Diagnostic Value of Video-Dermatoscopy in Patients with Systemic Sclerosis and Dermatomyositis with Its Relation to Serum Vascular Endothelial Growth Factor (S.VEGF)

Thesis

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Naglaa Fathy Salama Sayed

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LIST OF ABBREVIATIONS

Abb.		Full term
ALT	**:**	Alanine Amino-Transferase
AIF-1	**:**	Allograft Inflammatory Protein 1
ACR	**:**	American College of Rheumatology
ADM	**:**	Amyopathic Dermatomyositis
ACE	**:**	Angiotension Converting Enzyme
ACA	**:**	AnticentromerAntibody
ANA	**:**	Anti-Nuclear Antibody
AUC	**:**	Area under curve
AST	**:**	Aspartate Amino-Transferase
AZA	**:**	Azathioprine
CS	**:**	Corticosteroid
CK	**:**	Creatinine Kinase
CMV	**:**	Cytomegalovirus
DM	**:**	Dermatomyositis
DcSSc	**:**	Diffuse Cutaneous Systemic Sclerosis
DMARDs	**:**	Disease Modifying Anti-Rheumatic Drugs
EBV	**:**	Ebstien-Barr Virus
ET-1	**:**	Endothelin 1
ELISA	**:**	Enzyme-Linked Immunosorbent assay
EuLAR	**:**	European League Against Rheumatism
ENA	**:**	Extra-Nuclear Antibody
HMG B1	**:**	High Mobility Group Protein B1
IIM	**:**	Idiopathic Inflammatory Myopathy
IBM	**:**	Inclusion Body Myositis
IFN	**:**	Interferon
IL	**:**	Interleukin
ILD	**:**	Interstitial Lung Disease
IVIG	**:**	Inter-Venous Immunoglobulin
JDM	**:**	Juvenile Dermatomyositis
LDH	**:**	Lactate Dehydrogenase
LcSSc	**:**	Limited Cutaneous Systemic Sclerosis
MHC	**:**	Major Histocompatibility Complex
MDA-5	**:**	Melanoma differentiation indiced gene-5
MTX	**:**	Methotrexate
McTD	**:**	Mixed Connective Tissue Disease
MRSS	**:**	Modified Random Skin Score

LIST OF ABBREVIATIONS (CONT...)

Abb.		Full term
MCP-1	**:**	Monocyte Chemo-attractant Protein 1
MMF	**:**	Mycofenolate Mofetil
MAA	**:**	Myositis Associated Auto-antibody
MSA	**:**	Myositis Specific Auto-antibody
NVD	**:**	Nail fold Vedio-Dermatoscopy
NPV	**:**	Negative predictive value
NS	**:**	Non-significant
OD	**:**	Optical Denisity
PDE-5	**:**	Phosphodiesterase-5
PDGF	**:**	Platelet Derived Growth Factor
PM	**:**	Polymyositis
PPV	**:**	Positive predictive value
PG	**:**	Prostaglandin
PUVA	**:**	Psoralen Plus ultraviolet
RP	**:**	Raynaud's Phenomenon
T-reg	**:**	Regulatory T Cell
RA	**:**	Rheumatoid Arthritis
RTX	**:**	Rituximab
SP	**:**	Scleroderma Pattern
S. VEGF	**:**	Serum Vascular Endothelial Growth Factor
SLE	**:**	Systemic Lupus Erythematous
SSc	**:**	Systemic Sclerosis
Th	**:**	T-helper Cell
TIF-γ	**:**	Transcriptional intermediary factor
TGF	**:**	Transforming Growth Factor
TNF	**:**	Tumor Necrosis Factor
UVR	**:**	Ultraviolet Radiation
VD	**:**	Video-Dermatoscopy

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INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by essential vasomotor disturbances, fibrosis, subsequent atrophy of the skin, subcutaneous tissue, muscles and internal organs (e.g., alimentary tract, lungs, heart, kidney, CNS) with immunologic disturbances accompany these findings ***(Park et al., 2015).***

It is due to Excessive collagen deposition which causes skin and internal organ changes. Many factors, including environmental factors, can lead to immunologic system disturbances and vascular changes. Endothelial alterations may lead to a cascade of stimulatory changes that involve many cells, including fibroblasts, T lymphocytes, macrophages and mast cells. In turn, the activated cells secrete a variety of substances, including cytokines and their soluble receptors and enzymes and their inhibitors. These substances lead to changes in the extracellular matrix compounds, including fibronectin, proteoglycans and collagen types I, III, V, and VII. Increased collagen deposition in tissues is a characteristic feature of systemic sclerosis ***(Sakkas, 2005).***

Dermatomyositis (DM) is an idiopathic inflammatory myopathy with characteristic cutaneous findings, but may also affect the joints, the esophagus, the lungs and less commonly the heart ***(Callen and Wortmann, 2006).***

The cutaneous disease may precede the development of the myopathy in patients with dermatomyositis. In addition, the existence of another subset of patients with dermatomyositis that affects only the skin (amyopathic dermatomyositis) has been recognized. Finally, another subset of patients with dermatomyositis are those with controlled myopathy who continue to have severe and sometimes debilitating skin disease (postmyopathic dermato-myositis) ***(Bohan and Peter, 1975).***

The most common symptoms and signs of dermatomyositis include: a violet colored or dusky red rash which can be itchy or painful, most commonly on face, eyelids, knuckles, elbows, knees, chest and back "often it is the first sign of dermatomyositis" and progressive muscle weakness involves the muscles of both right and left sides closest to the trunk, such as those in hips, thighs, shoulders, upper arms and neck ***(Dalakas and Hohlfeld, 2003).***

The cause of dermatomyositis is unknown. However, genetic, immunologic, infectious and environmental factors have been implicated ***(Werth et al., 2002).***

Vascular endothelial growth factor (VEGF) is a sub-family of growth factors (the platelet-derived growth factor family of cysteine-knot growth factors) that are important signaling proteins involved in both vasculogenesis and angiogenesis ***(Senger et al., 1983).***

It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate such as in hypoxic conditions. VEGF's normal function is to create new blood vessels during embryonic development, new blood vessels after injury of muscle following exercise and new vessels (collateral circulation) to bypass blocked vessels ***(Palmer et al., 2014).***

When VEGF is over expressed, it can contribute to disease. Solid cancers cannot grow beyond a limited size without an adequate blood supply. However, cancers that can express VEGF are able to grow and metastasize. Moreover, Overexpression of VEGF can cause vascular disease in the retina of the eye and other parts of the body. Drugs such as aflibercept, bevacizumab and ranibizumab can inhibit VEGF and control or slow those diseases ***(Harmey, 2004).***

Furthermore, VEGF is dysregulated in patients with connective tissue diseases (CTDs) such as scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyositis, dermatomyositis and inclusion body myositis ***(Distler et al., 2011).***

Dermatoscopy (DE), also called dermoscopy, is a noninvasive technique that allows a rapid and magnified in vivo observation of the skin surface with the visualization of morphologic features invisible to the naked eye. It is performed using manual devices without computer assistance, which generally allows x10 magnifications. Videodermatoscopy (VD) represents the evolution of DE and is performed by a video camera

equipped with optic fibers and lenses that currently allow magnifications ranging from x10 to x1000; the images obtained are visualized on a monitor and stored using a specific software on a personal computer to identify and compare changes over time ***(Micali et al., 2009).***

Both DE and VD have been demonstrated to have further applications in dermatology apart from their use in the differential diagnosis of pigmented skin lesions, including some inflammatory diseases, cutaneous parasitoses, hair and nail abnormalities and a large variety of other dermatological conditions. In several disorders, they may be useful in differential diagnosis, prognostic evaluation and in evaluating the response to treatment ***(Micali et al., 2009).***

The evaluation of the skin microvasculature is important in the evaluation of connective tissue diseases. In patients affected by SSc, the most typical nailfold capillary pattern of microangiopathy, the so-called scleroderma pattern (SP), is commonly observed ***(Caramaschi et al., 2007).***

Three distinct nailfold capillary patterns of microangiopathy have been described in SSc patients: "early," "active," and "late," which do not normally coexist at the same time. "Early" SP is characterized by irregularly enlarged capillaries, a few giant capillaries and hemorrhages; capillary architecture is almost regular without signifcant loss of capillaries. In the "active" SP pattern, frequent giant capillaries and hemorrhages may be

observed with mild loss of capillaries and capillary architecture disorganization. Severe loss of capillaries with a few giant capillaries, avascular areas, capillary architecture disorganization, and ramifed capillaries are typical abnormalities of "late" SP. SSc patients with "late" capillary pattern show an increased risk for active disease and moderate/severe skin or visceral involvement, compared with patients with early and active patterns. The capillary features observed in dermatomyositis and in undifferentiated connective tissue disease are generally reported as being of the "scleroderma-like pattern" ***(Hoert et al., 2012).***