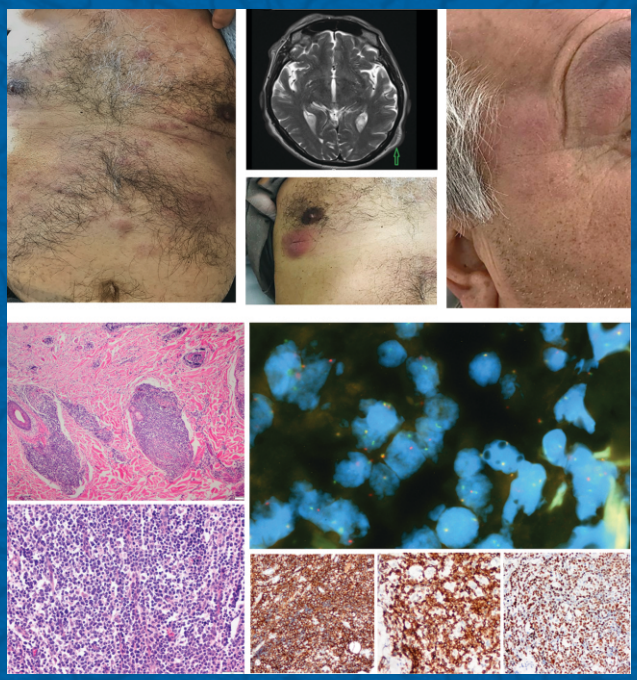
ISSN : 1307-7635

TURKISH JOURNAL OF DERMATOLOGY

VOLUME 15 • ISSUE 3 • JULY-SEPTEMBER 2021

www.tjdonline.org



TURKISH SOCIETY OF DERMATOLOGY 1968

An Official Publication of Turkish Society of Dermatology

Wolters Kluwer

Medknow

Volume No. 15 Issue No. 3 July-September 2021

Turkish Journal of Dermatology

An official publication of Turkish Society of Dermatology

EDITORIAL BOARD

Turkish Journal of Dermatology

An official publication of Turkish Society of Dermatology

General Information

The journal

Turkish Journal of Dermatology (TJOD) (ISSN: Print -1307-7635, Online - 1308-5255) is a peer-reviewed journal published on behalf of Turkish Society of Dermatology. The journal publishes articles related to clinical, epidemiological and research studies about dermatological and venereal diseases, reviews, interesting case reports, presentations like "what is your diagnosis?", articles related to clinical and practical applications, letters to the editor, and editorial reviews. The Journal is published in March, June, September and December.

Information for Authors

There are no page charges for TJOD submissions. Please check http://www.tjdonline.org/contributors.asp for details.

All manuscripts must be submitted online at https://review.jow.medknow.com/tjd

Advertising policies

The journal accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Wolters Kluwer India Private Limited, advertise@medknow.com

The journal reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal.

The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and/or its publisher of the quality or value of the said product or of claims made for it by its manufacturer.

Addresses

Editorial Office

Dr. Soner Uzun,
Editor-in-Chief,
Akdeniz University Faculty of Medicine,
Department of Dermatology, Antalya, Turkey
Phone: +902422406710
E-mail: sonuzun@hotmail.com
Website: www.tjdonline.org

Published by

Wolters Kluwer India Private Limited
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol,
Andheri (East), Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com; www.wolterskluwer.com

Turkish Journal of Dermatology

Volume No. 15 Issue No. 3 July-September 2021

CONTENTS

Turkish Journal of Dermatology on Web

https://review.jow.medknow.com/tjd

The Turkish Journal of Dermatology now accepts articles electronically. It is easy, convenient and fast. Check following steps:

1 Registration

- Register from https://review.jow.medknow.com/tjd as a new author (Signup as author)
- Two-step self-explanatory process

2 New article submission

- Read instructions on the journal website or download the same from manuscript management site
- Prepare your files (Article file, First page file and Images, Copyright form & Other forms, if any)
- Login as an author
- Click on 'Submit new article' under 'Submissions'
- Follow the steps (guidelines provided while submitting the article)
- On successful submission you will receive an acknowledgement quoting the manuscript ID

3 Tracking the progress

- Login as an author
- The report on the main page gives status of the articles and its due date to move to next phase
- More details can be obtained by clicking on the ManuscriptID
- Comments sent by the editor and reviewer will be available from these pages

4 Submitting a revised article

- Login as an author
- On the main page click on 'Articles for Revision'
- Click on the link "Click here to revise your article" against the required manuscript ID
- Follow the steps (guidelines provided while revising the article)
- Include the reviewers' comments along with the point to point clarifications at the beginning of the revised article file.
- Do not include authors' name in the article file.
- Upload the revised article file against New Article File - Browse, choose your file and then click "Upload" OR Click "Finish"
- On completion of revision process you will be able to check the latest file uploaded from Article Cycle (In Review Articles-> Click on manuscript id -> Latest file will have a number with 'R', for example XXXX_100_15R3.docx)

Facilities

- Submission of new articles with images
- Submission of revised articles
- Checking of proofs
- Track the progress of article until published

Advantages

- Any-time, any-where access
- Faster review
- Cost saving on postage
- No need for hard-copy submission
- Ability to track the progress
- Ease of contacting the journal

Requirements for usage

- Computer and internet connection
- Web-browser (Latest versions - IE, Chrome, Safari, FireFox, Opera)
- Cookies and javascript to be enabled in web-browser

Online submission checklist

- First Page File (rtf/doc/docx file) with title page, covering letter, acknowledgement, etc.
- Article File (rtf/doc/docx file) - text of the article, beginning from Title, Abstract till References (including tables). File size limit 4 MB. Do not include images in this file.
- Images (jpg/jpeg/png/gif/tif/tiff): Submit good quality colour images. Each image should be less than 10 MB) in size
- Upload copyright form in .doc / .docx / .pdf / .jpg / .png / .gif format, duly signed by all authors, during the time mentioned in the instructions.

Help

- Check Frequently Asked Questions (FAQs) on the site
- In case of any difficulty contact the editor

Review Article

Skin of Color – An Enigma: A Systematic Review

Sumit Sen, Kakali Mridha, Adrija Datta

Department of Dermatology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India

Abstract

The color of human skin varies according to race, ethnicity, and geographic location, which leads to differing appearances of the same cutaneous condition. The nonwhite population is projected to increase worldwide in the coming decades owing to globalization and changing demographics. Thus, this review aims to focus on the varying nature of cutaneous conditions in this population, which differ from traditional descriptions in textbooks. A thorough search of PubMed, MEDLINE, Cochrane, and Google Scholar databases was done for relevant articles focusing on appearances of various dermatoses in skin of color. Erythematous diseases such as psoriasis, pityriasis rosea, and atopic dermatitis presented with inconspicuous/less conspicuous erythema in individuals with colored skin. Postinflammatory pigmentary changes were frequent in individuals with Fitzpatrick Grading III to VI and in the darker phenotypes, the hyperpigmentation may be difficult to distinguish from normal skin color. Acne hyperpigmented macules are encountered as primary lesions in colored skin, causing a considerable amount of apprehension in affected individuals. Hypopigmented disorders such as arsenicosis, macular postkala-azar dermal leishmaniasis, and dhoti or saree-induced depigmentation were particularly observed in this population. A focused review addressing the visual aspects, especially the color of skin diseases in individuals with Fitzpatrick Grading III to VI is the need of the hour to sensitize dermatologists regarding the specific dermatoses and reaction patterns occurring in this population.

Keywords: Asian, hyperpigmentation, hypopigmentation, Indian, postinflammatory hyperpigmentation, skin of color

Introduction

Colors have fascinated human beings since time immemorial. Hence, it is only natural to delve into the various shades and hues that human skin present with. The color of human skin can be attributed to the interaction of visible light with skin components such as melanin and hemoglobin in dermis and epidermis and to some extent carotene and bilirubin. The dispersion of melanin in varying proportions in humans settling in different geographic locales gave rise to such differences in skin pigmentation. In 1975, Fitzpatrick classified human skin type based on their ability to react in response to sun exposure, initially into 4 types. Later Grade IV was expanded to Grades IV, V, and VI. In Western white nomenclature this latter group has been termed as having skin of color. According to racial differences and ethnicity, individuals having African American, African, Asian, Hispanic, Pacific Islander descent, and Native American descent have been considered to have skin of color.[1] Skin is a mirror for both internal and external insults to the body, with myriads of presentation visible to us in the form of changes in color and texture.

Study Rationale

For many years, dermatology training and textbooks had concentrated on dermatoses occurring in individuals with lighter skin color. However, with globalization and changing demographics, nonwhite individuals are projected to comprise more than half of the population worldwide. There is an unmet need to focus on the appearance and attributes of dermatoses occurring in nonfair-skinned individuals. There is dearth of data in our country as well as other Asian and African countries focussing solely in color of diseased skin in dark-skinned

Submission: 30-01-2021 **Revision:** 09-06-2021
Acceptance: 09-06-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_9_21

Address for correspondence: Dr. Adrija Datta, Department of Dermatology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India.
E-mail: adrijadatta@gmail.com

How to cite this article: Sen S, Mridha K, Datta A. Skin of Color – An enigma: A systematic review. Turk J Dermatol 2021;15:45-55.

individuals. Thus we aimed to collate all available data pertaining to the appearance of diseased skin in nonwhite population and fill up the void in our existing knowledge on the appearance of cutaneous conditions in skin of color.

Objectives

a. Primary objective: To compare the description of various cutaneous diseases in colored skin with that mentioned in textbooks
b. Secondary objective: To note the dermoscopic findings in such individuals.

Hypothesis

No difference exists between various skin diseases mentioned in standard dermatology textbooks and in individuals with color.

Methods

The protocol was devised in line with the preferred reporting items for systematic review and meta-analysis protocols statement. Diseases were chosen which were known to have distinct colored morphologics. Furthermore, tropical diseases endemic to the Indian subcontinent were selected, like leprosy, postkala-azar dermal leishmaniasis, arsenicosis.

Eligibility criteria

Inclusion criteria

Articles including reviews, observational studies, and longitudinal studies concentrating on appearance of skin color in various dermatoses were included.

Exclusion criteria

Articles reporting epidemiological and other clinical features and management of diseases in skin of color were excluded. Articles reporting no significant change in appearance in white and nonwhite skin were also excluded.

Information sources

PubMed, MEDLINE, Cochrane, Google Scholar databases and information pages of American Academy of Dermatology, Skin of Color Society as available on their websites, till November 30, 2020.

Search strategy

The search was conducted independently by 2 researchers who searched using the keywords and then filtered out only those relevant articles with full-text availability. Any discrepancy between the 2 researchers was resolved by a senior researcher, who was a part of the review. A thorough literature search prompted us to classify cutaneous diseases into erythematous, hyperpigmented, and hypopigmented diseases.

The Boolean operator AND was interposed between the key words "skin of color," "Indian," "Asian," "African" and different other diseases such as "acne," "acanthosis nigricans," "arsenicosis," "atopic dermatitis," "erythrasma," "hyperpigmentation," "hypopigmentation," "kwashiorkor," "leprosy," "melisma," "postinflammatory hyperpigmentation," "pityriasis alba," "pityriasis rosea," "pityriasis versicolor," "postinflammatory hyperpigmentation," "postinflammatory hypomelanosis," "post kala-azar dermal leishmaniasis," "psoriasis," "rosacea," "vitiligo" in these search platforms [Figure 1].

Data items

Only the difference in color of the diseased skin was noted.

Erythematous Cutaneous Diseases

Erythema is the most common change in skin color which can be readily understood on skin with less pigmentation. However, in darker skin types, this redness is perceived as a rather dusky violaceous hue.[2] This can be comprehended in the urticarial plaques of bullous pemphigoid, erythroderma, pityriasis rubra pilaris or even in extensive dermatophytosis. The enigma surrounding skin of color can be appreciated in the following cutaneous diseases, purportedly manifesting erythema.

Acne

Available literature projects acne vulgaris as a common infliction in skin of color. While there is no difficulty in recognizing the comedonal, papulopustular, or nodulocystic lesions, caution needs to be exercised while treating such patients as there is a higher propensity to develop postacne hyperpigmentation and keloidal scarring. In a survey conducted at the Skin of Color Centre in New York City, acne hyperpigmented macules were prominent in majority of African-Americans, Asians, and Hispanics and were of primary concern in many of them.[3] They primarily present like postinflammatory pigmented macules, with evidence of inflammation on histopathology and can persist for more than 4 months. In India, over 70% young adults with/with a history of acne vulgaris presented with postacne pigmentation, with recurring episodes inducing more intense and long-lasting pigmentation[4] [Figure 2a].

Atopic dermatitis

Atopic dermatitis is a global disease, with varying prevalence. In contrast to the easily visible erythema and flexural involvement in light-skinned individuals, skin of color individuals having atopic dermatitis have less conspicuous erythema, more scattered papular lesions, and extensor involvement, lichenification, and pigmentary

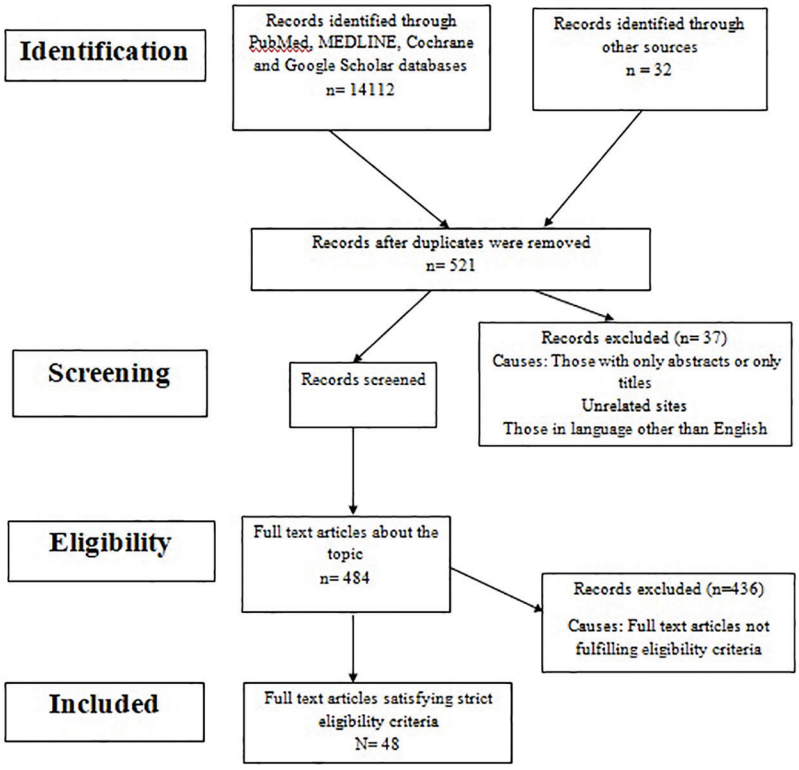


Figure 1: Flow diagram for the systematic review

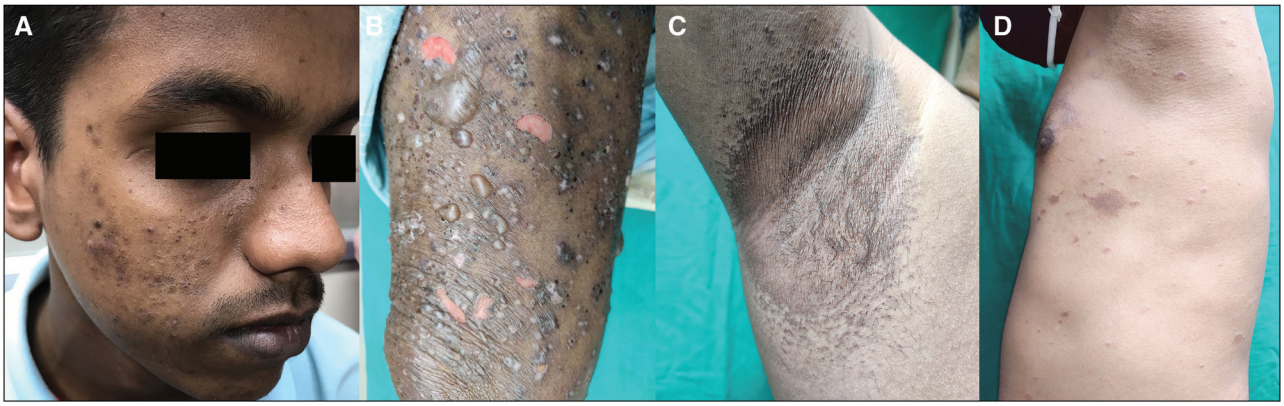


Figure 2: Erythematous diseases of skin: (a) Papular eruptions with hyperpigmented macules and postacne hyperpigmentation and scarring; (b) Tense bullae of bullous pemphigoid on a brownish base with accompanying erosions and prurigo-like hyperpigmented lesions; (c) Mild scaly brown patch of erythrasma in axilla (d) Multiple light brown papules of pityriasis rosea with a reddish-brown herald patch

changes.[5] In a London-based longitudinal study, Ben-Gashir *et al*. observed disease intensity to be more severe in dark-skinned children than their white counterparts, with erythema being a misleading factor in diagnosis.[6] Zhao *et al*. obtained excellent results using Eczema Area Severity Index (EASI) as an outcome measure in skin of color patients by adapting a grayscale instead of the erythema scale.[5]

Autoimmune bullous diseases

Tamazian and Simpson documented varied presentations of bullous diseases in individuals with skin of color. Bullous pemphigoid presented either with tense blisters without surrounding erythema or hyperpigmented patches with blisters in periphery. Hypopigmented and hyperpigmented plaques and patches with crusting, erosions, and blistering dominated the clinical picture in pemphigus foliaceus and vulgaris.[7] Histopathology and immunofluorescence were crucial in diagnosis in each case [Figure 2b].

Erythrasma

Erythrasma is a superficial bacterial infection presenting as well-defined red patches, which later become brown.

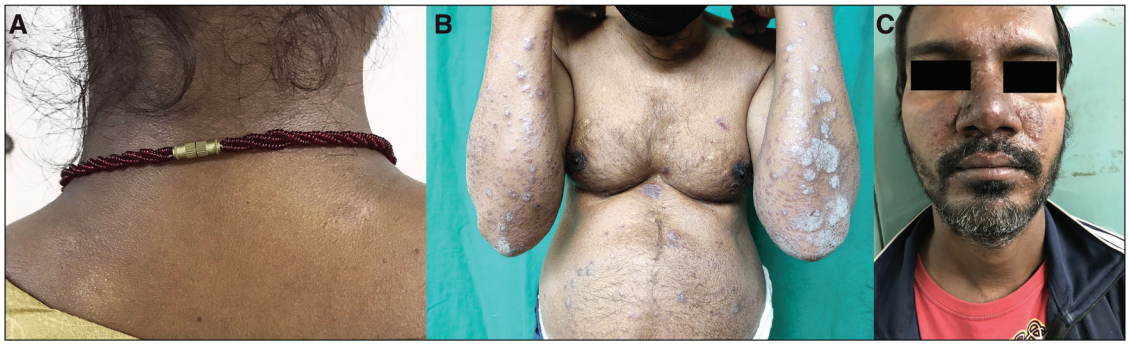


Figure 3: Erythematous diseases of skin (II): (a) Shiny hypopigmented papules of PMLE over nape of neck; (b) Thick scaly psoriatic lesions with minimal erythema, over extensors and trunk; (c) Papulopustular lesions of rosacea over central face

Badri *et al*. had described 16 cases of erythrasma from Tunisia with erythematous patches in 6 cases and yellowish patches in 10 cases.[8] In such cases, Wood's lamp and Gram stain facilitate confirmation of diagnosis [Figure 2c].

Pityriasis rosea

It has been described classically as a self-limiting disease of acute onset beginning with a well-defined erythematous plaque called herald patch followed by generalized eruption of "discrete oval lesions dull pink in color and covered by fine dry silvery-grey scales." Amer *et al*. described the condition in 50 black American children and found no discernible erythema. Rather profound scaling was visible. One-third of children had purely papular morphology and 4% had papulovesicular lesions and residual pigmentary changes were observed in 62% (31) of them.[9] In a clinicoepidemiological study from Varanasi, India, Sharma and Srivastava reported a cohort of 200 patients with pityriasis rosea, who had multiple erythematous to light brown lesions followed by pigmentary changes in nearly 50% (103) of them[10] [Figure 2d].

Polymorphic light eruption

Indian and Japanese literature have noted pinpoint variants of PMLE with 1–2 mm vesicular to erythematous papules. However, in darker Indian skin, it may appear as shiny hypopigmented papules over sun-exposed areas of elbow, nape of neck, and face.[1] A classical distribution and history aids in clinching the diagnosis [Figure 3a].

Psoriasis

It has been observed to be more in children with Malay and Indian descent than Africans. In contrast to the classical pictures, black Americans exhibit psoriatic plaques with less erythema but with increased thickness and scaling and more body surface area involvement.[11] The presence of hyperpigmented lesions[12] rather than the typical erythema may lead to inaccurate assessment of disease activity and PASI may be miscalculated. Dyspigmentation is a common occurrence post resolution [Figure 3b].

Rosacea

Classically rosacea has been characterized as a chronic entity with flushing and erythema as its prominent features. However, in European and North American countries, Asians and Africans often suffer a delay in diagnosis as the erythema and telangiectasia are barely discernible on darker pigmented skin. This may lead to improper treatment and increased risk of disfigurement like phymatous changes. The increasing incidence of rosacea in tropical countries may be related to risk factors such as hotter climate and prolonged sun exposure. In skin of color, there is female preponderance, increased frequency of papules and pustules, and associated demodiciosis.[13] Prior steroid use leading to rosacea-like features has consistently been reported from India[14] [Figure 3c].

Seborrheic dermatitis

Seborrheic dermatitis is typically described as a recurring dermatitis with erythematous patches and mild scaling affecting areas with prominent sebaceous glands. Hypopigmentation is a prominent feature of seborrheic dermatitis in skin of color. Arcuate and petaloid lesions involving the hairline are particularly observed in darker skin.[15]

Pigmentary Dermatoses

Pigmentary changes are found to be more frequent in skin of color and have a bearing on the psychosocial well-being of an individual. Asian skin including those from Far East, South-east Asia, and the Indian subcontinent tends to present with postinflammatory hyperpigmentation, melasma, lentigines, nevus of Ota, and Hori nevus.[16] In a cross-sectional study from Durban, South Africa, there was a 7.97% prevalence of pigmentary disorders of which vitiligo, postinflammatory hyperpigmentation, and melasma were found to be the most common.[17]

Hyperpigmented disorders

Acanthosis nigricans

Acanthosis nigricans has been typically described as symmetrical darkening having a velvety texture involving

the neck and other intertriginous areas, with underlying obesity and insulin resistance in majority and a higher prevalence in dark-skinned individuals.[18] Even though the clinical appearance remains similar in skin of color, the intensity of darkness varies and it tends to merge with constitutive skin color in those with darker skin. Unless there is a strong index of suspicion, the diagnosis may be missed [Figures 4a].

Clofazimine induced pigmentation

Clofazimine is an iminophenazine dye used in combination with dapsone and rifampicin as a component of multidrug therapy for leprosy. It is known to induce an orange-brown discoloration of skin within a month of initiating therapy. However, in the Indian skin, this color is barely appreciated and mostly appears as a reddish-brown hue. Chopra *et al*. observed a diffuse hyperpigmentation over the face and trunk, which on dermoscopy gave a honeycomb pattern of yellow and white globules in a dark backdrop.[19] An observational study from Brazil noted this as a dusky pigmentation[20] whereas a dark brown color was noted by Job and colleagues[21] [Figure 4b].

Lichen planus pigmentosus

Dr. Bhutani first reported this entity from India in 1974 and since then it has been reported in individuals with skin color Type IV–V from the Middle East, South America, and the Indian subcontinent. It is usually present as slate-grey to brownish-black pigmentation starting over the face as a consequence of photo-exposure.[22] Erythema dyschromicum perstans also has predilection for dark-skinned middle-aged individuals, in the photo-protected areas. Mustard oil has been postulated to induce similar pigmentary changes in Indians[23] [Figure 4c].

Melasma

Melasma is a common acquired hypermelanosis that presents as light to dark brown or grayish-brown pigmented macules or patches usually over face. In darker Indian skin types, these pigmented patches may not be evident unless closely inspected and may sometimes be indistinguishable from pigmentary demarcation lines. Wood's lamp and dermoscopy are useful tools to rule in a diagnosis of melasma in such cases[24] [Figure 5a].

Periorbital hyperpigmentation

Periorbital hypermelanosis is a common but ill-defined entity which presents with moderate to dark brown macules or patches in the periorbital skin. Despite a worldwide distribution, it is commoner in dark-skinned individuals, with the constitutive type being common in Indians and Malays[25] [Figure 5b].

Pigmented contact dermatitis/Riehl's melanosis

Pigmented contact dermatitis can often be found in the Indian setting induced by kumkum, bindi or sindoor. It may also present in the form of brown or slate gray pigmentation and lichen planus pigmentosus. Nath and Thappa noticed pigmented variant in 76.1% cases of kumkum-induced dermatitis.[26] Cultural and traditional practices are also responsible for pigmentary changes in the Middle-East, following the use of henna, kohl, threading, cupping, local remedies, and prayer marks.

Postinflammatory hyperpigmentation

Postinflammatory hyperpigmentation is a common pigmentary change usually observed in individuals with Fitzpatrick skin types III to VI as tan to black macules or patch, in the same distribution following a multitude of dermatoses like acne vulgaris, lichen planus, atopic dermatitis, psoriasis, and contact dermatitis, external stimuli (like photoexposure) and dermatologic procedures including lasers[27] [Figure 5c]. The ensuing pigmentation is more bothersome to the patient than the underlying inflammatory process and has a significant impact on the quality of life.

Figure 4: Disorders of hyperpigmentation: (a) Acanthosis nigricans over axilla, almost flushing with normal skin color; (b) Clofazimine-induced hyperpigmentation in a patient with Lepromatous leprosy; (c) Lichen planus pigmentosus affecting face and upper chest

Figure 5: Disorders of hyperpigmentation (II): (a) Dark brown patches and macules of melasma over nose, cheeks and part of forehead; (b) Dark brown periorbital hyperpigmentation; (c) Hyperpigmentation following burn injury over left side of forehead and temporal area

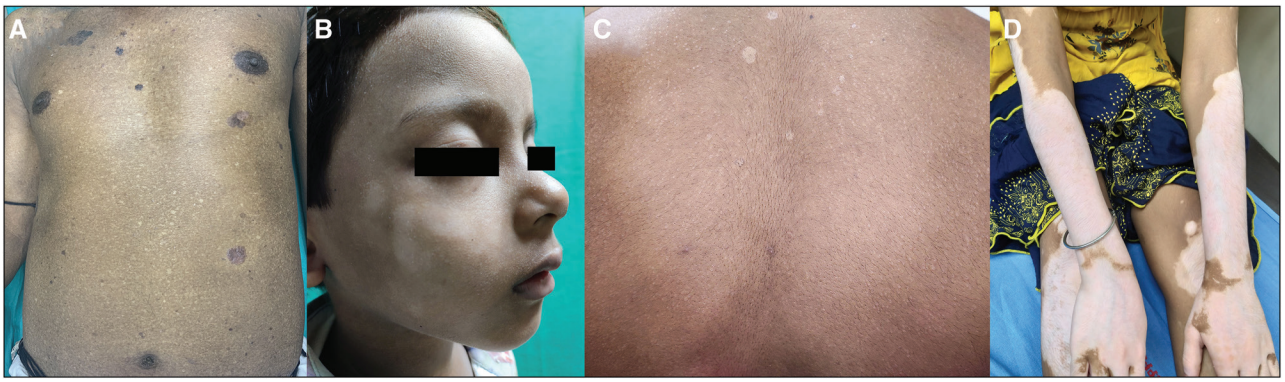


Figure 6: Disorders of hypopigmentation: (a) Hypopigmented macules of Arsenicosis in a dark background; (b) Mild scaly hypopigmented patches and macules of Pityriasis alba; (c) Hypopigmented perifollicular macules and patches of pityriasis versicolor; (d) Chalky white patches of vitiligo

Hypopigmented disorders

Arsenicosis

Arsenicosis is a distinct entity found in the lower Gangetic plains of India and Bangladesh. To the untrained eye, the discrete hypopigmented macules may be mistaken for idiopathic guttate hypomelanosis, especially in tanned individuals on a background of diffuse hyperpigmentation[28] [Figure 6a].

Bier spot (physiological anemic macule)

Bier spots are asymptomatic irregular white macules usually over the extremities and have mostly been reported in individuals of Chinese descent.[29]

Chronic sarcoidodsis

Young adults of Scandinavian or African descent have been reported to present with hypopigmented macules, patches, or plaques.[30] with hypopigmented alopecic patches over scalp being described as an unsual presentation of longstanding sarcoidosis.

Kwashiorkor

Undernutrition contributes to a huge disease burden in children of resource-poor countries in the form of kwashiorkor and protein-energy malnutrition. Skin manifestations of kwashiorkor have been described as blanchable erythematous, small dusky scattered petechiae-like spots, with depigmented alternate bands of pale and dark, dry, sparse, brittle, easily pluckable hair.[31]

Pityriasis alba

Pityriasis alba has been classically described as rounded oval or irregular hypopigmented patch which is usually not well marginated. Lesions are often slightly erythematous and have fine scaling. In a study by Vinod *et al*., Indian patients of pityriasis alba presented with hypopigmented macules and hypopigmented macules with central hyperpigmentation.[32] Hypopigmentation is most conspicuous in pigmented skin and lighter skin may become more evident after sun tanning[33] [Figure 6b].

Pityriasis versicolor

Pityriasis versicolor has been described as sharply demarcated macules which may be slightly erythematous but characterized by fine branny scaling. Ghosh *et al*. observed most lesions of Tinea versicolor to be hypopigmented, followed by mixed hypo and hyperpigmented lesions.[34] Wood's lamp examination revealed yellowish fluorescence. Jena and colleagues reported similar findings in children from Eastern India[35] [Figure 6c].

Vitiligo

Vitiligo is a discoloration of skin characterized by well-circumscribed ivory or chalky white macule which are flush to the skin surface. Patch looks startling especially in person with dark skin. The patch can be mistaken for dirty mark and considered a social deviance, In India, it is called *"safed dag"* or "*Kod"* and carries a social stigma[36] [Figure 6d].

Infective etiologies

Eruptive hypomelanosis

Within days to weeks after a prodromal coryza phase, symmetric discrete hypopoigmented macule (often with fine powdery scale) distributed over extensor surfaces, trunk and face are manifest.[37]

Indeterminate leprosy

A smooth well-defined hypopigmented macular patch on extremities or face is the presentation.[38]

Macular PKDL

It is found in East Africa or the Indian subcontinent. Prominent perioral hypopigmented macules, coalesce to form well-demarcated irregular patches are more common with Indian variant.[39] Hypopigmentation is so severe that it may mimic vitiligo. Lesion usually begins on face and then spread to other areas. Decrease in melanocytes is observed as well.

Neoplastic etiology

Mycoses fungoides

In Indian skin, it can present as hypopigmented or depigmented patches in children or young adult, with visible telangiectasia on surface.[40]

Postinflammatory hypomelanosis

Dhoti or saree depigmentation

Drawstring dermatitis is a frictional dermatitis due to a tightly worn string of a petticoat or salwar. It may result in lichenified grooves, postinflammatory depigmentation, and in some cases koebnerization of conditions like vitiligo.[41]

Radiation injury

Radiation therapy has been reported to induce depigmentation as well as vitiligo in Indian patients with breast cancer.[42]

Aging in skin of color

Signs of aging differ considerably in skin of color. Photoageing in Asian skin usually presents with mottled pigmentation and uneven skin tones and also solar lentigines and seborrheic keratoses.[43] These changes rather than fine lines and wrinkling should prompt clinicians to advise photoprotection and provide therapeutic options to treat aging skin [Figure 7].

The statement "looks can be deceptive" fits the current topic of review aptly. Our current knowledge regarding the visual aspects of various dermatoses is largely based on textbook descriptions based on Western literature. The appearance of color varies considerably in Indian skin and other individuals with skin of color [Tables 1-3]. The peculiarities observed in skin with increased melanin result are mostly pigmentary disturbances which are of immense concern in these groups of individuals. More than the underlying disorders, patients seek consultation for the resulting hyperpigmentation. India comprises the bulk of the global industry for skin-lightening agents and the rampant OTC availability and marketing of such agents containing steroids perpetuate the use of these agents in our population. Fitzpatrick classification of skin phototype is based on the response of skin to sun exposure, not to define race or ethnicity. Within the same race and ethnicity, the post-inflammatory pigmentary change may vary within individuals. Thus it is imperative to devise and validate new scales depending on the capacity of the skin to cause pigmentation following an inflammatory condition. The Taylor hyperpigmemtation scale may be useful in this regard to assess skin color and keep track of pigmentary changes with therapy.[49]

Conclusion

There is an increasing global population – people travel, visit and emigrate. Thus in this era of a world without borders, it is important to be accustomed to all skin types. An awareness of the exact morphology of the lesion, i.e., its texture, contours also the site should lead

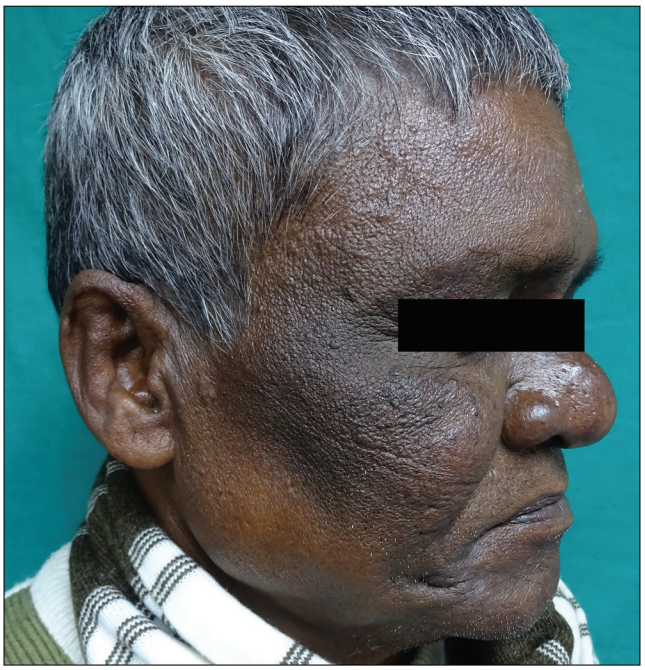


Figure 7: Ageing in Indian skin: solar elastosis, senile milia and seborrheic keratosis on a background of hyperpigmentation

Table 1: Comparison of classical findings with skin of color–erythematous diseases

Disease	Textbook description	Description in skin of color	Dermoscopic/wood's lamp finding
Acne	Erythematous papulopustular and nodular lesions	Hyperpigmented macule–may be primary or postacne hyperpigmentation	Round structured lesion with well-defined white center with thin brown border and erythematous periphery (inflammatory acne)
Atopic dermatitis	Easily visible erythema with flexural involvement	Erythema less conspicuous Lichenification and pigmentary changes are more pronounced	Yellow scales, dotted vessels in a patchy arrangement over a dull red background[44]
Erythrasma	Well defined red patches which later become brown	Dry brown slightly scaling patch	Coral red fluorescence
Pityriasis rosea	Salmon colored papular or macular lesions	Multiple erythematous light brown lesions	White scales at margins with patchy dotted vessels[44]
Psoriasis	Circumscribed, erythematous dry plaque, with silvery scaling	Less conspicuous erythema Hyperpigmented lesions common Postresolution dyspigmentation	Uniform dotted vessels in patchy distribution on pinkish backdrop and diffuse white scale[44]
Rosacea	Persistent erythema, telangiectasia, flushing	Erythema and telangiectasia barely discernible Dusky brown discoloration Yellowish-brown hard bumps around mouth, eyes or both	Arborizing vessels in a polygonal network[44]
Seborrheic dermatitis	Recurring dermatitis with erythematous patch		"Dotted vessels in a patchy distribution"[44]

Table 2: Comparison of classical findings with skin of color–hyperpigmented disorders

Disease	Textbook description	Description in skin of color	Dermoscopic/wood's lamp finding
Acanthosis nigricans			Hyperpigmented dots and sulcus cutis[45]
Clofazimine induced pigmentation	Orange-brown discoloration	Reddish-brown hue or dusky pigmentation	Honeycomb pattern of yellow and white globule in a dark background[19]
Lichen planus pigmentosus	Slate gray pigmentation	Slate gray to brown black pigmentation	Dot and/or globule in different patterns, with diffuse brownish pigmentation[45]
Melasma	Sharply demarcated brown patch typically on malar prominence	Light to dark brown or greyish brown pigmented macule	Diffuse light to dark brown dot granule, globule, arcuate and annular structure with sparing of perifollicular region[45]
Periorbital hyperpigmentation	Brown to dark color pigmentation in bilateral periorbital area	Moderate to dark brown macule and patches in the peri-orbital skin	Vascular – diffuse erythema Pigmented–multiple dot with different size and color or a diffuse network of pigment[46]
Post-inflammatory hyperpigmentation	Asymptomatic hyperpigmented macule and patch ranging from tan to dark brown (epidermal) to gray brown (dermal)		No consistent pattern, dermoscopy aids in determining epidermal or mixed type pigmentation[45]
Riehl's melanosis	Brownish gray facial pigmentation	Brown or slate graypigmentation	Diffuse pseudonetworks, gray dot/granule, liquefaction of basal cell incontinence of pigment[45]

a strong case for suspicion of a colored dermatological disorder though it may not be in alliance with the description in standard textbooks of the same skin disease. Bedside noninvasive tools like the Woods lamp and the dermoscope come in handy to strengthen the physician's suspicion in such cases and should be readily used to confirm a clinical suspicion.

Limitations

Full-text articles were not available for many suitable titles. Literature review was more focused on articles from the Indian subcontinent and other Asian countries. The current study could not focus on the appearances of autoimmune connective tissue diseases in skin of color due to paucity the literature. However, in the authors' experience, peculiar hyperpigmentation is particularly observed in patients with systemic sclerosis and systemic lupus erythematosus.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare no conflict of interest.

Table 3: Comparison of classical findings with skin of color–hypopigmented disorders

Disease	Textbook description	Description in skin of color	Dermoscopic/wood's lamp finding
Leprosy	Hypopigmented or reddish spot in skin (rare)	Well-defined hypopigmented macule or patch	Loss of hair and skin pigment along with absence of white dot[45]
Mycosis fungoides	Erythematous or brownish scaly patch, may show slight atrophy	Hypopigmented to depigmented patch (children, young adults)	Dotted and linear component (spermatozoa like structure)[44]
Parapsoriasis en plaque	Oval to circular erythematous to hyperpigmentedmacule and patch	Smooth or oval round hypopigmentedmacule or patch	Busy glomerular or dotted vessels, regularly arranged in a reddish background
Pityriasis alba	Irregular hypopigmented patch, not well-marginated, often slightly erythematous	Asymptomatic superficial hypopigmented macule	Ill-demarcated area with diffuse fine white scales[47]
Pityriasis versicolor	Sharply demarcated macule, sometimes slightly erythematous untanned white skin	Hypopigmented macule	Nonuniform pigmentation (in stripes/diffuse), with fine scaling[46]
Vitiligo	Amelanotic/hypomelanotic macule	Ivory or chalky white macule, looks striking in person with dark skin	White structureless area (absence of pigment network) –appear to glow, and perilesional pigmentation[45]
Sarcoidosis	Red brown macule and papule	Hypopigmented macule patch plaque (10%) along with other type of lesion	Orange yellow translucent globular like or structureless area or in combination with linear vessels[48]

References

1. Taylor F. Defining skin of color. Cutis 2002;69:435-7.
2. Elias M, Patel S, Schwartz RA, Lambert WC. The color of skin: Red diseases of the skin, nails, and mucosa. Clin Dermatol 2019;37:548-60.
3. Taylor SC, Cook-Bolden F, Rahman Z, Strachan D. Acne vulgaris in skin of color. J Am Acad Dermatol 2002;46:S98-106.
4. Nouveau S, Agrawal D, Kohli M, Bernerd F, Misra N, Nayak CS. Skin hyperpigmentation in Indian population: Insights and best practice. Indian J Dermatol 2016;61:487-95.
5. Zhao CY, Hao EY, Oh DD, Daniel BS, Martin LK, Su JC, *et al*. A comparison study of clinician-rated atopic dermatitis outcome measures for intermediate- to dark-skinned patients. Br J Dermatol 2017;176:985-92.
6. Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. Br J Dermatol 2002;147:920-5.
7. Tamazian S, Simpson CL. Autoimmune bullous disease in skin of color: A case series. JAAD Case Rep 2020;6:1173-8.
8. Badri T, Sliti N, Benmously R, Hammami H, Ben Jennet S, Mokhtar I, *et al*. Erythrasma: Study of 16 cases. Tunis Med 2014;92:245-8.
9. Amer A, Fischer H, Li X. The natural history of pityriasisrosea in black American children: how correct is the "classic" description? Arch Paediatr Adolesc Med 2007;161:503-6.
10. Sharma L, Srivastava K. Clinicoepidemiological study of pityriasis rosea. Indian J Dermatol Venereol Leprol 2008;74: 647-9.
11. Alexis AF, Blackcloud P. Psoriasis in skin of color: Epidemiology, genetics, clinical presentation, and treatment nuances. J Clin Aesthet Dermatol 2014;7:16-24.
12. Rizvi SA, Alvarez A, Alam R, Qureshi Z, Sikandar S, Khan S. Plaque psoriasis with severe hyperpigmentation in skin of color. Consultant 2019;59:125-6.
13. Alexis AF, Callender VD, Baldwin HE, Desai SR, Rendon MI, Taylor SC. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: Review and clinical practice experience. J Am Acad Dermatol 2019;80:1722-9.e7.
14. Manchanda K, Mohanty S, Rohatgi PC. Misuse of topical corticosteroids over face: A clinical study. Indian Dermatol Online J 2017;8:186-91.
15. Elgash M, Dlova N, Ogunleye T, Taylor SC. Seborrheic dermatitis in skin of color: Clinical considerations. J Drugs Dermatol 2019;18:24-7.
16. Chan IL, Cohen S, da Cunha MG, Maluf LC. Characteristics and management of Asian skin. Int J Dermatol 2019;58: 131-43.
17. Dlova NC, Akintilo LO, Taylor SC. Prevalence of pigmentary disorders: A cross-sectional study in public hospitals in Durban, South Africa. Int J Womens Dermatol 2019;5:345-8.
18. Chu AC, Teixeira F. Acquired disorders of epidermal keratinization. In: Griffith CE, Barker J, Blelker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology. 9th ed. UK: Wiley Blackwell; 2016. p. 87.2-5.
19. Chopra A, Mitra D, Agarwal R, Saraswat N, Talukdar K, Solanki A. Correlation of dermoscopic and histopathologic patterns in leprosy – A pilot study. Indian Dermatol Online J 2019;10:663-8.
20. Maia MV, Cunha Mda G, Cunha CS. Adverse effects of alternative therapy (minocycline, ofloxacin, and clofazimine) in multibacillary leprosy patients in a recognized health care unit in Manaus, Amazonas, Brazil. An Bras Dermatol 2013;88:205-10.
21. Job CK, Yoder L, Jacobson RR, Hastings RC. Skin pigmentation from clofazimine therapy in leprosy patients: A reappraisal. J Am Acad Dermatol 1990;23:236-41.
22. Mathews I, Thappa DM, Singh N, Gochhait D. Lichen planus pigmentosus: A short review. Pigment Int 2016;3:5-10.
23. Gutierrez D, Gaulding JV, Beltran AF, Lim HW, Pritchett EN. Photodermatoses in skin of color. J Eur Acad Dermatol Venereol 2018;32:1879-86.
24. Vashi NA, Wirya SA, Inyang M, Kundu RV. Facial hyperpigmentation in skin of color: Special considerations and treatment. Am J Clin Dermatol 2017;18:215-30.
25. Ranu H, Thng S, Goh BK, Burger A, Goh CL. Periorbital hyperpigmentation in Asians: An epidemiologic study and a proposed classification. Dermatol Surg 2011;37:1297-303.
26. Nath AK, Thappa DM. Kumkum-induced dermatitis: An analysis of 46 cases. Clin Exp Dermatol 2007;32:385-7.
27. Silpa-Archa N, Kohli I, Chaowattanapanit S, Lim HW, Hamzavi I. Postinflammatory hyperpigmentation: A comprehensive overview: Epidemiology, pathogenesis, clinical presentation, and noninvasive assessment technique. J Am Acad Dermatol 2017;77:591-605.
28. Schwartz RA. Arsenic and the skin. Int J Dermatol 1997;36: 241-50.

29. Mahajan VK, Khatri G, Singh R, Chauhan PS, Mehta KS. Bier spots: An uncommon cause of mottled skin. Indian Dermatol Online J 2015;6:128-9.
30. Khera P, English JC, Greek KE. Sarcoidosis. J Am Acad Dermatol 2001;44:725-43.
31. Mehta MN. Protein energy malnutrition. In: Parthasarathy A, editor. IAP Text Book of Pediatrics. 4thed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2009. p 136-57.
32. Vinod S, Singh G, Dash K, Grover S. Clinico epidemiological study of pityriasis alba. Indian J Dermatol Venereol Leprol 2002;68:338-40.
33. In SI, Yi SW, Kang HY, Lee ES, Sohn S, Kim YC. Clinical and histopathological characteristics of pityriasis alba. Clin Exp Dermatol 2009;34:591-7.
34. Ghosh SK, Dey SK, Saha I, Barbhuiya JN, Ghosh A, Roy AK. Pityriasis versicolor: A clinicomycological and epidemiological study from a tertiary care hospital. Indian J Dermatol 2008;53:182-5.
35. Jena DK, Sengupta S, Dwari BC, Ram MK. Pityriasis versicolor in the pediaric age group. Indian J Dermatol Venereol Leprol 2005;71:259-61.
36. Pandve HT. Vitiligo: Is it just a dermatological disorder? Indian J Dermatol 2008;53:40-1.
37. Chuh A, Zawar V, Maheshwari A, Bharatia P. A mini-epidemic of eruptive hypomelanosis in three children of the same family; the first piece of epidemiological evidence for an infectious cause of a novel paraviral exanthem. Clin Exp Dermatol 2016;41:680-1.
38. Talhari C, Talhari S, Penna GO. Clinical aspects of leprosy. Clin Dermatol 2015;33:26-37.
39. Zijlstra EE, El-Hassan AM. Leishmaniasis in Sudan. Post kala-azar dermal leishmaniasis. Trans R Soc Trop Med Hyg 2001;95 Suppl 1:S59-76.
40. Furlan FC, de Panla Pereira BA, de Silva LF, Sanches JA. Loss of melanocyte in hypopigmented mycosis fungoides, a study of 18 patients. J Cutan Pathol 2014;41:101-7.
41. Gupta D, Thappa DM. Dermatoses due to Indian cultural practices. Indian J Dermatol 2015;60:3-12.
42. Biswas A, Chaudhari PB, Julka PK, Rath GK. Radiation induced depigmentation disorder in two patients with breast cancer: Exploring a rare accompaniment. J Egypt Natl Canc Inst 2015;27:101-4.
43. Vashi NA, de Castro Maymone MB, Kundu RV. Aging differences in ethnic skin. J Clin Aesthet Dermatol 2016;9:31-8.
44. Taylor SC, Arsonnaud S, Czernielewski J; Hyperpigmentation Scale Study Group. The Taylor Hyperpigmentation Scale: A new visual assessment tool for the evaluation of skin color and pigmentation. Cutis 2005;76:270-4.
45. Errichetti E, Stinco G. Dermoscopy in general dermatology: A practical overview. Dermatol Ther (Heidelb) 2016;6:471-507.
46. Chatterjee M, Neema S. Dermoscopy of pigmentary disorders in brown skin. Dermatol Clin 2018;36:473-85.
47. Sarkar R, Das A. Periorbital hyperpigmentation: What lies beneath? Indian Dermatol Online J 2018;9:229-30.
48. Ankad BS, Koti VR. Dermoscopic approach to hypopigmentary or depigmentary lesions in skin of color. Clin Dermatol Rev 2020;4:79-83.
49. Chauhan P, Meena D, Hazarika N. Dermoscopy of sarcoidosis: A useful clue to diagnosis. Indian Dermatol Online J 2018;9:80-1.

Original Article

Examining the Effects of Melasma on Women's Quality of Life: A Study from Eastern Black Sea Region of Turkey

Sevda Önder, Yuhanize Taş Demircan[1], Sema Elibüyük Aksaç[2], Murat Ozturk[3], Fatma Etgü

Department of Dermatology, Ordu University Medical Faculty, Ordu Training and Research Hospital, Ordu, [1]Department of Dermatology, Seyhan State Hospital, Adana, [2]Department of Dermatology, Mersin City Hospital, Mersin, [3]Department of Dermatology, Van Training and Research Hospital, Health Sciences University, Van, Turkey

Abstract

Background/Aim: Melasma causes significant emotional and psychological effects in patients. Therefore, the investigation of the quality of life in patient with melasma has become increasingly important. In this study, we aimed to learn the demographic features of female patients with melasma in the north of Turkey, assess associated factors, and research how melasma affects quality of life. **Materials and Methods:** The demographic and etiological characteristics of 71 female patients with melasma were recorded. Dermatology Quality of Life (DQoL) index and Melasma Quality of Life Scale (MelasQoL-Tr) were completed by all patients in the presence of a dermatologist. **Results:** When the patients were evaluated according to age, marital status, education, duration of melasma, and age of onset melasma, there was no significant relationship in terms of MelasQoL. There was a statistically significant correlation in positive direction at moderate-good levels between MelasQoL and DQoL scores. **Conclusion:** Based on our study, melasma significantly affects quality of life in women. This situation clearly illustrates the need to give patients treatment not just based on clinical aspects but also including psychological features of the disease.

Keywords: Dermatology quality of life, melasma quality of life scale, melasma, Turkey

Introduction

Melasma is characterized by brown, symmetric, homogeneous, irregular macules mainly in areas exposed to sunlight and mostly on the face.[1] Melasma diagnosis is generally made clinically. However, the disease process is difficult due to being a chronic disease, progressing with frequent recurrences and lack of definite treatment.[2] It causes significant emotional and psychological effects in people.[3] For this reason, investigation of quality of life with this disease which affects physical appearance and emotional state has gained increasing importance.

A variety of factors are mentioned in melasma development; however, the definite cause is not fully known. In the literature, melasma is reported with pregnancy, hormonal treatment, hormonal contraceptives, cosmetics, photosensitizing medications, endocrinopathies, emotional stress, anticonvulsants, genetic tendency, and sunlight exposure.[1]

The prevalence of melasma varies linked to ethnic groups, skin phototype, and sun exposure. It is observed in all ethnic groups and populations. It is observed with higher prevalence in areas with intense ultraviolet (UV) radiation (UVR), especially in east Asia, India, Pakistan, the Middle East, Mediterranean Africa, America, Brazil, and Spain.[4] In Turkey, there is no study investigating the epidemiology of melasma and there are a few studies investigating the quality of life of melasma patients which are arranged as regional studies.[5,6] Our city is located in the north of Turkey in the Eastern Black Sea region and has relatively less UV exposure compared to other regions in Turkey. In this study, we aimed to learn the demographic features

Address for correspondence: Dr. Murat Ozturk, Department of Dermatology, Van Training and Research Hospital, Van, Turkey.
E-mail: chayacholic@hotmail.com

Submission: 29-04-2021 **Revision:** 04-06-2021
Acceptance: 18-06-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_33_21

How to cite this article: Önder S, Demircan YT, Aksaç SE, Ozturk M, Etgü F. Examining the effects of melasma on women's quality of life: A study from eastern black sea region of Turkey. Turk J Dermatol 2021;15:55-60.

of female patients with melasma in the north of Turkey, assess associated factors, and research how melasma affects quality of life.

Materials and Methods

Ethics committee approval obtained from Ordu University Training and Research Hospital. The study included 71 female patients with melasma attending our dermatology clinic in 2020. The study is a single-center prospective study.

The study was performed prospectively. Patient age, marital status, educational level, Fitzpatrick skin type, melasma duration, melasma onset age, melasma family history, thyroid disease history, sunscreen use habits, solar melasma activation, association of melasma with hormonal contraception, association of melasma with pregnancy were questioned and noted. The Dermatology Quality of Life (DQoL) index and the Melasma Quality of Life Scale (MelasQoL-Tr) validated by Dogramaci *et al*.[5] were completed by all patients accompanied by the dermatologist.

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 software SPSS (Chicago, IL, USA). Normal distribution of variables was investigated with analytic methods (Kolmogorov-Smirnov/Shapiro Wilk tests). Descriptive analyses present variables as mean and standard deviation and frequency and percentage. Variables obtained with measurements (continuous data) and with normal distribution (MelasQoL-Tr) were compared in independent groups (age and disease duration groups) using the independent *t*-test. Comparisons between educational levels used the one-way ANOVA test. The correlation between MelasQoL-Tr scale and DQoL index was investigated with Pearson correlation analysis. Situations with $P = 0.05$ were accepted as statistically significant.

Results

A total of 71 patients with melasma were evaluated in this study. The mean age of the patients was 37.7 ± 6.9 years (21–58). The mean duration of the disease was 7.2 years (range: 1–25 years). Of the patients, 73% were married and 27% were single. The majority of patients were primary school graduates (46.5%) and most were housewives (52.1%). Most of the patients had Fitzpatrick skin Types 3 and 4. Of patients, 52.1% did not use regular sunscreen. Melasma was associated with pregnancy in 45.1% of the patients. For 33.8% of patients, melasma was associated with hormonal contraception. There was family history among first-degree relatives in 36.6% of the patients. For 11.3% of patients, there was a history of thyroid disease. The DQoL index was 5.7 ± 5.7. MelasQoL-Tr was 38.6 ± 15.2. The demographic and clinical data for patients are given in Tables 1 and 2. When the patients with disease for longer or <5 years were compared, no significant difference was found in terms of MelasQoL ($P > 0.05$) [Table 3]. When the patients were evaluated as those above the age of 40 and under the age of 40, MelasQoL was found to be significantly higher in patients under the age of 40 ($P = 0.037$) [Table 4]. When the patients were evaluated according to age, marital status, education, duration of melasma, and age of onset melasma, there was no significant relationship in terms of MelasQoL ($P > 0.05$). There was a statistically significant correlation in positive direction at moderate-good levels between MelasQoL and DQoL scores ($P < 0.001$; $r = 0.689$).

For questions on the MelasQoL-Tr scale, in answer to the question about whether the appearance of their skin made them uncomfortable, 35.2% stated they were bothered most of the time. In answer to the question of whether they had concerns about the appearance of their skin, 36.6% stated that they were sometimes bothered. The question of whether they were embarrassed due to the state of their skin was answered with not bothered at all by 28.1%. The question of whether they felt melancholy and sad about the state of their skin was answered as sometimes bothered by 31%. For the question does the state of their skin affected their social relationships with family, friends, and neighbors, 46.5% stated they were not bothered at all. The question does the state of their skin affects their desire to be with other people was answered with not bothered at all by 49.3%. In answer to the question does the state of their skin prevent them showing interest in people, 57.7% stated they were not bothered at all. The question of whether they feel less attractive due to color changes in their skin was answered as sometimes bothered by 28.2%. In answer to the question do they feel less lively and productive due to color changes in their skin, 33.8% stated they were not bothered at all, while 31% stated they were sometimes bothered. The question of whether

Table 1: Descriptive statistics ($n=71$)

Parameters	Minimum–maximum	Mean±SD
Age	21–58	37.7±6.9
Duration of disease	1–25	7.2±5.8
DQoL score	0–24	5.7±5.7
MelasQoL-Tr	10–70	38.6±15.2
Age of onset	11–45	30.6±7.1

SD: Standard deviation, DQoL: Dermatology Quality of Life, MelasQoL-Tr: Melasma Quality of Life-Turkey

Table 2: Clinical features of patients

Parameters	Subgroups	Frequency, *n* (%)
Marital status	Married	52 (73.2)
	Single	19 (26.8)
Fitzpatrick skintype	2	7 (9.9)
	3	25 (35.2)
	4	27 (38.0)
	5	12 (16.9)
Education	None	1 (1.4)
	Primary	33 (46.5)
	Middle	13 (18.3)
	High school	11 (15.5)
	University	13 (18.3)
Job	Housewife	37 (52.1)
	Student	2 (2.8)
	Worker	16 (22.5)
	Nonworker	16 (22.5)
Using regularly sunscreen creams	Yes	34 (47.9)
	No	37 (52.1)
Association with pregnancy	Yes	32 (45.1)
	No	39 (54.9)
Exacerbation with oral contraceptives	Yes	24 (33.8)
	No	47 (66.2)
Family history	Yes	26 (36.6)
	No	45 (63.4)
Thyroid disease history	Yes	8 (11.3)
	No	63 (88.7)
Exacerbation with sun exposure	Yes	65 (91.5)
	No	6 (8.5)

Table 3: Compare of Melasma Quality of Life-Turkey score between time groups

Duration MelasQoL-Tr (years)	*n*	Mean	SD	SEM	*P*
<5	32	40.3	14.1	2.5	0.385
≥5	39	37.2	16.0	2.6	

Independent *t*-test was used and $P<0.05$ was considered significant. MelasQoL-Tr: Melasma Quality of Life-Turkey, SD: Standard deviation, SEM: Standard error of mean

it affected their feeling of freedom was answered with not bothered at all by 40.8% of women [Table 5].

Discussion

The MelasQoL is a quality-of-life scale used for patients with melasma. It was developed and validated by Balkrishnan *et al*. and was used for studies in many countries. The scale contains 10 questions. In order, it involves the assessment of questions about skin appearance, frustration with skin, embarrassment, feeling depressed, interaction with people, desire to be with people, showing affection, feeling unattractive, feeling less vital or productive, and affecting sense of freedom. Each question is scored from 1 to 7 and high scores show reduced quality of life.[7] In our study, the MelasQoL-Tr, translated to Turkish and validated by Dogramaci *et al*.,[5] was used and the effect on women with melasma living in a city in the Black Sea climate in the north of Turkey was investigated in light of the literature, along with demographic features, factors associated with disease and quality of life.

The mean age of women in our study was 37.7 ± 6.9 years. A global study had mean age 42.90 ± 9.60, a study in Indonesia had mean age 39.3 ± 4.7, and a study in Australia had mean age 41.4 ± 7.6.[8-10] The study by Balkrishnan *et al*.[7] had a mean age of 40 years, while in Turkey the study by Dogramaci *et al*.[5] had mean age 31.8 ± 7.3 years.

In our study, the MelasQoL score was 38.6 ± 15.2. When the literature is examined, some studies were identified to have higher scores. Scores were 55 ± 10.6 in an Australian study,[10] 44.4 ± 14.9 in a Brazilian study,[11] 42 in a Spanish study,[3] and 52.85 in an Iranian study.[12] When we look at these countries, they all have hot climates and intense exposure to UV light. Similar studies in other countries

Table 4: Compare of Melasma Quality of Life-Turkey score between age groups

Age MelasQoL-Tr	*n*	Mean	SD	SEM	*P*
<40	41	41.8	14.3	2.2	0.037
≥40	30	34.2	15.4	2.8	

MelasQoL-Tr: Melasma Quality of Life-Turkey, SD: Standard deviation, SEM: Standard error of mean

Table 5: Distribution of questions answers

Answer	Frequency, *n* (%)									
	1. The appearance of melasma	2. Frustration about melasma	3. Embarrassment about melasma	4. Feeling depressed about melasma	5. The effects on interactions with other people	6. Desire to be with people	7. Show affection	8. Feeling unattractive	9. Feel less vital or productive	10. Affecting sense of freedom
1	5 (7.0)	5 (7.0)	20 (28.2)	12 (16.9)	33 (46.5)	35 (49.3)	41 (57.7)	14 (19.7)	24 (33.8)	29 (40.8)
2	0	2 (2.8)	2 (2.8)	4 (5.6)	1 (1.4)	3 (4.2)	2 (2.8)	3 (4.2)	3 (4.2)	3 (4.2)
3	5 (7.0)	6 (8.5)	8 (11.3)	8 (11.3)	7 (9.9)	4 (5.6)	3 (4.2)	7 (9.9)	5 (7.0)	2 (2.8)
4	0	4 (5.6)	3 (4.2)	6 (8.5)	4 (5.6)	3 (4.2)	1 (1.4)	0	2 (2.8)	3 (4.2)
5	18 (25.4)	26 (36.6)	17 (23.9)	22 (31.0)	15 (21.1)	12 (16.9)	15 (21.1)	20 (28.2)	22 (31.0)	17 (23.9)
6	25 (35.2)	13 (18.3)	9 (12.7)	11 (15.5)	5 (7.0)	8 (11.3)	7 (9.9)	10 (14.1)	8 (11.3)	10 (14.1)
7	18 (25.4)	15 (21.1)	12 (16.9)	8 (11.3)	6 (8.5)	6 (8.5)	2 (2.8)	17 (23.9)	7 (9.9)	7 (9.9)

had lower MelasQoL scores compared to our study. For example, values were identified as 37.19 ± 18.15 in a study from India[13] and 34.40 ± 13.50, 37.5 ± 15.2 and 27.2 ± 13.4 in some Brazilian studies.[2,14,15] Studies by Balkrishnan *et al*.,[7] Misery *et al*.[16] and Dogramaci *et al*.[5] had lower scores compared to our study (36, 20.9, and 29.9, respectively). When we examine these countries, again there is higher UV exposure than our region; however, our results were higher. This leads to the consideration that results are affected by differences in the study groups and that quality of life is affected by other factors independent of melasma. We did not find a significant correlation between MelasQoL with marital status, education, duration of melasma, and age of onset melasma in our study ($P > 0.05$). Studies by Balkrishnan *et al*.,[7] in Spain[3] and Singapore[17] did not find statistical correlations between demographic variables and MelasQoL. When patients are assessed according to age, MelasQoL was affected more for patients under the age of 40 years, compared to patients over the age of 40 ($P = 0.037$). Misery *et al*.[16] found the MelasQoL scores were higher for those over the age of 45 and with long-term melasma. Balkrishnan *et al*.[7] found that patients in the 20–30 age group had significantly higher MelasQOL scores than patients in the 31–40 and >41 age groups.

In our study, the mean disease duration was 7.2 ± 5.8 years. There was no significant correlation between MelasQoL and disease duration in our study. When cases are assessed as those with disease for more than or <5 years, no significant difference was found in terms of MelasQoL. This again leads to the consideration that quality of life is affected independently of disease duration. Studies in the literature display different results. Mexican[11] and French[16] studies showed a positive correlation between MelasQoL and disease duration. A study in Australia found no significant correlation between duration and MelasQoL.[10]

In our study, the mean age at disease onset was 30.6 ± 7.1 years. In some studies, this value is higher than our study; in others, it is lower. Values in studies by Ortonne *et al*.[8] of 34 years, the Australian study[10] of 35.6 ± 6.7 and an Indian study[18] assessing 1001 patients of 34.57 ± 10.561 years were higher than our study. Studies with lower values include 27.5 ± 7.8 years in the study by Tamega Ade *et al*.,[1] and mean onset ages of 29.18 ± 7.05 years and 29.8 ± 8.8 years in some Brazilian studies.[2,19]

There was a family history among first-degree relatives in 36.6% of the patients in our study. There are different results in the literature. Studies have observed family history in 6%–54.7% of patients.[8]

In our study, 73.2% of the patients were married and 26.8% were single. This result is consistent with the literature. In the study by Balkrishnan *et al*.,[7] most patients were married (64%), for Dogramaci *et al*.[5] 78.1% were married and in a Spanish study[3] 75.8% were married. One study[20] investigating quality of life showed that quality of life was affected less in married patients; however, in our study, there was no significant difference between MelasQoL points between married and single participants.

In our study, 45.1% of cases had melasma associated with pregnancy. A global study identified the most frequent onset time for melasma was after pregnancy (42%). Another study in the same study had 20% rate of cases with melasma observed during pregnancy. Some studies show that melasma is triggered by pregnancy at rates from 16% to 45%.[8]

In our study, 11.3% of the patients had a history of thyroid disease. In a study, abnormal thyroid stimulating hormone hormonal profiles were present in 25.3%.[1] Another study found that thyroid disorders were present in 7.84% of patients.[2] Sacre *et al*.[21] found normal thyroid hormonal levels, prolactin, and gonadotrophic stores in their patients. There are different results in the literature and the relationship between melasma and thyroid diseases is not fully understood.

Exposure to UV light, especially in areas with intense UVR, increases melasma development by a significant degree.[22-24] In a study by Harumi and Goh, patients stated that the most frequent triggering factor was the sun (67.3%).[17] A study in India observed solar activation in 55.5% of cases.[25] In our study, activation by the sun was identified in 91.5% of patients and 52.1% of patients did not use sunscreen regularly in our study. This situation leads to the consideration that patients did not regularly and correctly use sunscreen. There are different results in the literature. In one study[10] regular sunscreen use was seen in 57.3%, while a study of 1001 patients found only 19.6% used sunscreen.[18] Our study mostly included primary school graduates (n = 33). Melasma patients with low educational levels may have deficient information about prevention and may have less desire to protect themselves from the sun due to the cost of sunscreen products.[26] In the literature, in studies by Freitag *et al*.[14] and Dominguez *et al*.[3] patients with low educational level had higher MelasQoL scores compared to patients with higher educational level. In our study, there was no significant difference in terms of MelasQoL when investigated in terms of educational level. Another study in our country by Dogramaci *et al*.[5] found no significant difference, similar to our study.

In our study, the DQoL index was 5.7 ± 5.7. Studies found the DQoL scores were 6.81 ± 1.40, 6.02 ± 4.94, and 4.5 ± 5.[6,17,27] There was a correlation between MelasQoL and DQoL scores in a study by Harumi and Goh.[17] In our study, a positive correlation was observed. When studies investigating other dermatological diseases in Turkey are examined, a study of psoriasis patients found DQoL Score 5.6 ± 4.2, a study of vitiligo patients found DQoL Score 5.6 ± 5.1 and in the same study the DQoL for acne patients was 6.4 ± 6.2.[28,29] When these studies are examined, it can be said that melasma affects quality of life to a similar degree as diseases such as psoriasis, vitiligo, and acne.

Limitations of this study are the low number of participants and the assessment of patients from only one city in Turkey.

Different results in studies may be due to group heterogeneity, disease severity, previous treatments, and cultural effects.

Conclusion

When melasma develops in visible areas, it may have significant effects on quality of life. Based on our study and other information in the literature, melasma significantly affects quality of life in women. This situation clearly illustrates the need to give patients treatment not only based on clinical aspects but also including psychological features of the disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tamega Ade A, Miot LD, Bonfietti C, Gige TC, Marques ME, Miot HA. Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. J Eur Acad Dermatol Venereol 2013;27:151-6.
2. Ikino JK, Nunes DH, Silva VP, Fröde TS, Sens MM. Melasma and assessment of the quality of life in Brazilian women. An Bras Dermatol 2015;90:196-200.
3. Dominguez AR, Balkrishnan R, Ellzey AR, Pandya AG. Melasma in Latina patients: Cross-cultural adaptation and validation of a quality-of-life questionnaire in Spanish language. J Am Acad Dermatol 2006;55:59-66.
4. Handel AC, Miot LD, Miot HA. Melasma: A clinical and epidemiological review. An Bras Dermatol 2014;89:771-82.
5. Dogramaci AC, Havlucu DY, Inandi T, Balkrishnan R. Validation of a melasma quality of life questionnaire for the Turkish language: The MelasQoL-TR study. J Dermatolog Treat 2009;20:95-9.
6. Uyanikoglu H, Aksoy M. Quality of life in patients with melasma in Turkish women. Dermatol Reports 2017;9:7340.
7. Balkrishnan R, McMichael AJ, Camacho FT, Saltzberg F, Housman TS, Grummer S, *et al*. Development and validation of a health-related quality of life instrument for women with melasma. Br J Dermatol 2003;149:572-7.
8. Ortonne JP, Arellano I, Berneburg M, Cestari T, Chan H, Grimes P, *et al*. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. J Eur Acad Dermatol Venereol 2009;23:1254-62.
9. Jusuf NK, Putra IB, Mahdalena M. Is there a correlation between severity of melasma and quality of life? Open Access Maced J Med Sci 2019;7:2615-8.
10. Anderson L, Rodrigues M. Quality of life in a cohort of melasma patients in Australia. Australas J Dermatol 2019;60:160-2.
11. Cestari TF, Hexsel D, Viegas ML, Azulay L, Hassun K, Almeida AR, *et al*. Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: The MelasQoL-BP study and improvement of QoL of melasma patients after triple combination therapy. Br J Dermatol 2006;156 Suppl 1:13-20.
12. Aghaei S, Moradi A, Mazharinia N, Abbasfard Z. The Melasma Quality of Life scale (MELASQOL) in Iranian patients: A reliability and validity study. J Eur Acad Dermatol Venereol 2005;19 Suppl 2:39.
13. Sarkar R, Garg S, Dominguez A, Balkrishnan R, Jain RK, Pandya AG. Development and validation of a Hindi language health-related quality of life questionnaire for melasma in Indian patients. Indian J Dermatol Venereol Leprol 2016;82:16-22.
14. Freitag FM, Cestari TF, Leopoldo LR, Paludo P, Boza JC. Effect of melasma on quality of life in a sample of women living in southern Brazil. J Eur Acad Dermatol Venereol 2008;22:655-62.
15. Purim KS, Avelar MF. Photoprotection, melasma and quality of life in pregnant women. Rev Bras Ginecol Obstet 2012;34:228-34.
16. Misery L, Schmitt AM, Boussetta S, Rahhali N, Taieb C. Melasma: Measure of the impact on quality of life using the French version of MELASQOL after cross-cultural adaptation. Acta Derm Venereol 2010;90:331-2.

17. Harumi O, Goh CL. The effect of melasma on the quality of life in a sample of women living in Singapore. J Clin Aesthet Dermatol 2016;9:21-4.
18. Sarkar R, Jagadeesan S, Basavapura Madegowda S, Verma S, Hassan I, Bhat Y, *et al*. Clinical and epidemiologic features of melasma: A multicentric cross-sectional study from India. Int J Dermatol 2019;58:1305-10.
19. Hexsel D, Lacerda DA, Cavalcante AS, Machado Filho CA, Kalil CL, Ayres EL, *et al*. Epidemiology of melasma in Brazilian patients: A multicenter study. Int J Dermatol 2014;53: 440-4.
20. Pollo CF, Miot LD, Meneguin S, Miot HA. Factors associated with quality of life in facial melasma: A cross-sectional study. Int J Cosmet Sci 2018;doi: 10.1111/ics.12464. Online ahead of print.
21. Sacre RC, Fernandes NC, Vaisman M, Tendrich M. Melasma idiopático: Avaliação das funções tireoidiana, prolactínica e gonadal feminina. An Bras Dermatol 1996;71:195-8.
22. Grimes PE. Melasma. Etiologic and therapeutic considerations. Arch Dermatol 1995;131:1453-7.
23. Sanchez NP, Pathak MA, Sato S, Fitzpatrick TB, Sanchez JL, Mihm MC Jr. Melasma: A clinical, light microscopic, ultrastructural, and immunofluorescence study. J Am Acad Dermatol 1981;4:698-710.
24. Kang WH, Yoon KH, Lee ES, Kim J, Lee KB, Yim H, *et al*. Melasma: Histopathological characteristics in 56 Korean patients. Br J Dermatol 2002;146:228-37.
25. Achar A, Rathi SK. Melasma: A clinico-epidemiological study of 312 cases. Indian J Dermatol 2011;56:380-2.
26. D'Elia MP, Brandão MC, de Andrade Ramos BR, da Silva MG, Miot LD, Dos Santos SE, *et al*. African ancestry is associated with facial melasma in women: A cross-sectional study. BMC Med Genet 2017;18:17.
27. Amatya B, Pokhrel DB. Assessment and comparison of quality of life in patients with melasma and vitiligo. Kathmandu Univ Med J (KUMJ) 2019;17:114-8.
28. Muştu Koryürek Ö, Karataş Toğral A, Koryürek MM, Ekşioğlu HM. The factors affecting quality of life in Turkish psoriasis patients. Turk J Dermatol 2015;3:123-7.
29. Salman A, Kurt E, Topcuoglu V, Demircay Z. Social anxiety and quality of life in vitiligo and acne patients with facial involvement: A cross-sectional controlled study. Am J Clin Dermatol 2016;17:305-11.

Original Article

Chemotherapeutic Drug-Induced Nail Changes: A Prospective Observational Study

Kallolinee Samal, Srigopal Mohanty[1], Smaranika Satapathy

Department of Skin and VD, SCB Medical College and Hospital, Cuttack, Odisha, [1]Department of Medical Oncology, Govt. Royapettah Hospital and Govt. Kilpauk Medical College, Chennai, Tamil Nadu, India

Abstract

Background: Nail changes associated with chemotherapeutic drugs are common and can compromise the quality of life of cancer patients if left overlooked by a clinician. **Aim:** The aim of this study was to study the common pattern of nail changes caused by chemotherapeutic drugs. **Materials and Methods:** A single-institutional prospective observational study was conducted for patients with histopathologically proven malignancy without prior nail changes undergoing first-line systemic chemotherapy. Analysis of frequency distribution and associations of categorical variables was performed by Chi-square test and multivariate analysis, using IBM SPSS statistics version 21 for Windows. $'R'' \leq '0.05$ was considered statistically significant. **Results:** The incidence of nail changes in the present study was 42% (182 out of 434 cases). Nail changes were commonly observed following 1–2 cycles of chemotherapy, and most of them were Grade 1 changes. The most common nail change observed was chromonychia (49%), followed by onychorrhexis (29%). Chemotherapeutic drugs frequently associated were taxane (65.3%) and platinum compounds (57.7%). Nail changes found associated with taxane included the largest varieties, i.e., chromonychia, onychorrhexis, splinter hemorrhage, Terry's nail, half-and-half nail, Beau's lines, onychodystrophy, and paronychia. Nail changes associated with platinum drugs were onychorrhexis and chromonychia. Adriamycin, bleomycin, vinblastine, and dacarbazine regimen was associated with leukonychia. Adriamycin and cyclophosphamide both were independently associated with chromonychia. **Conclusion:** A knowledge of chemotherapy-induced nail changes can avoid inadvertent diagnostic interventions and improve the quality of life by timely and proper patient counseling.

Keywords: Cancer, chemotherapy, drug, nail changes

Introduction

Cancer chemotherapeutic drugs are associated with different nail changes, which might result from one or more of the following proposed mechanisms: (i) damage to the nail matrix, causing aberrant nail plate growth; (ii) nail bed damage; (iii) damage to the proximal nail fold; and (iv) aberrant blood flow to the nail bed.[1,2] The chemotherapy-induced nail changes frequently mimic nail changes associated with many systemic diseases such as rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, psoriasis, pulmonary embolism, coronary thrombosis, cirrhosis, congestive cardiac failure, renal failure, nephrotic or nephritic syndrome, anemia, diabetes, porphyria, peripheral vascular disease, liver diseases, malnutrition, Addison's disease, hyperparathyroidism, and acquired immune deficiency infections.[3-8] Development of nail changes among these patients with terminal illness creates anxiety and apprehension and compromises the quality of life.[4] In view of limited prospective data available, we conducted a prospective observational study to find the association of frequent nail changes associated with chemotherapeutic drugs.

Materials and Methods

A prospective observational study was conducted in a tertiary cancer center in East India. The duration of the study was from August 2019 to March 2020. The study was conducted

Submission: 07-06-2021 **Revision:** 02-07-2021
Acceptance: 02-07-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_44_21

Address for correspondence: Dr. Srigopal Mohanty, Room No: 106A, 1st Floor, Cancer Block, Department of Medical Oncology, Govt. Royapettah Hospital and Govt. Kilpauk Medical College, Chennai - 600 014, Tamil Nadu, India.
E-mail: drsrigopal17@gmail.com

How to cite this article: Samal K, Mohanty S, Satapathy S. Chemotherapeutic drug-induced nail changes: A prospective observational study. Turk J Dermatol 2021;15:61-5.

as per the Declaration of Helsinki developed by the World Medical Association in 1964. Informed written consent from individual patients and institutional ethical committee approval were obtained prior to patient enrollment in the study. The inclusion criteria of study participants included patients with histopathologically proven malignancy undergoing first-line systemic chemotherapy. Exclusion criteria were dermatological diseases likely to involve nails or primary nail disorders, history of any occupational contact with any chemicals, and pulmonary, cardiac, renal, hepatic, endocrine disorders, which probably could cause the nail changes. Patients with history of drugs like retinoid in the last 6 months that could cause nail changes were also excluded. Co-administration of different drugs along with chemotherapy agents was noted. Nail changes were independently diagnosed clinically by two dermatologists to avoid bias. Baseline nail changes of the patients were noted and photographs were obtained. Patients were followed up during each chemotherapy cycle (every 3–4-week interval according to the chemotherapy protocols). Any new changes of the nail units were recorded and were documented during each follow-up. Grading of nail changes was done using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5 by a dermatologist. Nail discoloration, nail ridging, and asymptomatic nail loss were considered as Grade 1 changes, whereas symptomatic and painful nail loss was considered Grade 2 changes.[9] The statistical analysis was performed by using IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY, USA: IBM Corp). Chi-square test was used to evaluate the association of different nail changes with chemotherapy regimens. Multivariate analysis (MVA) using multivariate analysis of variance technique (with 95% confidence interval) was used to evaluate the association between nail changes and chemotherapeutic drugs, where a nail finding was observed with two or more chemotherapeutic drug-based regimens. *"R"*≤*"*0.05 was considered statistically significant.

Results

In the present study, the total number of cases enrolled after considering its inclusion and exclusion criteria was 434, out of which 182 (42%) developed nail changes during the chemotherapy treatment. The mean age of patients was 50.7 ± 10.5 years (ranges from 29 to 79 years). Male and female patients constituted 40.4% and 59.6%, respectively. Primary sites of malignancies were breast cancer (43.2%), head-and-neck cancer (18.6%), lung cancer (15.3%), cervical cancer (11.5%), ovarian cancer (9.3%), lymphoma (1.6%), and gastrointestinal cancer (0.5%). Different chemotherapeutic regimens found associated with nail changes in the study are illustrated in Table 1. The frequencies of different nail changes associated with chemotherapeutic drugs observed are depicted in Figure 1. The most common type of nail changes was chromonychia, followed by onychorrhexis. The nail changes were commonly observed after completion of 1–2 cycles of chemotherapy (77.6%), followed by completion of ≥3 cycles

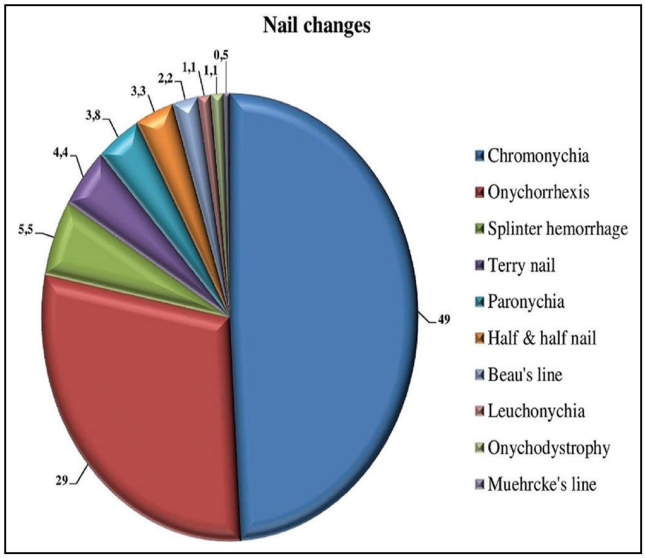


Figure 1: Frequency of different nail changes observed in the study

of chemotherapy (22.4%). Most of the chemotherapy-induced nail changes in the study were Grade 1, i.e., 97% (176) cases had Grade 1 and 3% (6 cases) had Grade 2 nail changes. Few of the common nail changes observed in the study are depicted in Figures 2-4. The association of different nail changes with chemotherapeutic drug-based regimens evaluated by MVA is depicted in Table 2.

Chromonychia was found in those patients who had received paclitaxel, paclitaxel + carboplatin, Adriamycin + cyclophosphamide, docetaxel + carboplatin, docetaxel, cisplatin, 5-fluorouracil + Adriamycin + cyclophosphamide, Adriamycin + cyclophosphamide + paclitaxel, cyclophosphamide + cisplatin, cyclophosphamide, and Adriamycin + bleomycin + vinblastine + dacarbazine regimen. MVA revealed that the drugs associated with chromonychia were paclitaxel, docetaxel, cyclophosphamide, and Adriamycin.

Onychorrhexis was observed in patients who had received cisplatin, paclitaxel + carboplatin, paclitaxel, and carboplatin. MVA revealed that the drugs associated with onychorrhexis were cisplatin and paclitaxel.

Splinter hemorrhage was observed in patients who had received paclitaxel, paclitaxel + carboplatin, and cisplatin. None of the single-agent carboplatin users developed this nail changes. Paclitaxel was associated with splinter hemorrhage in the study, which was not significant in MVA (probably due to lesser incidence of this nail finding).

Terry's nails were found in patients who had received paclitaxel and docetaxel.

Half-and-half nail was seen in patients who had received paclitaxel + carboplatin and paclitaxel whereas not observed among any patients who received single-agent carboplatin.

Table 1: Nail changed associated with different chemotherapeutic regimens

Nail changes	T, *n* (%)	D, *n* (%)	Ci, *n* (%)	Ca, *n* (%)	Cx, *n* (%)	AC, *n* (%)	TC, *n* (%)	DC, *n* (%)	FAC, *n* (%)	TAC, *n* (%)	CC, *n* (%)	ABVD, *n* (%)	*P*
Chromonychia	26 (29.2)	6 (6.7)	6 (6.7)	-	3 (3.4)	13 (14.7)	20 (22.5)	7 (7.9)	3 (3.4)	2 (2.2)	2 (2.2)	1 (1.1)	0.000
Splinter hemorrhage	5 (50)	-	1 (10)	-	-	-	4 (40)	-	-	-	-	-	
Onychorrhexis	6 (11.3)	-	34 (64.2)	4 (7.5)	-	-	9 (17)	-	-	-	-	-	
Terry's nail	5 (62.5)	3 (37.5)	-	-	-	-	-	-	-	-	-	-	
Half-and-half nail	3 (50)	-	-	-	-	-	3 (50)	-	-	-	-	-	
Onychodystrophy	2 (100)	-	-	-	-	-	-	-	-	-	-	-	
Beau's line	-	2 (50)	-	-	-	-	2 (50)		-	-	-	-	
Leukonychia	-	-	-	-	-	-	-	-	-	-	-	2 (100)	
Paronychia	2 (28.6)	2 (28.6)	-	-	-	-	3 (42.8)	-	-	-	-	-	
Muehrcke's line	-	1 (100)	-	-	-	-	-	-	-	-	-	-	

T: Paclitaxel, D: Docetaxel, Ci: Cisplatin, Ca: Carboplatin, Cx: Cyclophosphamide, AC: Adriamycin + cyclophosphamide, TC: Paclitaxel + cyclophosphamide, DC: Docetaxel + cyclophosphamide, FAC: 5-fluorouracil + Adriamycin + cyclophosphamide, TAC: Docetaxel + Adriamycin + cyclophosphamide, CC: Cyclophosphamide + cisplatin, ABVD: Adriamycin + bleomycin + vinblastine + dacarbazine

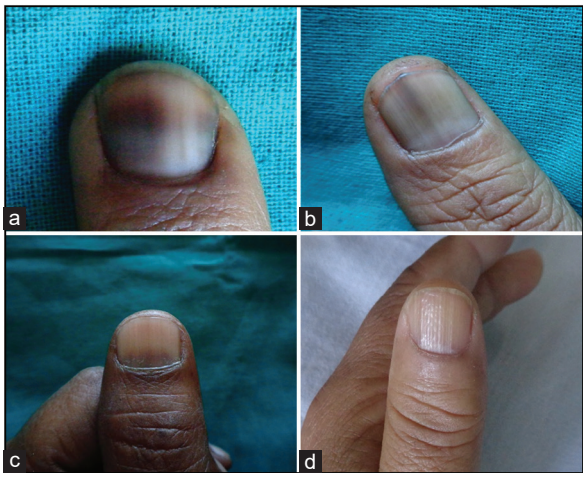


Figure 2: (a-c) Different patterns of chromonychia, (d) Onychorrhexis observed in a patient after receiving two cycles of cisplatin

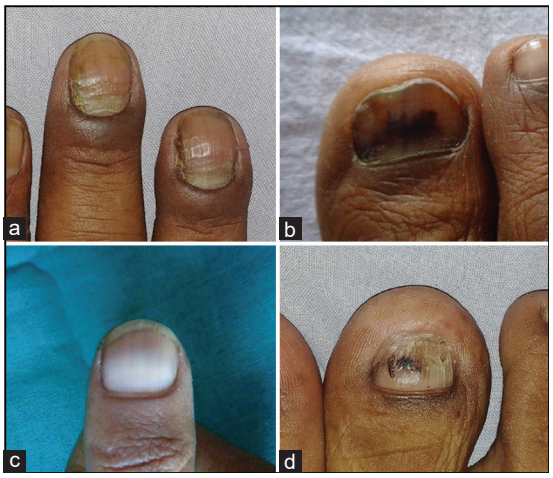


Figure 3: (a) Paronychia in a patient following three cycles of paclitaxel, (b) Splinter's hemorrhage observed in a patient following three cycles of paclitaxel, (c) Half-and-half nail observed in a patient following two cycles of paclitaxel, (d) Onychodystrophy observed in a patient following four cycles of paclitaxel

Beau's lines were observed in patients who had received docetaxel and paclitaxel + carboplatin, whereas it was not observed in any case who had received carboplatin. Onychomadesis was found in two patients after receiving paclitaxel.

Paronychia was observed in patients who had received paclitaxel + carboplatin, paclitaxel, and docetaxel but was not seen among any cases who received single-agent carboplatin.

- Onychodystrophy was observed in patients who had received paclitaxel
- Leukonychia was observed in patients who had received Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen
- Muehrcke's line was observed in one patient who had received docetaxel.

Discussion

The present study was conducted to identify some of the common nail changes and their causative chemotherapeutic agents.

Chromonychia results from activation of melanocytes of the nail matrix and increased production of melanin, although the exact underlying mechanism is not clear. It has been reported to be associated with chemotherapeutic drugs such as Adriamycin, cyclophosphamide, and hydroxyurea.[1,10-13] The drug-induced nail pigmentation proceeds from proximal to distal nail edge, which reverses in a similar fashion after withdrawal of the drugs.[14] The present study found that, in addition to the previous reports of cyclophosphamide and Adriamycin, the other drugs associated significantly with chromonychia were taxane (docetaxel and paclitaxel) and cisplatin. Chromonychia was the most common type of nail change observed in the present study, as similarly reported in the previous study.[15]

Onychorrhexis is multiple longitudinal lines or striations seen on nail plate.[1,16] Its association with specific chemotherapeutic drug is not yet reported to the best of our knowledge. In the present study, it was found to be significantly associated with cisplatin and paclitaxel.

Table 2: Multivariate analysis (95% confidence interval) showing chemotherapeutic drugs associated with specific nail changes

Nail changes	Chemotherapeutic drug-based regimen	*n* (%)	MVA (*P*)
Chromonychia	T	53 (56.4)	0.023
	D	18 (72)	0.013
	Ci	8 (18.6)	0.256
	Ca	34 (54.8)	0.334
	Cx	12 (100)	0.001
	Adriamycin	19 (90.5)	0.000
	ABVD	1 (33.3)	0.589
Splinter hemorrhage	T	8 (8.5)	0.216
	D	-	-
	Ci	1 (2.3)	0.299
	Ca	4 (6.5)	0.665
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-
Onychorrhexis	T	15 (16)	0.001
	D	-	-
	Ci	34 (79.1)	0.000
	Ca	15 (24.2)	0.354
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-
Paronychia	T	5 (5.3)	0.273
	D	2 (8)	0.247
	Ci	-	-
	Ca	-	-
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-
Terry's nail	T	5 (5.4)	0.470
	D	3 (12)	0.047
	Ci	-	-
	Ca	-	-
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-

MVA: Multivariate analysis, ABVD: Adriamycin + bleomycin + vinblastine + dacarbazine, T: Paclitaxel, D: Docetaxel, Ci: Cisplatin, Ca: Carboplatin, Cx: Cyclophosphamide

Splinter hemorrhage results from micro-injury to the nail bed capillaries.It presents as red, brown, black discolouration of nail, due to extravasation of blood from longitudinally oriented vessels of the nail bed. It is frequently reported after use of vascular endothelial growth factor receptor inhibitors (sunitinib and pazopanib).[1,10,17] In the study, this was found to be associated with paclitaxel, which was in concordance with the previous study report.[15]

Terry's nails are a type of apparent leukonychia, where narrow band of distal nail bed appears normal pink, leaving remaining proximal area of the nail opacified, obscuring the lunula. It is found in cirrhosis of liver, congestive cardiac failure, renal transplant cases, peripheral vascular disease, and type 2 diabetes mellitus.[1,10,18] In the present study, it was found to be associated with taxane (paclitaxel and docetaxel).

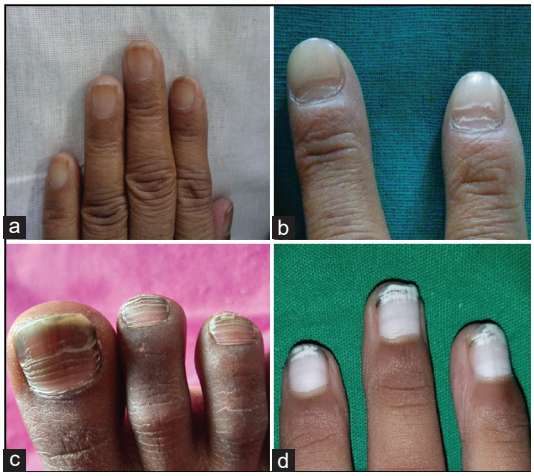


Figure 4: (a) Terry's nail observed in a patient following two cycles of docetaxel, (b) Onychomadesis observed in a patient following the first cycle of docetaxel, (c) Beau's lines observed in a patient following four cycles of docetaxel, (d) Leukonychia observed in a patient following three cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy

Half-and-half nails are a type of apparent leukonychia, where the abnormal white color of the proximal nail fold obscures the lunula. It is found commonly in chronic renal failure patients. It is a reversible nail change, which does not need any specific treatment and disappears after treatment discontinuation.[1,19] In the present study, it was found to be associated with paclitaxel.

Onychodystrophy results from damage to the nail matrix, and it can be congenital, caused by fungal or nonfungal infections, psoriasis, eczema, lichen planus, benign skin warts, or malignancies of skin.[20,21] In the present study, onychodystrophy was observed in two cases, and both cases developed dystrophy after four cycles of paclitaxel.

Leukonychia is white discoloration of nail plate, caused by impaired keratinization of distal nail matrix.This part of nail looks white as light is reflected from the parakeratotic layers of the nail.[1,2] In the present study, leukonychia was observed in two cases after completion of four cycles of chemotherapy with ABVD regimen.

Paronychia results from damage to the perionychium. It can be caused by bacterial or fungal infections secondary to trauma or moisture.[22] It has been reported to be associated with the use of anticancer-targeted therapies such as epidermal growth factor receptor and Erb-B inhibitors (afatinib and lapatinib, respectively) and less likely associated with chemotherapeutic agents (taxane).[10] In the present study, paronychia was found to be associated with taxane chemotherapy (paclitaxel and docetaxel).

Beau's lines are transverse linear depressions on the dorsum of nail plate, caused by temporary cessation of nail growth in the matrix. Multiple Beaus' lines in the same nail denote

multiple exposures to the drug, and the gap between the lines is proportional to the interval between the drug exposures. Beau's lines are reported to be associated with a taxane- and platinum-containing regimen.[1,10,15,23,24] Onychomadesis is an extreme degree of presentation of Beau's lines. In the present study, it was found associated with taxane chemotherapy (docetaxel and paclitaxel).

Muehrcke's line occurs due to abnormality in nail vascular bed and presents as double white transverse lines. It is commonly caused by hypoalbuminemia associated with liver disease, nephrotic syndrome, malnutrition, and chemotherapeutic drugs.[2] In the present study, it was observed in one patient who received docetaxel.

Conclusion

Chemotherapeutic drug-induced nail changes are quite common, which increases anxiety and apprehension among cancer patients. The present study adds information to the available literature on specific nail changes associated with particular chemotherapeutic drug or regimen, which can help a clinician to avoid unnecessary and at times invasive investigations to rule out probable systemic associations. Early diagnosis with appropriate patient counseling can improve the quality of life in these groups of patients with terminal disease.

Acknowledgment

We wholeheartedly thank all the study participants for their willingness and full cooperation in conducting the study. We thank Dr. Bhabani Shankar Tarini Prasad Singh, Associate Professor of the Department of Skin and VD, Sum Hospital, Bhubaneswar, Odisha, for his contribution in clinical diagnosis and his support in completing the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Piraccini BM, Alessandrini A. Drug-related nail disease. Clin Dermatol 2013;31:618-26.
2. Singh G. Nails in systemic disease. Indian J Dermatol Venereol Leprol 2011;77:646-51.
3. Hackbarth M, Haas N, Fotopoulou C, Lichtenegger W, Sehouli J. Chemotherapy-induced dermatological toxicity: frequencies and impact on quality of life in women's cancers. Results of a prospective study. Support Care Cancer 2008;16:267-73.
4. Gilbar P, Hain A, Peereboom VM. Nail toxicity induced by cancer chemotherapy. J Oncol Pharm Pract 2009;15:143-55.
5. Witkowska AB, Jasterzbski TJ, Schwartz RA. Terry's nails: A sign of systemic disease. Indian J Dermatol 2017;62:309-11.
6. Tully AS, Trayes KP, Studdiford JS. Evaluation of nail abnormalities. Am Fam Physician 2012;85:779-87.
7. Singh G, Haneef NS, Uday A. Nail changes and disorders among the elderly. Indian J Dermatol Venereol Leprol 2005;71:386-92.
8. Huang TC, Chao TY. Mees lines and Beau lines after chemotherapy. CMAJ 2010;182:E149.
9. Available from: http://ctep.cancer.gov/protocoldevelopment/electronic_applicatons/doc/CTCAE_V5_Quick_Reference_8.5x11.pdf. [Last accessed on 2020 Jul 26].
10. Robert C, Sibaud V, Mateus C, Verschoore M, Charles C, Lanoy E,*"gv"cn0* Nail toxicities induced by systemic anticancer treatments. Lancet Oncol 2015;16:e181-9.
11. Lopes M, Jordão C, Grynszpan R, Sodré C, Ramos-E-Silva M. Chromonychia secondary to chemotherapy. Case Rep Dermatol 2013;5:163-7.
12. Saha A, Arora N, Mehra N, Dubey NK. Cyclophosphamide-induced nail hyperpigmentation in a child. Indian J Nephrol 2012;22:149.
13. Kumar S, Dixit R, Karmakar S, Paul S. Unusual nail pigmentation following cyclophosphamide-containing chemotherapy regimen. Indian J Pharmacol 2010;42:243-4.
14. Ranawaka RR. Patterns of chromonychia during chemotherapy in patients with skin type V and outcome after 1 year of follow-up. Clin Exp Dermatol 2009;34:e920-6.
15. Zawar V, Bondarde S, Pawar M, Sankalecha S. Nail changes due to chemotherapy: A prospective observational study of 129 patients. J Eur Acad Dermatol Venereol 2019;33:1398-404.
16. Chessa MA, Lorizzo M, Richert B, Estebaranz JL, Rigopoulos D, Tosti A, *gv"cn* Pathogenesis, clinical signs and treatment recommendations in brittle nails: A review. Dermatol Ther 2020;10:15-27.
17. Roh MR, Cho JY, Lew W. Docetaxel-induced onycholysis: The role of subungual hemorrhage and suppuration. Yonsei Med J 2007;48:124-6.
18. Nia AM, Ederer S, Dahlem KM, Gassanov N, Er F. Terry's nails: A window to systemic diseases. Am J Med 2011;124:602-4.
19. Avhad G, Ghuge P. Half and half nail. Indian Dermatol Online J 2014;5:S67.
20. Oppel T, Korting HC. Onychodystrophy and its management. Ger Med Sci 2003;1:Doc02.
21. Tosti A, Piraccini BM. Treatment of common nail disorders. Dermatol Clin 2000;18:339-48.
22. Rockwell PG. Acute and chronic paronychia. Am Fam Physician 2001;63:1113-6.
23. Piraccini BM, Iorizzo M, Starace M, Tosti A. Drug-induced nail diseases. Dermatol Clin 2006;24:387-91.
24. Minisini AM, Tosti A, Sobrero AF, Mansutti M, Piraccini BM, Sacco C,*" gv"cn0*Taxane-induced nail changes: Incidence, clinical presentation and outcome. Ann Oncol 2003;14:333-7.

Original Article

Omalizumab in Chronic Urticaria; Real-life Data of 6-year-Experience

Adem Özdemir, Aslı Bilgiç, Mehmet Ali Koyuncu, Ertan Yılmaz

Department of Dermatology and Venereology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

Abstract

Background: Chronic urticaria (CU) is defined as the persistence of urticarial lesions for more than 6 weeks. Omalizumab, a human monoclonal anti IgE antibody, has been used as a new therapeutic option in CU patients unresponsive to high-dose second-generation antihistamines. **Aims and Objectives:** This study is aimed to examine the clinical and demographic characteristics of CU patients treated with omalizumab in our clinic and to define parameters related to therapeutic response. **Materials and Methods:** Patients who were followed up with the diagnosis of CU between January 2014 and June 2020 were evaluated retrospectively. The data obtained from patients' electronic files were analyzed using SPSS23 program. **Results:** 167 patients (125 female, 42 male) were included. The mean age was 45.34 ± 14.76 years. The mean disease duration at the onset of omalizumab was found to be 47.41 ± 63.26 months. Complete response to treatment was observed in 45.9%, 48%, and 52% of patients at 3rd, 6th, and 12th months of omalizumab treatment, respectively. The baseline total IgE level was evaluated in 107 patients and a statistically significant correlation was observed between complete response to treatment at 3rd month and higher baseline total IgE levels ($P < 0.001$). **Conclusion:** Omalizumab provided a significant therapeutic response and the patients did not need any other treatment, while patients with high pretreatment IgE levels showed a better and earlier response. These results may guide clinicians in predicting patients' response to omalizumab.

Keywords: Chronic spontaneous urticaria, chronic urticaria, inducible urticaria, omalizumab, treatment

Introduction

Urticaria is a skin disease characterized by itchy, erythematous, oedematous papules and plaques that appear suddenly and disappear spontaneously within 24 h. Angioedema might accompany to urticaria in a significant number of patients. Chronic urticaria (CU) is defined as the persistence of these urticarial lesions for more than 6 weeks. If symptoms occur without any external stimulus, it is classified as chronic spontaneous urticaria (CSU); if it occurs because of stimuli such as cold, heat, pressure, classified as chronic inducible urticaria (CIndU). In 10%–50% of patients, CSU occurs in combination with CIndU.[1,2]

Symptoms in CSU often last between one to five years (might continue for more than 5 years in 11%–14% of patients).[3] Second-generation H1 antihistamines are recommended as the first step in the treatment of CU and used up to 4 times in case of unresponsiveness, but even if the dose is increased, approximately 50% of patients do not respond.[4] Other therapeutic options frequently used are H2 antihistamines, leukotriene receptor antagonists, while systemic glucocorticoids are often used during acute urticarial flares. Omalizumab, which is a human monoclonal anti-IgE antibody and acts by reducing the level of free IgE and inhibiting mast cell and basophil activation, has been used as a new therapeutic option especially in CU in the last decade.[4] Omalizumab is recommended as the first treatment option in patients with CU unresponsive to high-dose second-generation antihistamines. It is generally used as 300 mg administered every 4 weeks. However, its effect is thought to be dose-dependent, so treatment

Submission: 07-06-2021 **Revision:** 18-07-2021
Acceptance: 22-07-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_45_21

Address for correspondence: Dr. Adem Özdemir, Department of Dermatology and Venereology, Akdeniz University, Faculty of Medicine, Dumlupınar Boulevard, Konyaaltı, Antalya, Turkey.
E-mail: dr.ademozdemir90@gmail.com

How to cite this article: Özdemir A, Bilgiç A, Koyuncu MA, Yılmaz E. Omalizumab in chronic urticaria; real-life data of 6-year-experience. Turk J Dermatol 2021;15:66-73.

response may vary in patients with different doses, thus the dose might be tailored according to the response.[5] The efficacy and safety of omalizumab in CSU treatment have been proven.[4] Omalizumab is also reported to be effective in CIndU such as cholinergic urticaria, cold urticaria, solar urticaria, symptomatic demographics, and late pressure urticaria. In addition, it increases the quality of life by reducing the development of angioedema and relapse after discontinuation of treatment in CU patients.[1,6] Other therapeutic options in resistant CU are cyclosporine, methotrexate, dapsone, hydroxychloroquine, and sulfasalazine, but data on the use of these treatments in CU are limited and these treatments can cause significant side effects.[7]

Materials and Methods

Patients who were followed up with the diagnosis of resistant CU between January 2014 and June 2020 in our clinic were retrospectively evaluated through the electronic patient files. Inclusion criteria of our study were patients who used omalizumab for at least 3 months, patients whose sociodemographic and clinical characteristics could be found from electronic patients' files. Data of patients with CSU with accompanying CIndU were also included in the study. Demographic data of the patients such as age, gender, duration of CU, history of CIndU, other accompanying diseases (autoimmune diseases, thyroid diseases, pernicious anemia, etc.), food or drug allergy, family history of urticaria or other allergic diseases (allergic rhinitis/conjunctivitis, allergic asthma, food allergy, drug allergy, etc.) were also scanned through the hospital records. In addition, the presence of accompanying angioedema was examined from the files in detail. Total serum IgE level, *Helicobacter pylori* antibody, Vitamin D, Vitamin B12, and thyroid hormone levels were retrospectively examined. Omalizumab dose and frequency of treatment and the effectiveness of treatment at 3rd, 6th, and 12th months were evaluated. Regarding the evaluation of therapeutic response to omalizumab, patients were divided into five groups; complete response to treatment (if there was no symptom and did not require the use of antihistamines), insufficiently controlled complete response (if occasional antihistamine use was present), partial response (if regularly using antihistamines), insufficient control (if needed systemic corticosteroids and/or cyclosporine in addition to regular antihistamines) and no significant improvement of complaints were accepted as unresponsiveness. Ethics approval was obtained from the Faculty of Medicine Clinical Research Ethics Committee (number: 70904504/459).

Statistical analysis

Data was analyzed using the SPSS 23 program. Descriptive statistics such as frequency distribution, mean, and standard deviation were used to define the sample. In cases where parametric test assumptions were not provided, "Mann–Whitney U" and "Kruskal–Wallis" tests were used. A 95% significance level (or $\alpha = 0.05$ margin of error) was used to determine the differences in the analysis.

Results

167 (125 [74.8%] female and 42 [25.2%] male) patients who received omalizumab treatment and met the inclusion criteria were included in the study, with a mean age of 45.3 ± 14.76 (age range: 17–86) years. The mean disease duration was 81.13 ± 69.86 (time range: 9–336) months. Sixty (56.1%) of them had a history of angioedema along with urticaria. Out of 80 patients whose history of CIndU was reached from patient files, 26 (32.5%) had both CSU + CIndU, while 54 (67.5%) only had CSU. Food allergy was found in 12 (15.4%) of 78 patients and drug allergy was detected in 15 (20%) patients out of 75 patients whom data was reachable from electronic files. Thyroid disease was detected in 20 (16.9%) of 118 patients. The sociodemographic characteristics of the patients are summarized in Table 1.

A total number of 152 (99.7%) patients had used antihistamines before omalizumab treatment. Since one patient had myasthenia graves, antihistamines could not be administered and omalizumab was started when urticaria could not be controlled with systemic corticosteroids. Systemic corticosteroids were used in 45 (49.15%) of the patients, whereas cyclosporine was used in 26 (30.2%) of them. Disease duration at the onset of omalizumab therapy was 47.41 ± 63.26 (range 1–300) months (n = 124 patients). The mean duration of omalizumab therapy was 12.64 ± 8.68 (range: 2–47) months (n = 148 patients). Complete response was observed in 68 (45.9%), 60 (48%), and 36 (52%) patients, respectively, at the 3rd, 6th, and 12th months of omalizumab therapy, and the response rates of omalizumab are summarized in Table 2. Treatment was discontinued in 120 (77.4%) patients, but relapse was observed in 86 (84.3%) of them with a period of 4.64 ± 5.43 months. When omalizumab was restarted, a good response was obtained in 66 (94.2%) patients, while 4 (5.71%) did not respond to treatment. 97 (85.6%) of the patients in our study were under control with treatment and remission without treatment was detected in 26 (24.3%) patients. There were 62 (54.9%) patients who are on omalizumab therapy during our data collection period. Baseline total IgE level was measured in 107 patients and found to have a mean value of 280.58 ± 361.81 IU/ml (mininimum: 1 and maximum: 2000). Higher baseline total IgE levels were detected in 67 (56.3%) patients. A statistically significant correlation was observed between discontinuation of omalizumab at the 3rd month and higher baseline total IgE levels ($P < 0.001$).

Discussion

Omalizumab is a human monoclonal antibody developed against IgE, acting by binding to free IgE in serum

Table 1: Sociodemographic and clinical characteristics of patients

Parameters (number of patients with data in electronic patient files)	Results, *n* (%)
Sex (*n*=167) (female/male)	42 (25.2)/125 (74.8)
Age (*n*=167)	45.34±14.76 (range:17–86)
Duration of disease (months) (*n*=167)	81.13±69.86
CU (*n*=80)	
CSU	54 (67.5)
CSU + CIndU	26 (32.5)
Concomitant diseases	
Angioedema (*n*=167)	60 (56.1)
Food allergy (*n*=78)	12 (15.4)
Drug allergy (*n*=75)	15 (20.0)
Allergic rhinitis/conjunctivitis (*n*=85)	18 (21.2)
Allergic asthma (*n*=73)	15 (20.5)
Thyroid diseases (*n*=118)	20 (16.9)
Anemia (*n*=126)	28 (22.2)
Vitamin D deficiency (*n*=62)	49 (79.0)
Vitamin B12 deficiency (*n*=61)	13 (21.0)
Autoimmune diseases (*n*=67)	8 (11.9)
Connective tissue disorders (*n*=65)	3 (4.6)
Total IgE levels	
Elevated IgE levels (*n*=119)	67 (56.3)
Mean value (*n*=107)	280.58±361.81
Treatment	
Antihistamines (*n*=153)	152 (99.3)
Systemic steroids (*n*=91)	45 (49.5)
Cyclosporine (*n*=86)	20 (30.2)

CU: Chronic urticaria, CSU: Chronic spontaneous urticaria, CIndU: Chronic inducible urticaria

Table 2: Response rates of omalizumab treatment according to different time frames

Response to omalizumab (number of patients evaluated)*	3rd month (*n*=148), *n* (%)	6th month (*n*=125), *n* (%)	12thmonth (*n*=69), *n* (%)
Complete response	68 (45.9)	60 (48.0)	36 (52.2)
Insufficiently controlled complete response	49 (33.1)	43 (34.4)	24 (34.8)
Partial response	20 (13.5)	16 (12.8)	4 (5.8)
Insufficient control	9 (6.1)	6 (4.8)	3 (4.3)
Unresponsiveness	2 (1.4)	0	2 (2.8)

*Complete response:If there was no symptom and did not require the use of antihistamines, insufficiently controlled complete response: If occasional antihistamine use was present, partial response: If regularly using antihistamines, Insufficient control: If taking systemic corticosteroids in addition to regular antihistamines, Unresponsiveness: No significant improvement in complaints

and preventing it from binding to FcεRI on mast cells and basophils. It reduces both the free IgE level and the number of receptors and prevents mast cell activation.[8] The efficacy and safety of omalizumab in CU have been demonstrated in placebo-controlled studies, but real-life data are limited. Maurer *et al*. revealed that omalizumab reduced symptoms in patients with CSU resistant to H1 antihistamines in their placebo-controlled randomized phase-3 studies.[9] In another study, the effectiveness of omalizumab was evaluated retrospectively in patients with CSU and CIndU, and it was concluded that omalizumab acts fast with high efficacy and safety in both groups.[10] Our results also showed 32.5% of patients had both CSU + CIndU, while 54 (67.5%) only had CSU. This was similar to the study by Maurer *et al*. in which no identifiable trigger factors for the symptoms were present in a large proportion of affected subjects.[11] Furthermore, in our study, omalizumab had a good therapeutic effect in both patients with CSU + CIndUand with CSU only, and no significant difference was found in terms of age, sex, the duration of omalizumab therapy, and the duration of relapse time after omalizumab discontinuation. However, relapses after omalizumab cessation were significantly more common in patients with CSU + CIndU ($P = 0.021$) than in CSU only ($P = 0.009$) and complete remission without any therapy was significantly higher in patients with CSU only.

In a recent study by Chen *et al*., a total of 138 patients (87 with CSU alone, 33 with different forms of CIndU, and 18

Table 3: Literature data regarding IgE levels and therapeutic response to omalizumab

Studies/year	Number of patients	Mean IgE levels (parameter)	Response rate, *n* (%)	IgE level after therapy	Relapse rate	Is total IgE a good marker of response?
Marzano *et al*.[5]/2019	470	Responders: 131.6 (507) KUA/L	425 (90.4)	-	First relapse: 60.2%-Second relapse: 66.3%**	Yes
		Non responders:42.1 (299) KUA/L*	45 (9.6)			
Metz *et al*.[10]/2014	44	CR: 110 (7–1667) KUA/L***	CR: 35 (79.54)	-	-	No
		PR or NR: 111 (5–882) KUA/L	PR+ NR: 9 (20.45)			
Nettis *et al*.[14]/2018	322	231.4 ± 506.6 KUA/L	4th week: 188 (58.4)	-	40.8%	Yes
			12th week: 232 (73.4)			
			20th week: 255 (84.2)			
			40th week: 107 (61.8)			
Ertaş *et al*.[20]/2018****	113	CR: 73.7 (19.5–153.8) IU/ml	43 (38.1)	CR: 290.5 (121.5–637.5) IU/ml	-	Yes
		PR: 82.0 (46.2–126.5) IU/ml	55 (48.6)	PR: 298 (205.8–543.5) IU/ml		
		NR: 17.9 (17.0–55.0) IU/ml	15 (13.3)	NR: 17.9 (17.4–86.2) IU/ml		
Cugno *et al*.[21]/2018	25	CR: 148 ± 114 KUA/L	-	-	-	Yes
		PR: 115 ± 432 KUA/L				
		NR: 16 ± 24 KUA/L				
Salman *et al*.[22]/2019	72	Group 1: 205.4±368.4 (9-2284) IU/ml*****	-	-	-	Yes
		Group 2: 261.2 ± 459.1 (0-1446) IU/ml				
Straesser *et al*.[24]/2018	137	1st quartile: 0–15.2 IU/ml†	48.4%	-	-	Yes
		2nd quartile: 15.3–68.8 IU/ml	86.1%			
		3rd quartile: 68.9–168.0 IU/ml	88.2%			
		4th quartile: 168.1–4261 IU/ml	94.1%			
Deza *et al*.[25]/2017	47	Responders: 151 (66–311) KUA/L	38 (80.9)	-	-	Yes
		Non responders: 20 (5–59) KUA/L	9 (19.1)			
Weller *et al*.[26]/2018‡	85	CR: 204.0IU/ml, (113.8-437.5)	43 (50.5)	-	-	Yes
		PR: 56.7IU/ml, (9.9-242.0)	23 (27)			
		NR: 16.7IU/ml, (8.4-32.4)	19 (22.3)			
Asero *et al*.[27]/2019§	76	Responders:183.5 KUA/L(87-372)	62 (81.5)	-	-	Yes (in non-atopic patients)
		Non responders: 58.5 KUA/L(8-452)	14 (18.5)			
Çildağ *et al*.[28]/2018‖	41	152 (42–444) mg/dl	CR:17 (41.4)	386 (159–1282) mg/dl	-	No
			SI: 21 (51.2)			
			NSI: 3 (7.3)			

Table 3: Continued

Studies/year	Number of patients	Mean IgE levels (parameter)	Response rate, *n* (%)	IgE level after therapy	Relapse rate	Is total IgE a good marker of response?
Magen *et al*.[29]/2019	106	CR: 146 ± 94 IU/ml PR: 159 ± 72 IU/ml NR: 109 ± 85 IU/ml	CR: 63 (58.9) PR: 27 (27.2) NR: 16 (14.9)	-	-	No

*Non-responder: Defined as a <30% reduction of UAS7 or an exacerbation at week 12, **In this study authors described first (within 2 months after first 24 weeks omalizumab treatment course) and second relapse (within 3 months after second 20 weeks omalizumab treatment course), ***KUA/L: Kilo Units per litre, Measurement of serum IgE levels according to the manufacturer's instructions (ImmunoCAP; ThermoFisher, Uppsala, Sweden), ****Patients with IgE levels that exceeded the upper assessment limit (1100 IU/ml) were excluded from analyses (*n*=17), *****Patients divided into two groups according to omalizumab dose; Group 1 includes patients with omalizumab 300 mg/4w and group 2 includes patients with omalizumab 450 mg/4w, †Subdivided into quartiles according to IgE levels, ‡Complete response (CR), partial (PR) and non-response (NR) was defined as the reduction of signs and symptoms by ≥90%, by ≥30% but <90%, and by <30% (physicians' global assessment), respectively, after 2 four-weekly injections of omalizumab 300 mg, §Nonresponse to omalizumab was defined as the absence of any change (i.e., >20%) in UAS-7 values 3 months after the start of the treatment. A fast response to omalizumab was defined as the disappearance or a reduction >50% of the UAS-7 score within 4 weeks after the first administration. A response was defined as slow if it occurred within 1 and 3 months after the first administration of the drug,‖"Complete response" to omalizumab was defined as a reduction of 90% or more in the UAS-7, a "significant improvement" as a reduction in the UAS-7 of 90% – 30% and "no significant improvement" as less than 30% reduction in the UAS-7. CR: Complete responders, PR: Partial responders, NR: Nonresponders; SI: Significant improvement, NSI: Not any significant improvement. UAS-7: Urticaria Activity Score-7

with both) were retrospectively examined. The response to omalizumab therapy were 86.2% in CSU alone (*n* = 75), 90.9% in CIndU (*n* = 30) and 83.3% in CSU + CindU (*n* = 15) and the speed of onset of omalizumab effect was comparable among patients with CSU, CIndU or both. However, complete response (defined by Urticaria Control Test = 16 during the period of treatment with omalizumab, with/without H1-antihistamine therapy) rate in patients with CSU only (69.0%, *n* = 60/87) or CIndU only (72.7%, *n* = 24/33) were significantly higher (*P* = 0.009) than that of patients with both CSU + CIndU (33.3%, *n* = 6/18).[1] Moreover, Türk *et al*. showed that comorbidity of CindU was linked to longer disease duration and higher disease activity.[2] Thus, it is important to document triggering factors and inducible urticaria if it accompanies to CSU.

Our study demonstrated high response (including complete response, insufficiently controlled complete response, and partial response) rate of 92.5% at the 3rd month and 92.8% at the 12th month of omalizumab therapy. However, we could not evaluate response with urticarial control test (UCT) due to retrospective design and lack of data. A recent meta-analysis of real-world data including 45 studies reported an average complete response rate of 72.2% and an average partial response rate of 17.8% for CSU.[12]

In CU, grouping patients according to omalizumab therapeutic response and revealing clinical and laboratory parameters that will predict the response may facilitate better management of CU. In several studies, the indicators of good response to omalizumab therapy in CSU were reported as the absence of angioedema, negative histamine release test, advanced age, short disease duration, no history of systemic immunosuppressive therapy, higher levels of total IgE, a reduction of plasmatic D-dimer and serum IL-31 levels, higher expression of FceRI and the absence of serum stimulating activity of expression of CD203c on basophils.[13-16] On the other hand, a positive basophil histamine release assay (BHRA), a positive autologous serum skin test, and the presence of eosinopenia are shown to predict a slow or poor response.[15-17]

Delineation of different categories of responders to omalizumab as well as the investigation of both biological and clinical markers predictive of response to omalizumab could ameliorate the management of CSU patients.[5] Elevated IgE levels in patients with CU have been noted previously.[18] In a study, Kessel *et al*. showed that one-third of patients with CU had significantly elevated levels of total IgE compared with the control group. In addition, they found 93% of CU patients with elevated IgE had moderate to severe urticaria.[19]

In a prospective study, Ertaş *et al*. evaluated if response rates to treatment with omalizumab in patients with CSU are linked to their baseline IgE levels, their IgE levels after omalizumab treatment, and the ratio of on treatment IgE/baseline IgE levels [Table 3]. They found nonresponders to omalizumab had significantly lower baseline IgE levels than partial responders and complete responders. After 4 weeks of omalizumab treatment, non-responders have lower total IgE levels than responders. As a result, authors suggested IgE levels of CSU patients and their change can predict the outcome of omalizumab treatment.[20] Similarly, in other studies, initially high IgE level was associated with good treatment response as seen in our results.[5,21-23] Similar findings were reported by Straesser *et al*. (*n* = 137, CSU patients) retrospectively and they observed an association between the lack of serum IgE and a lower likelihood of omalizumab response. They also subdivided serum IgE levels into quartiles and response to omalizumab differed significantly according to quartiles. A low baseline serum IgE ≤15.2 IU/mL was shown to predict a lower likelihood of response to omalizumab.[24] In a retrospective study of 332 CSU patients, Nettis *et al*.

showed that higher pretreatment IgE levels (above 48 KUA/L) were significantly less likely to be associated with a Urticaria Activity Score-7day (UAS7) score > 6 (non-responders) at the end of the 24-week treatment period. They also reported that cyclosporine use, angioedema history, and duration of CSU were also associated with nonresponder group.[14]

Marzano *et al*. reported that baseline IgE correlated to a good response to omalizumab since levels were significantly higher in responders than nonresponders. Among responders, there was no significant difference in terms of clinical response categories, namely early complete responders (the disappearance of symptoms within 1 week from the start of omalizumab), late complete responders (disappearance of symptoms within 12 weeks from omalizumab starting), and late partial responders (defined as an at least 30% reduction of UAS7 as compared to baseline, evaluated at week 12).[5] Although a relationship was found between the length of the disease duration and the development of primary and secondary relapse in the same study, a similar relationship was not observed in our study. In their study, Marzano *et al*. found female gender associated with treatment unresponsiveness.[5] However, no relationship was found between gender and therapeutic response in our study.

In a prospective study, Deza *et al*. investigated immunological predictors of response to omalizumab therapy.[25] They reported responders (defined as an improvement in the patients' signs and symptoms achieving UAS7≤ 6 or ≥90% reduction in the UAS7 at 6 months of treatment) showed higher baseline total IgE levels in comparison with nonresponders but authors implied that there is not enough argument to believe in the assessment of total IgE as a good therapeutic predictor in CSU. This is due to the wide range (and therefore overlap) of IgE values observed in responders (16–683 kU/l) and nonresponders (1–100 kU/l).[25] Weller *et al*. showed notably elevated IgE levels in the majority (77. 5%) of CR, in 31.8% of PR and only in 20.0% of NR. They emphasized elevated total IgE levels were common in CR and only rarely detectable in NR to omalizumab. Normal and particularly low normal total IgE levels were prevalent in NR and only rarely detectable in CR. However, normal and low total IgE levels were found in all responder types as a result authors suggested total IgE levels cannot be used as a stand-alone predictor of response to omalizumab.[26]

In a small study population, Cugno *et al*. also found nonresponders have significantly lower baseline IgE levels than partial and complete responders.[21] Since the atopic status is often associated with elevated levels of total IgE, in an exploratory study by Asero *et al*., evaluated the role of atopic status in modifying the predictive value of total IgE levels. When total IgE was analyzed, omalizumab responders and nonresponders did not differ significantly regarding the baseline levels. However, if atopic patients were excluded from the analysis, omalizumab responders showed much higher total IgE levels than nonresponders.[27] Authors implied analyzing the atopic status of CSU patients is important because atopic status acts as a factor modifying the ability of total IgE levels in predicting the response to omalizumab. In the same study, within the responders' group, fast responders showed much higher mean total IgE levels than slow responders.[27] However, they suggested that one should be cautious to accept this laboratory parameter as a predictive factor of response because several CSU patients with high total IgE levels are also nonresponders to omalizumab.

Çildağ *et al*. could found no significant differences in baseline IgE levels between patients with a complete response and without ones.[28] Magen *et al*. reported higher levels of total IgE in patients with CSU with partial responders to omalizumab than nonresponders, but this was not statistically significant, maybe due to the small number of patients in their study.[29]

Similarly, two retrospective studies by Metz *et al*. and Viswanathan *et al*. did not show significant differences in serum IgE concentrations between omalizumab responders and nonresponders.[10,30] Hence, there are conflicting results about baseline IgE level and its predictive role in omalizumab treatment response in the literature [Table 3]. We observed a statistically significant correlation between discontinuation of omalizumab at the 3rd month and higher baseline total IgE levels ($P < 0.001$) and this result was compatible with previous literature.

In a prospective study, increased serum total IgE levels are linked to faster relapse of CSU after discontinuation of omalizumab.[23] However, we found no significant relationship between the relapse time after omalizumab discontinuation and the baseline IgE level. In our study, 84.3% of the patients had relapses in an average of 4.64 months with omalizumab discontinuation; however, when omalizumab restarted again, the treatment was effective in 94.2% of the patients. This result was consistent with other studies in the previous literature.[10,31]

Complete response rates for omalizumab treatment were 45.9% at 3rd month, 48% at 6th month, and 52.2% at 12th month in our study. The complete response rates in the 3rd month of our study were found to be higher than ASTERIA I (44%), ASTERIA II (35.8%), and GLACIAL (34%), which are randomized phase-3 studies involving groups using omalizumab with a dose of 300 mg/month.[9,32,33] Data on the long-term use of omalizumab in CU are limited, and in the randomized placebo-controlled XTEND-CIndU study, patients were followed for a 48-week treatment period and showed evidence for the benefits of regular use of omalizumab to prevent recurrence of symptoms and sustainable disease control. In addition, it was stated that real-life data on long-term use of

omalizumab are needed.[34] Har *et al*. evaluated 10 patients with persistent CU who had been using omalizumab for more than 1 year; they recommend that omalizumab is effective and safe in the use of more than 1 year and that the spontaneous remission status should be evaluated by discontinuing the treatment from time to time.[35] This may be related to omalizumab reducing FcεRI levels on mast cells and basophils in 12–16 weeks by acting on free IgE.[36] In the study of Kaplan *et al*., patients were divided into two groups according to omalizumab therapeutic response as early responders (those who respond in the first 4–6 weeks) and late responders (those who respond in 12–16 weeks). Terminating the treatment before the 12th week causes a group of patients who will respond to the treatment to miss this opportunity. In addition, a response may occur after 24 weeks in late responders and may be observed within the first week in early responders.[37] In a study that retrospectively evaluated the effectiveness of omalizumab in 110 patients, complete response or significant improvement was achieved at a rate of 80.8% and disease control was achieved in 60% without the need for any other medication. In this study, omalizumab was discontinued in 37.3% of the patients due to complete remission but relapse occurred in 47.5% of them and when omalizumab was restarted and a complete response was obtained again at a rate of 90%.[38] However, different therapeutic protocols were used and therapeutic responses by specific time points were not determined.[38] In our study, omalizumab was discontinued at a higher rate (n = 120, 77.4%) and relapse rate was also higher (86 [84.3%]). When omalizumab was restarted, a good response was obtained in 66 (94.2%) patients, while 4 (5.71%) did not respond to treatment. Therefore, it was observed that the effect did not decrease when omalizumab was restarted in our study.

In our study, accompanying thyroid disease was found in 20 patients (16.9%). This result was consistent with previous studies,[31,39,40] which reflects autoimmune characteristics of both diseases. The angioedema was detected in 60 (56.1%) patients. This was in line with the study of Maurer *et al*. in which 58.5% (394 of 673) of patients had CSU-associated angioedema.[11] Although Ghazanfar *et al*. observed that the absence of concomitant angioedema was associated with a good omalizumab response,[13] no relationship was found between therapeutic response and the presence of angioedema in our study. In addition, it has been reported that the 300 mg/monthly dose of omalizumab is effective in controlling angioedema.[9]

In our study, the duration of omalizumab use in patients with a history of triggering medication was found to be significantly shorter (24.12 months) than those without it (39.73 months) (P = 0.016). Various drugs can trigger the development of CU through nonallergic hypersensitivity.[4] Therefore, when a triggering drug is detected, its use should be discontinued. Furthermore, in our study, the time between discontinuation of omalizumab and relapse was shorter than those without a history of food allergy (17.5 months; 26.3 months, respectively), but this value was not statistically significant (P = 0.059). It is extremely rare for an IgE-mediated food allergy to cause CU. If the nutrient relationship is detected and eliminated, the symptoms regress within 24 h. No other study was found in the literature comparing the triggering drug with the duration of omalizumab use and the relationship between food allergy and relapse. Thus, this relationship needs to be further investigated. Following omalizumab discontinuation, patients usually relapse within a few months, while rapid remission occurs when omalizumab is started again. Higher baseline IgE levels have been associated with faster relapse following omalizumab discontinuation.[23] In addition, baseline UAS7 was significantly correlated with the risk of developing first relapse but not the second one.[5] As far as we know, there is no other marker that indicates when and which patient relapses after discontinuation of treatment.

Omalizumab was generally well tolerated in the study group, with tachycardia observed in only one patient. Our study was limited by its retrospective nature and being a small sample, which might limit the breadth of our analysis. In addition, data retrieval also represented a possible limitation in our study as in some cases we could not reach all the information from the medical chart.

Conclusion

Our study which is the real-life data of a tertiary center, omalizumab is a safe and effective therapeutic option in patients with CU who are unresponsive to antihistamines. Although there are some markers that will predict the treatment outcome, new studies are needed to reveal their validity. Furthermore, determining omalizumab response patterns may lead us to better understand the pathophysiology of the disease and to apply personalized treatments in future.

Financial support and sponsorship

Nil.

Conflicts of interest

There is no conflict of interest nor financial support or sponsorship.

References

1. Chen Y, Yu M, Huang X, Tu P, Shi P, Maurer M, *et al*. Omalizumab treatment and outcomes in Chinese patients with chronic spontaneous urticaria, chronic inducible urticaria, or both. World Allergy Organ J 2021;14:100501.
2. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgereit T, Maurer M. How to treat patients with chronic spontaneous urticaria with omalizumab: Questions and answers. J Allergy Clin Immunol Pract 2020;8:113-24.

3. Gaig P, Olona M, Muñoz Lejarazu D, Caballero MT, Domínguez FJ, Echechipia S, *et al*. Epidemiology of urticaria in Spain. J Investig Allergol Clin Immunol 2004;14:214-20.
4. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, *et al*. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
5. Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, *et al*. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: A study of 470 patients. J Eur Acad Dermatol Venereol 2019;33:918-24.
6. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, *et al*. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. J Allergy Clin Immunol 2018;141:638-49.
7. Maurer M, Church MK, Gonçalo M, Sussman G, Sánchez-Borges M. Management and treatment of chronic urticaria (CU). J Eur Acad Dermatol Venereol 2015;29 Suppl 3:16-32.
8. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fc epsilon RI expression and function. J Allergy Clin Immunol 2004;114:527-30.
9. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, *et al*. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368:924-35.
10. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis. J Dermatol Sci 2014;73:57-62.
11. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, *et al*. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy 2017;72:2005-16.
12. Tharp MD, Bernstein JA, Kavati A, Ortiz B, MacDonald K, Denhaerynck K, *et al*. Benefits and harms of omalizumab treatment in adolescent and adult patients with chronic idiopathic (spontaneous) urticaria: A meta-analysis of "real-world" evidence. JAMA Dermatol 2019;155:29-38.
13. Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: Evaluation of 154 patients. Br J Dermatol 2016;175:404-6.
14. Nettis E, Cegolon L, Di Leo E, Lodi Rizzini F, Detoraki A, Canonica GW, *et al*. Omalizumab in chronic spontaneous urticaria: Efficacy, safety, predictors of treatment outcome, and time to response. Ann Allergy Asthma Immunol 2018;121:474-8.
15. Sánchez-Borges M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, *et al*. The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations. World Allergy Organ J 2021;14:100546.
16. Sánchez-Borges M, González Díaz S, Ortega-Martell JA, Rojo MI, Ansotegui IJ. Current and potential biological drugs for the treatment of chronic urticaria. Immunol Allergy Clin NA 2020;40:609-23.
17. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, *et al*. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol 2017;139:1059-61.e1.
18. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, *et al*. Clinical and laboratory parameters in predicting chronic urticaria duration: A prospective study of 139 patients. Allergy 2004;59:869-73.
19. Kessel A, Helou W, Bamberger E, Sabo E, Nusem D, Panassof J, *et al*. Elevated serum total IgE – A potential marker for severe chronic urticaria. Int Arch Allergy Immunol 2010;153:288-93.
20. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy 2018;73:705-12.
21. Cugno M, Genovese G, Ferrucci S, Casazza G, Asero R, Marzano AV. IgE and D-dimer baseline levels are higher in responders than non-responders to omalizumab in chronic spontaneous urticaria. Br J Dermatol 2018;179:776-77.
22. Salman A, Comert E. The real-life effectiveness and safety of omalizumab updosing in patients with chronic spontaneous urticaria. J Cutan Med Surg 2019;23:496-500.
23. Ertas R, Ozyurt K, Ozlu E, Ulas Y, Avci A, Atasoy M, *et al*. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. J Allergy Clin Immunol 2017;140:1749-51.
24. Straesser MD, Oliver E, Palacios T, Kyin T, Patrie J, Borish L, *et al*. Serum IgE as an immunological marker to predict response to omalizumab treatment in symptomatic chronic urticaria. J Allergy Clin Immunol Pract 2018;6:1386-8.e1.
25. Deza G, Bertolín-Colilla M, Pujol RM, Curto-Barredo L, Soto D, García M, *et al*. Basophil FcεRI expression in chronic spontaneous urticaria: A potential immunological predictor of response to omalizumab therapy. Acta Derm Venereol 2017;97:698-704.
26. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, *et al*. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy 2018;73:2406-8.
27. Asero R, Ferrucci S, Casazza G, Marzano AV, Cugno M. Total IgE and atopic status in patients with severe chronic spontaneous urticaria unresponsive to omalizumab treatment. Allergy 2019;74:1561-3.
28. Çildağ S, Şentürk T. The effect of omalizumab treatment on IgE and other immunoglobulin levels in patients with chronic spontaneous urticaria and its association with treatment response. Postepy Dermatol Alergol 2018;35:516-9.
29. Magen E, Chikovani T, Waitman DA, Kahan NR. Factors related to omalizumab resistance in chronic spontaneous urticaria. Allergy Asthma Proc 2019;40:273-8.
30. Viswanathan RK, Moss MH, Mathur SK. Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. Allergy Asthma Proc 2013;34:446-52.
31. Türkmen M, Çoban M, Doğan S, Uygur F, Soylu-Hakkı İ. The efficacy of omalizumab therapy in chronic spontaneous urticaria: A retrospective analysis. Turkderm Turk Arch Dermatol Venereol 2019;53:65-7.
32. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, *et al*. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101-9.
33. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, BülbülBaskan E, Bradley MS, *et al*. Efficacy and safety of omalizumab in patients with chronic idiopathic/ spontaneous urticaria who remain symptomatic on H1 antihistamines: A randomized, placebo-controlledstudy. J Invest Dermatol 2015;135:67-75.
34. Maurer M, Kaplan A, Rosén K, Holden M, Iqbal A, Trzaskoma BL, *et al*. The XTEND-CIU study: Long-term use of omalizumab in chronic idiopathic urticaria. J Allergy Clin Immunol 2018;141:1138-9.e7.
35. Har D, Patel S, Khan DA. Outcomes of using omalizumab for more than 1 year in refractory chronic urticaria. Ann Allergy Asthma Immunol 2015;115:126-9.
36. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fce psilon RI expression and function. J Allergy Clin Immunol 2004;114:527-30.
37. Kaplan A, Ferrer M, Bernstein JA, Antonova E, Trzaskoma B, Raimundo K, *et al*. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J Allergy Clin Immunol 2016;137:474-81.
38. Labrador-Horrillo M, Valero A, Velasco M, Jáuregui I, Sastre J, Bartra J, *et al*. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: Analysis of 110 patients in real-life practice. Expert Opin Biol Ther 2013;13:1225-8.
39. Nazik H, Mülayim MK, Öztürk P. Omalizumab usage in chronic urticaria and atopic dermatitis: Data from South-East province of Turkey. Postepy Dermatol Alergol 2019;36:734-8.
40. Mandel VD, Guanti MB, Liberati S, Demonte A, Pellacani G, Pepe P. Omalizumab in chronic spontaneous urticaria refractory to conventional therapy: An Italian retrospective clinical analysis with suggestions for long-term maintenance strategies. Dermatol Ther (Heidelb) 2018;8:291-301.

Case Report

An Unusual Case of Biotinidase Deficiency with Fingertip Desquamation

Asburçe Olgaç, Sebile Kilavuz[1], Mustafa Kılıç, Rıza Köksal Özgül[2], Çiğdem Seher Kasapkara[3]

Department of Pediatric Metabolic Diseases, Ankara Dr. Sami Ulus Children's Hospital, Ankara, [1]Department of Pediatric Metabolic Diseases, Van Bölge Training and Research Hospital, Van, [2]Department of Pediatric Metabolic Diseases, Hacettepe University, Ankara, [3]Department of Pediatric Metabolic Diseases, Ankara Yıldırım Beyazıt University, MD, Ankara, Turkey

Abstract

Biotinidase deficiency (BD) is an autosomal recessively inherited inborn error of metabolism that causes multisystemic manifestations, including developmental delay, seizures, hypotonia, vision problems, hearing loss, ketolactic acidosis, and various cutaneous findings at the early stages of life. Treatment consists of oral biotin that is effective in the prevention of complications. We present a case of a 4-year-old boy with partial BD with fingertip desquamation that could be resolved by increasing biotin dosage.

Keywords: Biotin, biotinidase deficiency, desquamation

Introduction

Biotin is a water-soluble vitamin that is the coenzyme of several enzymes that play an essential role in carboxylation reactions. Biotinidase is responsible for the cleavage of biotin from biocytin and dietary sources. Biotinidase deficiency (BD) is an autosomal recessively inherited inborn error of metabolism (IEM) that causes multisystemic manifestations, including cutaneous findings.[1,2]

We present a case of a 4-year-old boy with partial BD deficiency with fingertip desquamation that could be resolved by high-dose oral biotin.

Case Report

A 4-year-old boy with known partial BD (biotinidase level: 1, normal level >4.2 nmol/ml/s) was admitted due to fingertip desquamation [Figure 1]. He was the first child of consanguineous parents (first-degree cousins). BD was diagnosed in the neonatal period by neonatal birth screening (NBS), and oral biotin 10 mg/day was initiated. He had no history of fever or infection, hair loss, or seizures. He denied contact with any chemicals or irritants. Desquamation was only limited to the fingertips of hand, not involving the palms and soles. Initial diagnosis of the desquamation was attributed to eczema, and discontinuation using liquid soap was suggested. Moreover, topical steroid was administered for 10 days. He was referred to the metabolism department for further evaluation, since the desquamation persisted despite treatment. Upon admission, he was in good condition. His height and weight were within normal centiles. He did not have any other cutaneous finding apart from desquamation of fingertips. Laboratory analyses revealed normal complete blood count, antistreptolysin O antibody titer, ferritin, plasma zinc level, and vitamins A and E. Incompliance to biotin treatment was denied by parents.

Genetic analysis of BTD gene performed in our center revealed a compound heterozygous mutation (c.98–104del7ins3 and c.1330G>C, p.D444H).

Since the finger desquamation persisted, biotin dosage was increased to 20 mg/day. Interestingly, the desquamations reappeared when the patient could not get biotin for a couple of days since he was out of supply, also involving

Submission: 04-05-2021 **Revision:** 08-06-2021
Acceptance: 09-06-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_34_21

Address for correspondence: Dr. Asburçe Olgac, Division of Metabolism, Pediatric Metabolic Unit, Dr. Sami Ulus Children's Hospital, Ankara, Turkey.
E-mail: mabolgac@yahoo.com

How to cite this article: Olgac A, Kilavuz S, Kılıç M, Özgül RK, Kasapkara ÇS. An unusual case of biotinidase deficiency with fingertip desquamation. Turk J Dermatol 2021;15:74-6.

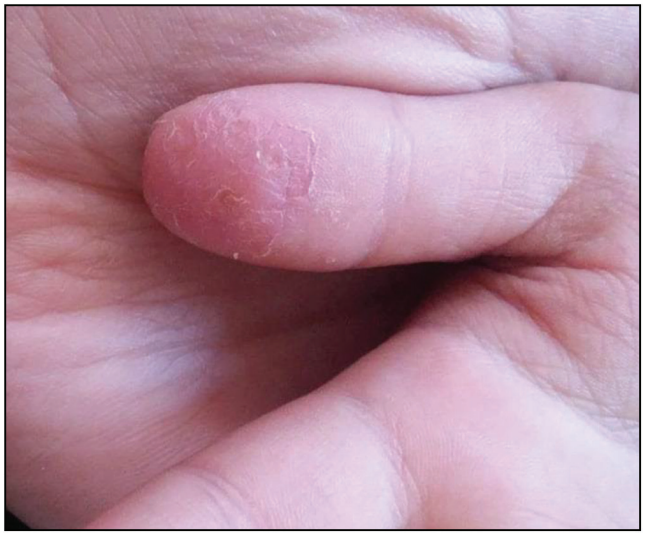


Figure 1: Fingertip desquamation of the presented case

the palms [Figure 2], and again resolved after restarting of therapy.

Discussion

BD is an autosomal recessively inherited disorder with variable symptoms, especially with neurological and dermatological involvement.[1] Biotin is a cofactor of many carboxylases including pyruvate carboxylase, propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase. Due to the deficient activity of these enzymes, the processing of proteins, fats, and carbohydrates is altered in BD that affects the energy metabolism and leads to multisystemic symptoms.[2]

The incidence is suggested to be 1 in 60,000 and may be higher in countries where consanguineous marriages are prevalent, as in Turkey.[2] In many countries, patients are diagnosed at the newborn period by NBS.[3]

The responsible gene for the disease is BTD that is located on chromosome 3p25. Three hundred and sixty-four different variants have been reported up-to-date. Genotype–phenotype correlation is difficult due to the variability of symptoms.[4]

BD is categorized as profound or partial, according to the residual enzyme activity (<10% in profound deficiency, between 10% and 30% in partial deficiency). Although patients with profound BD usually have a mild clinic, severe symptoms have been reported if untreated.[5] Profound BTD deficiency occurs due to the homozygous or compound heterozygous mutations.[4] The underlying mutations are the determinants of the enzyme activity and thus the severity of symptoms.[2] Canda *et al*.[6] have reported the largest cohort of BD from Turkey in 2012, where p.D444H, p.R157H, and c.98_104delinsTCC were the most commonly detected variants. Our patient is found to be compound heterozygous for the two most commonly reported mutations in Turkey.

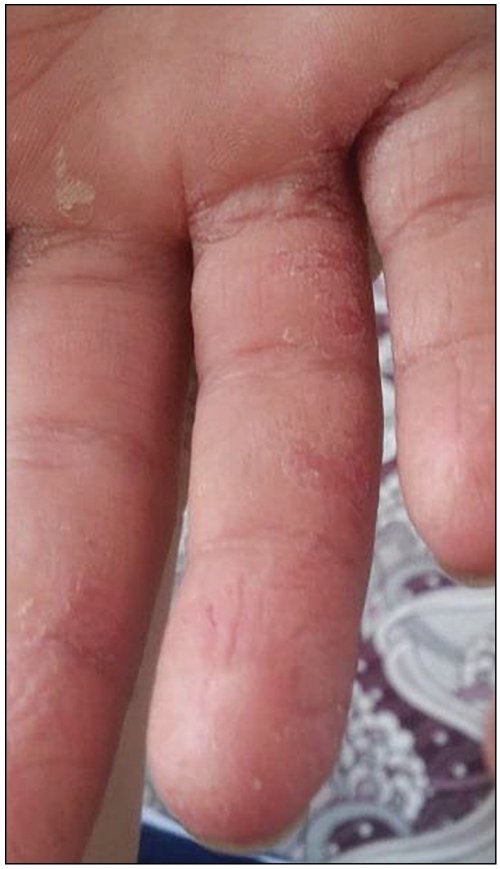


Figure 2: Finger desquamation during noncompliance to treatment

Cutaneous signs related to BD include rash, eczema, alopecia, scaly erythematous plaques over the flexors and perioral areas, and seborrheic dermatitis-like eruptions.[7] Lichenification, crusting, and secondary *Candida* infections may be seen in severe cases. Thin hair, total or partial alopecia have also been reported.[8] The skin changes of BD are suggested to be related to abnormalities in lipid metabolism, since the accumulating propionyl-CoA metabolites due to PCC deficiency may cause an increase in odd-chain fatty acids. Supplementation of biotinidase-deficient mice with omega-6-polyunsaturated fatty acid has been shown to prevent dermatological manifestations of BD.[2]

Diagnosis is usually made by the determination of biotinidase activity in plasma or serum by colorimetric assay method.[2] The exact diagnosis is made by the molecular genetic analysis of BTD.[1-3]

Standard treatment of profound BD is 10–20 mg/day oral biotin therapy that is usually sufficient for the prevention of irreversible neurological symptoms including optic atrophy, hearing loss, or cognitive disability.[5] Treatment may improve or resolve mild symptoms that may reoccur due to noncompliance with biotin treatment.

Many metabolic disorders present with cutaneous findings.[9] Well-known IEMs that lead to skin findings are summarized in Table 1. Periorificial desquamation involving moist areas is most commonly defined in IEMs involving pathways

Table 1: Inborn errors of metabolism that cause skin eruptions

Disease name	Type of skin lesion	Additional clinical findings
Biotinidase deficiency	Desquamative, periorificial eruptions	Massive ketosis and acidosis, stridor, convulsions, hypotonicity, mental retardation, optic atrophy, and sensorineural deafness
Holocarboxylase synthetase deficiency	Desquamative, periorificial eruptions	Similar to biotinidase deficiency, more severe
3-MCC deficiency	Similar to biotin deficiency	
Methylmalonic aciduria/ propionic aciduria	Desquamative, periorificial eruptions, psoriasiform lesions, and alopecia (skin lesions are mainly due to natural protein restriction)	
Mevalonic aciduria/hyper-IgD syndrome	Morbilliform rashes and erythematous macules	Dysmorphic features, global developmental delay, cataract, arthralgias with periarticular edema, recurrent febrile crises with lymphadenopathy, hepatosplenomegaly, vomiting, and diarrhea
Homocystinuria	Skin ulceration due to thromboembolic disease	
Acrodermatitis enteropathica	Bullous, pustular dermatitis on extremities and periorificial areas	Diarrhea and zinc deficiency
Sulfite oxidase deficiency	Eczema	
Prolidase deficiency	Lower extremity ulcers	Mental retardation, ophthalmoplegia, splenomegaly, dysmorphic features, and susceptibility to infections. Severe immunological abnormalities
Lysinuric protein intolerance	Lupus-like lesions	Hyperammonemia, failure to thrive, severe renal involvement, and pulmonary involvement
Tyrosinemia type II	Hyperkeratotic lesions of palms and soles	Corneal ulcers

3-MCC: 3-Methylcrotonyl-CoA carboxylase

related to biotin metabolism.[7] Any relationship between fingertip desquamation and BD has not previously been reported in the literature, and reports of atypical cases are limited. For example, Navarro *et al*. have reported an infant with erythematous scaling in the lumbosacral region.

Fingertip desquamation is a frequently encountered condition in childhood that is usually benign. Various diseases may cause desquamation of fingertips including eczema, exfoliative keratolysis, allergic contact dermatitis, and psoriasis. Periungual desquamation is also a hallmark of Kawasaki disease. Congenital syphilis and bacterial toxin-mediated disorders are also known to cause desquamation of hands and feet.[10]

In the presented case, although scaling of the fingertips may not be directly related to BD, the refractive nature of the lesions may be due to the disease since topical treatment did not have any effect. Furthermore, they may be an atypical presentation of BD. Nevertheless, increasing the dosage of biotin has resolved the lesions.

Conclusion

Cutaneous findings of a patient with known metabolic disorder may suggest inadequate treatment or poor metabolic control.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Wolf B. Clinical issues and frequent questions about biotinidase deficiency. Mol Genet Metab 2010;100:6-13.
2. Canda E, Kalkan Uçar S, Çoker M. Biotinidase deficiency: Prevalence, impact and management strategies. Pediatric Health Med Ther 2020;11:127-33.
3. Wolf B. Biotinidase deficiency: If you have to have an inherited metabolic disease, this is the one to have. Genet Med 2012;14:565-75.
4. Hymes J, Stanley CM, Wolf B. Mutations in BTD causing biotinidase deficiency. Hum Mutat 2001;18:375-81.
5. Wolf B. Why screen newborns for profound and partial biotinidase deficiency? Mol Genet Metab 2015;114:382-7.
6. Canda E, Yazici H, Er E, Kose M, Basol G, Onay H, *et al*. Single center experience of biotinidase deficiency: 259 patients and six novel mutations. J Pediatr Endocrinol Metab 2018;31:917-26.
7. Mock DM. Skin manifestations of biotin deficiency. Semin Dermatol 1991;10:296-302.
8. Navarro PC, Guerra A, Alvarez JG, Ortiz FJ. Cutaneous and neurologic manifestations of biotinidase deficiency. Int J Dermatol 2000;39:363-5.
9. García-Cazorla A, Wolf NI, Mochel F, Hoffmann GF. Neurological disease. In: Hoffman GF, Zschocke J, Nyhan WL, editors. Inherited Metabolic Diseases: A Clinical Approach. Berlin Heidelberg: Springer; 2017. p. 251-92.
10. Mancini AJ, Krowchuk DP. Pediatric Dermatology: A Quick Diagnosis Deck. 2nd ed. Itaska, IL: American Academy of Pediatrics; 2020.

Case Report

Polyneuropathy as Paraneoplastic Syndrome in a Patient with Metastatic Diffuse Large B-Cell Lymphoma

Ecem Bostan, Adam Jarbou, Neslihan Akdogan, Aysegul Uner[1], Altan Kavuncuoglu[1]

Departments of Dermatology and Venereology, [1]Pathology, Hacettepe University, School of Medicine, Ankara, Turkey

Abstract

Paraneoplastic syndromes are multisystemic diseases that are seen in association with solid organ tumors and lymphomas. Immune-mediated polyneuropathy, encephalopathy, cerebellar degeneration, and Guillain–Barre syndrome have all been described as paraneoplastic neurologic disorders. Clinical symptoms may appear before the diagnosis of associated malignancy creating diagnostic confusion. Tumor-derived peptides, hormones, and mediators are shown to be associated with paraneoplastic syndromes. Herein, we present an unusual case of stage 4 diffuse large B-cell lymphoma with cutaneous metastatic nodules presenting initially as paraneoplastic polyneuropathy.

Keywords: B-cell lymphoma, paraneoplastic, polyneuropathy

Introduction

Paraneoplastic syndromes are defined as a group of systemic disorders that most commonly develop in association with solid organ tumors and lymphomas.[1] Tumor-related hormones, peptides, mediators as well as immune cross-reaction between normal and tumoral tissues are held responsible for paraneoplastic syndromes.[1,2] Manifestations of systemic involvement may develop during the course of paraneoplastic syndromes.[3] Diffuse large B-cell lymphomas (DLBCL) are known to be associated with paraneoplastic neurologic disorders (PNDs).[4] We present an extraordinary case of stage 4 DLBCL with skin metastases presenting initially as sensory and motor polyneuropathy.

Case Report

A 63-year-old man with a history of hyperlipidemia, benign prostate hyperplasia, and hypertension was referred to us due to enlarging erythematous nodules involving the chest. The patient had pain and numbness sensation radiating from bilateral first, second, third, and fifth fingers to elbows and hypoesthesia between first and second toes 20 days before. Electromyography (EMG) findings results showed prolonged distal motor latencies of bilateral median and right tibial nerve; decreased motor conduction velocities of the right median, tibial and left ulnar nerves; and motor conduction blocks of bilateral median and left ulnar nerve. With EMG findings, he was diagnosed with demyelinating polyneuropathy accompanied by secondary axonal degeneration in both sensory and motor fibers. A provisional diagnosis of multifocal acquired demyelinating sensory and motor polyneuropathy was considered. Diffusion magnetic resonance imaging (MRI) of the brain showed T2 hypointensities, prominent diffusion restriction, and increased signal contrast involving the left parietooccipital, bilateral frontal scalp extending to bilateral temporal subcutaneous tissue [Figure 1B]. However, no pathological enhancement was noted. Cervical MRI showed pathological linear enhancement in the posterior roots of the right T1 nerve, bilateral C7, and C8 nerves; T2 hypointense enhancing soft-tissue lesion was apparent in the right maxillary area. MRI findings

Submission: 17-05-2021 **Revision:** 08-06-2021
Acceptance: 08-06-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_38_21

Address for correspondence: Dr. Ecem Bostan, Department of Dermatology and Venereology, Hacettepe University, Faculty of Medicine, Ankara, Turkey.
E-mail: bostanecem@gmail.com

How to cite this article: Bostan E, Jarbou A, Akdogan N, Uner A, Kavuncuoglu A. Polyneuropathy as paraneoplastic syndrome in a patient with metastatic diffuse large B-cell lymphoma. Turk J Dermatol 2021;15:77-9.

were compatible with primarily lymphomal involvement. Cerebrospinal fluid analysis showed an increased number of lymphomononuclear cells. The patient reported to have no B symptoms; full blood count and biochemistry were normal. Autoimmune markers and viral markers were all negative. Beta-2 microglobulin and lactate dehydrogenase levels were normal. Seven days after his hospitalization, he developed non-tender violaceus-erythematous nodules involving the anterior chest and right zygomatic area [Figure 1]. He denied any prior history of similar cutaneous nodules. A 4-mm-punch biopsy was performed from the right subcostal area which showed blastic, medium-sized lymphoid aggregates demonstrating diffuse infiltration pattern [Figure 2]. Mitotic activity was high and neoplastic cells were diffusely and strongly positive with CD20 and BCL-2 (B-cell lymphoma 2); BCL-6 (B-cell lymphoma 6) and MUM-1 (multiple-myeloma 1) were found positive in more than 30% of the neoplastic cells [Figure 2]. Ki-67 proliferation index was 70%–80%. EBER (Epstein–Barr virus-encoded small ribonucleic acids) *in situ* hybridization was negative. FISH (fluorescent *in situ* hybridization) analysis revealed MYC (myelocytomatosis) gene translocation but no aberrations in *BCL-2* and *BCL-6* genes [Figure 2]. Bone marrow aspiration biopsy was normal. Thoracoabdominal computed tomography (CT) showed aortocaval and conglomerated right hilar lymph nodes. Radiologic imaging studies suggested the diagnosis of lymphoproliferative disorder. The patient was diagnosed with stage 4 DLBCL, as the presence of pathologic lymph nodes involving thoracoabdominal region was

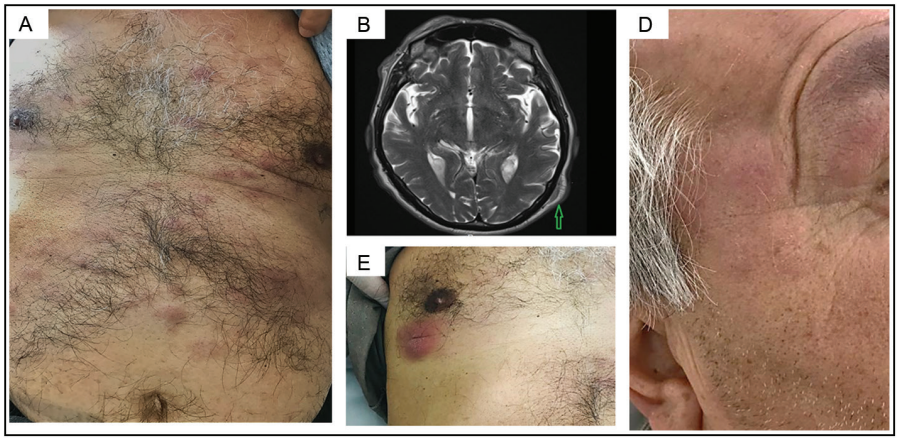


Figure 1: Dermatologic examination revealing widespread erythematous nodules involving the anterior chest (A), most prominent on the right inframammarian area (C) and the right face (D). T2-weighted magnetic resonance imaging showed iso-hyperintense lesions in the left temporoparietal area (arrow, B)

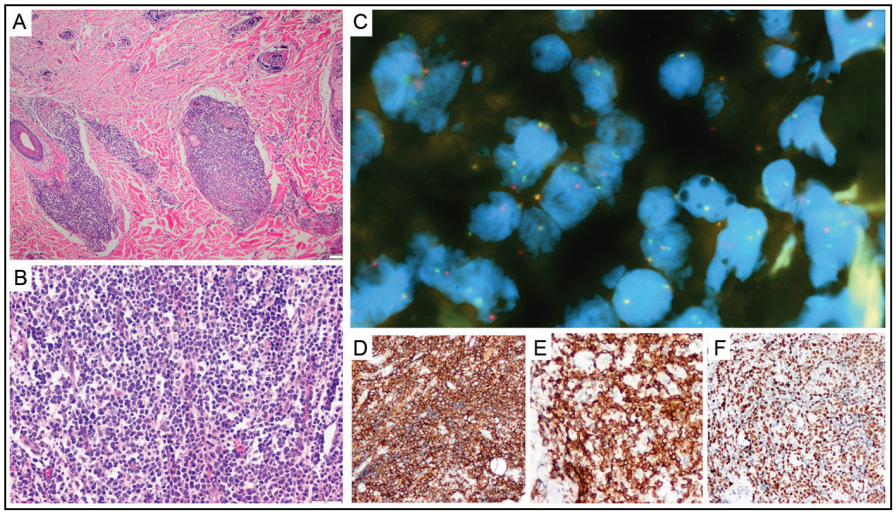


Figure 2: On low-power lymphoid neoplasm centered around skin adnexae in dermis with concomitant subcutaneous fat involvement was seen (A) (HandE, 40X). Neoplastic population was composed of medium-sized atypical lymphoid cells with blastic chromatin, irregular nuclear contours and small nucleoli (B) (HandE, 200X). Immunohistochemically these cells were diffusely and strongly positive with CD20 (D, 400X), Bcl-2 (E, 400X). Ki-67 proliferation index was relatively (%80) high (F, 400X). Findings supported a high-grade B cell lymphoma, for further subclassification FISH was performed. On FISH examination neoplastic cells showed a pattern consistent with MYC gene translocation (C, 1000X). Together with the immunophenotypic and morphological findings the patient was finally diagnosed as *MYC-positive diffuse large B cell lymphoma*

supported by CT and disseminated erythematous nodules were accepted as cutaneous metastases given that they appeared simultaneously 7 days ago. He was started on rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy regimen and a total dose of 30 mg intravenous immunoglobulin was administered over 5 days which resulted in diminution of neurologic symptoms.

Discussion

PNDs developing in association with solid organ malignancies or lymphoid malignancies may present themselves in a wide spectrum of syndromes.[5] Frequently reported neurological syndromes are encephalomyelitis, cerebellar degeneration, autonomic neuropathies, subacute sensory neuronopathies, and optic neuritis.[5] PNDs are shown to be associated with antineuronal autoantibodies such as anti-Hu, anti-Ri, anti-Ma, and anti-mGluR1 produced in the setting of underlying neoplasm.[6] Primary cutaneous B-cell lymphomas and systemic lymphomas presenting with cutaneous metastases are reported to be associated with various PNDs.[7] Ho *et al*.[7] reported a rare case of mononeuritis multiplex observed in a patient diagnosed with primary cutaneous large B-cell lymphoma of the leg and breast. In addition, Jiang *et al*.[8] described another case of DLBCL which presented as a painful lump on the cheek and was associated with sensorimotor demyelinating polyneuropathy, which is very similar to our case. These cases show that primary cutaneous lymphomas or skin involvement of the systemic lymphomas may also present with neurologic symptoms before the diagnosis. In conclusion, we present an extraordinary case of stage 4 DLBCL with widespread metastases to skin, developing demyelinating sensory and motor polyneuropathy involving upper, lower limbs. Before the appearance of metastatic skin lesions, the relationship between DLBCL and neurologic symptoms was not able to be established. Therefore, skin biopsy was the fundamental diagnostic approach for the underlying lymphoid neoplasm. An associated malignancy should always be considered in patients presenting with progressive sensory or motor polyneuropathy of unknown origin. Full-body dermatologic examination should always be completed to detect any visible cutaneous metastases which could provide physicians a hint for the right diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Pelosof LC, Gerber DE. Paraneoplastic syndromes: An approach to diagnosis and treatment. Mayo Clin Proc 2010;85:838-54.
2. de Beukelaar JW, Sillevis Smitt PA. Managing paraneoplastic neurological disorders. Oncologist 2006;11:292-305.
3. Ma GM, Chow JS, Taylor GA. Review of paraneoplastic syndromes in children. Pediatr Radiol 2019;49:534-50.
4. Nevison S, Rizek P. Anti-CV2-associated paraneoplastic hemichorea secondary to diffuse large B-cell lymphoma. Can J Neurol Sci 2019;46:480-1.
5. Rosenfeld MR, Dalmau J. Update on paraneoplastic neurologic disorders. Oncologist 2010;15:603-17.
6. Graus F, Dalmau J. Paraneoplastic neurological syndromes. Curr Opin Neurol 2012;25:795-801.
7. Ho SL, Tang BY, Chai J, Tan SH. Cutaneous large B-cell lymphoma of the leg: Presenting initially as mononeuritis multiplex. Singapore Med J 2009;50:e158-60.
8. Jiang Z, Ju W, Luo S, Yang Y. Diffuse large B-cell lymphoma involving peripheral nervous system with IgM antibodies against GM1 and GD1B: A case report. Medicine (Baltimore) 2019;98:e15049.

Segmental Leiomyoma: A Report of Two Cases

Introduction

Leiomyomas are a rare form of benign smooth muscle tumors. The most common site of occurrence is the uterus (95%), followed by the skin. Cutaneous leiomyoma accounts for 75% of the extrauterine leiomyomas.[1] The pathogenesis of cutaneous leiomyoma is unknown. Based on their site of origin, they are classified as piloleiomyoma, angioleiomyoma, and genital leiomyoma.[2] Piloleiomyoma is the most common variant arising from the arrector pili muscle.[3] Segmental leiomyomas represent the mosaic manifestation of cutaneous leiomyomas.[2] We present two cases of Type 1 segmental leiomyoma, which are rare and unique.

Case Report 1

A 27-year-old man presented with a history of multiple intermittently painful skin-colored raised lesions limited to the right side of the back region for 3 years. The patient experienced increased pain whenever lesions came in contact with cold water. Cutaneous examination revealed multiple, firm, tender, skin-colored to pale red papules and nodules. The lesions are grouped over the right side of the posterior trunk in a segmental distribution [Figure 1a]. Incisional skin biopsy revealed a well-circumscribed lesion composed of spindle cells arranged in a whorled pattern in the deep dermis [Figure 2a]. Masson trichrome stained the smooth muscle bundles in the dermis as red color [Figure 2b]. He was started on oral nifedipine and advised regular follow-up.

Case Report 2

A 26-year-old man presented with painful raised lesions over his left upper arm since 1 year. He experienced an increased intensity of pain upon friction. Cutaneous examination showed three well-defined, firm, tender, skin-colored to erythematous nodules of varying sizes. These nodules were present over the antero-medial aspect of the upper left arm [Figure 1b]. Based on the distinct clinical and pathological findings, he was diagnosed to have segmental leiomyoma and the lesions were excised.

Discussion

Piloleiomyomas commonly manifest between the first and third decades of life with no gender predilection.[4] It clinically presents as skin-colored to red-brown dermal papules or nodules, mainly distributed over the proximal extremities, followed by trunk, face, and neck.[3] The pain in leiomyoma may either be spontaneous or induced, secondary to cold, pressure, emotional stress, and friction.[3] The pain may be of burning, stabbing, or pinching in nature which could be attributed to pressure of the tumor on the underlying nerves or smooth muscle fiber contraction and infiltration of mast cells. Pain is more commonly observed in diffuse and segmental pattern.[5]

Piloleiomyomas can either be solitary or multiple. Multiple leiomyomas are more common and are termed as leiomyomatosis. When the leiomyoma lesions are more than 5000, it is known as myomatosis cutis miliaris.[6] Usually, multiple piloleiomyomas are commonly observed between 10 and 30 years of age, whereas solitary piloleiomyomas are seen with advancing age.[1] Multiple piloleimyomas are transmitted in an autosomal dominant fashion, which may be associated with uterine leiomyomas (Reed's syndrome/MCUL—multiple cutaneous and uterine leiomyomatosis) and hereditary leiomyomatosis and renal cell carcinoma (HLRCC). A predisposing factor to MCUL and HLRCC is the gene encoding fumarate hydratase mutation on chromosome 1q42.3–43.[7] Multiple lesions in the leiomyoma may present in different patterns, such as disseminated/diffuse, blaschkoid, and segmental/zosteriform.[1,6] The other reported forms are grouped, linear, and symmetrical pattern.[8]

Segmental leiomyomas are of two types: (i) Type 1 and (ii) Type 2. Both are inherited as autosomal dominant pattern of inheritance.[2] The salient features of the two types have been summarized in Table 1.[6] Cutaneous leiomyomas have to be differentiated from other painful cutaneous tumors such as the dermatofibroma, angiolipoma, eccrine spiradenoma, schwannoma, and neuromas.[6] Other painful conditions in segmental distribution are given in Table 2.[9-14]

The piloleiomyoma is histopathologically characterized by poorly demarcated interlacing bundles of smooth muscle cells with varying amounts of intermingling collagen fibers in a low-power field. The muscle fibers are usually straight, with centrally located long, thin, "eel-like nuclei."[8] The histopathological differential diagnosis includes other spindle tumors such as dermatofibroma, leiomyosarcoma, neurofibroma, and schwannoma.[8] Masson trichome stain and immunohistochemistry are helpful in differentiating piloleiomyomas from other spindle cell tumors.[1,8]

The treatment aspects for leiomyomas are not satisfactory. Avoiding trauma and exposure to cold can prevent the pain in leiomyoma.[3] Surgical excision can be done when

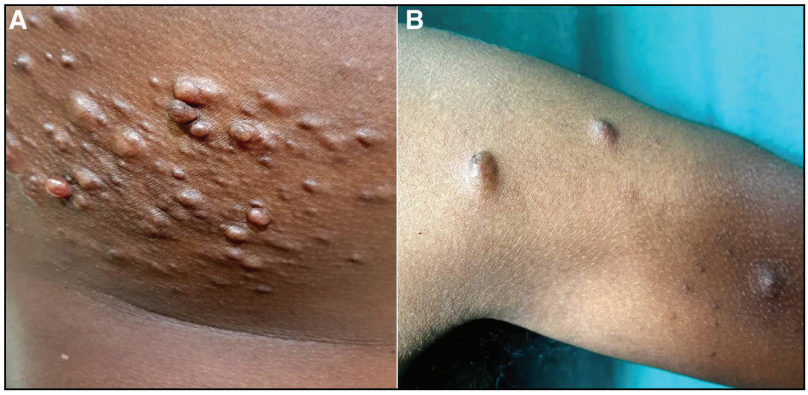


Figure 1: (a, b) Multiple skin-colored to red-colored papules and nodules in a segmental distribution

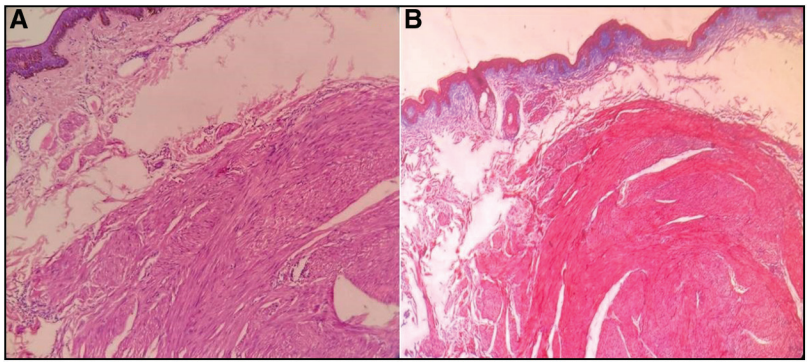


Figure 2: (a) HPE 10×—A circumscribed tumor with fascicles of smooth muscle bundles. (b) Masson trichrome stain (4×)—Red color highlights the smooth muscle bundles in the dermis

Table 1: Difference between Type 1 and Type 2 segmental leiomyomas

Type 1 segmental leiomyomas	Type 2 segmental leiomyomas
Due to the heterozygosity of the postzygotic mutation	Loss of heterozygosity causes homo/hemizygosity of the underlying mutation
Clinical features resemble non-mosaic phenotype	Causes pronounced segmental lesion superimposed on non-segmental phenotype
More common	Less common
Less severe	More severe

lesions are few; however, recurrence is common.[4] In case of multiple lesions, where excision is not possible, liquid nitrogen cryotherapy, electrocoagulation, and CO_2 laser ablation can be considered. Drugs such as nifedipine, doxazosin, gabapentin, antidepressants, and topical 9% hyoscine hydrobromide are helpful in relieving the pain.[5] Recently, botulinum toxin has been used for pain management.[15]

To conclude, leiomyoma cutis Type I is a rare but painful tumor that can affect the quality of life. The cornerstone of management is planning the treatment appropriate to the patient.

Acknowledgments

Nil.

Table 2: Segmental painful cutaneous tumor

- Eccrine spiradenoma
- Blue rubber bleb nevus
- Dermatofibroma
- Eccrine angiomatous hamartoma
- Glomangioma
- Schwannoma

Author Contribution

Arumugam Iswarya has contributed to the content, literature search, manuscript preparation, and submitted the article.

Palaniappan Vijayasankar has contributed to the design and literature search of the article.

Kaliaperumal Karthikeyan has planned the concept, manuscript preparation, manuscript editing, manuscript review, and is the guarantor of this article.

Vijayaraghavan Sriram has contributed to the histopathology part.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will

not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Arumugam Iswarya[1], Palaniappan Vijayasankar[1], Kaliaperumal Karthikeyan[1], Vijayaraghavan Sriram[2]

[1]Departments of Dermatology, Venereology, and Leprosy, [2]Pathology, Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India

Address for correspondence: Dr. Kaliaperumal Karthikeyan, Department of Dermatology, Venereology, and Leprosy, Sri Manakula Vinayagar Medical College and Hospital, Puducherry 605107, India.
E-mail: karthikderm@gmail.com

References

1. Malhotra P, Walia H, Singh A, Ramesh V. Leiomyoma cutis: A clinicopathological series of 37 cases. Indian J Dermatol 2010;55:337-41.
2. Tsoitis G, Kanitakis J, Papadimitriou C, Hatzibougias Y, Asvesti K, Happle R. Cutaneous leiomyomatosis with type 2 segmental involvement. J Dermatol 2001;28:251-5.
3. Albuquerque MM, Rocha CF, Costa IS, Maia Rda R, Branco FJ, Gonçalves Hde S. Piloleiomyoma with segmental distribution—Case report. An Bras Dermatol 2015;90:178-80.
4. Kura MM, Parsewar S. Skindia quiz 19: Soft tumors in segmental fashion. Indian Dermatol Online J 2015;6:302-3.
5. Vasani RJ. Unilateral segmental type II leiomyomatosis: A rare occurrence. Indian J Dermatol Venereol Leprol 2012;78:521.
6. Lang K, Reifenberger J, Ruzicka T, Megahed M. Type 1 segmental cutaneous leiomyomatosis. Clin Exp Dermatol 2002;27:649-50.
7. Choudhary S, McLeod M, Torchia D, Romanelli P. Multiple cutaneous and uterine leiomyomatosis syndrome: A review. J Clin Aesthet Dermatol 2013;6:16-21.
8. Suwattee P, Dakin C. Bilateral segmental leiomyomas: A case report and review of the literature. Cutis 2008;82:33-6.
9. Englander L, Emer BJ, McClain D, Amin B, Turner RB. Segmental eccrine spiradenomas. J Clin Aesthet Dermatol 2011;4:38-44.
10. Happle R. Type 2 segmental manifestation of "blue rubber bleb nevus syndrome": A reappraisal of 5 case reports. Eur J Dermatol 2010;20:266-8.
11. Bhabha FK, Magee J, Ng SY, Grills CE, Su J, Orchard D. Multiple clustered dermatofibroma presenting in a segmental distribution. Australas J Dermatol 2016;57:e20-2.
12. Patterson AT, Kumar MG, Bayliss SJ, Witman PM, Dehner LP, Gru AA. Eccrine angiomatous hamartoma: A clinicopathologic review of 18 cases. Am J Dermatopathol 2016;38:413-7.
13. Cabral CR, Oliveira Filho Jd, Matsumoto JL, Cignachi S, Tebet AC, Nasser Kda R. Type 2 segmental glomangioma—Case report. An Bras Dermatol 2015;90:97-100.
14. Cherian A, Baheti NN, Sarada C, Iype T, Mathew M. Segmental schwannomatosis: An uncommon cause of crural monoparesis. J Neurosci Rural Pract 2012;3:420-1.
15. Onder M, Adişen E. A new indication of botulinum toxin: Leiomyoma-related pain. J Am Acad Dermatol 2009;60:325-8.

Submission: 15-06-2021 **Revision:** 05-08-2021
Acceptance: 09-08-2021 **Web Publication:** 29-09-2021

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_50_21

How to cite this article: Iswarya A, Vijayasankar P, Karthikeyan K, Sriram V. Segmental leiomyoma: A report of two cases. Turk J Dermatol 2021;15:80-2.