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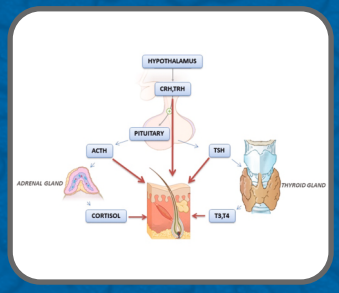

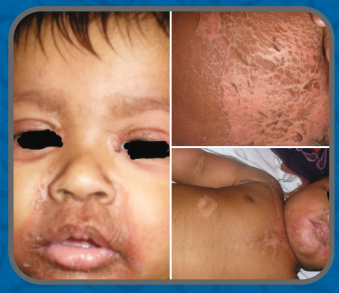

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Review Article

Brain–Skin Connection: The Contemporary Perspective through Neuroendocrinology

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Abstract

This review summarizes the novel and precious data on the direct effects of ancient neuroendocrinologic molecules on the skin and hair and additionally the active production of these hormones by resident skin cells. The data are extracted from PubMed using the keywords neuroendocrinology, hormones, skin, hair follicle, pituitary, hypothalamus, thyroid, and prolactin. The most important neuroendocrinologic axis is composed of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol (CRH–ACTH–cortisol) and is related to stress. The CRH–ACTH–cortisol axis is demonstrated to be fully functional in the skin. This review furthermore points out to a possible neuroendocrinologic mechanism likely to explain the association between psychological stress and skin and hair diseases.

Keywords: Hair follicle, hormones, neuroendocrinology, skin

Introduction

The skin serves as a barrier isolating the organism from the external environment. Besides the mechanic protective function, a wide range of different functions are established and increasingly recognized. Even recently, epidermis is proposed to be the third brain after the accepted opinion on the digestive system as the second brain of the body.[1] Skin is not only the primary end organ for environmental stimulators but also produces various hormones and neuromediators.

In this review, we briefly focused on the intimate relationship between brain activities such as reception and processing of external information and skin reactions including immune, endocrine, and inflammatory responses.

The Arousal of Skin Neuroendocrinology

The connection between the skin and the brain is recognized even in the prehistorical times as the aggravation of many dermatological diseases by psychological stress. Furthermore, the alterations of quality of life and mood disorders are commonly observed and defined by clinicians throughout the dermatological practice. The elevated levels of inflammatory molecules such as cytokines, neuromediators, and neurotrophins due to skin diseases such as psoriasis, atopic dermatitis, and hidradenitis suppurativa were also hypothesized to be the cause of psychiatric comorbidities in dermatological patients.[2,3]

The skin can serve both affective and effective properties attending crucial functions through the intertalk between the body and the external environment.

As an ordinary sensory organ, the skin collects the signals from the environment in an appropriate way and as an exceptional finding can process these data and react to stressful events independent from the nervous system. In other words, the skin, itself, has the potential either to initiate an emotional response to the changing environmental conditions or evoke adaptive physiological responses by the contribution of keratinocyte-derived molecules. The neuroendocrine system begins to work out from the beginning in the reception step by the regulation of the intensity of environmental signals – the

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differentiation of environmental noise from appropriate signals – and only can be activated upon receiving signals above the activation threshold levels. The environmental signals clearly induce significant alterations of the immune and pigmentary systems of the skin. Thus, these systems were once accepted as fundamental independent responders to different types of stress. The skin neuroendocrine system is found to serve important implications on these abovementioned systems also with a potential to enter the systemic circulation and cause systemic effects.[1]

The skin has various receptors for neuronal and endocrine ligands, but its active production of hormones and neurotransmitters is an outstanding discovery and the cause for increased attention on neuroendocrinology.

The acquired data changed the position of the skin from a passive player in whole-body homeostasis to an active one.

Developmental Biology of the Skin: An Emphasis on Shared Origin with the Nervous System

Epidermis and dermis substantially derive from different embryonal layers as the ectoderm and mesoderm, respectively. Adnexal structures arising from the precise mesenchymal–epithelial interactions are also ectoderm derived. The central and peripheral nervous system, retina, and medulla of the adrenal gland derive from the ectoderm, making an intimate connection, in other words, a common molecular syntax reasonable for the epidermis and adnexa with these structures.

Keratinocytes, the complete structure of the hair follicle including the sebaceous and apocrine glands and also eccrine sweat glands, derive from the ectoderm-originated embryonal outer epithelium.

Similarly, the anterior lobe of hypophysis derive from the outer epithelium.[4] This common ancestral relationship with the anterior hypophysis gland is noteworthy, as growing evidence indicates the existence of identical hypothalamic–pituitary–end organ axes in the skin with relevant feedback mechanisms.

Fundamental Concepts in Skin Neuroendocrinology

General neuroendocrinology describes several central axes through which the brain controls the endocrine glands. Prior to the introduction of these well-known molecules with unfamiliar properties related to the skin, these principles should be kept in mind:

The skin itself can express these molecules and include their receptors in the adjacent layers in the apparent absence of strict compartmentalization as observed in the pituitary gland.

Current evidence suggests that drugs, the skin microbiome, and physical stimulants such as ultraviolet radiation, oxidative stress, and also psycho-emotional stress may directly interact with the intracutaneous production of hormones and neuromediators.[5]

Even both epidermal and hair follicle keratinocytes express hormones, neuromediators, and neurotrophins; the regulation and effects of these molecules are distinct for hair follicle and epidermal cells. For example, thyrotropin-releasing hormone (TRH) is shown to serve significant melanogenic stimulation in the hair follicle, which did not appear to be alike in the epidermal cells. Through the contribution of hair follicle organ cultures without the need for animal studies, the science of skin neuroendocrinology is preferentially evolving in the hair follicle.[6] Peripheral nerves in the skin influence skin function through secreted neuroinflammatory molecules.

Neuroendocrine axes pose critical regulatory roles for the hair cycle. The characteristic distribution of androgen-sensitive and androgen-resistant hair follicles in different genders is responsible for the typical phenotype of androgenetic alopecia, which is also valid for different hormones. A typical example is the differential effect of prolactin on the hair cycle; while it promotes occipital catagen hair in males, it stimulates hair growth in female frontotemporal hair follicles.[6]

Many hormones also work as a cytokine or a neuromodulator. Thus, the distinctions between hormones, neuropeptides, neurotransmitters, and cytokines are less clear.

A lot of broad questions cover up the field as to what extent the skin equivalents communicate with or depend on their central neuroendocrinologic axes.

Regarding the huge amount of cell number including epidermal and hair follicle cells, Paus *et al*. suggested that even the production of hormones was defined at a minimal level, there might still be a theoretical risk of contributing to systemic neurohormone levels, which had to be investigated further.[6]

Hypothalamus–Pituitary–End Organ Axis with Corresponding Skin Equivalents

The skin includes a full-functional hypothalamus–pituitary–adrenal axis (HPA), and the hypothalamus–pituitary–thyroid (HPT) axis of the skin is regarded as a partial equivalent of the central counterpart.[7,8] Despite the absence of an end organ, due to the structural integrity with HPT axis through its central control by TRH, the evidence on the functions of prolactin related to the skin will also be discussed in this context.

Hypothalamus–pituitary–adrenal axis

Upon exposure to stress, hypothalamic neurons secrete some hormones. HPA involves subsequent upregulation of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol [Figure 1]. Following the discoveries on the expression of different elements belonging to HPA axis in the skin, the fully functional peripheral equivalent of HPA axis is first demonstrated in 2005 in microdissected, organ-cultured scalp hair follicles.[9,10] CRH induces the secretion of proopiomelanocortin-derived neuropeptides

such as alpha-melanocyte-stimulating hormone (α-MSH), β-endorphin, and ACTH in the pituitary gland. In addition to the roles of CRH, ACTH, and cortisol, α-MSH and β-endorphin have distinct functions in the skin [Figure 2].

CRH attends a wide range of actions in the skin including both proliferative and anti-proliferative or inflammatory and non-inflammatory features depending on the resident cell type. CRH is produced by epidermal and hair follicle keratinocytes, mast cells, and melanocytes. The skin involves two types of CRH receptors such as CRH-R1 and CRH-R2. The expression of CRH-R1 is widespread in epidermis, dermis, and subcutaneous tissue, whereas CRH-2 is only expressed in hair follicle keratinocytes and papillary fibroblasts.[11]

As a downstream molecule of HPA pathway, ACTH reaches to the adrenal cortex's outer layer and exerts pro-inflammatory features and stimulates corticosteroid production through melanocortin-2-receptor. ACTH mainly induces the production of cortisol in the surreal cortex as a stress hormone and concurrently stimulates a pro-inflammatory cytokine, interleukin-18 in epidermal keratinocytes as a T-cell activator.

This axis is unique in skin neuroendocrinology due to three different aspects. First, the most prominent neurohormonal response to psychological stress occurs through HPA axis; thus, this axis embraces important issues mainly including the connection of skin diseases and stress. Second, the skin HPA axis has profound suppressive implications on the immune system, mainly described as the suppression of Th1-mediated immunity with a shift toward Th2-mediated humoral immunity, admixing the effects of neuroendocrinology with skin immunology. The third perspective includes as a very commonly used drug in dermatological practice, topical corticosteroids may impact the intrafollicular HPA axis equivalent.

Hypothalamus–pituitary–thyroid axis

Recently, the discoveries on the HPT axis equivalent of the skin pointed out to exciting different roles of this axis that could be translated to general neuroendocrinology.

Slominski *et al*. first described the expression of members belonging to this axis including TRH, thyroid-stimulating hormone (TSH) and thyroid hormones (T3 and T4), and the receptor transcripts of TRH and TSH.[12]

The established functions of HPT axis hormones are summarized in Table 1.

Table 1: The functions of hormones belonging to the hypothalamus-pituitary-thyroid axis equivalent of the skin

Hormone	Effects on the skin and the hair follicle
TRH	Effects on epidermal hormone expression
	Stimulation of epidermal TSH expression
	Regulation of intracutaneous prolactin expression
	Stimulation of hair pigmentation
	Intrafollicular melanin synthesis
	Tyrosinase gene expression and activity
	Dendrite formation by hair follicle melanocytes
	Increased melanosome transfer to keratinocytes
	Possibly occurs through upregulation of MITF
	Keratinocyte mitochondrial function
	Enhanced mitochondrial activity and biogenesis
	Regulation of keratin expression
	Hair keratins
	Stem cell keratins (K15, K19)
	Effects on the hair cycle
	Anagen promotion
TSH	Keratinocyte mitochondrial function
	Enhanced mitochondrial activity and biogenesis
	Regulation of keratin expression
	Hair keratins
	Stem cell keratins (K15, K19)
T3, T4 (generated mainly outside the skin)	Regulation of keratin expression
	Effects on hair cycle
	Anagen promotion
	Improved wound healing
	Regulation of epidermal stem cell functions

TRH: Thyrotropin-releasing hormone, TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, MITF: Microphthalmia-associated transcription factor

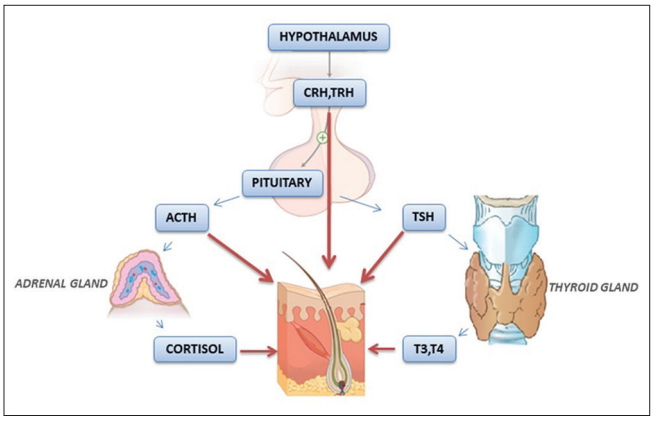

Figure 1: The schematic representation of the hypothalamic–pituitary–thyroid and hypothalamic–pituitary–adrenal axes with established effects on the skin

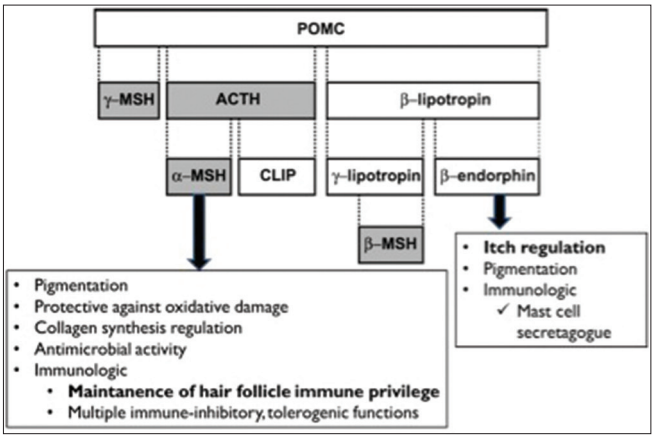

Figure 2: Proopiomelanocortin-derived hormones with their relevant functions on the skin and hair follicle

The novel function of TRH on melanocytes as a strong melanogenic agent is demonstrated in hair follicle organ cultures, but this effect was not replicated for epidermal cells.[13] These findings together can be translated to the clinical setting as the selective effect on hair follicle pigmentation points out to a possible therapeutic role to prevent or even reverse existent hair graying.

The effects of TRH and TSH on keratinocyte mitochondrial functions were detected in both epidermis and hair follicle keratinocytes.[7,8] These results gave the first hints about the regulatory role of neuroendocrinology on mitochondrial functions and served as a research frontier for the possible role of TRH/TSH in other tissues with high-energy demands. Starting from the mitochondrial theory of aging, the modulation of decreasing mitochondrial function in senescent hair follicles and other tissues by therapeutic strategies targeting TRH/TSH is suggested to be possible.[6]

An intensively searched function of HPT axis related to the skin includes the control of keratin gene and protein expression in human epidermis and hair follicle.[14] Keratins attend a wide range of regulatory functions for epithelial cell proliferation, differentiation, migration, apoptosis, wound healing, carcinogenesis, and hair follicle cycling beyond their mechanical properties in order to form a scaffold for keratinocytes.[15] Triiodothyronine (T3) was the first of various hormones revealing a regulatory effect on keratin expression. Hypothyroid mice exhibit decreased K6 expression and the exposure of cultured keratinocytes to T3 resulted in increased gene expressions of K6, K16 and K17.[16] Subsequent studies, especially designed on human hair follicle cultures, reported the differential expression of keratin sets by different molecules including TRH/TSH, prolactin, CRH, endorphins, catecholamines, and parathyroid hormone-related peptide.[17-26] The effects of these hormones on keratin expression are not fully understood. For example, in the human hair follicles, despite the widespread presence of TRH immunoreactivity including the outer root sheath (ORS), the TRH-R immunoreactivity is confined to the inner root sheath. Nevertheless, TRH strongly regulates the expression of keratins in ORS such as keratin.[6,14,17]

The regulation of stem cell-associated keratins is especially reported with prolactin and TRH. However, the consequences of this affiliation and whether it could serve as a therapeutic strategy are unknown.[6]

Hypothalamic control of prolactin

The stimulating effects of TRH on prolactin were reported both in general and skin neuroendocrinology.[27,28] Prolactin is reported to be involved in hair cycle and sebum production and also as discussed previously in HPT axis attend regulatory roles in keratin expression.

The function of prolactin on hair cycle is gender and species specific and is a typical example demonstrating why the data derived from animal studies should not be generalized to human situations. Prolactin is found to promote catagen in mouse hair follicles.[29] The promotion of occipital catagen hair in males and conversely stimulation of hair growth in frontotemporal hair follicles in females were reported in human studies.[30]

Neuroendocrine Stress Response Systems in Human Skin

The relationship between dermatological diseases and psycho-emotional stress was explained through the psychoanalytical perspective and also immunological measures such as cytokine levels. Exposure to sound, restraint, and foot-shock stress caused remarkable perifollicular neurogenic inflammation and suppressed hair growth in mouse studies, suggesting a possible explanation for stress-induced hair loss.

The detection of increased nerve–mast cell contacts in inflammatory skin diseases such as psoriasis and atopic dermatitis is a starting point for the adaption of skin neuroendocrinology into this model, designated by the phrase of "stress-induced neurogenic skin inflammation."

Stress-induced neurogenic inflammation gathers neuroendocrinology and neuro-immunology together in order to contribute to the pathogenesis of many skin diseases and reveals skin mast cells as the central player leading to a vicious cycle of inflammatory events upon activation. The activation and degranulation of mast cells occur upon increased levels of mediators including CRH, ACTH, nerve growth factor, and substance P.

Conversely, endogenous and exogenous agonists of cannabinoid receptor 1 (CB-1) suppress both the maturation and degranulation of mast cells and hold promise as a therapeutic approach for the epidemic of allergic diseases related to the skin, lungs, and upper respiratory airway. The endocannabinoid system involves three main parts including the endogenous ligands such as anandamide and 2-arachidonoylglycerol, the enzymes responsible for the synthesis and metabolism of these products, and the receptors such as CB-1 and CB-2. Tonic CB-1 signaling is essential for the prevention of excessive mast cell activation and degranulation.

The involvement of sympathetic–adrenal–medullary axes to the systemic stress response is also appreciated, and the skin also involves a peripheral catecholamine system equivalent. Originally, the role of catecholaminergic signaling pathway in dermatologic diseases relies on the long line of research demonstrating the role of β-adrenergic signaling in atopic eczema about five decades ago.[31] Apart from the appreciated production of catecholamines from skin nerve endings, epinephrine is also synthesized by keratinocytes and additionally adrenergic receptors are expressed in epidermal keratinocytes and melanocytes.[32] The activation of β-2 adrenergic signaling in keratinocytes with epinephrine induces the production of cyclic adenosine monophosphate though protein kinase C activation, and the result is increased calcium

concentration. Hence, calcium level has important regulatory functions on both epidermal proliferation and differentiation; catecholaminergic signaling is expected to influence epidermal health.[33] Dermal fibroblast functions including migration and collagen production are also demonstrated to be influenced by catecholaminergic signaling in the presence of beta-adrenergic receptors, suggesting a possible mechanism for the detrimental effect of stress on wound healing.[34] Recently, the inhibition of adrenergic signaling with timolol is shown to result in improved healing in burn and radiation wounds.[35]

The brain is considered to be protected by the blood–brain barrier and assumed as a master of the organism collecting inputs and sending unidirectional commands throughout the body for decades. Recently, animal studies confirmed the clear effects of chronic systemic inflammation on the brain by neuroimaging findings. The brain inflammation is somehow triggered by chronic inflammatory diseases. There is an open field for the investigation of the possible effects of chronic skin inflammation on brain inflammation and functioning, and researches are likely to occupy the arena in dermatology in the near future. The interaction between skin and general neuroendocrinology might be a mechanism for such an association.

Conclusion

Neuroendocrinologic molecules may represent more biological activities than their conventional features, including the effects on epithelial and mesenchymal growth and regeneration, possibly related to wound healing and tissue homeostasis. In future, the cumulative data on these ancestral functions may serve as a therapeutic tool and can be translated for targeted therapies in various dermatological disorders.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Confusing Acquired Macular Pigmentation of Unknown Etiology in Children: Retrospective Analysis of 10 Years in Single Tertiary Center

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Abstract

Acquired Macular Hyperpigmentation: Ashy dermatosis (AD), lichen planus pigmentosus (LPP), erythema dyschromicum perstans (EDP), and idiopathic eruptive macular pigmentation (IEMP) are the spectrum of acquired macular pigmentation of unknown etiology (MPUE). The aim of this study is to investigate and reevaluate our pediatric patients who had clinically and histopathologically been diagnosed with aforementioned disorders, in consideration of the global consensus statement on acquired MPUE. **Materials and Methods:** A retrospective chart review of 23 pediatric cases that had applied to the dermatology unit between the years 2007 and 2017 and diagnosed with any of the acquired macular pigmentation was performed. **Results:** Of 23 patients, 16 were diagnosed with AD, 4 with LPP, and 3 with IEMP. In AD patients, major site of presentation at onset was the trunk (13/16) and brownish (15/16) were the most prominent coloring. Dermal melanophages (16/16), perivascular lymphohistiocytic infiltrate (14/16), and pigment incontinence (7/16) were the most prominent features. Upper limbs (3/4) were the most predilection area in LPP patients. Perivascular lymphohistiocytic (4/4), lichenoid infiltration (3/4), basal vacuolar degeneration (4/4), and dermal melanophages (4/4) were observed. The trunk was the major site of presentation (3/3) in IEMP patients. Brownish (2/3) and ashen-gray (1/3) was the coloring of lesions. Basal layer pigmentation (3/3) and dermal melanophages (3/3) were the most prominent findings. No basal vacuolar changes (0/3) were observed. **Conclusion:** Clinical and histopathological distinction between these conditions is challenging. We reevaluated our patients in this context. We predict that we have achieved more accurate terminology with the global consensus statement. Such a terminology might allow that these disorders may be compared with a collective terminology in the literature.

Keywords: Ashy dermatosis, erythema dyschromicum perstans, hyperpigmentation, idiopathic eruptive macular pigmentation

Introduction

Acquired macular pigmentation of unknown etiology (MPUE) is a new term for acquired macular pigmentation of the skin with unknown etiology in the absence of preceding or concurrent inflammatory lesions. This umbrella term encompasses ashy dermatosis (AD), lichen planus pigmentosus (LPP), erythema dyschromicum perstans (EDP), and idiopathic eruptive macular pigmentation (IEMP).[1-6] The overlapping clinical and histological features of these skin disorders identified under the terminology, turn differential, and formal diagnostic stages into a rather challenging process.[2,5-9] A consensus on the terminology of these disorders was a long-felt need. This was achieved by the global consensus forum, established after the 22nd International Pigment Cell Conference, in Singapore in 2014. Kumarasinghe *et al*. reported the consensus statement of the forum and reviewed the available literature in 2019.[3] Herein, we report 23 pediatric cases of acquired MPUE in consideration of global consensus statement.[3]

Materials and Methods

Retrospective review of 23 pediatric cases with acquired MPUE which had applied to the dermatology unit of the children's hospital between 2007 and 2017, was conducted.

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This center provides medical services primarily to Caucasian individuals from the Aegean region but also receives referrals from other parts of Turkey. Patients, histopathologically and clinically diagnosed with acquired MPUE, without any previous or concurrent inflammatory lesions were included in the study. In addition, we re-examined photo documentation of patients whenever possible. Hematoxylin and eosin, crystal violet or Congo-red, and toluidine blue stained archival tissue sections of patients were reevaluated. Hence, mastocytosis and amyloidosis were excluded at the process of differential diagnosis. If there is not erythematous border in the past or current, these conditions were not labeled EDP.

Data regarding clinical location of lesions, presenting symptoms, duration of the disease, sociodemographic characteristics of subjects such as gender, age, history of drug intake, and observed distinct histopathological features were noted.

Results

In this study, from 23 children, 16 were diagnosed with AD, four with LPP, and three with IEMP, while none of the patients had the diagnosis of EDP. The average age of children was 9, 5 (6 months –16 years). The gender distribution of the cases was 11 females and 12 males. The demographical, clinical, and histopathological features of all cases in the context of diagnosis have shown in Tables 1 and 2.

Children with AD, neither simultaneous erythematous border nor the history of erythematous border were found [Figure 1].

Histories of drug use that might be suspected were noted. (2/amoxicillin-clavulanate, 1/pyrantel pamoate, 1/nonsteroidal anti-inflammatory drugs, 1/methylphenidate, and 1/montelukast-desloratadine); summarized in Table 1.

Dermal melanophages (16/16), perivascular predominantly lymphohistiocytic infiltrate (14/16), and pigment incontinence (7/16) were the most prominent features, followed by basal layer pigmentation (5/16) and basal vacuolar changes (5/16) [Table 2 and Figure 2]. Among preliminary diagnoses of the 16 patients, AD/EDP had also been considered.

Of LPP patients, none of the patients had the history of preceding erythema, vesicles, or scaling before the onset of hyperpigmentation or the history of papules of typical lichen planus lesions. Only one patient had had a prior history of medication (naproxen sodium). One of the female patient's lesions was on flexural areas [Figure 3]. Perivascular lymphohistiocytic (4/4) and lichenoid infiltration (3/4), acanthosis (2/4) hypergranulosis (1/4), basal vacuolar degeneration (4/4), and dermal melanophages (4/4) were observed [Table 2 and Figure 2].

In IEMP patients, no erythematous patches had been found, and there was no history of preceding dermatosis and no history of medications [Table 1 and Figure 4]. Basal layer pigmentation (3/3) and dermal melanophages (3/3) were the most prominent findings. No basal vacuolar changes (0/3) were observed [Figure 2].

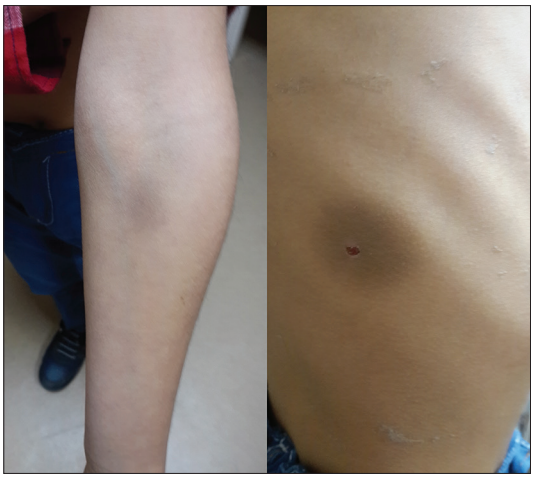

Figure 1: Cutaneous macules in colors with various shades of gray in ashy dermatosis patient

Discussion

AD, EDP, LPP, and IEMP are potential differential diagnoses.[1-3,5,6,9-14] Some authors consider them as a part of the same nosological spectrum of a unique entity, while others argue that they are different diseases. A consensus on the terminology of these lesions with various morphologies was a long-felt need. This was achieved by the global consensus forum, established after the 22nd International Pigment Cell Conference in Singapore in 2014. Thirty-nine experts presenting 18 countries participated in the deliberations.

Kumarasinghe *et al*., in 2019, reviewed the available literature and reported the consensus statement of the forum. In this study, we tried to determine the clinical and histopathological features of 23 children due to this consensus to obtain similar terms.

Many dermatological and medical diseases can cause acquired macular hyperpigmentation as a sequel. In order to be identified as acquired MPUE, it is crucial to prove that encountering pigmented macules do not appear following a known disease, and they do not have any preceding and concurrent prior inflammatory skin lesion.[1,3]

Initially described in 1961, Venezuela by Convit, EDP is characterized by asymptomatic, slowly progressing, ashy-gray, expanding macular hyperpigmentations with slightly raised, erythematous border at presentation.[15] Yet, Ramirez had reported a novel pigmentary disorder characterized by an eruptive, asymptomatic rash consisting of ash-colored macules without erythematous border, in 1957.[16] The same author had reported 139 patients with ash-colored and grayish macules, where some lesions presenting with an easily observable, nonelevated erythematous border, in 1967.[17] This disorder had been identified as AD or dermatosis cenicienta.[5,17] Henceforth, although some clinical features might slightly differ, many authors and most textbooks have regarded these two as identical conditions.[5,9] Zaynoun suggested separate classification to be used for differential diagnoses of EDP

Table 1: Sociodemographic and illness-specific characteristics of 23 cases with acquired macular pigmentation of unknown etiology

Patient number	Age/sex	Duration	Location	Drug intake/ infection	Clinical features	Most prominent histopathologic features	Clinical and histological diagnosis
1	4/male	8 months	Trunk, neck, upper limbs	+(pyrantel pamoate)/-	Ashen-gray brownish, color macula, no erythematous border	Papillomatosis, increased basal melanocytes in focal areas, dermal melanophages, pigment incontinence	AD
2	7/female	1 month	Upper and lower limbs	-/-	Ashen-gray brownish, color macula, no erythematous border	Focal basal vacuolar changes, eosinophilic colloid body, lichenoid infiltrate, perivascular lymphohistiocytic infiltrate, dermal melanophages, pigment incontinence	LPP
3	13/ female	2 months	Armpit, pubic area, neck, inguinal folds	+(naproxen sodium)/-	Brownish, color macula, no erythematous border	Basal vacuolar changes, perivascular lymphohistiocytic infiltrate, lichenoid infiltrate, dermal melanophages, pigment incontinence	LPP
4	11/male	8 months	Trunk, lower limbs, back	+(montelukast-desloratadine)/-	Ashen-gray color macula, no erythematous border	Increased basal layer pigmentation, perivascular lymphocytic infiltrate	AD
5	11/male	1 year	Trunk, upper and lower limbs	-/-	Brownish, color macula, no erythematous border	Increased basal layer pigmentation, dermal melanophages, pigment incontinence	IEMP
6	6/male	6 months	Back of the trunk, upper limbs	-/-	Ashen-gray brownish, color macula, no erythematous border	Increased basal layer pigmentation, dermal melanophages, pigment incontinence	IEMP
7	16/ female	2 months	Trunk	-/-	Brownish, color macula, no erythematous border	Perivascular lymphocytic infiltrate, dermal melanophages, pigment incontinence	AD
8	9/female	6 months	Trunk, upper and lower limbs	-/-	Brownish, color macula, no erythematous border	Increased basal layer pigmentation, basal vacuolar changes, perivascular lymphohistiocytic infiltrate, dermal melanophages, pigment incontinence	LPP
9	9/female	5 months	Trunk, upper and lower limbs	+(amoxicillin-clavulanate)/+	Brownish, color macula, no erythematous border	Basal vacuolar changes, perivascular lymphocytic infiltrate, dermal melanophages, pigment incontinence	AD
10	9/female	1 month	Trunk, upper and lower limbs	+(amoxicillin-clavulanate)/+	Brownish, color macula, no erythematous border	Dermal melanophages, pigment incontinence, mild lymphocytic infiltrate	AD
11	16/ female	2 years	Trunk, upper limbs	-/-	Ashen-gray brownish, color macula, no erythematous border	Basal vacuolar changes, dermal melanophages, pigment incontinence, mild lymphocytic infiltrate	AD
12	12/ female	1 year	Trunk, lower limbs, back	-/-	Brownish and ashen-gray color macula, no erythematous border	Perivascular lymphocytic infiltrate, dermal melanophages, pigment incontinence, basal vacuolar changes	AD
13	6/male	1 month	Trunk, upper and lower limbs	+(nonsteroidal anti inflammatory drugs)/-	Brownish color macula, no erythematous border	Increased basal layer pigmentation, dermal melanophages, pigment incontinence, mild lymphocytic infiltrate	AD
14	9/female	5 months	Trunk, upper and lower limbs	-/-	Brownish color macula, no erythematous border	Perivascular mild lymphocytic infiltrate, a small number of dermal melanophages	AD
15	13/male	5 months	Shoulders, back of the trunk	-/-	Brownish color macula, no erythematous border	Perivascular mild lymphohistiocytic infiltrate, a small number of dermal melanophages	AD
16	5 months/ male	4 months	Trunk	Unknown	Brownish color macula, no erythematous border	Increased melanin in the basal layers, perivascular sporadic melanophages	IEMP
17	8/female	1 month	Back of the trunk	Unknown	Brownish color macula, no erythematous border	Increased basal layer pigmentation, perivascular mild lymphohistiocytic infiltrate	AD

Contd...

Table 1: Contd...

Patient number	Age/sex	Duration	Location	Drug intake/ infection	Clinical features	Most prominent histopathologic features	Clinical and histological diagnosis
18	8/male	5 months	Trunk, upper and lower limbs	Unknown	Brownish color macula, no erythematous border	Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate dermal melanophages	AD
19	10/male	5 months	Trunk	Methylphenidate/-	Brownish color macula, no erythematous border	Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate, and melanophages	AD
20	12/male	1 year	Trunk, upper and lower limbs	Unknown	Brownish color macula, no erythematous border	Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate, and melanophages	AD
21	3/male	1 month	Lower limbs	Unknown	Brownish color macula, no erythematous border	Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate, and melanophages	AD
22	9/female	9 months	Neck, trunk, upper limbs	Unknown	Brownish color oval macula, no erythematous border	Mild lymphohistiocytic infiltrate and melanophages in the superficial dermis	AD
23	8/male	1 year	Trunk, upper limbs	Unknown	Brownish, color and mild elevated macula, no erythematous border	Irregular acanthosis of the epidermis, hypergranulosis and sporadic necrotic keratinocytes, basal vacuolar changes, lymphohistiocytic infiltrate in the papillary dermis, pigment-containing melanophages	LPP

AD: Ashy dermatosis, LPP: Lichen planus pigmentosus, IEMP: Idiophatic eruptive macular pigmentation

and AD.[5] Inoue proposed that only cases with marginal erythema be considered as EDP.[9,18] Global consensus on acquired MPUE forum reached a consensus on EDP and AD; if there is an erythematous border in the past or current, these conditions should be labeled EDP.[3] The erythematous border indicates the presence of an inflammatory process that is caused by T lymphocyte infiltration. Although AD patients in this study had perivascular predominantly lymphohistiocytic infiltrate (14/16), neither prior nor simultaneous erythematous border had been detected [Table 2]. This observation gives rise to the thought that AD and EDP are distinct diseases.

In numerous studies, AD/EDP has shown similar histopathological findings. Prominent histological findings include pigment incontinence and melanophages in the dermis, along with mild-to-moderate superficial perivascular lymphohistiocytic infiltration.[1,4,5,9] According to Chang *et al*., EDP/AD can be subdivided into active and inactive lesions. In active lesions, basal vacuolar degeneration and lymphocytic infiltration, in inactive lesion melanophages, and pigment incontinence are the most prominent findings.[4] We observed basal vacuolar changes and also lymphohistiocytic infiltrates in patients with prolonged disease duration of one and 2 years (patients 11 and 12). These findings suggested that the disease could continue with attacks.

The underlying pathomechanism of EDP or AD remains unclear, however, an immunological basis along with possible genetic susceptibility have been suggested. Parasitic infections, human immunodeficiency virus infections, and hepatitis C, exposure to chemicals such as ammonium nitrate, barium sulfate, antibiotics, benzodiazepines, pesticides, and environmental allergens have been as well listed among predisposing factors.[4,5,9] In this study, the positive history of drug use was detected in 6, and the history of infection (upper respiratory infection) was detected in 2 of our AD patients. These factors may be triggers of the aforementioned disease. Therefore, possible triggering factors should be evaluated in addition to the content of this consensus.

IEMP is a rare disease that has been reported mostly in children and young adults.[6,8,11,19] In this study, three of the patients had the diagnoses of IEMP. It has been reported initially by Degos;[20] however, initial diagnostic criteria for the disorder were defined by Sanz de Galdeano.[6,8,10,11,21] In 2007, nine cases that clinically fulfilled the diagnostic criteria for this entity, with comorbid papillomatosis were reported. These lesions had been reported to contain velvety surfaces with prominent papillomatosis, that resembled the presentation of acanthosis nigricans.[8] The authors proposed to classify IEMP as an eruptive form of acanthosis nigricans.[8] Epidermal hypermelanosis and marked basal cell pigmentation have been regarded as the predominant finding of IEMP, by many authors.[1,3,6] Joshi *et al*. have re-evaluated 48 cases identified as IEMP in a total number of 24 case reports.[6] They have suggested that IEMP was an epidermal hypermelanotic condition, that sometimes was comorbid with papillomatosis (pigmented papillomatosis).[6] The authors have reported 9 cases had been misdiagnosed as IEMP.[6] According to the global consensus forum's conclusions; histology of IEMP is characterized by hyperpigmentation of the basal layer of the epidermis and prominent dermal melanophages without visible basal layer damage or inflammatory infiltration. The condition described as IEMP with papillomatosis appears to be a different entity to typical IEMP.[3] We proposed the same definition through the histopathology of IEMP patients in

Table 2: Histopathologic examination of 23 cases with acquired macular pigmentation of unknown etiology

Diagnosis	Acanthosis	Hyperkeratosis	Hypergranulosis	Papillomatosis	Basal pigmentation	Basal vacuolar changes	Eosinophilic colloid body	Perivascular lymphohistiocytic infiltrate in the superficial dermis and melanophages in the superficial dermis	Perivascular lymphohistiocytic mild	Perivascular lymphohistiocytic/ lymphocytic prominent infiltrate	Lichenoid infiltrate	Mild infiltrate	Pigment incontinence and dermal melanophages
Ashy dermatosis (n=16)	1	4	0	1	5	5	0	12/9		0/3	0	12	7/8
Lichen planus pigmentosus (n=4)	2	2	1	0	1	4	1	0/1		4/0	3	0	3/4
Idiophatıc eruptive macular pigmentatıon (n=3)	1	0	0	0	3	0	0	0/1		0/0	0	0	2/2

this study who had no papillomatosis and no velvety surface clinically of three cases.

Bhutani *et al*.[16,22] described LPP lesions with similar pigmentation to that described by Ramirez, some of whom had lichen planus concomitantly in 1974.[16,22] These lesions had histopathological findings similar to lichen planus with epidermal vacuolization and lichenoid infiltration. In 2003, Kanwar *et al.* conducted a large study and suggested that LPP, a distinct clinical entity, should be considered in the spectrum of lichenoid disorders as a variant of lichen planus.[23] However, mostly, such cases never develop typical lichen planus concurrently or hereinafter. According to the global consensus forum conclusions, it is thought that LPP may not be etiopathologically related to lichen planus. If the hyperpigmentation is limited to areas of previous lichen planus lesions and lesions of lichen planus present, it is best to tend labeling with post-inflammatory hyperpigmentation.[3]

LPP involves the head and neck in most cases, the next common area of involvement is the flexures, particularly armpit. With time the upper extremities and upper part of the back and trunk may also be involved. LPP lesions are found on sun-exposed areas as well as nonsun-exposed areas.[3,23,24] In our LPP patients, upper limbs (3/4) were the most predilection area, and one of the female patients' lesions was on intertriginous folds.

The most distinctive feature of MPUE is the unknown etiology in the absence of preceding or concurrent inflammatory lesions. Simply post-inflammatory hyperpigmentation due to known conditions may be determined easily, whereas other possible conditions may be challenging. For instance, pigmented contact dermatitis and pigmented cosmetic contact dermatitis that may occur following noneczematous mild inflammatory dermatosis should be kept in mind. The patch test application might be beneficial in such cases. Other causes of pigmentation, such as medicinal drugs, food additives, and food coloring should be carefully excluded as the pigmentation can be insidious.

Conclusion

We believe that triggering factors, histopathological examinations, and the novel global consensus classifications reported by Kumarasinghe, need to be taken into consideration throughout formal diagnostic processes.

As a result of this study, we propose a diagnostic algorithm [Figure 2]. Thus, a collective terminology for this disease spectrum could be established in the literature with such a diagnostic consensus.

Declaration of patient consent

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

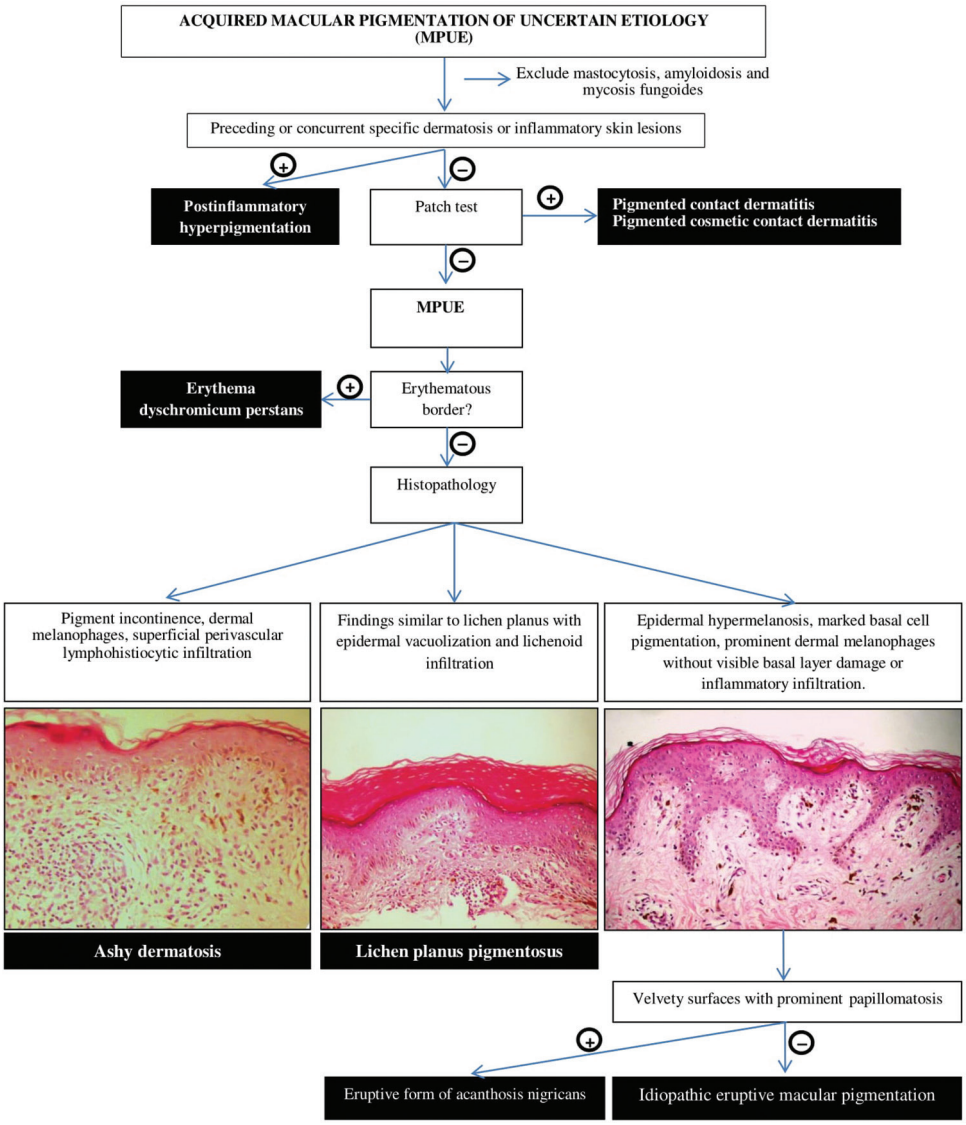

Figure 2: Clinicopathological algorithm of acquired MPUE

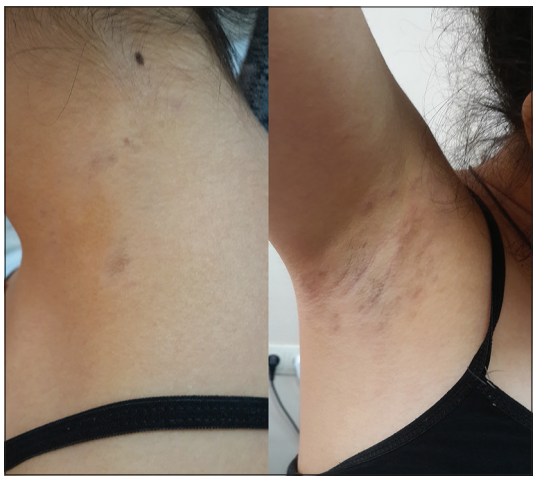

Figure 3: Cutaneous macules in colors with various shades of brown in lichen planus pigmentosus patient in intertriginous areas

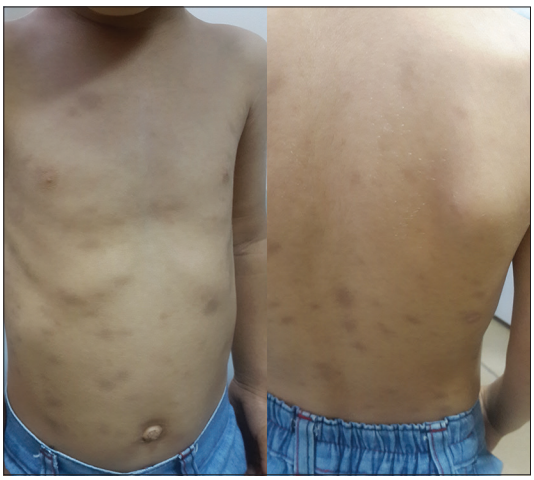

Figure 4: Cutaneous macules in colors with various shades of brown in eruptive macular pigmentation patient

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Conflicts of interest
There are no conflicts of interest.

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Original Article

The Relationship between Direct Immunofluorescence Findings and Clinical and Laboratory Parameters in Patients with Cutaneous Small Vessel Vasculitis

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Abstract

Objective: Cutaneous small-vessel vasculitis (CSVV) is a disease characterized histologically by leukocytoclastic vasculitis (LCV) and immune-complex deposition in small vessel walls. We aimed to evaluate the type of deposited immune complexes in patients with LCV and to determine the relationship between the immune-complex types and clinical and laboratory parameters. **Materials and Methods:** Patients who had been diagnosed as LCV histopathologically between 2000 and 2018 were retrospectively evaluated. Patients' medical records and pathology databases were reviewed to determine the demographic characteristics, clinical, laboratory, and histopathological findings. Direct immune fluorescence (DIF) findings to determine the immune-complex subtypes, including immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG) or C3 deposition, were evaluated. **Results:** Sixty-eight patients were included in the study. A total of 36 (53%) patients had deposition in the perivascular or vessel walls, with at least one of IgA, IgM, IgG, or C3. IgA deposition was detected in 29 (42.6%) patients, IgM in 13 patients (19.1%), IgG in four patients (5.9%), and C3 in 31 patients (45.6%). Clinical features of the patients, including triggering factors, extracutaneous involvement, lesion localization, and skin findings, were compared with DIF findings. It was found no statistically significant difference between DIF-positive and DIF-negative groups ($P > 0.05$, for all). There was also no statistically significant difference in terms of laboratory findings between the groups ($P > 0.05$, for all). **Conclusions:** Our study showed that DIF findings did not play a role in determining the clinical findings, and they did not affect laboratory parameters in CSVV.

Keywords: Direct, fluorescent antibody technique, vasculitis

Introduction

Cutaneous small-vessel vasculitis (CSVV) is a vasculitic process that involves primarily the dermal postcapillary venules and is characterized histologically by leukocytoclastic vasculitis (LCV). Although CSVV with LCV can be seen in the setting of mixed (small- and medium-sized vessel) vasculitides, the term CSVV is generally reserved for small-vessel vasculitis of the skin without medium-sized vessel involvement, irrespective of the clinical severity of the skin disease or the underlying etiology.[1] CSVV is often idiopathic in nature but maybe secondary to an underlying cause such as drugs, infections, malignancies, and systemic inflammatory diseases have been implicated in the etiology.[2]

Clinically, the typical finding is palpable purpura, which is located on the lower extremities, but also, different types of lesions may be seen in different localizations such as upper extremity and trunk. CSVV mainly affects the skin, but the renal, musculoskeletal, and gastrointestinal system (GIS) may also be involved. Patients with no systemic findings at the time of diagnosis are less likely to develop extracutaneous involvement during the disease.[2]

The primary process in the pathogenesis of CSVV is the immune complex deposition in small vessel walls. This

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is associated with the activation of complement cascade and production of C5a, which is a neutrophil polymorph chemoattractant. After polymorph influx, lysosomal enzymes are released, and this leads to blood vessel wall damage, fibrin deposition, and the release of red blood cells (purpura) into the perivenular connective tissue. There are convincing findings about the immune-complex mediated pathogenesis of the disease, one of which is that the immune complexes can usually be detected between the basal membranes of endothelial cells and the pericytes of postcapillary venules.[3]

In the literature, there are conflicting reports about the most common immune complex type in LCV and its relationship with clinical and laboratory parameters. In this study, it was aimed to evaluate the presence of immune complex deposition and its subtype, clinical, and laboratory findings in patients with CSVV and to determine whether immune complex deposition detected by direct immune fluorescence (DIF) examination is a risk factor for the development of extracutaneous involvement.

Materials and Methods

Patients

Patients who were examined with the diagnosis of CSVV between January 1, 2000, and February 28, 2018, in the Department of Dermatology were included in the study. The database of the pathology department using the term "LCV" and "DIF"were retrospectively searched. All cases of LCV with DIF findings were reviewed by a dermatologist. Other types of vasculitis or patients diagnosed only with clinical findings were excluded. Patients' medical records were analyzed by another dermatologist to determine their demographic characteristics, clinical, laboratory, and histopathological findings. The patients' medical data such as the age at the time of diagnosis, gender, triggering factors, extracutaneous involvement, lesion localization, skin findings, laboratory parameters, and DIF findings were noted on the standardized paper forms. For extracutaneous involvement, symptoms related to joint, GIS, and kidney were reviewed from the patient's medical history or clinical follow-up records. Laboratory parameters to determine extracutaneous involvement, triggering factors, or underlying causes were reviewed. Joint involvement was defined as the presence of arthritis or arthralgias in medical history or examination. Abdominal pain, melena, hematochezia, or the presence of occult blood in the stool was described as GIS involvement. Renal involvement was defined as the presence of elevated blood creatinine levels, hematuria, spot or 24-h urinary proteinuria, or renal biopsy findings. Laboratory parameters include white blood cell (WBC), hemoglobin, blood urea nitrogen, creatinine, transaminase levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antistreptolysin-O, Complement 3 (C3) and Complement 4 (C4), rheumatoid factor (RF), antinuclear antibody (ANA), extractable nuclear antibody, perinuclear antineutrophilic cytoplasmic antibody (ANCA), cytoplasmic ANCA, urinalysis, occult blood stool (OBS), and 24-h urine protein values were recorded. Immune complexes examined on DIF included immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), and C3.

This study was approved by the Ethics Committee of the university and is registered under the following number GO 18/336-02.

Statistical analyses

Statistical analyses were performed with the Statistical Package for the Social Sciences, software version 22.0. (SPSS Inc., Chicago, IL, USA). Numerical variables were summarized as mean ± standard deviation or median (minimum–maximum). Categorical variables were given as frequencies and percentages. Categorical variables were compared by Chi-square test or Fisher's exact test. A value of $P < 0.05$ was considered statistically significant.

Results

The study included 68 CSVV patients (27 males and

Table 1: Clinical characteristics of the leukocytoclastic vasculitis patients in direct immune fluorescence positive and direct immune fluorescence negative groups

Characteristics	DIF positive ($n=36$) (%)	DIF negative ($n=32$) (%)	P*
Triggering factors			
Drug	47	50	1.00
Infection	42	41	1.00
Vaccine	0	3	N/A
Bypass surgery	3	0	N/A
Extracutaneous involvement			
Renal	53	50	1.00
Joint	64	50	0.363
GI	39	16	0.062
Neurological	3	0	N/A
Scrotal	3	0	N/A
Pulmoner	3	0	N/A
Eye	3	0	N/A
Lesion localization			
Lower extremity	97	100	N/A
Upper extremity	42	44	1.00
Glutea	39	47	0.675
Trunk	33	34	1.00
Face	6	9	0.660
Skin finding			
Macule	44	25	0.155
Papule	36	38	1.00
Plaque	19	13	0.655
Patch	39	22	0.210
Petechia	11	25	0.238
Purpura	33	53	0.161
Echymoses	3	6	0.598
Bullae	17	9	0.484
Necrosis	6	13	0.410

*Chi-square test or Fisher's exact test. N/A: Not applicable, GI: Gastrointestinal, DIF: Direct immune fluorescence

41 females) with a mean age of 34.7 ± 21.9 years (range: 2–70 years). The median time from the appearance of the rash to the time of biopsy was 14 days (range: 1–3650 days).

A total of 36 (53%) patients had deposition in the perivascular area and/or on vessel walls, with at least one of IgA, IgM, IgG, or C3. The relationship between the clinical features of the patients and DIF findings were analyzed and presented in Table 1. The differences in the triggering factors, extracutaneous involvement, lesion localization, and skin findings between DIF-positive and DIF-negative groups were not statistically significant ($P > 0.05$, for all). DIF positive group was evaluated in detail according to the deposited immune-complex subtypes and summarized in Table 2. IgA deposition was detected in 29 (42.6%) patients, IgM in 13 patients (19.1%), IgG in 4 patients (5.9%), and C3 in 31 patients (45.6%). There was no statistically significant difference between IgA, IgM, IgG, and C3 positive and negative groups in terms of triggering factors, extracutaneous involvement, lesion localization, and skin findings (all, $P > 0.05$). Laboratory findings of patients were compared, and no significant differences were found between DIF positive and DIF negative groups, as shown in Table 3. There was also no statistically significant difference in terms of laboratory findings with respect to the subtypes of the immune complexes, as shown in Table 4 (all, $P > 0.05$). Due to inadequate number in the IgG group, it was not evaluated statistically.

Discussion

Multiple factors have been reported in the etiology of CSVV, but approximately 40% of cases are idiopathic.[4] In the literature, 15%–20% of cases have been associated with infections and 10%–15% with drugs. In our study, no underlying cause was found in 41% of cases.[5] The history of the drug was determined by 49% and infection in 41%. Since some patients had taken a newly started drug during the infection, both the drug and infection were defined as triggering factors in the patient. Therefore, the prevalence of drugs and infection in our study might be higher than in the literature.

Table 2: Comparison of clinical characteristics according to immune complex subtypes in direct immune fluorescence positive group

Characteristics	IgA			IgM			C3		
	Positive (*n*=29) (%)	Negative (*n*=39) (%)	*P**	Positive (*n*=13) (%)	Negative (*n*=55) (%)	*P**	Positive (*n*=31) (%)	Negative (*n*=37) (%)	*P**
Triggering factors									
Drug	48	49	1.00	62	46	0.462	45	51	0.791
Infection	45	39	0.781	62	36	0.179	36	46	0.532
Vaccine	0	3	N/A	0	2	N/A	0	3	N/A
Bypass surgery	3	0	N/A	8	0	N/A	3	0	0.532
Extracutaneous involvement									
Renal	55	49	0.778	54	51	1.00	48	54	0.824
Joint	69	49	0.155	77	53	0.202	58	57	1.00
GI	38	21	0.190	46	24	0.166	36	22	0.319
Neurological	3	0	N/A	0	2	N/A	3	0	N/A
Scrotal	0	3	N/A	0	2	N/A	3	0	N/A
Pulmoner	0	3	N/A	8	0	N/A	3	0	N/A
Eye	0	3	N/A	8	0	N/A	3	0	N/A
Lesion localization									
Lower extremity	97	100	N/A	100	100	N/A	97	100	N/A
Upper extremity	35	49	0.354	46	42	1.00	39	46	0.723
Glutea	48	39	0.575	54	40	0.551	39	46	0.723
Trunk	38	31	0.720	54	29	0.111	36	32	0.994
Face	7	8	1.00	15	6	0.241	3	11	0.366
Skin finding									
Macule	52	9	0.029	46	33	0.520	48	24	0.070
Papule	31	41	0.555	39	36	1.00	36	38	1.00
Plaque	14	18	0.747	23	15	0.428	16	16	1.00
Patch	38	26	0.412	31	31	1.00	39	24	0.310
Petechia	14	21	0.691	15	18	1.00	10	24	0.208
Purpura	31	51	0.155	31	46	0.515	32	51	0.180
Ecchymoses	3	5	1.00	8	4	0.477	3	5	1.00
Bullae	21	8	0.156	31	9	0.060	10	16	0.494
Necrosis	7	10	1.00	15	7	0.322	3	14	0.209

*Chi-square test or Fisher's exact test. N/A: Not applicable, GI: Gastrointestinal

Table 3: Laboratory findings of the leukocytoclastic vasculitis patients in direct immune fluorescence positive and direct immune fluorescence negative groups

Parameter	DIF positive (%)	DIF negative (%)	*P**
Anemia	36	34	1.00
High WBC	28	38	0.297
High ESR	53	45	0.698
High CRP	69	70	1.00
High ASO	36	33	1.00
High creatinine	14	7	0.485
High transaminases	23	23	1.00
Low C3	10	4	0.494
Low C4	24	19	0.227
RF positivity	25	11	0.621
ANA positivity	38	40	1.00
Anti-dsDNA positivity	0	0	N/A
ANCA positivity	8	0	0.501
ENA positivity	0	0	N/A
HBV positivity	4	0	1.00
HCV positivity	0	0	N/A
Proteinuria	51	60	0.658
Hematuria	31	39	0.626
OBS	30	35	0.951

*Chi-square test or Fisher's exact test. N/A: Not applicable, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, ASO: Antistreptolysin O, C3: Complement 3, C4: Complement 4, RF: Rheumatoid factor, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA, ANCA: Anti-neutrophil cytoplasmic antibody, ENA: Extractable nuclear antigen, HBV: Hepatitis B virus, HCV: Hepatitis C virus, OBS: Ocult blood stool, DIF: Direct immune fluorescence

As extracutaneous involvement, 57% of the patients had joint involvement, followed by renal involvement with 52% and GIS involvement with 28%. In the literature, it has been reported that systemic symptoms may develop in 5%–25% of the patients with CSVV, joint involvement in 15%–65% of the patients as being most commonly, genitourinary in 3%–7% and GIS involvement in 3%–5% of the patients.[6] The prevalence of joint involvement in our study was consistent with the literature, but renal and GIS involvements were found to be higher than in the literature. Patients with Henoch-Schönlein purpura (HSP) were also included in our study. It is known that the prevalence of genitourinary involvement in patients with HSP is as high as 40%–50%, and GIS involvement may be seen in 35%–65% of the patients.[7] We think that the high prevalence rates of renal and GIS involvements might be related to the inclusion of patients with HSP in our study. Nearly all of our patients (99%) had lesions on the lower extremities, which are classical localization sites for CSVV.[7] Face, which is an unusual localization site, was also affected in 7% of the patients. Purpura was the most common skin finding with 43% of the patients and this was consistent with usual lesion type in CSVV. In patients with CSVV, mild-to-moderate inflammation may be observed. WBC, ESR, and CR*P* values may be increased, but there is a greater increase in inflammation markers in case of systemic involvement. In our study, 32% of the patients had an elevation in WBC, 47% in ESR, and 63% in CRP levels, and these results support the systemic inflammatory process in the disease.[7] There is also a known relationship between CSVV and autoimmune connective tissue diseases, and it is considered as the underlying cause in 15%–20% of the patients in the literature.[5] In this study, the laboratory parameters related to autoimmunity showed that 39% of the patients had ANA positivity, 20% had RF positivity, and 4% had ANCA positivity. These autoimmunity markers, which were detected in a large number of our patients, support the necessity to investigate and follow-up patients for autoimmune connective tissue diseases.

Vessel wall injury is related to immune complex deposition in CSVV.[6] In the literature, there are conflicting reports about the most common immune complex type in DIF.[6,8-11] In the study of Lath *et al*.,[10] DIF was positive in 60% of the patients, with the deposition of IgA being the most common, followed by C3. Nandeesh and Tirumalae[12] reported that 39% of patients were positive for DIF and they reported the most common immune complex subtype as C3, IgA, IgG, and IgM, in descending frequency. DIF positivities and the most common immune complex subtypes differ among different studies in the literature. In this study, the most common immune complex was C3 in 47% of patients, followed by IgA in 43%, IgM in 19%, and IgG in 6% of patients. There are many reports which indicate the close relationship between DIF positivity and timing of biopsy.[13-16] Because of the differences in the biopsy time and the faster dissipation of immunoglobulins compared to the complement, deposited immune -complex types were thought to differ between our study and other studies in the literature. C3 is expected to be deposited in late-stage lesions of vasculitis.[17] DIF findings are usually negative and unreliable in biopsies taken from older lesions of >48 h.[18] Therefore, early lesions should be preferred for biopsy. In this study, the age of the lesion, which was sampled, was not detected. This is one of the limitations which may have affected the DIF results. Another limitation is that it was not considered whether the biopsy site was exposed to the sun or not. It might have an effect on immune-complex depositions.[19] Biopsy site is also an important factor for stasis-related immune complex depositions.[20] IgA deposition can be detected in other dermatological diseases related to stasis,[20] but this limitation was not considered in the study when investigating DIF findings.

In our study, no statistically significant difference was found between DIF-positive and DIF-negative groups in terms of triggering factors, extracutaneous involvements, lesion localizations, and skin findings. There was also no statistically significant difference in the same parameters between immune-complex subtype groups. Takatu *et al*.[11] reported the association between IgM deposition and connective tissue disease or inflammatory comorbidities in LCV. In our study, laboratory parameters, including ANA, RF, ANCA, C3, and C4 levels, which are well-known autoimmunity markers,

Table 4: Comparison of laboratory findings according to immune complex subtypes in direct immune fluorescence positive group

Parameter	IgA			IgM			C3		
	Positive (%)	Negative (%)	*P**	Positive (%)	Negative (%)	*P**	Positive (%)	Negative (%)	*P**
Anemia	38	33	0.892	46	32	0.520	39	32	0.776
High WBC	28	36	0.413	23	35	0.560	29	35	0.447
High ESR	55	44	0.542	69	44	0.193	50	49	1.00
High CRP	69	69	1.00	100	61	0.006	69	70	1.00
High ASO	33	35	1.00	50	32	0.592	31	38	1.00
High creatinine	18	5	0.268	7	12	0.800	16	6	0.371
High transaminases	29	18	0.499	39	19	0.152	19	26	0.748
Low C3	9	6	0.811	18	5	0.341	12	3	0.420
Low C4	26	19	0.118	27	21	0.584	28	17	0.196
RF positivity	25	15	0.645	33	16	0.562	21	18	1.00
ANA positivity	46	34	0.592	42	38	1.00	40	38	1.00
AntidsDNA positivity	0	0	N/A	0	0	N/A	0	0	N/A
ANCA positivity	10	0	0.192	18	0	0.056	9	0	0.489
ENA positivity	0	0	N/A	0	0	N/A	0	0	N/A
HBV positivity	5	0	0.476	0	3	1.00	5	0	1.00
HCV positivity	0	0	N/A	0	0	N/A	0	0	N/A
Proteinuria	55	56	1.00	62	54	0.852	47	63	0.290
Hematuria	34	35	0.741	38	34	0.459	23	44	0.129
OBS	30	33	1.00	50	28	0.256	27	38	0.619

*Chi-square test or Fisher's exact test. N/A: Not applicable, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, ASO: Antistreptolysin O, C3: Complement 3, C4: Complement 4, RF: Rheumatoid factor, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA, ANCA: Anti-neutrophil cytoplasmic antibody, ENA: Extractable nuclear antigen, HBV: Hepatitis B virus, HCV: Hepatitis C virus, OBS: Ocult blood stool

were not statistically different between DIF-positive and DIF-negative groups. Takatu *et al*.[11] found a statistically significant difference with respect to ANA, SSA (anti-Ro)/SSB (anti-La) antibodies, C3/C4 levels, and IgM deposition and also with respect to ANCA and IgG deposition. Alalwani *et al*.[21] showed the correlation between DIF positivity and autoimmune markers, as well. Our study and contradictory data in the literature show that further studies are needed to elucidate the relationship between DIF findings and autoimmunity. In this study, no any association was found between extracutaneous involvement and DIF results, as in the study of Sais *et al*.[8] Unlike our results, Barnadas *et al*.[22] showed IgA deposition in patients with renal involvement and also, Alalwani *et al*.[21] detected IgA deposition in renal and GIS involvements. Takatu *et al*.[11] reported an association between C3 deposition and renal involvement, and between IgM deposition and autoimmune diseases. In our study, laboratory parameters, including blood creatinine levels, hematuria, spot or 24-h urinary proteinuria and OBS, showing renal or GIS involvement, were also not correlated with DIF findings.

The skin findings of this study were found to vary from petechiae, purpura, macule, and patch to more severe lesions, including papules, plaques, ecchymoses, bullae, and necrosis. No association between DIF findings and skin findings indicates that immune complex deposition does not affect the severity of skin lesions, and DIF findings cannot be predicted by lesion type.

It has been reported that the lesions located above the waist might be related to IgA deposition and organ involvement.[23] In this study, variable descriptions for skin findings and localizations were used. Because of the retrospective nature of the study, the objectivity of these variables might be limited. In addition to this limitation, there is a disequilibrium between the numbers of groups, which may lead to question the negative results of the study.

IgA deposition on DIF examination is an important diagnostic criterion for only HSP,[24] not for other vasculitis. This laboratory test should be requested to differentiate HSP from other small vessel vasculitis. Therefore, performing DIF examination only with IgA, not with other antibodies, fibrinogen, or complement, maybe enough for the diagnosis of HSP.

Conclusion

Based on the reports in the literature and our results, we think that DIF results did not play a role in determining the clinical findings and laboratory parameters in patients with CSVV. Therefore, the necessity of DIF examination, which is an expensive method, should be clarified with the prospective, large patient series.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Assessment of Acne Rosacea Prevalence and Quality of Life between Individuals Aged 18 Years and Over in Mahmudiye District Center, Eskisehir, Turkey (A Population-Based Study)

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Abstract

Objective: The aim of this study was to determine the prevalence of acne rosacea among adults, examine some related variables and evaluate the quality of life. **Methods:** This cross-sectional study including 2226 individuals with an age of 18 years old-above who lived in Mahmudiye-Eskisehir, Turkey. The study group was visited in their houses individually and agreed to participate the study. The researchers completed the survey forms during face-to-face interviews, performed the examinations. The Short Form-36 scale was used to assess the quality of life. The Chi-square, Mann-Whitney U test, Logistic Regression Analysis were used in the statistical analyses. **Results and Conclusions:** Of the study group 910 (40.9%) were male. Their ages ranged from 18-95 years (Mean age: 47.2±16.7). The prevalence of acne rosacea was 22.6% (n = 504). Being over the age of 55, obesity, primary school or lower education, history of complaints related to the face, family history of acne rosacea and personal history of head and/or neck treatment were identified as important risk factors for acne rosacea. Participants with acne rosacea had low quality of life based on the physical function subscale. It may be useful to perform intermittent screening, directing suspect cases to a specialist physician for early diagnosis- treatment and raise awareness.

Keywords: Acne rosacea, population-based study, quality of life, Turkey

Introduction

Acne rosacea (AR) is a common skin disorder with a not completely known etiology and usually beginning in the range of 30 and 50 years.[1] The standard diagnostic criteria of AR are one or more of the findings of transient-persistent erythema, telangiectasia, papules, and pustules, symmetrically located on the face.[2,3] The AR prevalence was reported between 4% and 22% in different studies.[4-8] AR affects every skin type and is more common in women and individuals with fair skinned.[1,9]

Although different theories have been proposed, still precise etiology and pathophysiologic mechanisms of AR remain unknown. The development of AR is multifactorial and may occur by genetic factors, environmental factors (ultraviolet[UV] radiation, reactive oxygen species, including superoxide and hydroxyl radicals, hydrogen peroxide, hot or cold, etc.), infectious reasons (*Helicobacter pylori*, *Demodex folliculorum*), gastrointestinal system (GIS) disease (dyspepsia, gastric hypochlorhydria), and psychological factors (such as major stressful life events and anxious and immature personality).[10-14] As AR primarily affects the face, it can cause patients to lose their emotional state, causing feelings of shame, anxiety, loss of self-esteem, and depressed feelings. In addition, findings such as papules, pustules, and redness may lead to physical discomfort.[15]

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Health-related quality of life, which is significantly affected by physical and mental well-being, deteriorates in these patients because both physical and psychological factors accompany with AR.[15]

There is no community-based prevalence study with AR patients in Turkey population. For this reason, the aim of this study was to determine the prevalence of AR among adults living in Mahmudiye district center, to examine some variables thought to be related with AR, and to evaluate the quality of life.

Materials and Methods

The study was a cross-sectional study that conducted between November 1, 2014, and February 28, 2015, in a study group of individuals aged 18 years and above living in Mahmudiye district center of Eskisehir. Eskisehir is a province located in Central Anatolia (near the capital of Turkey) with a total population of 844,842 people and is a reflection of the developed regions of Turkey. Eskisehir has 14 districts in total and 87% of the total population living in two districts, the city center. In Mahmudiye, one of the periphery districts of Eskisehir, the total population of 18 years and over is 3455.[16]

The ethical committee approval was taken by before the study. The rules of the Declaration of Helsinki were complied with when collecting data.

A questionnaire was prepared using the literature of the study.[17-21] The questionnaire contains information about individuals of the sociodemographic characteristics, the presence of AR and variables thought to be related, and the questions about the health-related quality of life scale short form (SF) 36. A total of 2226 people (64.4%), each of whom were visited in their home and who agreed to participate in the study, formed the study group during the study period. After being informed about the subject and the purpose of the study, verbal approvals were received from those who agreed to participate in the study. Questionnaires were filled via face-to-face. In our study, it was accepted as "AR exists" in case of at least one of the presence of lesions of erythema-telengiectasia, papules, pustules, or granulomatous lesions on the face.[2] The examinations were carried out by researchers who have been educated about the subject by a dermatologist; the patients diagnosed with AR reexamined again by the dermatologist.

Skin-type evaluation was done according to the Fitzpatrick Skin Type Classification. This scale has six skin types. The most lighted skin tones are defined as type 1, while the darkest tones are defined as type 6.[22]

SF-36 health-related quality-of-life scale was used to assess the quality of life in this study. This scale was developed by Ware and Sherbourne in 1992.[23] The validity and reliability study in Turkey were conducted by Kocyigit *et al*. in 1999.[24] The SF-36 is a self-assessment scale, based on the status of individuals within the last 4 weeks. There are eight subscales of the scale and the scores that can be taken from each subscale range from 0 to 100. As the scores get higher, the quality of life increases.

Employees who are actively involved in any income-generating business in our study are defined as "working." The family income situation was evaluated as "good, moderate, and bad," according to the individual's own perceptions. In this study, smokers smoking at least 1 cigarette per day on a regular basis were considered "smoking."[25] Those who consume more than 30 g of ethyl alcohol per week were defined as "consuming alcohol."[26] Those who consume 1 cup of coffee per day regularly were evaluated as "consuming coffee."

The presence of at least one of the complaints of redness, burning, stinging, and itching on the face was evaluated as "there is a complaint on the face." At least one of the treatment methods such as cauterization, cryotherapy, laser therapy, radiotherapy, and surgical operation for any reason in the head-and-neck region has been defined as "having any treatment story about the head-and-neck region."

The age groups were grouped as ≤34, 35–54, and ≥55 years considering the literature data and ethnicity.

Analysis of the obtained data was done in the Data were analyzed using SPSS 15.0 statistical software (SPSS Inc, Chicago, Illinois, United States). The data of the study group were given as measures of central tendency (proportion, mean, and ratio) and dispersion (standard deviation and range). Chi-square test and Mann–Whitney U-test were used for the analyses. Logistic regression analysis was also applied to determine the factors that affect AR. The level of statistical significance was accepted as $P \leq 0.05$.

Results

Of the study group, 910 (40.9%) were male and 1316 (59.1%) were female. Their ages ranged from 18 to 95 years, with a mean of 47.2 ± 16.7 years. The AR prevalence in this study was 22.6% (n = 504). There was flushing in 149 (26.5%), erythema-telangiectasia in 359 (63.8%), papulopustular in 45 (8.0%), and granulomatous lesions in 10 (1.7%) people. The distribution of AR and non-AR according to some sociodemographic characteristics in the study group is given in Table 1 and according to some diseases and complaints is given in Table 2.

The results of logistic regression analysis comprised from the variables (age group, education status, complaints on the face, AR history in the family, and a treatment for head-and-neck region) related with AR, which were detected by the analyses performed, are presented in Table 3.

Approximately two-thirds of the participants in the study group had skin types 3 and 4. No individuals with skin-type 6 were encountered. Distribution of AR and non-AR according to the skin type in the study group is given in Table 4.

In the study group, the median scores of those with AR from the "physical functioning" subscale of the SF-36 scale were

Table 1: Distribution of acne rosacea and non-acne rosacea according to some sociodemographic characteristics in the study group

Sociodemographic features	Acne rosacea			Test value (χ^2; *P*)
	No, *n* (%)[a]	Yes, *n* (%)[a]	Total, *n* (%)[b]	
Age group				
≤34	508 (84.9)	90 (15.1)	598 (26.9)	39.763; 0.000
35-54	665 (78.3)	184 (21.7)	849 (38.1)	
≥55	551 (70.7)	228 (29.3)	779 (35.0)	
Gender				
Male	696 (76.5)	214 (23.5)	910 (40.9)	0.820; 0.365
Female	1028 (78.1)	288 (21.9)	1316 (59.1)	
Education				
Primary and lower	882 (72.8)	329 (27.2)	1211 (54.4)	38.331; 0.000
Middle school	199 (78.3)	55 (21.7)	254 (11.4)	
High school	326 (82.5)	69 (17.5)	395 (17.7)	
University	317 (86.6)	49 (13.4)	366 (16.4)	
Family type				
Nuclear	1523 (77.7)	437 (22.3)	1960 (88.1)	0.773; 0.679
Extended	171 (76.0)	54 (24.0)	225 (10.1)	
Broken	30 (73.2)	11 (26.8)	41 (1.8)	
Family income situation				
Good	224 (80.3)	55 (19.7)	279 (12.5)	2.769; 0.250
Normal	1347 (77.4)	393 (22.6)	1740 (78.2)	
Bad	153 (73.9)	54 (26.1)	207 (9.3)	
Smoking status				
Smoking	475 (77.9)	135 (22.1)	610 (27.4)	3.760; 0.153
Nonsmoking	1087 (78.1)	305 (21.9)	1392 (62.5)	
Given up	162 (72.3)	62 (27.7)	224 (10.1)	
Alcohol				
No	1593 (77.6)	460 (22.4)	2053 (92.2)	0.320; 0.572
Yes	131 (75.7)	42 (24.3)	173 (7.8)	
Coffee				
No	1154 (77.2)	340 (22.8)	1494 (67.1)	0.110; 0.740
Yes	570 (77.9)	162 (22.1)	732 (32.9)	
Total	1724 (77.4)	502 (22.6)	2226 (100.0)	

[a]Percentage of row is taken, [b]Percentage of column is taken

lower than those without AR. The distribution of the median scores of subscales of the SF-36 scale in the study group with and without AR is given in Table 5.

Discussion–Conclusions

Nowadays, the increasing prevalence of AR is an important health problem because it affects the external appearance of the people, causing cosmetic worries and affecting the quality of life related to health negatively.[27]

In our study, the AR prevalence was found to be 22.6%. The AR prevalence has been reported as 22% in Estonia, 12.3% in Germany, 11% in the USA, 10% in Sweden, and 5% in Russia.[5-8] The reasons for having different prevalence in the literature include the differences in the classification/diagnostic methods and the different genetic structure and skin type of the study population.

It is generally accepted that AR peaked in over 30 years of age.[2] In our study, the AR prevalence increased as the age progressed. We found that over 55 years of age in the study group was a significant risk factor for AR. Moustafa *et al*. in the US and Abram *et al*. in Estonia also reported similar results.[6,8] Among the reasons for increased AR prevalence with increasing age are increased exposure to environmental and climatic factors playing a role in the etiopathogenesis of AR and increased prevalence of chronic diseases.

AR is reported to be more frequent in females than in males.[1] In our study, there was no difference in the AR prevalence between males and females. Furue *et al*. reported that the AR prevalence in hospital-based studies in Japan was twice as high as that in females; on the other hand, the studies conducted in community-based studies have been reported equal prevalence between female and male in consistent with our results.[6,8,10] The reason for the higher prevalence of AR in hospital-based studies in women may be due to more cosmetic anxiety and more frequent medical treatment, as AR affects mainly the facial region.

Table 2: Distribution of patients with and without acne rosacea according to some diseases and complaints in the study group

Some diseases/complaints	Acne rosacea			Test value (χ^2; *P*)
	No, *n* (%)[a]	Yes, *n* (%)[a]	Total, *n* (%)[b]	
Complaint on the face				
No	1478 (85.4)	253 (14.6)	1731 (77.8)	280.680; 0.000
Yes	246 (49.7)	249 (50.3)	495 (22.2)	
Irritant substance exposure				
No	824 (77.3)	242 (22.7)	1066 (47.9)	0.026; 0.871
Yes	900 (77.6)	260 (22.4)	1160 (52.1)	
Gastrointestinal system complaints				
No	960 (78.6)	262 (21.4)	1222 (54.9)	1.916; 0.166
Yes	764 (76.1)	240 (23.9)	1004 (45.1)	
Presence of any skin disease other than acne rosacea				
No	1600 (77.9)	455 (22.1)	2055 (92.3)	2.581; 0.108
Yes	124 (72.5)	47 (27.5)	171 (7.7)	
Family history of acne rosacea				
No	1692 (77.8)	482 (22.2)	2174 (97.7)	6.812;0.009
Yes	32 (61.5)	20 (38.5)	52 (2.3)	
Any treatment history about the head-and-neck region				
No	1647 (78.1)	461 (21.9)	2108 (94.7)	10.608; 0.001
Yes	77 (65.3)	41 (34.7)	118 (5.3)	
Chemotherapy history				
No	1706 (77.5)	496 (22.5)	2202 (98.9)	0.083; 0.773
Yes	6 (25.0)	18 (75.0)	24 (1.1)	
Total	1724 (77.4)	502 (22.6)	2226 (100.0)	

[a]Percentage of row is taken, [b]Percentage of column is taken

Table 3: Results of logistic regression analysis (final step 4) generated with variables determined to be related to acne rosacea

Variables	β	SE	*P*	OR	CI
Age range (reference: ≤34 age)					
35-54	0.345	0.169	0.042	1.412	1.013-1.968
≥55	0.816	0.187	0.000	2.261	1.567-3.262
BMI (reference: Weak)					
Normal	1.166	0.627	0.063	3.210	0.940-10.960
Overweight	1.076	0.627	0.086	2.933	0.858-10.019
Obese	1.504	0.631	0.017	4.499	1.305-15.507
Education (reference: University)					
High school	0.370	0.219	0.091	1.448	0.942-2.226
Middle School	0.671	0.240	0.005	1.956	1.223-3.130
Ground school and lower	0.710	0.200	0.000	2.034	1.375-3.008
Complaints on the face (reference: None)					
Yes	1.918	0.123	0.000	6.810	5.352-8.665
Family history of acne rosacea (reference: none)					
Yes	0.715	0.330	0.030	2.045	1.070-3.908
Any treatment history about the head and neck region (reference: None)					
Yes	0.535	0.225	0.018	1.708	1.098-2.656
Constant	−3.989	0.635	0.000	-	-

SE: Standard error, OR: Odd's ratio, CI: Confidence interval, BMI: Body mass index

AR, which is characterized by chronic relapses and has a complex and long treatment, is a chronic disease that can be triggered by environmental (exposure to temperature extremes, hot or cold, moving to a warm or hot environment from a cold one, cold wind, and heat from sunlight and severe sunburn) factors.[28] For this reason, one of the most important steps of AR administration is patient education. Treatment compliance becomes complicated for those with a low level of education.

In our study, the AR prevalence in the primary and lower education levels was higher than the university graduates.

Cigarette smoking is a very common addictive habit and is well known for its harmful health effects. Cigarette smoking is a risk factor for many chronic diseases.[29] Smoking seems to prevent the development of several immune-mediated diseases and granulomatous diseases.[30,31] In our study, there could not be found any difference between smokers and nonsmokers in terms of the AR prevalence, while Abram *et al*. reported that the prevalence of AR was lower in smokers than nonsmokers.[6] This may be thought to be due to the anti-inflammatory effect of the cigarette affecting the onset or activation of AR.[19,32]

Drinks such as tea and coffee have been shown to trigger the AR after changes in the vascular structure with increased oral temperature rather than the caffeine they contain. For this reason, it is recommended to avoid hot drinks.[33] There was no correlation between caffeine intake and AR in the study. In Estonia, a similar result to ours was reported.[6]

Alcohol can trigger AR by dilating cutaneous vascular structures.[34] There was no difference in the AR prevalence between those who consumed alcohol and those who did not. Gupta *et al*. reported that there was no relationship between alcohol consumption and AR.[14] This result may be due to the low frequency of alcohol consumption in our study.

Table 4: Distribution of acne rosacea and nonacne rosacea according to skin types in the study group

Skin type	Acne rosacea		
	No, *n* (%)[a]	Yes, *n* (%)[a]	Total, *n* (%)[b]
1	40 (69.0)	18 (31.0)	58 (2.6)
2	203 (64.9)	110 (35.1)	313 (14.1)
3	629 (73.3)	229 (26.7)	858 (38.5)
4	755 (84.4)	140 (15.6)	895 (40.2)
5	97 (95.1)	5 (4.9)	102 (4.6)
Total	1724 (77.4)	502 (22.6)	2226 (100.0)

χ^2=81.872; *P*=0.001, [a]Percentage of row is taken, [b]Percentage of column is taken

It was found that those with complaints such as "burning," "stinging," "itching," and "reddening" on the face were higher than those without AR. According to the logistic regression analysis, the complaint rate on the face increases the AR prevalence by 6.8 times. A study in Korea reported an association between focal acantholytic dyskeratosis and AR, and this association was linked to common etiologic factors such as UV–sun exposure.[35] Li *et al*. reported that basal cell carcinoma was more frequent in the skin of patients with AR in the USA.[36]

The relationship between GIS diseases and AR can be explained by the fact that diet and hormonal factors affect the structure of GIS enzymes, impair bacterial flora, and therefore prolong the duration of digestion time.[37] In a community-based cohort study conducted by Egeberg *et al*. in Denmark, AR has been found to be associated with GIS disorders such as Crohn's disease, celiac disease, ulcerative colitis, and *H. pylori* infection.[38] In our study, there was no difference between the patients with and without GIS complaints. As the diagnosis of GIS diseases is not elaborated and it is handled through GIS complaints, the relation may not be established.

Genetic susceptibility plays an important role in the etiology of AR. In the study done by Yazici *et al*., it was revealed that there is a relationship between some genes and AR.[39] Thus, AR presence in any of the family members increases the risk of other family members. One of the risk factors for AR in our study was the presence of familial AR history. The study conducted by Abram *et al*. also supports our study result.[6] The fact that family members have similar genetic makeup and that they are exposed to similar environmental effects (UV and sun exposure) and dietary factors could lead to this conclusion.

Therapeutic methods (radiation and cryotherapy) applied to the head-and-neck region may induce leukocyte activation and thus the formation of histopathological changes of AR by stimulating the inflammatory process in the skin.[40] In our study, we found 1.7 times more AR prevalence in those who had a local treatment of head-and-neck region. Treatment

Table 5: Distribution of median scores of subscales of the short form-36 scale among those with and without acne rosacea in the study group

Domains	SF-36 score			Test value (*Z*; *P*)
	Acne rosacea, median (minimum-maximum)			
	No	Yes	Total	
Physical functioning	95.0 (0.0-100.0)	90.0 (0.0-100.0)	90.0 (0.0-100.0)	2.022; 0.043
Role-physical	50.0 (0.0-50.0)	50.0 (0.0-50.0)	50.0 (0.0-50.0)	1.214; 0.225
Bodily pain	74.0 (0.0-100.0)	74.0 (0.0-90.0)	74.0 (0.0-100.0)	1.419; 0.156
General health perception	65.0 (0.0-100.0)	67.0 (0.0-100.0)	67.0 (0.0-100.0)	1.196; 0.232
Vitality	65.0 (0.0-100.0)	65.0 (0.0-100.0)	65.0 (0.0-100.0)	0.363; 0.717
Social functioning	100.0 (0.0-100.0)	100.0 (0.0-100.0)	100.0 (0.0-100.0)	0.180; 0.857
Role-mental	100.0 (0.0-100.0)	100.0 (0.0-100.0)	100.0 (0.0-100.0)	0.504, 0.614
Mental health	68.0 (0.0-100.0)	68.0 (8.0-100.0)	68.0 (0.0-100.0)	0.262; 0.793

SF: Short form

methods such as radiation and cryotherapy applied to the head-and-neck region in the study group may have caused this result by stimulating the inflammatory process.

UV radiation and chemicals have been shown to be associated with chronic inflammatory skin diseases. Irritants cause the formation of free oxygen radicals and can initiate the inflammatory process by creating vascular and dermal matrix damage. In addition, UV can cause areas such as telangiectasia in AR's histopathology by increasing cutaneous angiogenic factors (vascular endothelial growth factor–fibroblast growth factor).[41] It is therefore expected that AR patients with fair skinned will be more affected by UV damage. In our study, there was no difference between patients with and without irritant exposure, and the highest prevalence of AR was found in skin type 2 patients. In a study conducted in Estonia, it was reported that having type 1 and 2 in terms of skin type increased AR risk by 2.76-fold.[6]

Because AR affects mostly the face region, emotional disturbances can occur in people due to physical appearance, decreased self-esteem, and social phobia. In all these aspects, the health-related quality of life of the people is degraded.[15]

The scores of the SF-36 quality-of-life scale from the physical function subscale were lower than those without the AR. However, for the other subscale of the SF-36 scale, no difference was found between those with and without AR. In the study conducted by Salamon *et al*., SF-36 scores were reported to be lower on physical function, general health, mental health, emotional state, and pain subscale in patients with AR.[42] In a study conducted by Aksoy *et al*. in Turkey, it has been shown that AR affects the quality of life of people negatively.[21] AR may have altered the quality of life of the physical subdomain in a negative way, since it affects people's physical appearance and disrupts their daily work.

There are limitations of the present study. First, it was performed in a single district; therefore, the sample may not be representative of Turkish population. Second, limitation is that this study was a cross-sectional study.

AR is an important health problem among adults. Participants with acne rosacea had low quality of life based on the physical function subscale. It may be useful to perform intermittent screening for early diagnosis and treatment, directing the suspected cases to a specialist physician, and conducting informative studies to raise awareness.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

A Case of Pemphigus Vulgaris Developing after Platelet-rich Plasma Treatment

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Abstract

Platelet-rich plasma (PRP) which is peripheral blood originated product contains high concentrated platelet and many growth factors. It has been used in dermatology for many indications, including alopecias and chronic nonhealing wounds. Pemphigus vulgaris (PV) is a chronic autoimmune bullous disease of the skin and mucous membranes. We report a case of PV induced after the treatment of PRP for female pattern hair loss. The first lesions of PV occurred on the application site of PRP in this case. The diagnosis of mucocutaneous PV was established according to the clinical, cytological, and serological findings. Many physical agents and drugs were reported to induce PV. As far as is known, there is no PRP-related PV case in the literature. An *in vitro* study demonstrated that PRP may trigger the acantholysis in a genetically susceptible patient and may lead to pemphigus. Virtually, there is no enough evidence showing PRP to cause pemphigus. However, PRP treatment should be performed carefully in such patients.

Keywords: Pemphigus vulgaris, platelet-rich plasma, treatment

Introduction

Platelet-rich plasma (PRP) which is a peripheral blood originated product contains high concentrated platelet and many growth factors. It has been widely used for the treatment of chronic ulcers, orthopedic surgery, and dentistry.[1-3] In dermatology, PRP has been used for the facial rejuvenation, treatment of striae, androgenetic alopecia, alopecia areata, and scars and its utilization is getting increased more and more.[4] Pemphigus vulgaris (PV) is a chronic autoimmune bullous disease of the skin and mucous membranes. The pathogenesis of blistering in PV is based on developing autoantibodies against desmosomal adhesion proteins.[5] We present a case developed pemphigus lesions on scalp after PRP application.

Case Report

An 42-year old woman referred to our outpatient clinic for eroded lesions on her head, trunk, and mouth in February 2016. The lesions first started on her scalp 10 months before the first admission. The patient was treating with PRP for female pattern hair loss bimonthly in another hospital for a year. The first eroded lesions appeared on the scalp after a month from the last and 6th session of the PRP therapy. The patient was treated with various topical drugs and oral antibiotics without any improvement. A parenteral corticosteroid injection temporarily stopped the enlargement of the lesions. However, new blisters occured on the back, in the nose and eventually in the mouth after 3, 6, and 9 months subsequent to scalp lesions, respectively. There was no history of autoimmune disease with her family. Dermatological examination revealed eroded lesions with serous drainage on vertex and on back, erosions on the buccal mucosa and the ventral surface of the tongue [Figure 1].

A Tzanck smear from the lesions demonstrated acantholytic cells. The histopathological examination from the scalp lesions revealed suprabasal and intraepidermal acantholysis [Figure 2].

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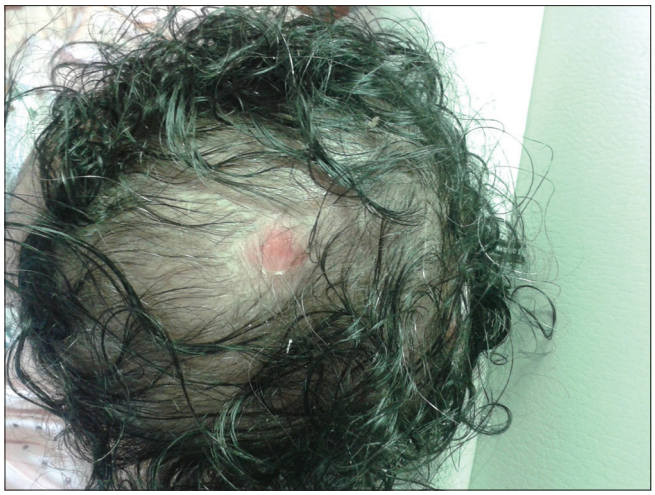

Figure 1: The eroded lesion on vertex. Female pattern hair loss is prominent

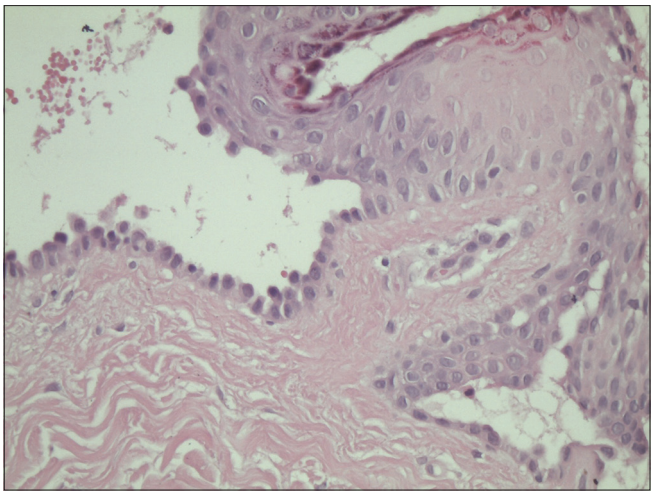

Figure 2: Intraepidermal acantholysis along with suprabasal dissociation (H and E, ×400)

Direct immunofluorescence examination was negative, but anti-desmoglein 1 and anti-desmoglein three antibody titers were 75 and 194 IU/ml with ELISA, respectively. The diagnosis of mucocutaneous PV was established according to the clinical, cytological, and serological findings. The disease was controlled by a moderate dose of oral methylprednisolone, and the patient is on complete remission with minimal therapy until now.

Discussion

Many physical agents and drugs were reported to induce PV, including surgery, dental procedures, blunt trauma, radiotherapy, angiotensin-converting enzyme inhibitors, D-penicillamine, and calcium channel blockers.[6] However, blood cell-containing products such as erythrocytes and platelets have not been reported to induce PV. Moreover, PRP has been used to cure resistant oral ulcers of PV patients and has found to be as effective as intralesional triamcinolone.[7] Furthermore, Šijan *et al*. treated a traumatic intractable leg ulcer of a PV patient in remission using homolog platelet gel.[8] The study of Hunziker *et al.,* in which the platelet-derived materials demonstrated to enhance the acantholysis caused by plasma of the pemphigus patient, points that platelets may have an effect on PV.[9] In the present case, the first lesions of PV started on vertex, where the PRP was applicated. Then, the lesions got widespread on the other skin areas and also occurred on the oral mucosa. It can be hypothesized that PRP may trigger the acantholysis in a genetically susceptible patient and exposing the antigens caused to produce anti-desmoglein antibodies, which lead to widespread skin and mucosal erosions. Another assumption is that PRP microneedling could make Nikolsky effect on the patient with subclinical disease of PV without any influence of platelets. Current findings imply that the platelet-derived products should be used with caution in the patients of PV.

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

A Case of Acrodermatitis Enteropathica Misdiagnosed as Staphylococcal Scalded Skin Syndrome

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Abstract

Acrodermatitis enteropathica (AE) is a rare genetic autosomal recessive disorder, characterized by periorificial dermatitis, alopecia, and diarrhea due to zinc deficiency. We report a case of a 9-month-old baby boy with hair loss for 2 months, diarrhea for 1.5 months, skin peeling starting around mouth, nose, anus, gradually spreading all over body over 1 month, and fever for 10 days. Due to superadded bacterial infections and altered clinical picture, he was diagnosed as a case of staphylococcal scalded skin syndrome. With low serum zinc levels and improvement of skin lesions and diarrhea within 8 days of starting oral zinc therapy, it was confirmed to be a case of acrodermatitis enteropathica. It is important to consider AE as one of the differential diagnoses in pediatric chronic diarrhea cases with acral and/or periorificial skin lesions to prevent delay in the zinc supplementation treatment and mortality.

Keywords: Acrodermatitis, periorificial dermatitis, zinc deficiency

Introduction

Acrodermatitis enteropathica (AE) is a recessively inherited defect of intestinal zinc absorption, caused by mutation in zinc transporter protein, zinc-ligand binding protein 4 (ZIP4), encoded by the gene solute carrier family 39 member 4 (SLC39A4).[1,2] Zinc is an essential co-enzyme for metal enzymes such as alkaline phosphatase, and it is also an important structural component of gene regulatory proteins required for the intracellular binding of tyrosine kinase to T-cell receptors. AE usually appears during infancy after weaning of breastfeeding. Signs and symptoms in infancy include diarrhea, mood changes, anorexia, and neurological disturbance. Eczematous/desquamative/bullous/vesicular skin lesions evolve predominantly on the extremities and periorificially. In toddlers and school-going children, zinc deficiency is characterized by growth retardation, alopecia, hypogonadism, neuropsychiatric abnormalities, and recurrent infections.[3] Spontaneous remission or death due to multiple organ failure are known to occur.[3,4] For diagnosis, zinc levels in the serum, urine, or hair are considered, but they are neither specific nor sensitive. In individuals with the typical clinical picture, decreased zinc plasma levels (<70 mg/dL) corroborate the diagnosis of AE.[4] Zinc absorption tests are cumbersome and genetic testing which are confirmatory (defect in 8q24, gene SLC39A4), are not easily available, or are not affordable to the patients. Most dermatologists/pediatricians therefore rely on immediate results of a therapeutic zinc supplementation (1–3 mg/kg body weight/day) as a confirmation of the diagnosis.[3,4]

Case Report

A 9-month-old male infant, product of a nonconsanguinous marriage, full-term normal delivery, exclusively breast fed till the age of 6 months and weaned off over the next 2 months, achieved milestones for age, and 7.5 kg body weight, presented with loss of hair for 2 months, diarrhea for 1.5 months, and peeling of skin all over body ×1 month. Mother noticed gradual

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loss of scalp hair over the last 2 months. The baby started having watery, yellowish-greenish stools, 10–12 times/day for 1.5 months. After a few days, the baby started developing erythematous scaly lesions over the feet and hands and later around mouth and perianal area. The baby was given some topical applications by the village quack. He developed pustules over the existing lesions and also in the groin and axillae. In a few days, the baby developed skin peeling almost all over the body and fever [Figure 1]. He was diagnosed as staphylococcal scalded skin syndrome (SSSS) in a pediatric hospital and was given intravenous antibiotics and hydrocortisone. The baby's condition improved, fever subsided, and pustules regressed. However, by day 5, baby developed fever again and continued to have skin peeling and diarrhea. When the baby was brought to our institute, he was lethargic, irritable, febrile and had tachycardia, anasarca, and pallor. Other systemic examination did not reveal any abnormalities.

Dermatological examination revealed extensive exfoliation of skin and erythema over the entire body in sheets with denuded areas over the perioral region, flexures, flanks, and perianal region. Perioral tightening of the skin was noticed. There was no skin tenderness. Nikolsky's sign was negative. No mucosal lesions were seen. Although the clinical picture had altered, depending on the onset of lesions postweaning, their first appearance being periorificially, and on feet, alopecia, and chronic diarrhea, provisional diagnosis of sepsis with underlying nutritional deficiency of Zinc was established. Other diagnoses such as congenital bullous ichthyosiform erythroderma, SSSS, and Steven–Johnson's syndrome were also considered [Figure 2 shows a patient of SSSS for comparison, treated at our institute, few months before this case].

The baby was shifted to the pediatric intensive care unit and was given barrier nursing. The baby was started on broad-spectrum Intravenous (IV) antibiotics, oral zinc sulfate syrup was given in the dose of 2 mg/kg body weight/day (15 mg)[3] along with multivitamin and oral protein supplements. He was given topical therapy with potassium permanganate compresses over oozy areas, topical antibiotic and antifungal creams for raw areas, and emollients over dry scaly areas.

The investigations revealed anemia (Hb: 4.2 g/dl), leukocytosis (18,700 cells/cumm – neutrophil predominance), hypoproteinemia (4.4 g/dl), hypoalbuminemia (2.4 mg/dl), and low serum alkaline phosphatase: 46U/L. C-reactive protein was positive. Pus culture and sensitivity revealed *Escherichia coli* and *Pseudomonas aeruginosa* growth. Serum zinc levels were low – 45 μg/dl (normal range 70–120 μg/dl).[5] Ultrasonography of the abdomen showed fatty liver. Skin biopsy showed parakeratosis, extensive vacuolization of the upper epidermal cells, acanthosis and spongiosis in the epidermis, and perivascular lymphocytic infiltration in the papillary dermis [Figure 3].

Chest X-ray, remaining liver function and renal function tests, urine and stool examination, blood culture, and urine and stool culture did not reveal any abnormality. ELISA for HIV, venereal disease research laboratory test, and antibodies for hepatitis B and C were negative. Genetic mutation testing was not performed due to unaffordability of the parents.

IV albumin and packed red blood cell transfusion were given in view of anasarca and anemia. Antibiotics were changed as per culture and sensitivity report. The baby was afebrile by day 5 of admission. Diarrhea improved by day 8. Erosions started healing by day 10. Erythema and scaling regressed by day 14. By day 20, the child was afebrile, playful, and smiling, his vitals were stable, and skin lesions had completely regressed [Figure 4]. The child was discharged with the counseling to

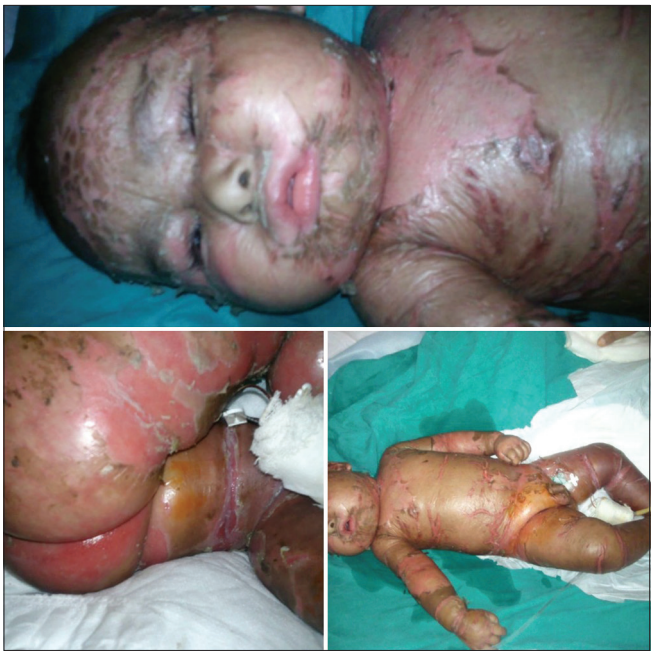

Figure 1: Periorificial dermatitis with skin peeling all over the body

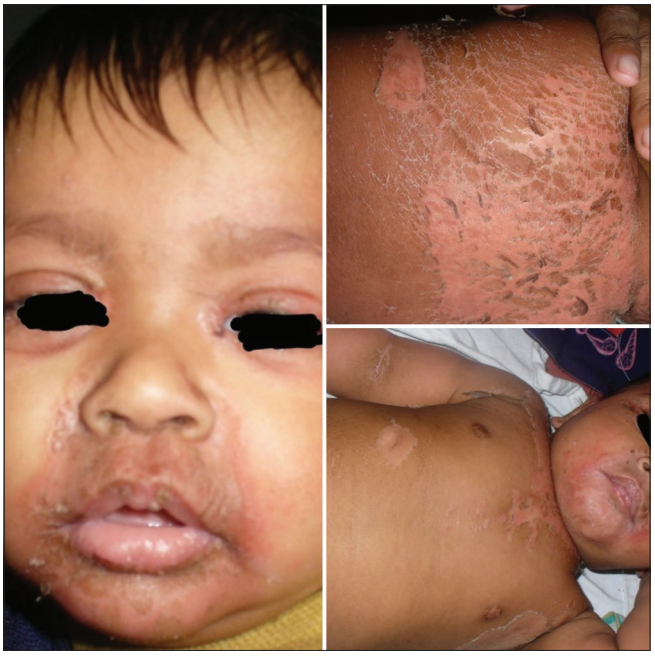

Figure 2: A case of staphylococcal scalded skin syndrome

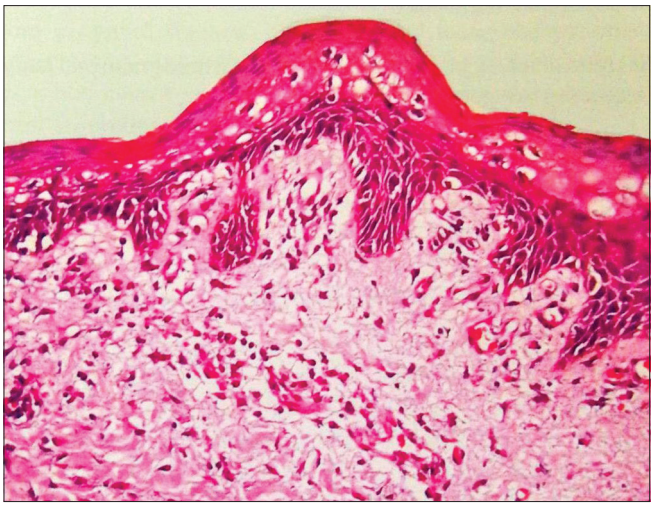

Figure 3: Histopathological image showing parakeratosis, extensive vacuolization of the upper epidermis, acanthosis and spongiosis in the epidermis and perivascular lymphocytic infiltration in the papillary dermis

the parents regarding continuation of syrup zinc lifelong. They were also advised to include seafood, liver, eggs, meat, legumes, nuts, whole grains, and leafy vegetables in the child's diet, which are good sources of zinc.

The oatient was brought to follow-up after 2 months, and he was perfectly fine, growing well. The parents were following the advice of zinc supplementation diligently.

Discussion

Zinc is an essential trace element required for the adequate functioning of the cells and plays an important role in the metabolism of proteins, carbohydrates, and Vitamin A.[1] It is a cofactor of various enzymes such as alkaline phosphatases, alcohol dehydrogenase, and RNA polymerase.[2] Zinc deficiency can be acquired or inherited. The causes of acquired zinc deficiency include premature infants, low birth weight, zinc deficiency in maternal milk, exclusive parenteral nutrition, malabsorption syndromes such as Crohn's disease and celiac disease, alcoholism, low calcium and phytate diet, and kwashiorkor.[3]

The inherited deficiency of zinc is classically known as "AE." It is caused by an autosomal recessive mutation of SLC39A4) gene on chromosome 8q24.3, which leads to a congenital partial or total deficiency of the zinc transporter protein ZIP 4.[4]

The clinical manifestations of acquired zinc deficiency and AE are similar and consist of three main symptoms: periorificial dermatitis, alopecia, and diarrhea. This clinical triad is observed in only 20% of patients with AE.[5] The lesions that usually start as erythematous, eczematous lesions are rarely vesiculobullous or pustular lesions, located around perioral, anogenital, and acral areas. Without treatment, skin lesions become erosive and spread to other periorificial areas of the face (eyes, nose, and ears), neck, lower abdomen, back, inguinal area, and thighs. Diffuse alopecia, loss of eyelashes and eyebrows, glossitis,

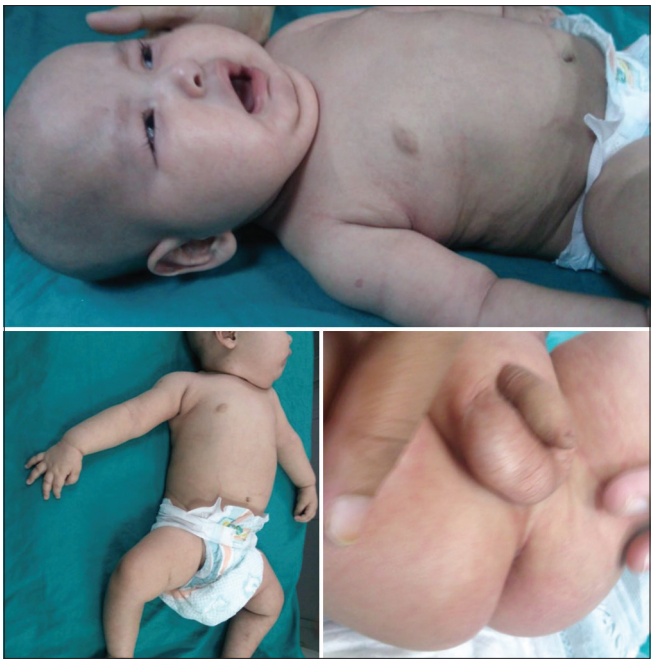

Figure 4: A case of staphylococcal scalded skin syndrome

gingivitis, stomatitis, onychodystrophy, onycholysis, and pachyonychia are observed in long-standing untreated cases.[6] In our case, the classical triad was observed in the form of alopecia, diarrhea, and skin lesions starting periorificially.

Diarrhea can be intermittent or totally absent. Children with prolonged watery diarrhea in AE usually manifest neuropsychological symptoms, such as irritability, lethargy, depression, and anorexia. Growth retardation, anemia, and ophthalmic symptoms of photophobia, blepharitis, and conjunctivitis are commonly seen.[7] Secondary bacterial infections and candidiasis (*Candida albicans*) can modify the clinical picture. In our case also, the child was only being treated for skin infections and not the underlying condition before presenting at our institute. The clinical findings of AE present with a broad spectrum and make the diagnosis challenging. The diagnosis is established by clinical symptoms, with or without low plasma zinc levels and rapid clinical response to zinc supplementation.[8]

Low hemoglobin, serum alkaline phosphatase and serum zinc levels, hypoproteinemia, skin lesions starting periorificially, alopecia, and diarrhea led us to the diagnosis of AE, which was further confirmed by dramatic clinical response to oral zinc supplementation within a few days.

The differential diagnoses to consider are superficial bacterial and fungal skin infections, napkin psoriasis, atopic dermatitis, seborrheic dermatitis, contact dermatitis, Langerhans cell histiocytosis, and cystic fibrosis.[9] Once the diagnosis is established, the treatment consists of daily oral zinc supplementation in the dose of 1–3 mg/kg, which leads to a rapid disappearance of the symptoms within a few days. With treatment, the survival rate is 100% and children show

normal growth physically and neurologically.[10] Parents need to be counseled regarding life-long treatment and monitoring of this condition.

Conclusion

AE mimics many dermatological diagnoses in pediatric patients such as SSSS, congenital bullous ichthyosiform erythroderma, Steven–Johnson's syndrome, and other dietary deficiencies. Hence, pediatric patients of chronic diarrhea, skin lesions, and growth retardation should be evaluated for serum zinc levels and given a trial of zinc supplementation therapy to prevent mortality.

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.

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Conflicts of interest

There are no conflicts of interest.

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