Evaluation of Vasular Changes in Morphea patients: A Dermoscopy Guided Immunohistochemical Study

A Thesis
Submitted For Partial Fulfillment of
Master Degree in Dermatology

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2015

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Acknowledgement

First and for most, I am always indebted to **GOD**, *the source of all human's knowledge.*

I would like to express my deepest gratitude to ***Prof. Dr. Manal Abdel Wahed Bosseila,*** *Prof of Dermatology, Faculty of Medicine, Cairo University, for her masterful teaching, continuous support, enthusiastic encouragement and correction. It was a great honor as a master student to work under her supervision and learn from her how to make a research. To me, she is so more than a professor, she is an idol.*

I am deeply indebted to ***Dr. Marwah Saleh Adly****, assistant Lecturer of Dermatology, Faculty of Medicine, Cairo University. Her meticulous and continuous supervision was of great help for me throughout this work.*

I would like to thank ***Prof. Dr.Safinaz Salah El-Din Sayed****, Professor of histology, Cairo University, her support and valuable advice will always be appreciated.*

I would like to thank all the staff members and colleagues at the department of Dermatology, for their sincerity, keenness and for setting an excellent example by just being who they are.

I would like to thank my patients for this research work and for their patience and cooperation.

Abstract

Background: Morphea is a rare autoimmune, inflammatory and fibrosing skin disorder that leads to sclerosis of the dermis and subcutaneous tissue. The underlying pathogenesis of the disease remains unknown, but is likely initiated by vascular injury that terminates in increased collagen production and decreased collagen destruction.

Objectives: Evaluation of vascular changes in morphea patients by dermoscopy and immunohistochemistry.

Methods: Twenty patients who fulfilled the clinical and histological findings of morphea were included in this study. Patients were subjected to clinical examination, scoring of morphea lesions as well as dermoscopic examination using Dermlite II Hybrid. Two biopsies were taken from each patient: one from the morphea lesion and the second from the non-lesional skin. Paraffin sections were stained by vascular endothelial growth factor (VEGF) to identify blood vessels.

Results: Dermoscopic evaluation showed that morphea lesions exhibited a characteristic dermoscopic pattern showing the linear blood vessels with areas of shiny and hypopigmented fibrosis.

The total number of blood vessels positive for VEGF in morphea lesions (1.85± 1.94) was comparable to non-lesional skin of same patients (1.88 ± 1.23, p=0.475). The active morphea lesions had higher no. of total blood vessels positive for VEGF (range: 0.8 – 7.6, mean 3.35±2.95) than indurated morphea lesions (range: 0.0 - 4.2, mean 1.68±1.55) and atrophic morphea lesions (range: 0.0 - 4.8, mean 1.28±1.54) but was not statistically significant. A weak inverse significant

correlation was found between the disease duration and the total number of blood vessels positive for VEGF (r=-0.481, p=0.032).

Conclusions: Morphea lesions have specific dermoscopic criteria, which can aid in diagnosing localized scleroderma cases and morphea is not associated with neoangiogenesis.

Key words: Angiogenesis, dermoscopy, vascular endothelial growth factor, morphea.

List of Abbreviations

Abbreviation	Full term
ANA	Antinuclear antibody
B. burgdorferi	Borrelia burgdorferi
CLASI	Cutaneous lupus erythematosus activity and severity index
CMV	Cytomegalovirus
ECDS	En coup de sabre
ECM	extracellular matrix
ECS	Endothelial cells
EPC	Endothelial precursor cells
FGF	Fibroblast growth factor
ICAM-1	Intercellular adhesion molecule-1
IFN-γ	Interferon gamma
IL	Interleukin
LOCUS	Localized Scleroderma Clinical and Ultrasound Study Group
LoSCAT	Localized Scleroderma Cutaneous Assessment Tool
LoSDI	localized scleroderma skin damage index
LoSSI	localized scleroderma skin severity index
LSEA	Lichen sclerosus et atrophicus
MM	Malignant melanoma
MMPs	matrix metalloproteinases
MRI	Magnetic Resonance Imaging
mRSS	modified Rodnan skin score
MSS	Modified Skin Score
NRP	Neuropiline
PDGF	platelet-derived growth factor
PlGF	Placental growth factor
SCC	Squamous cell carcinoma
SLE	Systemic lupus erythematosus
SSC	Systemic sclerosis
TGF-β	Transforming growth factor beta
Th	T-helper
TNF-α	Tumor necrosis factor alpha
VCAM-1	Vascular cell adhesion molecule-1
VEGFR	Vascular Endothelial growth factor receptor
VPF	Vascular permeability factor

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INTRODUCTION and AIM OF WORK

Morphea (localized scleroderma) is an excessive collagen deposition disorder that leads to thickening of the dermis, subcutaneous tissues or both ***(Laxer and Zulian, 2006).*** It may affect children or adults. It is characterized by shiny, ivory-white sclerotic area surrounded by purple erythema which gradually fades with time ***(Zulian et al., 2006).***

There are three main variants of morphea: cicumscribed, generalized morphea , and linear scleroderma ***(Nicole and Werth, 2011).***

The interplay of autoimmune, endothelial, and collagen abnormalities is the postulated pathogenesis of morphea. ***(Leitenberger et al., 2009).***Histopathologically, the microscopic picture of early morphea is characterized by lymphocytic and plasma cells infiltrate in addition to increased interstitial mucin deposition. On the other hand, fully developed lesion is characterized by sclerotic collagen fibres and decrease in the number of adnexal structures ***(Helmbold et al., 2004).*** Skin biopsy specimens provide information about the activity (degree of inflammation), the depth of involvement and morphea disease stages which is useful in therapeutic decision making ***(Succaria et al., 2013).***

Angiogenesis is the production of new blood vessels from an existing vascular network. Angiogenesis is also the underlying pathological process in all the major diseases ***(Carmeliet and Jain, 2011).***

VEGF is one of the most important proangiogenic molecules in the skin. It is also a potent vasodilator, as it increases vascular permeability, it is found to be overexpressed in most physiological and pathological angiogenetic state ***(Bao et al., 2009).***

Dermoscopy is a useful tool that improves diagnostic accuracy in the evaluation of pigmented skin lesions and assessment of vascular structures ***(Argenziano and Zalaudek, 2007)***.

Dermatoscopic features of morphea have been reported only twice in published literature and consisted of accentuated fibrotic beams crossed by spreading telangiectases in the centre of the lesion ***(Campione et al, 2009).***

Aim of work:

In this study we aim to evaluate the vascular changes in morphea patients and correlate them to the disease stage by dermoscopic examination and immunohistochemical staining using vascular endothelial growth factor.

CHAPTER I

MORPHEA

Morphea, also known as localized scleroderma, is a rare fibrosing disorder of the skin and underlying tissues, but in some cases may also extend to the fascia, muscle, and underlying bone ***(Nicole and Werth, 2011).***

Morphea and systemic sclerosis share the same inflammatory and immunologic pathways that are finally responsible for the vascular changes, increased collagen production, and extracellular matrix proliferation ***(Kahaleh, 2008)***.

EPIDEMIOLOGY:

The incidence of morphea is 0.4 to 2.7 per 100,000 people. Although morphea affects all races, it is more common in caucasian. A female predominance of 2.4 to 4.2:1 has been reported ***(Zulian et al., 2006).***

The prevalence of morphea is equal in adults and children; however linear morphea is the more common in children than adults. Patients with morphea are more likely to have a positive family history of morphea and other autoimmune diseases ***(Murray et al., 2002).***

Etiology:

The underlying etiology of morphea remains unknown. The development of morphea is a multifactorial process. The following factors

have all been associated with the formation of morphea: trauma, radiation, medications, infection, and autoimmunity ***(Nicole and Werth, 2011).***

History:

Lesions of morphea occur insidiously. As they are usually asymptomatic, and the early stages of the disease are nonspecific, seeking medical advice is often delayed. Moreover, lack of awareness with this condition further adds to delay in diagnosis and treatment. Significant delay has been described ranging from 6 months up to years ***(Nouri et al., 2013).***

Clinical picture:

Morphea has an asymmetric distribution and is frequently limited to one body area; therefore it is also defined as localized scleroderma ***(Marzano et al., 2003).***

Lesions of morphea have an initial inflammatory (active) stage of erythematous to violaceous patches or plaques. Over time, the center becomes white and sclerotic, and the borders of the lesions take on the characteristic ‘‘violaceous ring.’’ As the active stage subsides, the resultant damage manifests as white sclerotic patches or plaques with post inflammatory hyperpigmentation. The overabundant collagen deposition destroys lesional hair follicles and adnexal structures, resulting in hairless, anhidrotic plaques; recognition of the level of activity of the lesion is very important in the therapeutic decision ***(Laxer and Zulin, 2006)***.

CLASSIFICATION:

Morphea is classified according to clinical presentations, different classifications have been suggested but the most clinically applicable