Dermoscopic and Immunohistochemical Changes in Acquired Melanocytic Nevi following Narrow Band Ultraviolet-B Therapy

Thesis submitted for partial fulfillment of M.D degree of Dermatology

By:

Nanees Abdel Aleem Abdel Monem Ragab

Supervised by

Dr/ Hesham Abdel Moety ZaherProfessor of Dermatology
Cairo University

Dr/ Safinaz Salah Al Din Sayed Professor of Histology Cairo University

Dr/ Dalia Ahmed BassionyAssistant professor of Dermatology
Cairo University

Dr/Rania Mohamed MonirAssistant Professor of Dermatology
Cairo University

Faculty of medicine Cairo University-2015

Abstract

Background: Acquired Melanocytic Nevi (AMN) have been reported to undergo morphological and dermoscopic changes following exposure to NB-UVB radiation.

Objectives: To study the clinical, dermoscopic and immunohistochemical changes in AMN exposed to NB-UVB radiation.

Patients and Methods: 40 patients diagnosed with different dermatological conditions were enrolled in the study. Three sessions of suberythemogenic NB-UVB per week were delivered for a total of 30 sessions. For each patient a minimum of 2 nevi were selected. One nevus was surgically removed prior to sessions as control, for the other nevus/nevi dermoscopic images were captured before and after NB-UVB sessions. The images were evaluated for morphological and dermoscopic changes. At the end of the irradiation cycle another nevus was surgically removed. Immunohistochemical assessment of Ki67 (marker of proliferation) and Melan A (marker of melanogenesis) were done for the biopsy specimens.

Results: Our study showed a statistically significant increase in the size of AMN after NB-UVB radiation (P<0.001). Benign dermoscopic changes in the form of an increase in the overall darkening, width of network, number and size of brown dots and blurring were observed. A statistically significant positive correlation was found between the darkening of brown color and the total cumulative dose of NB-UVB. A statistically significant positive correlation was found between the width of network and the total cumulative dose of NB-UVB. Immunohistochemical analysis did not show any significant change in exposed AMN in comparison to unexposed controls

Conclusion: AMN irradiated with repeated suberythemogenic doses of NB-UVB showed benign morphological and dermoscopic changes and this was confirmed by our immunohistochemical study.

Key words

DETECTION OF EXTENDED SPECTRUM BETA-LACTAMASE AND Ampc BETA-LACTAMASE-PRODUCING ENTEROBACTERIACEAE CLINICAL ISOLATES AND TESTING THEIR SUSCEPTIBILITY TO NOVEL ANTIBIOTICS

Dermoscopic and Immunohistochemical Changes in Acquired Melanocytic Nevi following Narrow Band Ultraviolet-B Therapy

Thesis submitted for partial fulfillment of M.D degree of Dermatology

By:

Nanees Abdel Aleem Abdel Monem Ragab

Supervised by

Dr/ Hesham Abdel Moety Zaher
Professor of Dermatology
Cairo University

Dr/ Safinaz Salah Al Din SayedProfessor of Histology
Cairo University

Dr/ Dalia Ahmed BassionyAssistant professor of Dermatology
Cairo University

Dr/Rania Mohamed MonirAssistant Professor of Dermatology
Cairo University

Faculty of medicine Cairo University-2015

Abstract

Background: Acquired Melanocytic Nevi (AMN) have been reported to undergo morphological and dermoscopic changes following exposure to NB-UVB radiation.

Objectives: To study the clinical, dermoscopic and immunohistochemical changes in AMN exposed to NB-UVB radiation.

Patients and Methods: 40 patients diagnosed with different dermatological conditions were enrolled in the study. Three sessions of suberythemogenic NB-UVB per week were delivered for a total of 30 sessions. For each patient a minimum of 2 nevi were selected. One nevus was surgically removed prior to sessions as control, for the other nevus/nevi dermoscopic images were captured before and after NB-UVB sessions. The images were evaluated for morphological and dermoscopic changes. At the end of the irradiation cycle another nevus was surgically removed. Immunohistochemical assessment of Ki67 (marker of proliferation) and Melan A (marker of melanogenesis) were done for the biopsy specimens.

Results: Our study showed a statistically significant increase in the size of AMN after NB-UVB radiation (P<0.001). Benign dermoscopic changes in the form of an increase in the overall darkening, width of network, number and size of brown dots and blurring were observed. A statistically significant positive correlation was found between the darkening of brown color and the total cumulative dose of NB-UVB. A statistically significant positive correlation was found between the width of network and the total cumulative dose of NB-UVB. Immunohistochemical analysis did not show any significant change in exposed AMN in comparison to unexposed controls

Conclusion: AMN irradiated with repeated suberythemogenic doses of NB-UVB showed benign morphological and dermoscopic changes and this was confirmed by our immunohistochemical study.

Acknowledgment

I would like to express my profound gratitude and deep thanks to **Prof. Dr. Hesham Abdel moety Zaher**, Professor and Head of the Department of Dermatology, Faculty of Medicine, Cairo University, who no words can meet his kind supervision, his guidance and endless support through this work

I would like to thank A. **Prof. Dr. Dalia Ahmed Bassiouny**, Assistant Professor of Dermatology, Faculty of Medicine, Cairo University, for her guidance, sincere help and continuous supervision which helped me accomplish this work.

I would like to thank A. **Prof. Dr. Rania Mohamed Mounir**, Assistant Professor of Dermatology, Faculty of Medicine, Cairo University, for her guidance, supervision and support throughout all the stages which helped me accomplish this work.

I would like to thank **Prof. Dr. Safinaz Salah El Din Saied**, Professor of Histology, Faculty of Medicine, Cairo University, for her help, guidance, sincere help and her efforts in immunohistochemistry and image analysis which helped me a lot accomplish this work

I would like to thank **Dr Nesrine Samir** for her cooperation and assistance in the clinical work which helpd me a lot accomplish this work

Contents

	Page
List of Abbreviations	•••••
List of tables	•••••
List of figures	•••••
Introduction & Aim of the Study	1
Review of Literature	•••••
Chapter 1: Melanocytic Nevi	3
Acquired Melanocytic Nevi	3
Atypical/Dysplastic Melanocytic Nevi	15
Congenital Melanocytic Nevi	17
Melanoma Simulators	18
Chapter 2: Dermoscopy	23
Principal and design	23
Indications	24
Dermoscopic criteria	25
Dermoscopic Alogarithim	25
Dermoscopic appearance of Nevi	30
Dermoscopic differential diagnosis of melanocytic nevi	33
Benign or Malignant	36
Analysis techniques of melanocytic lesions	39
Chapter 3: Melanoma	43
Epidemiology	43
Types of Primary Melanomas	48

Other melanoma Variants49
Histopathology51
Immunopathology52
Chapter 4: Narrow Band UVB phototherapy59
Principals and Mechanisms59
Treatment Protocols60
Efficacy of Narrow band in treatment of Dermatological Diseases62
Containdications65
Side Effects66
Mechanisms of Melanoma development following UVR exposure69
Chapter 5 Melanocytic Nevi and NB-UVB73
Melanocytic Nevi and NB-UVB Therapy73
Vitiligo and Melanoma75
Mycosis fungoids and Melanoma76
Psoriasis and Melanoma76
Patients and Methods77
Results81
Discussion
Conclusion and Recommendations108
Summary109
Master Tables111
References
Arabic Summary

List of Tables

	Table Title	Page
Table 1	Triggers for the development and/or growth of	4
	Melanocytic Nevi	
Table 2	Melanocytic Nevus Phenotypes	16
Table 3	Assessment of atypical spitz nevus (tumor) in	19
	children and adolescence for risk of metastasis	
Table 4	Risk of melanoma in different types of	21,22
	melanocyytic nevi and indication of excision	
Table 5	Dermoscopic colors and their pathologic	25
	correlates	
Table 6	Dermoscopic Structures	27,28,29,30
Table 7	Dermoscopic Classification of Nevi	32
Table 8	Benign Dermoscoic Patterns	36,37
Table 9	Melanoma Specific structures and their	38,39
	pathological correlates	
Table 10	Analysis of Patterns	41
Table 11	Risk Factors for the development of Cutaneous	44
	Melanoma	
Table 12	Criteria for Histopathologic diagnosis of	52
	Melanoma	
Table 13	Melanocyte-associated markers that have been	53,54
	suggested as being useful in the diagnosis of	
	melanoma	
Table 14	Proliferation markers for distinguishing	56,57
	melanoma from benign nevi and prognosis for	
	melanoma	
Table 15	NB-UVB treatment protocols	61
Table 16	Other indications for NB-UVB	65
Table 17	Size of melanocytic nevi before and after NB-	83
	UVB sessions	
Table 18	Dermoscopic changes in AMN after NB-UVB	84

	Table title	Page
Table 19	Ki67 and MA immunohistochemical expression before and after NB-UVB sessions	85
Table 20	Correlation between Age and Clinical, Dermoscopic and Immunohistochemical Changes following NB-UVB Therapy	86
Table 21	Association between skin phototype and Clinical, Dermoscopic, Immunohistochemical changes following NB-UVB Therapy	87
Table 22	Association between Dermatological Diagnosis and Type of nevus, Dermoscopic and Immunohistochemical Changes following NB-UVB Therapy	88,89
Table 23	Association between Site of Nevus and Dermoscopic and Immunohistochemical Changes following NB-UVB Therapy	90
Table 24	Correlation between Cumulative dose and Clinical, Dermoscopic and Immunohistochemical Changes following NB- UVB Therapy	92
Table 25	Correlation between Different Dermoscopic Criteria, immunohistochemical and size changes following NB-UVB Therapy	93,94
Table 26	Clinical Data and Cumulative dose	113,114
Table 27	Clinical and Dermoscopic Features of Acquired Melanocytic Nevi before and after NB-UVB Therapy	115, 116, 117
Table 28	Ki67 and MA before and after NB-UVB sessions	118,119

List of Figures

	Figure Title	Page
Figure 1	Clinical picture of Lentigo Simplex	5
Figure 2	Histopathology of Lentigo Simples	6
Figure 3	Clinical picture of Junctional nevus	6
Figure 4	Histopathology of Junctional nevus	7
Figure 5	Clinical picture of Compound melanocytic Nevus	7
Figure 6	Histopathology of Compound melanocytic Nevus	8
Figure 7	Clinical picture of Dermal melanocytic nevus	9
Figure 8	Histopathology of Dermal Melanocytic nevus	9
Figure 9	Clinical picture of Spitz Nevus	16
Figure10	Clinical picture of Reed Nevus	20
Figure 11	Pigment Network	26
Figure 12	Globular Pattern	26
Figure 13	Actively growing nevus	31
Figure 14	Dermoscopic picture of solar lentigen	33
Figure 15	Dermoscopic picture of freckles	33
Figure 16	Dermoscopic picture of seborrehic keratosis	34
Figure 17	Dermoscopic picture of Dermatofibroma	34
Figure 18	Thymidine dimer formed by ultraviolet exposure	70
Figure 19	Percentage of Males and Females in the study	81
Figure 20	Percentage of the different Dermatological Diagnoses in the study	82
Figure 21	% of the different dermoscopic types of Nevi	82
Figure 22	Mean size of nevi before and after NB-UVB	83
Figure 23	Dermoscopic changes following NB-UVB	84
Figure 24	Mean Ki67 and MA before and after NB-UVB	85
Figure 25	Changes in brown dots in relation to different dermatological	89
	diagnoses	
Figure 26	Dermoscopic changes in relation to size of nevus	91
Figure 27	Dermoscopic images of a reticular nevus before & after NB-UVB	94

Figure 28	Dermoscopic images of a reticular nevus before and after NB-UVB	94
Figure 29	Dermoscopic images of a reticular nevus before and after NB-UVB	95
Figure 30	Dermoscopic images of a reticular nevus before and after NB-UVB	96
Figure 31	Dermoscopic images of a reticular nevus before and after NB-UVB	97
Figure 32	Dermoscopic images of Brown Dots before and after NB-UVB	98
Figure 33	Dermoscopic images of globular nevus before and after NB-UVB	98
Figure 34	Dermoscopic images of Brown Dots before and after NB-UVB	99
Figure 35	MA before and after NB-UVB	100
Figure 36	Ki 67 before and after NB-UVB	101
Figure 37	MA before and after NB-UVB	102
Figure 38	Ki67 before and after NB-UVB	103

List of Abbreviations

ALM: Acral Lentigenous Melanoma

AMN: Acquired Melanocytic Nevi

BB-UVB: Broad Band Ultraviolet B

C: Cytosine

CDKN2A: Cyclin Dependant Kinase Inhibitor 2A

CMN: Congenital Melanocytic Nevi

CTCL: Cutaneous T- Cell Lymphoma

HIV: Human Immunodeficiency virus

HMB: Human Melanoma Black

IL: Interlukin

LMM: Lentigo Maligna Melanoma

LOH: Loss of Heterozygosity

MA: Melan A

MAL: Melanoma associated Leucoderma

MART: Melanocyte antigen recognized by T cells

MC1R: Melanocortin 1 receptor

MED: Minimal erythema Dose

Mel-CAM: Melanoma cell adhesion molecuole

MF: Mycosis Fungoids

MITF: Microphthalmia associated transcription Factor

MMR: Mammalian mismatch repair

NB-UVB: Narrow Band ultraviolet- B

NGFR: Nerve Growth Factor receptor

NM: Nodular Melanoma

NMSC: Non Melanoma Skin Cancer

PASI: Psoriasis Area and severity Index

PTEN: Phosphate and Tensin Homologue

PUVA: Psoralen+Ultraviolet-A

SL: Solar Lentigens

SSM: Superficial Spreading Melanoma

T: Thymine

TH17: T helper 17

TNFα: Tumor Necrosis Factor Alpha

TP53: Tumor Protein 53

UV: Ultraviolet

UVA: Ultraviolet A

UVR: Ultraviolet Rays

Introduction

Phototherapeutic modalities are commonly used for the treatment of skin diseases. Previous studies have reported that repeated solar and artificial UVB (280–320 nm) and UVA (320–400 nm) exposure can modify the clinical, dermoscopic and histological features of acquired melanocytic nevi. However, it is unclear whether the changes are caused by molecular events with a carcinogenic potential (**Manganoni et al., 2011**).

Previous studies revealed an increased risk of non melanoma skin cancers following UV therapy. Studies of the risk of melanoma following UV therapy revealed controversial results (Archier et al., 2012).

Distinction between benign and malignant melanocytic lesions may be difficult even for highly skilled dermatopathologists emphasizing the importance of advanced diagnostic tools such as immunohistochemistry and dermoscopy (Nielsen et al., 2011).

Ki67 "which is a nuclear protein and a cellular marker of proliferation" is the most important marker in distinguishing benign from malignant melanocytic tumors (Ohsie et al., 2008).

MART1 (melanoma antigen recognized by T cells 1) also known as Melan A is a protein antigen found on the surface of melanocytes. It is another marker highly specific for melanoma. Ki67/MART1 stains are valuable diagnostic tools to distinguish melanomas and nevi with a large degree of certainty (**Nielsen et al., 2011**).

Dermoscopy is a noninvasive, in vivo method for the early diagnosis of malignant melanoma and the differential diagnosis of pigmented lesions of the skin. By allowing visualization of sub-macroscopic pigmented structures that correlate with specific underlying histopathologic structures, dermoscopy provides a more powerful tool than the naked-eye examination for clinicians to determine the need to excise a lesion (Roldan-Marin et al., 2012).