Estimation of Serum IL-33 Level in Vitiligo and its Relation with the Activity of the Disease

Thesis

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Amany Magdeldin Mohamed

بسم الله الرحمن الرحيم

﴿ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا ﴾

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
8-MOP	8-methoxypsoralen
ACD	Allergic contact dermatitis
AD	Atopic dermatitis
ANA	Antinuclear antibody
bFGF	Basic fibroblast growth factor
BSA	Body surface area
CASP7	Caspase 7
CCR6	C-C chemokine receptor type 6
CMV	Cytomegalovirus
CTL	Cytotoxic T lymphocytes
CTLA-4	Cytotoxic T-lymphocyte antigen-4b
CXCL10	C-X-C motif chemokine ligand 10
CXCR3	C-X-C motif chemokine receptor 3
DCs	Dendritic cells
DDR1	Discoidin domain receptor-1
EASI	Eczema Area and Severity Index
EBV	Epstein-Barr virus
ER	Endoplasmic reticulum
ET	Endothelin
FDA	Food and Drug Administration
Foxp3	Forkhead box P3
GM-CSF	Granulocyte-macrophage colony-stimulating factor
H2O2	Hydrogen peroxide
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immune deficiency virus
ICAM	Intercellular adhesion molecule
IFN-γ	Interferon-γ
IL	Interleukin
iNKT	Invariant natural killer T
JAK	Janus kinase
MBEH	Monobenzyl ether of hydroquinone

List of Abbreviations cont…

Abb.	Full term
MDA5	Melanoma differentiation-associated protein 5
MELAS	Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
NB-UVB	Narrow band ultra-violet light
NK	Natural killer
NSV	Non-segmental vitiligo
PASI	Psoriasis area and severity index
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
PUVA	Psoralen plus ultra-vilolet A
QSR	Q-Switched Ruby
ROS	Reactive oxygen species
SA-VES	Self assessment vitiligo extent score
SCF	Stem cell factor
SLE	Systemic lupus erythematosus
STAT	Signal transducer and activator of transcription
SV	Segmental vitiligo
T reg	T regulatory
TCs	Topical corticosteroids
TGF-β	Transforming growth factor-beta
Th2	T helper 2
TNF-α	Tumor necrosis factor-α
TSH	Thyroid-stimulating hormone
Tyrp-1	Tyrosinase-related protein 1
UV	Ultra-vilolet
VASI	Vitiligo Area Severity Index
VES	Vitiligo extent score
VETF	Vitiligo European Task Force
VETI	Vitiligo Extent Tensity Index
VGICC	Vitiligo global issues consensus conference
VIDA	Vitiligo Disease Activity Score

INTRODUCTION

Vitiligo is a disorder of pigmentation characterized by the presence of depigmented skin macules due to chronic and progressive loss of melanocytes. Large population surveys have shown a worldwide incidence of 0.5–2%, with the disease beginning before the age of 20 years in 50% of cases. Susceptibility to vitiligo is not thought to be linked to gender. Furthermore, there is a hereditary factor as 6–38% of patients have family members with the disease **(Rezaei et al., 2007).**

The etiology of vitiligo is unclear, and several theories (including autoimmune, neural, self-destruction and inherent defect theories) have been proposed to explain its pathogenesis (**Namian et al., 2008).**

The autoimmune theory proposes that alterations in humoral or cellular immunity result in destruction of melanocytes **(Alkhateeb et al., 2003).** Moreover, there is growing evidence that cytokines that are important in autoimmunity may play a role in depigmentation **(Moretti et al., 2002).**

Interleukin-33 (IL-33) is one of the interleukins that is incriminated in the pathogenesis of vitiligo. It was identified as the ligand for the orphan receptor ST2 **(Schmitz et al., 2005).** IL-33 is expressed mainly by cells of barrier tissues as the epithelial and endothelial cells, suggesting a central role for this

cytokine in barrier tissue defence. Through mechanisms that are poorly understood, IL-33 seems to be released as an alarmin. IL-33 may be an important cytokine in the initiation and perpetuation of inflammation **(Liew et al., 2010).**

Li et al. (2015); Vaccaro et al. (2016) observed that serum IL-33 was raised in patients with active vitiligo. **Li et al. (2015)** reported that IL-33 and ST2 expression was increased in lesional skin. However, serum levels of IL-33 were not investigated in stable versus active vitiligo.

Interleukin-33 seems to be a key interleukin in the pathogenesis of vitiligo through its interaction with other important cytokines. However, scarce studies are found regarding the role of Il-33 in vitiligo and its relation to the activity status of the disease.

Aim of the Work

The aim of this work was to estimate the serum levels of IL-33 in vitiligo patients versus healthy controls to demonstrate its proposed role in the pathogenesis of vitiligo.

Our study also aimed at comparing between IL-33 level in active versus stable cases and correlating its level with other different disease characteristics (e.g., age, sex, body surface area (BSA) and type of vitiligo).

Chapter One

VITILIGO OVERVIEW

Epidemiology

Vitiligo is a chronic acquired disorder of pigmentation, characterized by destruction of epidermal melanocytes. Prevalence is noticed as being between 0.5 to 1% of general population. Onset of vitiligo occurs in childhood or young adulthood with a peak age at 10–30 years **(Yaghoobi et al., 2011).** Among patients diagnosed as having the disease, about a third present before the age of 12 years, and half before the age of 20 **(Ezzedine et al., 2015a).** Both sexes have shown equal predilection for the disease. Though, female predominance was reported in some studies **(Lee et al., 2015)**. Severe sunburn, pregnancy **(Mason and Gawkrodger, 2005),** skin trauma **(Mehta et al., 1973)** and emotional stress **(Manolache and Benea, 2007)** were reported to precede the disease.

Clinical Presentation

Vitiligo usually presents with asymptomatic achromic macules or patches with convex borders surrounded by normal skin. Lesions exhibit variations in size and shape **(Ortonne, 2008).** Typical sites include fingers, wrists, axillae, groin and body orifices. Elbows, knees, digits and flexor wrists are involved on extremities **(Anbar et al., 2008).** Vitiligo is

common on sites of repeated trauma, friction or pressure as koebnerization is a feature of the disease **(Gauthier and Benzekri, 2010).**

Leukotrichia may coexist with skin lesions. Additionally, it was reported that leukotrichia isn't correlated to the disease activity as follicular melanocytes are usually spared in vitiligo **(Ortonne and Passeron, 2012).** Nevertheless, leukotrichia marks the loss of melanocyte stem cells from the bulge area **(Anbar et al., 2009).**

Vitiligo has an insidious onset. Clinical course of the disease is unpredictable. It may show spontaneous regression, stabilization, slow progression or acute exacerbation. Vitiligo lesions may be active or stable. A stable lesion is one that has not changed in a year **(Ezzedine et al., 2012a).**

An acquired nevus of melanocytic origin may be seen in vitiligo patients; halo nevus. It is surrounded by a halo of depigmentation. It may be solitary or multiple and can occur alone or in combination with vitiligo. The relation between halo nevi and vitiligo is not clear **(Patrizi et al., 2013) (Figure 1).**

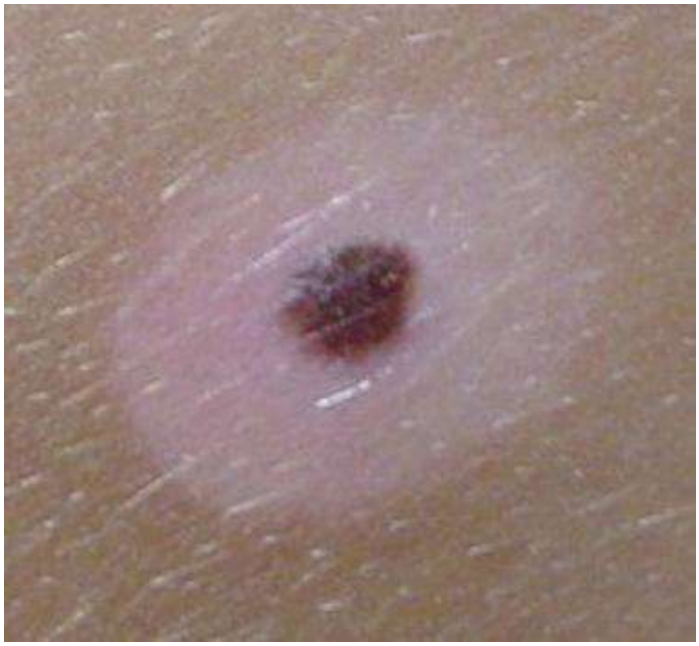

Figure (1): Halo nevus **(Zabawski, 2016)**

Classification of vitiligo

According to vitiligo global issues consensus conference (VGICC) classification, vitiligo is classified into:

Table (1): Classification of vitiligo **(Ezzedine et al., 2012a).**

Non-segmental vitiligo	▪ Acrofacial ▪ Mucosal (more than one site) ▪ Generalised ▪ Universal ▪ Mixed (non-segmental + segmental) ▪ Rare variants
Segmental vitiligo	▪ Uni-segmental ▪ Bi-segmental ▪ Pluri-segmental
Un-classifiable vitiligo	▪ Focal ▪ Mucosal (one site)

Generalized vitiligo is the most abundant form of vitiligo. It is characterized by symmetrical lesions involving the face, trunk and extremities **(Figure 2).** Regarding universal vitiligo, depigmentation occurs in more than 80 % of the BSA and poliosis is common. However, sun-exposed areas may exhibit pigmentation **(Ezzedine et al., 2012a).**

Acrofacial vitiligo is confined to the face, head, hands and feet. Involvement of the distal fingers and facial orifices is often present. It may evolve into generalized vitiligo **(Kemp et al., 2001) (Figure 3).** Mixed vitiligo refers to segmental vitiligo (SV) which has been followed by non-segmental vitiligo (NSV) with a delay of at least 6 months **(Ezzedine et al., 2011).** In addition, the segmental part of the disease is usually more resistant to treatment. Risk factors for the progression of segmental to mixed vitiligo include the presence of halo nevi and leukotrichia **(Ezzedine et al., 2012b).**

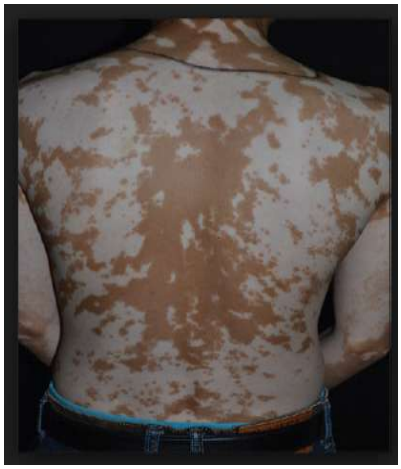

Figure (2): Generalized vitiligo **(Tang et al., 2015).**