of lesions: (……….. %)**

Lymph Node Examination: …………………………………………………………......
………………………………………………………………………………………..

Investigations:
CXR:……………………………………………………………………………………
………………………………………………………………………………………………
Abd/US:……………………………………………………………………………………………...
………………………………………………………………………………………..
Skin biopsy: …………………………………………………………………………
Staging:

Stage	Description
I. Ia Ib	Only cutaneous Patches or Plaques <10% of body surface >10%, Generalized plaques, lichenoid, erythrodermic
IIa IIb	Plaques and / or dermatopathic lymphadenopathy Tumors and / or dermatopathic lymphadenopathy
III	L.N and / or deep involvement (no other Viscera)
Iva IVb	Plaques or tumors / pathological L.N. involvement / Visceral involvement Plaques or tumors / clinical and pathological L.N. / Visceral involvement
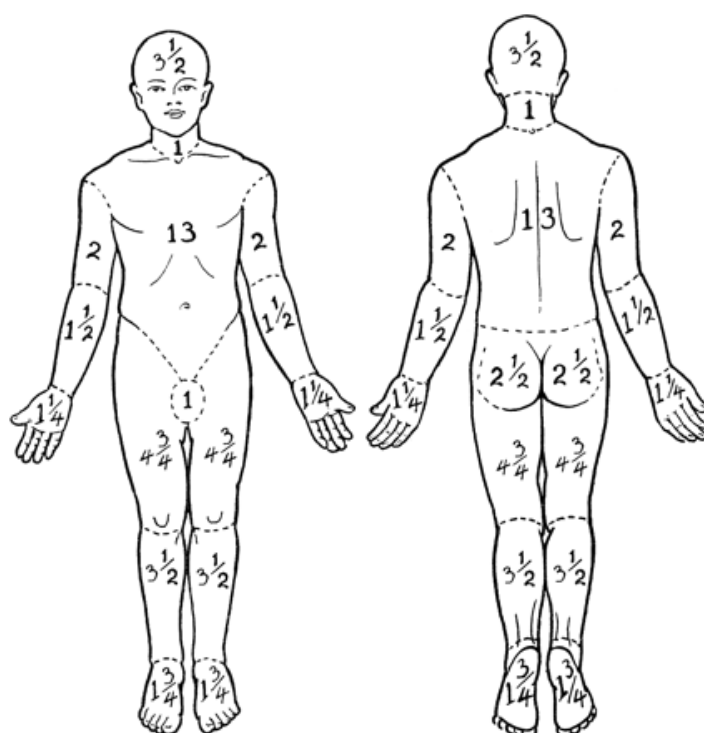
DISCUSSION

The natural history of MF is characterized by an indolent progression through four stages: patch, plaque, tumor, and visceral involvement *(30)*. The diagnosis of MF in its early stages is very challenging *(13)*

Endocan emerged in the past decade as a promising prognostic factor and therapeutic target in many cancers *(17)*. Experimental evidence implicates that Endocan plays a major role in the regulation of major processes such as cell adhesion, inflammatory disorders and tumor progression *(18)*.

In the present study, tissue Endocan expression was elevated in MF patients than in controls in a statistically significant manner. Some studies demonstrated that, Endocan is over-expressed at the mRNA and/or protein levels in several tumor types *(31-34, 29)*.A study by Pedersen & colleaguesproved that

CTCLs display increased levels of angiogenic factors such as VEGF which may explain the significant increase of tissue Endocan expression in our MF patients *(35)*

We also found that serum Endocan expression was elevated in MF patients than in controls, however the difference was not statistically significant. This finding could be explained by the tissue specific nature of mycosis fungoides which is primarily a cutaneous T-cell lymphoma with skin homing preference of malignant T-lymphocytes *(36)*, and also characterized by an indolent course and slow progression till visceral or blood invasion *(30)*.

The current work also showed a statistically significant difference in tissue Endocan levels and the stages of MF. Likewise, a statistically significant positive correlation

between tissue Endocan levels in MF patients and the stage of the disease, as well as the extent of lesions was demonstrated. Previous studies reported that over expression of endocan was found to increase tumor progression *(37).*

The high mRNA levels of endocan have also been regarded as one of the worst prognostic factors in several types of cancer including melanoma, breast, lung, ovarian cancers and HCC *(17)*

Moreover, another study found that the inhibition of Endocan expression through its siRNA, inhibited cell invasion *(38).* We assume that the relationship between Endocan and MF progression is mediated through Endocan's relationship with angiogenesis and with the NFκB pathway in MF

As regards NFκB pathway in MF carcinogenesis and tumor progression, increased activity of NFκB was proven to initiate the expression of anti-apoptotic genes in CTCL cells, leading to increase in their proliferation, survival, angiogenesis and metastasis and contributed to the immune-suppressive nature of *(39).* Another study confirmed the increased activity of the NFκB pathway in MF *(40).* The expression of Endocan was shown to increase tumorous cell survival through the inhibition of NFκB pathway *(28)*

Angiogenic growth factors such as VEFG, HGF/SF, and FGF-2, expressed in tumors promote Endocan expression, which in turn promotes their expression in a positive feedback mechanism. The net result is an acceleration of the vascular endothelial cells proliferation and the vasculogenic mimicry process amongst different tumors *(21).*

Also, no statistically significant correlation was found between serum endocan levels in MF patients and the stage of the disease. This could be explained as previously mentioned by the tissue specific nature of the disease, its indolent course, slow progression, and the absence of patients with advanced stages in this study

We also found that tissue Endocan levels were higher than its serum levels in MF patients in a statistically significant manner, and a positive weak significant correlation was detected between the tissue and serum Endocan levels in MF patients .Therefore, the current study proposes that in MF, when tissue Endocan expression increases, serum Endocan expression increases too, however as previously mentioned serum Endocan levels could not be properly

assessed in the late stages of the disease in the current work, which was a study limitation.

CONCLUSION

This study aimed to assess the serum and tissue levels of endocan in mycosis fungoides and to prove that tissue endocan levels are elevated in mycosis fungoides, and to prove that tissue endocan levels correlated positively with the stage of mycosis fungoides, suggesting that tissue endocan level could be a possible prognostic factor in MF.

In conclusion, the current study sheds the light on the possible role of endocan as a prognostic factor in mycosis fungoides, and also provides an insight about the possible role of endocan in the pathogenesis of mycosis fungoides, and its progression mediated through Endocan's role in angiogenesis, and through its interaction with the NFκB pathway in MF which offers better options for mycosis fungoides monitoring &management.

The current study also delivers Endocan as a new therapeutic target for mycosis fungoides, since it has been found that Endocan may be a therapeutic target in cancer patients *(41).*

However, further studies are required to elucidate more on such roles of endocan in mycosis fungoides and to confirm suggested assumptions and theories.

Appendix1:
History & clinical examination sheet applied for the patient group

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