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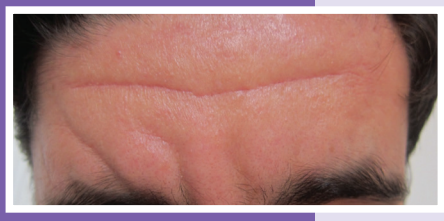

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References:

Mareledwane NG. A randomized, open-label, comparative study of oral doxycycline 100 mg vs. 5% topical benzoyl peroxide in the treatment of mild to moderate acne vulgaris. Int J Dermatol 2006; 45: 1438-1439. PMID: 17184250

Doger FK, Dikicioglu E, Ergin F, Unal E, Sendur N, Uslu M. Nature of cell kinetics in psoriatic epidermis. J Cutan Pathol 2007; 34: 257-263. PMID: 17302610

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Journal of the Turkish Academy of Dermatology

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REVIEW

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Cutaneous Findings of COVID-19: A Review of the Literature

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ABSTRACT

Many different cutaneous findings have been reported in coronavirus disease 2019 (COVID-19) patients. It is still uncertain whether these findings are associated with disease. On the other hand, lesions had different features, time of onset and prognostic relations. We reviewed published data in PubMed database with keywords of "COVID-19" and "cutaneous". We found out 34 articles consisted with 563 patients. Urticarial rash was the most common followed by chilblain-like and vesicular lesions. However, total number non-specified maculopapular rashes were higher than other lesions according to one article which included both confirmed and suspected patients. Livedo-like lesions and acro-ischemia tent to appear in severe COVID-19 patients. Chilblain-like lesions were reported more frequently in young patients at late periods of disease and also, in young normal population without history of COVID-19. Petechial and purpuric lesions were developed either true vasculitis or thrombogenic vasculopathy. Vesicular eruptions resembled to herpes simplex virus and varicella-zoster virus infections and these infections should strongly be considered. More studies and reports are needed to determine non-specific maculopapular and rare lesions such as mottling. Although many reports and classifications exist about cutaneous findings of COVID-19, their exact relationships remain to be elucidated especially for maculopapular and urticarial lesions which can also be seen in other viral exanthems and drug eruptions. Furthermore, clinical data and histopathologic features weren't reported in several articles. In conclusion, varied types of cutaneous lesions can be seen in COVID-19 and beneficial for suspicion of disease and prognosis.

Keywords: COVID-19, Cutaneous, Skin, Dermatology, Livedo-like lesions, Chilblain-like lesions, Maculopapular, Urticaria, Vesicular rash

Introduction

Since it was first reported in China on December 2019, coronavirus disease 2019 (COVID-19) has spread throughout the world rapidly [1]. Consequences were terrible and dreadful as it causes more than 250,000 deceased people in more than 180 countries worldwide [1]. World Health Organization (WHO) declared this out-brake as pandemic and governments took precautions which resulted huge impacts on socio-economic status of communities [1,2]. Suspected virus was described by WHO as Severe Acute Respiratory syndrome Coronavirus-2 (SARS-COV-2) that belongs to family of *Coronaviridae*, the same family of SARS and MERS out-brakes' agents [1,3]. It is single stranded RNA virus with envelope and transmits by inhaling of expelled droplets from patients by coughing and sneezing. Contact and carry of droplets to respiratory mucosa and conjunctiva is another important transmission path. Virus uses angiotensin-converting enzyme 2 (ACE-2) to hold on and invade respiratory epithelium [1]. Median incubation period is 5.2 (4-14) days. In most cases disease begins with fever, cough, fatigue in whom dyspnea, hypoxemia may accompany. Mortality is usually resulted by respiratory failure after 6-41 days from beginning of symptoms [4]. Diagnosis is confirmed by reverse-transcriptase polymerase chain reaction (PCR) test [1]. Although respiratory system is mostly involved, other organs can also be affected especially gastrointestinal tract [1,4]. It is not surprising because ACE-2 is expressed in many organs, particularly in small intestines [1]. The

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first report about skin findings is from China in which prevalence was reported as 0.2% [5]. Since then many cases with varied types of skin lesions were published however, it is not certain whether these findings were associated with disease [5,6]. Some of these are relatively specific to COVID-19 such as varicella like lesions on the other hand, maculopapular rash and urticarial rash are not and can be seen in other viral infections [6]. Lesions may appear before other symptoms and recognition is essential in such cases for early diagnosis and precautions [7,8]. It was also speculated that several of these lesions may predict complications and poor outcome [9]. Furthermore, not all articles presented photographs of patients and described pathological features [5]. In this paper we aimed to review reported skin lesions of COVID-19 confirmed patients in whom these lesions related to disease. We also intent to categorize these and search for existence of photographs and histopathologic investigation.

We searched for articles about skin findings of COVID-19 infection in PubMed database on May 27th, 2019. We use keyword combination of "COVID-19" and "cutaneous". All accessible articles that were written in English were evaluated. We reviewed articles that reported patients with confirmed COVID-19 infection and associated skin lesions. Articles that were reviews, not relevant with skin findings of COVID-19, written in other than English, with non-confirmed COVID-19 patients, reported skin findings not related with COVID-19 were excluded. Skin lesions that was evaluated by tele-dermatology were excluded too. We extracted demographic, clinical, histopathological data of patients and categorized them according to type of skin findings that were described by Wollina et al. [5]. Onset time of skin lesions was measured from beginning of respiratory signs of COVID-19 infection. If onset time of lesions was pointed according to hospital admission or COVID-19 diagnosis, it was also pointed in review. We also pointed existence of photographs.

Review of Cutaneous Findings of COVID-19

Searching of database reveled 85 articles. After evaluation 34 articles fulfilled the criteria and were included to the review. Six of them were studies and large case series, others were small case series and reports. Frequencies, which were reported in studies and large case series, were showed in Table 1. Characteristics of reported patients were shown in Table 2. Erythematous rash evaluated as different group due to several reports in which non-specific erythematous lesions were reported under this nomenclature.

Maculopapular Rash

In our review we reached seven articles about maculopapular rash which consisted of 14 patients. Eight females and six males were reported. Female patients' mean age was 63.2 (range: 32-84) and males was 51.6 (6-88). Onset time of rash varied between 2 and 33 days from COVID-19 symptoms. Pictures of almost all lesions existed in papers [10,11,12,13,14,15,16]. Herrero-Moyano et al. [16] performed histopathological examination in 8 patients and observed varied findings. These were spongiosis, non-follicular sub-corneal pustules, neutrophilic interstitial infiltrates and exocytosis, rare eosinophils. They reported signs of vascular injury, microthrombi in capillaries, erythrocytes extravasation in several patients. They excluded existence of infectious agents [16]. Duration of lesions were varied between 4-16 days [10,11,12,13,14,15]. Avellana Moreno et al. [14] reported patient treated with intravenous corticosteroid and antihistamines whom lesions resolved in five days on the other hand, Morey-Olive et al. [13] reported lesions that healed in five days without treatment.

Erythematous Rash

Erythematous rash were reported by seven articles in our screen. Fifty-eight patients were reported in these papers. Age and gender data were missing in some patients [17,18,19,20,21,22,23]. De Giorgi et al. [22] reported frequency in their series as 70 percent (37 patients over 53). Most of these patients had mild itch. In one report 39-year-old female developed non-pruritic, annular fixed, erythematous and edematous plaques that located on upper extremities, chest, abdomen, neck and palms. Rash resolved in seven days and no therapy was reported in that patient [18].

Pityriasis Rosea Like Eruption

We found only two reports about Pityriasis Rosea like eruption. Galvan Casas et al. [24] reported 47 patients over 375 but, no clinical features were reported. Ehsani et al. [25] reported 27-year-old man developed erythematous and scaly annular plaques. These located on forearm, trunk and upper extremities and scattered like pine-tree branches. Rash had appeared three days after from low grade fever and non-specific symptoms and continued to appear five

Table 1. Reported frequencies of cutaneous findings in COVID-19 patients from studies and case series

Author	Frequency of skin findings in COVID-19 (reported from studies and case series) Number of patients and percentages
Fernandez-Nieto et al. [40]	24/53 (NR)
Hedou et al. [20]	5/103 (NR)
Recalcati [21]	18/88 (20.4%)
De Giorgi et al. [22]	53/678 (7.8%)
Guarneri et al. [23]	13/125 (10.4%)
Herrero-Moyano et al. [16]	8/1177 (0.7%)

NR: Non-reported, COVID-19: Coronavirus disease 2019

Table 2. Demographics and clinical characteristics of COVID-19 patients with cutaneous findings

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Cepeda-Valdes et al. [28]	2	50 F 20 F	Urticaria (2)	No	No	Soon after fever	2 days	No	Antihistamines and moisturizers	Yes	NR
Llamas-Velasco et al. [35]	1	61 M	Purple ischemic lesions and livedoid Purplish retiform patches on both feet and hands (livedo-like lesions with acro-ischemia)	No	No	Simultaneously	17 days	Yes	NR	Yes	Followed in ICU
Janah et al. [26]	2	17 M 29 M	- Erythematous maculopapular atypical targetoid eruption on palms (1) - Urticarial targetoid lesions on his palms (1) (atypical erythema multiforme)	No	Yes	+15 days +12 days	NR	No	NR	NR	NR
Gunawan et al. [29]	1	51 M	- Urticaria	No	No	+5 days	1 day	NR	Loratadine	NR	No
Jimenez-Cauhe et al. [27]	4	66.75 (58-77) Females	- Coalescing erythematous papules on upper trunk which progressively turned to erythemato-violaceous patches with a dusky center and a pseudo-vesicle in the middle and spread to back, face and limbs (4) - Accompanied typical target lesions (2) (EM-like lesions)	Palatal macules and petechia (3)	No	+19.5 (16-24)	2-3 weeks	Yes	Systemic corticosteroids	NR	NR
Fernandez-Nieto et al. [40]	24	40.5 (19-62). F/M:18/6	- The diffuse pattern is polymorphic with papules, pustules, vesicles and has a tendency to a widespread distribution on trunk, palms and soles (18) - The localized pattern is monomorphic with vesicles and only involves the trunk (6) (vesicular pattern)	No	2/24 -15 (10-20)	+14 days* (4-30) 3 patients with symptomes	10 days (4-22)	2/24	NR	Yes	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Sachdeva et al. [10]	3	71 F 77 F 72 F	- Maculopapular itchy rash appeared on the trunk resembling a grover disease - Maculopapular exanthem (morbilliform) on the trunk - Papulo-vesicular, pruritic eruption appeared on sub-mammary folds, trunk and hips (maculopapular rash)	No	NR	10 days NR 4 days	NR NR 10 days	NR	NR	Yes	NR
de Masson et al. [36]	25+	NR	- Acral lesions (7) - Chilblain-like lesions (NR)	NR	NR	NR	NR	NR	NR	NR	NR
Castelnovo et al. [30]	2	NR	- Widespread urticarial rash on thigh and perimalleolar area (1) - Vasculitic purpura on legs with erythematous rash (1)	NR	NR	NR	2 days	NR	Steroid	Yes (vasculitic purpura)	NR
Ehsani et al. [25]	1	27 F	- Erythematous and scaly annular plaque on left form arm which progressed to widespread papules and plaques. (pityriasis rosea like eruptions)	NR	No	+3 days*	NR	NR	Topical corticosteroid and antihistamine (cetirizine)	Yes	NR
Paolino et al. [11]	1	37 F	Craniocaudal spreading erythematous maculopapular rash on the trunk, neck, and face, nummular erythematous lesions with a peripheral slight white halo, assuming an urticaria-like feature on the lower limbs.	NR	No	+3 days	8 days	NR	NR	Yes	NR
Zengarini et al. [17]	1	67 F	Itchy erythematous confluent rash.	No	No	+1 mo*	7 days	Yes	NR	Yes	NR
Ahouach et al. [12]	1	57 F	Diffuse fixed erythematous maculopapular rash, which was asymptomatic over the limbs and trunk, but, burning on the palms.	No	No	+2 days	9 days	Yes	NR	NR	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Galvan Casas et al. [24]	375⊥	NR	- Itchy or painful acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%) - Itchy vesicular eruptions on trunk and limbs (9%) - Itchy urticarial lesions on trunk (19%) - Other maculopapular eruptions: Perifollicular, pityriasis rosea like; Erythema elevatum diutinum like, Erythema multiforme like eruptions on extremities (47%) - Livedo or necrosis on trunk or acral sites (6%).	NR	Yes 22/275	NR	12.7 days 10.4 days 6.8 days 8.6 days NR	NR	NR	Yes	Less severe: Pseudo-chillbalin; More severe: Urticarial, maculopapular, livedo or necrosis
Morey-Olive et al. [13]	2	6 M, 2 mo F	- Erythematous, confluent, nonpruritic maculopapular rash began on trunk and neck, spread to cheek, extremities, palms and soles (1) - Itchy urticaria (1)	No	Without COVID-19 symptom	Without COVID-19 symptom	5 days	NR	No spesific treatment	Yes	NR
Tammaro et al. [41]	3	NR	- Pruritic isolated herpetiform lesions on their trunk (2) - Vesicular isolated lesions on her back (1) (vesicular eruption due to HSV)	NR	NR	NR +8 days*	NR	NR	NR	NR	NR
Avellana Moreno et al. [14]	1	32 F	- Pruritic, sudden-onset, generalized morbilliform rash that progressed cephalocaudally.	Yes	No	+6 days	4 days	NR	i.v. corticosteroid and antihistamines	Yes	NR
Amatore et al. [18]	1	39 M	Febrile, erythematous and edematous non-pruritic annular fixed plaques on upper limbs, chest, neck, abdomen and palms (febrile erythematous rash).	No	No	At same time with fever	7 days	Yes	NR	Yes	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Van Damme et al. [31]	1	71 F	- Extensive acute urticaria	NR	Yes Few days	- Few days	Started to improve but die	No	Bilastine	No	NR
Gianotti et al. [19]	3	59 F 89 F 57 M	- Widespread erythematous macules on arms, trunk and lower limbs (1) - Exanthem on trunk and arms (1) - Widespread, pruritic erythematous macules and papules (1) (erythematous rash).	NR	No	3 days* Admission 2 days	5-10 days	Yes	NR	Yes	NR
Hedou et al. [20]	5	F/M: 71/32; 47 (20-88)	- Itchy erythematous rash on face and upper body (2) - Urticaria on face and upper body (2) - HSV activation (1)	NR	Yes. Urticarial rash (1)	During illness (4) Prod-rome (1)	Median: 2 days (1-6)	NR	NR	NR	NR
Magro et al. [34]	3	32 M 66 F 40 F	- Retiform purpura with extensive surrounding inflammation on buttocks (1) - Dusky purpuric patches on palms and soles (1) - Purpuric reticulated eruption with livedo racemosa on chest legs and arms (1) (purpuric eruption, livedo-like eruption).	NR	No	11 days 19 days 14 days	11-19 days	Yes	NR	Yes	NR
Henry et al. [32]	1	27 F	Pruritic disseminated erythematous plaques particularly located on face and acral sites (urticarial rash).	NR	Yes, 2 days	-2 days	NR	No	Antihistamines	Yes	NR
Estebanez et al. [48]	1	28 F	Pruritic red yellow confluent papules on heels which hardened and progressed to plaques (non-specified).	NR	No	13 days*	NR	NR	Topical steroid	Yes	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Fernandez-Nieto et al. [33]	1	32 F	Urticarial rash	NR	No	6 days	5 days	Yes	Oral antihistamines	Yes	NR
Kamali Aghdam et al. [42]	1	15 M	Mottling	NR	No	Exist at admission	2 days	NR	NR	NR	NR
Recalcati [21]	18	NR	- Erythematous rash (14) - Urticaria (3) - Chickenpox-like vesicle on trunk (1) - Itching was observed but, not in all patients.	NR	NR	8 at onset 10 after hospitalization	Few days	NR	NR	NR	NR
Dominguez-Santas et al. [38]	1	71 F	Pruritic purpuric macules and papules on thighs, legs and ankles (purpuric eruption).	No	No	7 days	3 weeks	Yes	Topical betamethasone propionate	Yes	NR
De Giorgi et al. [22]	53	M/F: 60/40; 55.9 (28-69)	- Itchy erythematous rash (70%) - Diffuse urticaria (2%) - Vesicular eruption (4%) - Petechiae, purpura and acro-ischemia (13) Lesions located on trunk and upper limbs.	NR	Yes (44%) Exist at diagnosis	+2-23 days* (56%)	Mean: 3 days (2-5)	NR	NR	NR	NR
Mayor-Ibarguren et al. [39]	1	83 F	- Palpable purpura and serohaematic blisters on lower legs, feet, toes (petechia and purpura).	NR	No	+1 mo	10 days	Yes	30 mg/day prednisone	Yes	NR
Guarneri et al. [23]	13	NR	- Widespread urticarial rash (2) - Panniculitis (3) - Erythematous rash (2) - Chilblains-like lesions (1) - Acro-cyanosis in (2); one resulted with amputation - Itchy urticaria with angioedema (1) Lesions located on trunk, upper and lower limbs.	NR	NR	Exist at admission in 2 patients	3-18 days (erythematous rash)	NR	NR	NR	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Papa et al. [37]	1	11 F	Erythematous chilblain-like lesions and several ulcers on feet. Dyschromia of the nails.	NR	NR	NR	15 days	NR	Parasetamol and mupirocin ointment	Yes	NR
Putra et al. [15]	1	29 M	Multiple, discrete, 3 mm sized, lenticular redness papules on extremities with sensation of pins and needles on tips. Tips thickened and exfoliated (maculopapular rash).	Aphthous stomatitis	No	3 days	10 days	NR	NR	Yes	NR
Herrero-Moyano et al. [16]	8	F/M: 4/4 72.2	Ill-defined erythematous and coalescent maculopapular rash on trunk, back and folds. Pustules and desquamation appeared after.	NR	No	27.6 days	Mean: 11.6 days	Yes	NR	Yes	NR

NR: Non-reported, COVID-19: Coronavirus disease 2019, M: Male, F: Female, ICU: Intensive care unit, HSV: Herpes simplex virus, mo: Month, i.v.: Intravenous
*: Onset time was reported according to admission or diagnosis, not beginning of symptoms
⊥: Both confirmed and suspected cases were included
+: Confirmed patients with cutaneous findings but, only few patients' lesions were explained

days, became pruritic and disseminated. Patient were treated with topical steroids and cetirizine.

Erythema-multiforme Like Lesions

Three articles reported erythema-multiforme like lesions. Janah et al. [26] reported two patients with ages of 17 and 29. Both developed atypical targetoid lesions on palmar regions. No mucosal lesions and history of recurrent herpes virus infection was reported. Rash appeared after 12 and 15 days from COVID-19 symptoms. Photographs existed in papers but histopathological features didn't. Jimenez-Cauhe et al. [27] reported four patients with varied ages between 58-77. They developed rash after 16-24 days from COVID-19. However, in three of them lesions appeared after discharging from clinic. All patients had lesions on face, trunk, extremities but not on palmoplantar regions. Mucosal lesions as macules and petechia, especially on palatal sites, were reported in three patients. Histopathological features were similar in all patients. These were basket-weave stratum corneum, mild-moderate spongiosis, dilated vessels filled with neutrophils, extravasation of red blood cells, perivascular and interstitial lymphocytes. Basal vacuolar changes and lymphocytic exocytosis were observed in each different patient. All patients' lesions subsequently resolved in 2-3 weeks with systemic corticosteroids. Galvan Casas et al. [24] also reported erythema-multiforme like lesions in their series consisted of 375 patients but, however, clinical data were lack.

Urticarial Rash

Urticarial lesions were reported in 104 patients by 11 articles that consisted of five case series and six case reports. One patient developed urticarial rash accompanied with angioedema. These patients were included 79 confirmed and 24 suspected cases [13,21, 22,23,24,28,29,30,31,32,33]. Age and gender data were available in several articles. In these articles urticarial rash tent to be more frequent in females and ages were varied between two months and 71 years [13,31]. Development time of lesions were highly varied in reports. In series of Galvan Casas et al. [24] 73 patients with COVID-19 and urticarial rash were reported. In this series three patients developed lesions before and 43 at the same time with COVID-19 symptoms, 25 did after that. Henry et al. [32] reported lesions appeared before

two days, on the other hand, in case report of Fernandez-Nieto et al. [33] after six days from COVID-19 symptoms. Furthermore, Morey-Olive et al. [13] reported two-month-old infant with only fever and urticarial lesions in absence of other COVID-19 symptoms. Mean time of duration of symptoms was reported 6.8 days [standard deviation (SD): 7.8] by Galvan Casas et al. [24], seven of them were treated with systemic corticosteroid. Gunawan et al. [29] reported duration time as one day. Histopathologic investigation revealed upper dermal edema, perivascular lymphocytic infiltrates and some eosinophils [33]. There was lack of data about relation between prognosis and rash.

Vascular Lesions

Many lesions that concerning vascular involvement have been reported in COVID-19 patients. These are livedo-like lesions, chilblain-like lesions, ischemic ulcers, petechia, purpura and necrotic lesions [5]. Histopathological investigations of several COVID-19 patients revealed vascular injury with or without vasculitis, microthrombi and also complement system activation and deposition in both lesions and normal skin [34].

Few varied reports exist about livedo-like, ischemic and necrotic lesions on acral sites. Livedo-like lesions consist of livedo racemosa, purple round or reticular patches located on trunk, thigh, legs, arms feet and hands [24,34,35]. Accompanied acral ischemia and retiform purpura were also reported [34,35]. Skin symptoms varied in reports from asymptomatic to painful, burning and itchy

Table 3. Types and patient numbers of cutaneous findings

Type of cutaneous finding	Number
Total patient number	563
Urticarial rash	104
Maculopapular rash	14
Erythematous rash	59
Vesicular lesions	64
Petechiae, purpura, acroischemia, livedo, necrosis	43
Chilblains-like lesions	73
Perifollicular; pityriasis rosea like; erythema elevatum diutinum like, erythema multiforme like eruptions	183
Acral lesions	7
HSV activation	3
Panniculitis	3
Grover disease-like lesions	1
Pruritic red yellow confluent papules on heels (non-specified)	1
Chickenpox-like vesicle on trunk	1
Mottling	1

HSV: Herpes simplex virus

[24,34,35]. In a study of Galvan Casas et al. [24], which included both confirmed and suspected COVID-19 patients, together these and acro-ischemic lesions were reported in 29 patients (6% percent). This group patients showed higher mortality on the other hand, patients that showed transient lesions experienced mild disease. In that study mean age of these patients were 63.1 with SD of 17.3 and 10 of them were females (48%). Also confirmed cases were much more compared to suspected ones (81% vs. 19%). Eighteen of them (86%) developed lesions at the same time with other symptoms, 1 before, 2 after and in 8 data wasn't reported. Mean time of duration of lesions 9.4 days with SD of 5.4. Llamas-Velasco et al. [35] reported 61-year-old male patient with livedo-like lesions on hands and accompanied acro-ischemia which appeared at the same time with COVID-19 symptoms. Followed in intensive care unit (ICU), lesions showed some improvement after 19 days. Magro et al. [34] reported three patients with skin lesions concerning vascular involvement. One of them, 40-year-old female developed retiform purpura and livedo racemosa on chest, legs and arms. Lesions noted at admission and she had had symptoms for 14 days. Exact time of appearance and duration of lesions and progress of disease weren't reported but, d-dimer and INR levels were elevated. Histopathological features were reported in only two reported cases. Magro et al. [34] reported in their patient perivascular lymphocytic infiltrate and microthrombi without vasculitis in venules of the deep dermis. They also investigated patients for complement activation and observed vascular C5b-9 and C4 deposition in both lesion and normal skin biopsy that obtained from deltoid area. Llamas-Velasco et al. [35] also observed deep-dermis seated thrombi but, in larger arterial vessels that were surrounded with limited neutrophils and showed focal fibrinoid necrosis. Additionally, dilated vessels that were filled with thrombi and surrounded by mild neutrophilic components were seen in papillary dermis. Upper dermis and eccrine sweat gland necrosis, particularly in secretory parts, were also accompanied.

Acro-ischemic changes without livedo-like lesions were also reported. These lesions consisted of finger and toe cyanosis [23]. Aforementioned study from Spain included acro-ischemic lesions without livedo into livedo/necrosis group and as mentioned before, reported frequency was six percent [24]. Guarneri et al. [23] reported two patients with leg thrombosis. One of them experienced amputation due to thrombosis. De Giorgi et al. [22] reported 13 patients with petechia, purpura, acro-ischemia. These group consisted of more severe patients several of whom were cared in ICU and had clotting disorders.

Chilblain-like lesions consisted of erythematous and edematous lesions which located on acral sites. Accompanied vesicles or pustules were also reported. Skin symptoms of itch, pain or burning can be seen. Galvan Casas et al. [24] reported 71 patients

(19%) in their series. Mean age of these patients was 32.5 (SD: 21.8) and 48 of them were females (68%). Most of them developed the lesions after COVID-19 symptoms (42 patients, 59%). Twenty-four patients (34%) developed lesions at the same time of disease symptoms and 5 patients (7%) before. Mean duration of lesions were 12.7 days and more frequently seen in mild patients. Forty-two of these patients (59%) weren't confirmed by virologic tests. Guarneri et al. [23] reported 1 confirmed patient with chilblain-like lesion but, clinical features weren't pointed. On the other hand, they did research with tele-dermatology for chilblain-like lesions. They found 22 patients who were scanned for COVID-19 with rhino-pharyngeal swab samples. Mean age was 14.3 with a range of 6-30 and 19 were children. COVID-19 diagnosis was confirmed in 6 of them of whom 5 were children. de Masson et al. [36] reported several cases in their series. Papa et al. [37] reported 11-year-old girl with chilblain-like lesions with erythema and several ulcers. They also observed dyschromia on nails. There was no sign of any disease in her medical history. SARS-COV-2 wasn't detected in nasopharyngeal swab but, IgG antibodies against virus was. Lesions completely resolved with topical antibiotics and analgesic in 15 days.

Petechia and Purpuric Rash

Reported petechial and purpuric rashes could be induced by either vasculitis or vascular occlusion without inflammation [34,38]. It consisted of palpable purpura, dusky purpuric patches or retiform purpura surrounded by inflammation located on lower extremities and palms and soles [30,34,38,39]. Pruritus was reported in several patients and Koebner phenomenon in one [30,38]. De Giorgi et al. [22] reported 13 patients with petechia, purpura and acro-ischemia over 53 COVID-19 patients which was pointed above. These patients were more severe and association with coagulation disorders was observed. Magro et al. [34] reported two patients; 32-year-old male with retiform purpura with surrounding inflammation located on thighs and 66-year-old female with dusky purpuric patches located on palms and soles. Lesions appeared after 11 and 19 days from COVID-19 symptoms, respectively. Castelnovo et al. [30] reported one patient with itching purpura on legs which suggested vasculitis. Erythematous rash accompanied to lesions. This patient developed severe respiratory failure. Lesions resolved in few days with steroid treatment. Dominguez-Santas et al. [38] reported 71-year-old man with pruritic purpuric macules and papules on both legs which extended from ankle to thighs. Koebner phenomenon was positive. Lesions appeared seventh day of COVID-19 symptoms and resolved in three weeks with topical steroid. Mayor-Ibarguren et al. [39] reported 83-year-old woman with palpable purpura and serohaematic blisters on lower legs, feet and toes with a history of five days. This patient didn't have COVID-19 symptoms at admission but, she had experienced pharyngeal complaints one-month before from admission. Serologic evaluation revealed IgG and IgM antibodies against SARS-COV-2. Lesions healed in 10 days with systemic steroid treatment. Histopathologic features were depending on lesion type. Palpable purpura was characterized by basal layer necrosis, small vessel injury with fibrinoid necrosis, neutrophilic infiltration vessel walls, leukocytoclasia and erythrocyte extravasation [38,39]. Purpuric patches and retiform purpura showed vascular ectasia, thrombi in deep-seated vessels and thrombogenic vasculopathy with perivascular and interstitial neutrophilic infiltration with leukocytoclasia. Extensive necrosis of epidermis, adnexal structures and eccrine coil was also accompanied [34]. Complement deposition were observed in both types of lesions [34,38].

Vesicular Eruption

Two specific clinical patterns have been reported about vesicular eruptions. Fernandez-Nieto et al. [40] performed a study about vesicular rashes that developed in COVID-19 patients and they observed two main specific eruptions in 24 individuals: diffuse pattern and localized pattern. Diffuse pattern was seen in 18 patients and characterized with widespread polymorphic lesions consisted with 7-8 mm sized papules, vesicles, pustules mainly located on trunk, palms and soles. Localized pattern consisted with monomorphic, 3-4 mm sized vesicles involved more than one region but, primarily trunk. No difference in demographics, clinical features and COVID-19 severity was found between two groups. In total mean age was 45 (range: 19-65) and 18 of them were females. Two patients developed rash before COVID-19 symptoms and three with at the same time of symptoms began. Nineteen patients' lesions appeared after COVID-19 symptoms with a mean latency period of 14 days (4-30). Mean duration of lesions were 10 days (4-22). COVID-19 RNA was searched in four patients' vesicles but, it wasn't presented. Ten patients developed pneumonia and one of them required ICU. Others showed mild disease. Galvan Casas et al. [24] reported 34 patients over 375 suspected and confirmed COVID-19 patients (9%). Lesions consisted with itching monomorphic vesicles located on trunk and limbs which progressed bigger and diffuse lesions with serohemorrhagic content in several patients. Patients were middle-aged (mean: 45.6; SD: 20) and 19 of them were female (56%). Five of them developed lesions before and 10 patients after COVID-19 symptoms (15%). Nineteen at the same time with COVID-19 symptoms. These patients tent to show COVID-19 in moderate severity. Duration of lesions were 10.4 (SD: 9.3) days. Recalcati [21] reported one patient with chickenpox-like vesicles over 84 COVID-19 patients. De Giorgi et al. [22] reported two patients with varicelliform, scattered, vesicles in whom herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections were excluded by PCR analysis. Vesicular lesions due to HSV infection

were also reported in COVID-19 patients. Hedou et al. [20] reported HSV type 1 activation in intubated patient cared in ICU. Tammaro et al. [41] reported three patients from two hospitals. Two of them had itchy herpetiform vesicles with erythematous halo on trunk. Other patient had numerous vesicles on back. They suggested lesions were caused by agents belonging to *Herpesviridae* family. Reported histopathologic features were acantholysis, intraepidermal vesicles and ballooned keratinocytes [40].

Mottling

Only one patient has been reported with mottling. Fifteen-day-old neonate in whom fever, tachycardia (heart rate: 170 beat per minute), tachypnea (respiratory rate: 66 per minute), mild subcostal retractions were accompanied to rash at admission. He was care in ICU because of respiratory distress. He was discharged after six days [42].

Discussion

In our review we found 34 relevant articles which consisted of 563 COVID-19 patients with cutaneous findings (Table 3). Details of articles and authors can be found in Table 2. The most frequent cutaneous findings were urticarial rashes followed by chilblain-like lesions. Other frequent skin findings were vesicular lesions, erythematous rash, livedo-like lesions and acro-ischemia, respectively. Interestingly, in case series of Galvan Casas et al. [24] the total number of other maculopapular lesions such as perifollicular lesions, pityriasis rosea like lesions, erythema elevatum diutinum like lesions, erythema-multiforme like lesions were higher than all other eruptions.

Urticarial and maculopapular rashes are common lesions and may be related to many different conditions. Most important differential diagnosis is drug eruptions and lots of COVID-19 patients had already taken drugs before rashes appeared. Galvan Casas [24] suggested that these lesions weren't enough for diagnosis but, on the other hand, rash usually onset with COVID-19 symptoms therefore, they might be beneficial for suspecting COVID-19. Although these authors reported that these lesions tent to be developed in more severe patients, De Giorgi et al. [22] didn't observe correlation between these lesions and prognosis [24].

Reports of livedo-like lesions and acro-ischemia are few and reported demographic and clinical features were varied. Although specific data of age were varied and missing in several articles, it seems that lesions were observed in patients around age of 60 [24,35]. On the other hand, these lesions might be related with severe disease, requirement of ICU, increased mortality [9,24,34,35]. Galvan Casas et al. [24] reported mortality of these patients as 10 percent [35]. But, however, reports were few. Due to reticulated pattern and cyanosis, vascular involvement was suspected [34,35]. Magro et al. [34] reported patient with altered coagulation markers and complement deposition which might lead to further activation of coagulation in tissues. Reported histopathological feature in two patients revealed thrombosis in deep dermal vessels without obvious vasculitis [34,35]. Also, two reported patients with acro-ischemia showed leg thrombosis [23]. It is not surprising because hypercoagulable state and tendency to clotting is well-known features of COVID-19 disease and can be responsible for this skin manifestations through released cytokines [9,24,34].

Chilblain-like lesions were one of the most argued cutaneous findings of COVID-19 for its nomenclature and association with disease. Due to its acral involvement these lesions were mostly confused with acro-ischemia. Of course, vascular involvement possibly existed but, necrosis was absent. Furthermore, features of these lesions were similar with chilblains. Finally, literature review and suggestion has been made by Piccolo and Bassi [43] who concluded that lesions were different from acro-ischemia and should be called "chilblain-like lesions". Other argued aspect is specifity for COVID-19. In a study of Galvan Casas et al. [24] both confirmed and suspected (couldn't had been confirmed by virologic tests) patients were reported. In their report only 41% of patients with chilblain-like lesions had got certain diagnosis of COVID-19. As aforementioned before, tele-dermatologic observation of individuals with chilblain-like lesions by Guarneri et al. [23] showed only 26.3% positivity in PCR analysis of nasopharyngeal swabs. Docampo-Simon et al. [44] prospectively followed 58 individuals with acral lesions during pandemic. Forty-two of them (72.4%) had chilblain-like lesions. Thirty-nine of them were tested with PCR and only one of them resulted positive whom lesions regarded as not to be related with COVID-19. de Masson et al. [36] reported 106 individuals with chilblain-like lesions. Only several of them gave positive result for SARS-COV-2. Recalcati et al. [45] reported 11 children and three adults with chilblain-like lesions. Only three of them gave history of cough and fever before three weeks from appearance of rash. Some of these individuals were negative for COVID-19 and others weren't tested. All lesions resolved in 2-4 weeks and no etiologic factors were found. Cordoro et al. [46] reported six adolescents with chilblain-like lesions. Each three of them were clustered in two families. They reported viral upper respiratory infection symptoms 1-2 weeks before onset of rash. All were negative for SARS-COV-2 PCR test. Due to few data and individuals with negative PCR tests, several authors suggested that chilblain-like lesions weren't related with COVID-19 [44]. However, some of these individuals were seen in relatively warmer weathers which was unexpected because nature of chilblains suggests triggering by cold [24,36,43]. Furthermore, clustered cases with chilblain-like lesions into same families were also reported [24,45,46]. On the other hand, it seems that this kind

of lesions tent to be develop in younger patients and later period of COVID-19 which might explain negative PCR results [9,24,45]. Chilblain-like lesions seem to be suggestive for COVID-19, seen in younger patients, developed in later periods of disease, and may aid to find out asymptomatic and mild patients.

Petechial and purpuric lesions may be occurred due to vasculitis or thrombogenic vasculopathy [5]. Pathologic features of vasculitis consisted of leukocytoclastic vasculitis and may be caused by immune response against viral antigen accumulation [38,39]. Dominguez-Santas et al. [38] searched for SARS-COV-2 RNA in lesions but, they couldn't find out. They explained that finding with responsible immune complexes didn't contain compact viruses. Although absence of absence of viral RNA in lesions they suggested that reported patient related to COVID-19 and any cutaneous small vessel vasculitis observed during pandemic shouldn't be regarded as idiopathic unless COVID-19 ruled out. Thrombogenic vasculopathy related purpura might be caused by complement activation due to either systemic cytokine escape or direct induction of viral particles seated on lesions [9,30,34]. Magro et al. [34] showed co-localization of SARS-COV-2 spike and envelope proteins with Complement 4d and C5b-9 membrane attack complexes on vessels of lungs. They also suggested that focally activated complement system subsequently lead to microvascular injury coagulation and fibrin deposition. They also reported elevated d-dimer levels in serum of their patients. Although reported age and related COVID-19 prognosis were varied in articles, it seems that these kinds of lesions tend to occur in advanced aged patients with coagulation problems and poor prognosis [22,30,39].

Pathologic features of vesicular rash in COVID-19 patients resembled other viral infections and acantholysis seemed to be important mechanism in intra-epidermal blistering. Although Fernandez-Nieto et al. [40] couldn't detect SARS-COV-2 RNA in blister fluid, they pointed that drug usage before appearance of lesions existed in few patients and medical history of patients strongly suggested that vesicles were related with COVID-19. They explained undetected RNA in vesicle contents with false negativity of PCR and absence of standardized methods. However, several authors related their patients' lesions to herpes virus infections, and they suggested that these kinds of lesions weren't specific to COVID-19 [20,41]. Nevertheless, both chicken pox like vesicles and monomorphic scattered lesions were observed in many COVID-19 patients in most of whom drug eruption was unlikely and relationship with disease was strongly suggested [24,40,47]. Therefore, more studies and reports were required to reveal relationship between this kind of lesion type and COVID-19 [41].

In conclusion, reported cutaneous findings in COVID-19 were varied in their clinical appearance. Classification seems to be beneficial to identify these lesions however, different categorizations and nomenclatures exist in articles. Also, association of these lesions with COVID-19 is still speculative and more studies are needed to clarify. Maculopapular and urticarial rash can be seen in other viral exanthems and drug eruptions. But, nevertheless, these conditions were searched, and association was suggested in reports. Livedo-like lesions and acro-ischemia may be related hypercoagulable state in COVID-19 patients and also predict poor prognosis. Chilblain-like tend to appear young patients at late stages of mild diseases. Interestingly, these lesions were also reported in clustered normal patients during warm weathers unexpectedly. These patients might had exposed to subtle or asymptomatic disease before admitted to health-care centers. Thus, chilblain-like lesions may be beneficial to catch asymptomatic patients. Petechial lesions seem to be relatively specific to COVID-19 and can occurred due to either true vasculitis or thrombogenic vasculopathy. The latter condition may be associated with severe disease. HSV, VZV and other viral infections should be considered for vesicular lesions that appeared in COVID-19. More articles and studies are needed to determine features of other maculopapular lesions and less frequently reported cutaneous findings such as erythematous rash, mottling, erythema multiforme-like lesions and pityriasis rosea like lesions. We observed that different classifications, lack of patient and clinical data and photographs in some articles, scarcity of histopathological investigations. These needed to be updated and reorganized and caused limitations to our review. Other limitations were searching articles in only one database, couldn't access publications with languages other than English and databases for COVID-19. More specific studies, extended case series and reports with histopathological examination are necessary to clarify characteristics, pathogenesis and relations with COVID-19.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.C.K., H.S., Design: M.C.K., H.S., Data Collection or Processing: M.C.K., H.S., Analysis or Interpretation: M.C.K., H.S., Literature Search: M.C.K., H.S., Writing: M.C.K., H.S.

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Serum Apelin Levels in Psoriasis: A Case-controlled Prospective Study

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ABSTRACT

Background: Psoriasis is a chronic, inflammatory skin disease which is closely associated with obesity, cardiovascular diseases (CVD), diabetes and metabolic syndrome. Adipokines are a large of group bioactive substances secreted from adipose tissue which are involved in various metabolic diseases including psoriasis. Apelin is a very new described adipokine in this group. We aimed to evaluate the difference of serum apelin levels in patients with psoriasis vulgaris and healthy volunteers.

Materials and Methods: Fourty volunteers and 37 patients with psoriasis vulgaris were recruited in this study. Healthy adults, with no known diagnosis of cancer, CVD, diabetes mellitus, kidney failure and hematologic disorders were included in control group. Psoriasis was diagnosed according to physical and histopathological examination. Venous blood was collected into serum separate or tubes with clot activator. Biochemical analyses including fasting glucose, homeostatic model assessment-insulin resistance (HOMA-IR), insulin, erythrocyte sedimentation rate, C-reactive protein (CRP), hemoglobin A1c (HbA1c), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG) were done. Serum fasting apelin concentration was measured with the ELISA assay.

Results: The mean ages of participants of psoriasis were 43 years, and 23 male, 14 female. The mean ages of a control group were 41 years, 17 male and 23 female. There were no statistically significant differences between patient and control groups according to serum levels of total cholesterol, LDL, HDL, TG, glucose, HbA1c, CRP, and erythrocyte. The mean value of serum apelin concentration in control and patient groups were 0.13 and 0.10 pg/mL, respectively, and there were statistically significant differences. Serum apelin concentration was only correlated with age. There was no correlation between serum apelin concentrations and other biochemical parameters and HOMA-IR values.

Conclusion: In our study, we found a statistically significant difference between two groups according to serum apelin concentrations.

Keywords: Adipokine, Apelin, Inflammation, Psoriasis

Introduction

Psoriasis is a chronic, T cell mediated, inflammatory skin disorder which is affecting 2-3% of the population [1]. In the long term follow up psoriatic patients were shown to have an increased prevalence of different comorbidities including obesity, cardiovascular disease (CVD), inflammatory bowel disease, psychiatric disorders, metabolic syndrome and its components [1,2,3,4,5]. The mechanism between psoriatic skin inflammation and systemic comorbidities is still unknown, but recently psoriasis is accepted as a part of the systemic inflammation named as "psoriatic march" more than being only a single organ disease [2].

The association of psoriasis with metabolic syndrome and obesity has been reported in several studies in the literature [6]. The exact mechanism is still unknown, but long lasting chronic inflammation

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and inflammatory mediators are considered as the initiators of the development of metabolic syndrome. Moreover hypertension, dyslipidemia, insulin resistance and obesity are reported to be independently related to psoriasis other than as components of metabolic syndrome [4]. Adipose tissue is not only protecting the internal organs also it is a dynamic endocrine organ secreting multiple bioactive proteins - or adipocytokines - promoting inflammation and affecting glucose metabolism and vascular endothelial biology [6,7].

Adipokines are big family secreted by white adipose tissue which is mainly located around internal organs and subcutaneous fat tissue. Not only adipocytes but also other cells present in the adipose tissue, mainly macrophages, contribute to the secretion of adipokines [7]. Secretion of these peptides elevates with increasing adiposity. Some of these peptides act as proinflammatory molecules, and some of them called as good adipokines and have the antiinflammatory role. Proinflammatory adipokines may drive insulin resistance, disturbance of glucose and lipid metabolism, vascular dysfunction, and immune cell tissue infiltration and activation. Although this role is more clearly shown in metabolic syndrome, obesity or diabetes they also role on psoriasis by contribution to the inflammation in skin and skin cell dysfunction [7,8,9,10].

Apelin is a newly identified adipokine with peptide origin was first described by Tatemoto et al. [11] in 1998 with a widespread distribution over such variety of tissues such as kidney, heart, lung, adipose tissue, liver, endothelium, and human plasma. It mainly role in the regulation of cardiovascular and gastrointestinal system such as regulation of angiogenesis and endothelial and smooth muscle cell apoptosis, immune functions, as well as in bone physiology, fluid homeostasis and cardiovascular system embryonal development [12]. It has also been shown to enhance the sensitivity of cells to insulin and delay the development of metabolic disorders associated with obesity, to a large extent strong positive inotropic, hypotensive effect and cardioprotective effects [13]. The role of apelin is well defined in cardiopulmonary disorders and apelin pathway targeted therapies were considered as a new therapeutic approach in CVD [13,14]. The role of apelin is not well known in dermatologic diseases.

Apelin has a key regulator role on glucose and lipid metabolism and may be associated with insulin resistance, and similarly psoriasis is known to be associated with increased insulin resistance and other metabolic disorders such as dyslipidemia, hypertension, endothelial dysfunction and reduced vascular compliance and atherosclerosis; in this study we aimed to investigate if there is a significant difference in serum apelin levels between psoriasis patients and healthy controls.

Materials and Methods

Patients and Healthy Subjects

A prospective case-control study was conducted on 37 consecutive patients (23 males and 14 females) with psoriasis vulgaris and 40 healthy controls (17 male, 23 female). The study was conducted in the light of the declaration of Helsinki and followed a protocol approved by our institutional localboard (Ethical approval 2015/0048). Patients were recruited in the study after being given informed consent. Patients who have moderate to severe plaque-type psoriasis were included the study. Psoriatic patients who have diabetes, metabolic syndrome or obesity were not included in this study. Healthy adults, with no known diagnosis of cancer, CVD, diabetes mellitus, renal failure and hematologic disorders were included in the control group. The study was carried out in accordance with the World Medical Association Declaration of Helsinki and was approved by the Local Ethics Committee.

Sample Collection

Samples were collected from the patients and healthy volunteers. Each participant was present at the laboratory in the morning of sampling day, after fasting for 8-12 hours. Each participant was seated in an upright posture before venipuncture and throughout specimen collection. The tourniquet was taken off by the phlebotomist immediately to prevent hemolysis and hemoconcentration.

Venous blood was collected into serum separator tubes (BD Vacutainer; BectonDickinson, Meylan, France) with clot activator. Samples were centrifuged at 2000x g for 10 min with refrigerated bench top centrifuge and stored in -80 °C until analysis.

Biochemical analyses of total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), glucose, hemoglobin A1c (HbA1c), C-reactive protein (CRP), and erythrocyte sedimentation rates (ESR) were done with AU 680, Beckman Coulter, USA. The methodology and intra/inter-assay analytical CV's were determined for two levels.

The serum apelin concentration was measured with the ELISA assay (Phoenix, Apelin12, California, USA).

Statistical Analysis

Statistical analyses were carried out using the "Statistical Package for the Social Sciences (SPSS) 15.0 for Windows (SPSS Inc., Chicago, IL, USA) software. Categorical variables were expressed as percentages and continuous variables as the mean±standard deviation (SD). The distribution of variables were assessed by Kolmogorov-Smirnov test. Differences between two groups were analyzed using "Student's t-test" (parametric distributed variables) and "Mann-Whitney U test" (nonparametric distrubuted variables) for continous variables and Pearson chi-square for categorical variables.

For the analysis of correlation coefficients, Pearson and Spearmen correlation tests were used for normally and non-normally distributed variables, respectively.

Results

In total, the data of 77 patients were analyzed. The mean ages of participants were 43 (SD±12) and 41 (SD±13) years in patient and control group, respectively. Baseline characteristics of both groups were comparable and shown in Table 1.

There were not statistically significant differences between patient and control groups according to serum levels of total cholesterol, LDL, HDL, TG, glucose, HbA1c, CRP and ESR.

There were statistically significant differences between two groups according to serum apelin concentrations. The mean value of serum apelin concentration in control and patient groups were 0.13 and 0.10 ng/mL, respectively ($p<0.05$). The box plots of serum apelin concentrations are shown in Figure 1.

The correlation between serum apelin concentrations and other parameters were evaluated. Serum apelin concentration was only correlated with age. The correlation between serum apelin concentration and age are shown in Figure 2. There was no correlation between serum apelin concentrations and other biochemical parameters, psoriasis area and severity index scores, and homeostatic model assessment-insulin resistance (HOMA-IR) values. Expectedly, there was association between serum total cholesterol level and ESR, HbA1c and HOMA-IR values. Serum TG concentration was correlated with HbA1c and HOMA-IR values. There was also the correlation between serum LDL concentration and HbA1c levels.

Discussion

Apelin is a newly defined adipokine with anti-inflammatory, antiatherogenic and cardioprotective effects [15]. It is a hypoxia inducible peptide, produced and secreted by adipocytes, stromal vascular structure, and cardiovascular tissues [16]. In addition to hypoxia, secretion of this peptide is controlled by different factors including tumor necrosis factor (TNF)-alpha and insulin [16,17]. The link between apelin and insulin was studied in different clinical studies, and challenging results have been reported in the literature. Some authors claim that when compared to normal

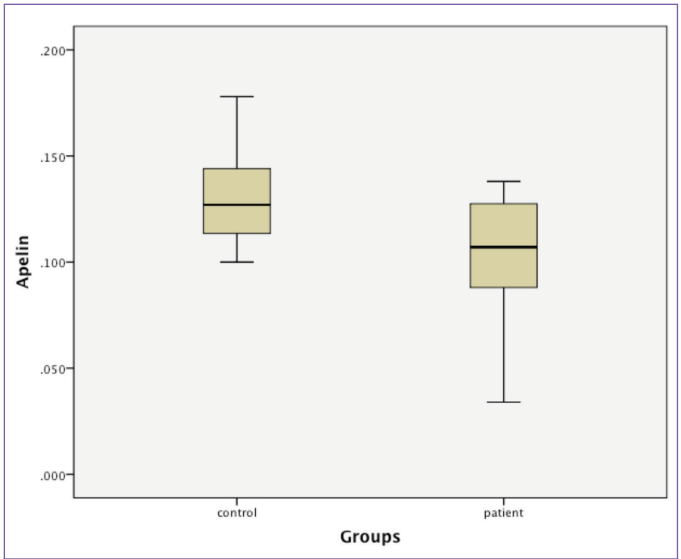

Figure 1. The boxplots of serum apelin concentrations according to the groups ($p<0.001$)

Table 1. Baseline characteristics of both groups

	Patients (n=37)	Control (n=40)	p value
Gender (F/M)	14/23 (37.8%/57.5%)	23/17 (62.2%/42.5%)	0.084$^{\$}$
Age	43±12	41±13	<0.001$^{\&,\#}$
Triglycerides	158±136	162±91	0.334*
HDL cholesterol	51±16	50±14	0.3*
LDL cholesterol	130±53	129±38	0.668*
Total cholesterol	209±60	211±42	0.882$^{\#}$
Sedimentation	20.7±16	20.6±18.1	0.976*
CRP	0.7±0.8	1.02±1.7	0.796*
HOMA-IR	2.35±7.73	2.05±4.61	0.879
HbA1c	5.3±1.8	5.9±0.7	0.053*
Glucose	104±36	102±19	0.75*
Apelin (ng/mL)	0.106±0.03	0.130±0.02	<0.001$^{\&,\#}$

F: Female, M: Male, LDL: Low density lipoprotein, HDL: High density lipoprotein, CRP: C-reactive protein, HbA1c: Hemoglobin A1c, HOMA-IR: Homeostatic model assessment-insulin resistance.
Data are expressed as mean±standard deviation or as number of patients.
*p value is based on Mann-Whitney U test; $^{\$}$p value is based on chi-square test; $^{\#}$p value is based on Student's t-test $^{\&}$p<0.05 compared to control group

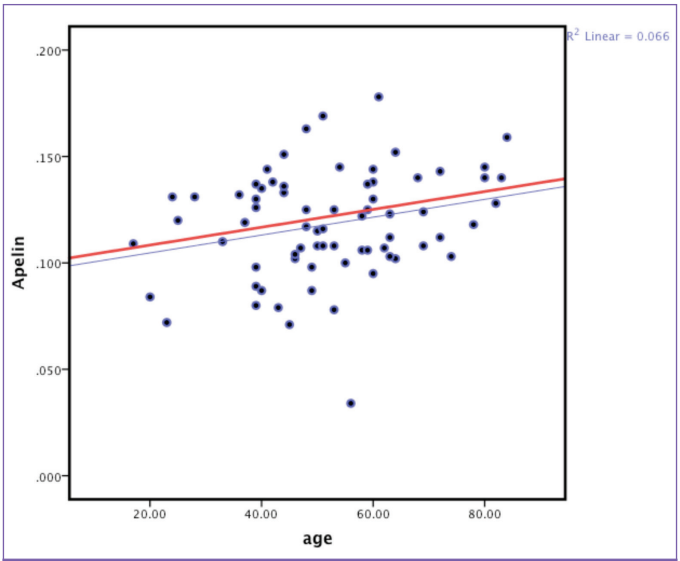

Figure 2. Correlation analysis of serum apelin concentration and age (p=0.031)

controls, plasma apelin concentration was reported to be increased in insulin resistant subjects, as well as in morbid obese individuals with type 2 diabetes mellitus and metabolic syndrome while in some studies lower concentrations of apelin was detected in obese patients [18,19,20,21,22]. The role of obesity in apelin secretion was reported to be mainly associated with increased hypoxia in adipose tissue. In our study, we did not include obese individuals or patients with metabolic syndrome for not to affect the apelin levels independently.

Decreased levels of apelin have been reported mainly in cardiovascular disorders, preeclamptic women and in polycystic ovary syndrome and were considered as novel biomarker for cardiovascular disorders [23,24,25,26]. Positive inotropic, antiatherogenic and cardioprotective effects have also been emphasized in these studies.

The role of apelin in skin disorders has been reported in few studies in the literature [27,28,29]. Dertlioglu et al. [27] reported increased levels of apelin in psoriasis patients, but they did not exclude patients with metabolic syndrome in their study. Also incerased levels of apelin have been reported in systemic scleroderma patients with conflicting results [28,29]. Kovacs et al. [30] investigated the expression of the major adipokines in sebaceoud glands of healthy skin samples and they did not detect apelin expression in sebocytes.

As mentioned above adipose tissue produces both pro- and anti-inflammatory mediators that influence local and systemic inflammation and expressions of these peptides may change according to the underlying metabolic situation. Major adipokines such as adiponectin, leptin, resistin and visfatin that are known to be dysregulated in obesity and obesity-induced chronic inflammation. They were also found to be abnormal in psoriasis. However, in some studies, controversial data shows that the alterations of adipokine levels are similar to changes found in obesity but independently associated with psoriasis. Adiponectin, C1q/TNF-related proteins (CTRPs), omentin, and secreted frizzled-related protein 5 (SFRP5) are anti-inflammatory adipokines produced by adipose tissue and their low levels have been shown in psoriatic patients in several studies [31]. Also, increased levels of proinflammatory adipokines such as leptin, chemerin and resistin have also been reported in psoriasis patients in different studies [31,32,33].

Study Limitation

The small sample size is the main limitation of our study.

Conclusion

In our study, we detected decreased levels of apelin which has an anti-inflammatory role in psoriasis patients when compared to healthy controls. According to these results, we believe that in psoriasis patients chronic inflammation of psoriasis may also lead dysregulation of adipokines independently from obesity. We also think that decreased levels of apelin seem be related to chronic inflammation of psoriasis that induces hypoxia leading to adipose tissue dysfunction and adipose tissue fibrosis and may result in decreased release of anti-inflammatory adipokines. Decreased levels of apelin in psoriasis patients may be associated with this mechanism of adipose tissue dysfunction and adipose tissue fibrosis that result in decreased release of apelin. To prove this further effect studies with the larger population are needed.

Ethics

Ethics Committee Approval: The study was conducted in the light of the declaration of Helsinki and followed a protocol approved by our institutional localboard (Ethical approval 2015/0048).

Informed Consent: Patients were recruited in the study after being given informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.K.Ü.U., H.E., A.S.K., N.A., Concept: T.K.Ü.U., H.E., Design: T.K.Ü.U., H.E., Data Collection or Processing: T.K.Ü.U., H.E., Analysis or Interpretation: T.K.Ü.U., H.E., N.A., Literature Search: T.K.Ü.U., A.S.K., Writing: T.K.Ü.U., A.S.K.

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Assessment of the Efficacy of Narrow-band UVB Treatment and Correlated Factors in Cutaneous Lichen Planus

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ABSTRACT

Background: Lichen planus (LP) is a papulosquamous skin disorder that affects less than 1% of the general population. As the cutaneous disease has a benign course, treatment depends on the location of the lesions; and the severity of the symptoms such as itching and hyperpigmentation. Narrow-band ultraviolet-B (nbUVB) has various cutaneous immunosuppressive effects, which makes it a potentially good treatment modality for cutaneous LP that is an immune-driven disease.

Materials and Methods: We present a total of 49 cutaneous LP patients treated with nbUVB three times weekly and have achieved complete remission. The age of the patient, the disease duration and the total number of sessions needed to achieve remission were noted. Spearman correlation coefficient was calculated.

Results: A total of 49 patients were included in this study. The mean age of the patients was 46 (9-71) years. The mean disease duration was 43.27 (1-300) months with a standard deviation of 75.4 months. The mean number of nbUVB sessions needed to achieve remission was 27.5 (12-63) sessions with a standard deviation of 9.6. No correlation between the number of sessions needed to achieve remission and the patient's age or disease duration were detected.

Conclusion: nbUVB treatment is a safe and effective treatment modality in cutaneous LP patients; and the number of sessions needed to achieve remission is independent of the patient's age and disease duration.

Keywords: Dermatology, Lichen planus, Phototherapy

Introduction

Lichen planus (LP) is a papulosquamous disorder, affecting less than 1% of the general population and mainly affects adult patients; however rare cases of pediatric LP have also been reported [1]. The mean age of diagnosis of cutaneous disease is 40 to 45 years of age; and 50 to 60 years of age for oral disease [2]. The disease has no gender predilection [1]. There are some reports of the disease having a female predilection, though. The disease has a self-limiting course; often resolving in a time period of a month to 7 years [3]. Infections, especially hepatitis C virus; environmental and genetic factors; and immune dysregulation are the possible etiologic factors for LP [1].

The clinical presentation of the disease varies according to the area involved. Mainly there are mucosal and cutaneous presentations. The cutaneous lesions are flat topped violaceus polygonal papules [1,2]. The papules may coalesce into large plaques. Both the papules and the plaques may have a white reticulation superimposed on them; which is referred to as the Wickham striae. Extremities are the most commonly affected areas; flexor wrists and ankles leading them all. The cutaneous lesions may have a zosteriform, blaschkoid or inverse distribution as well. The patients may complain of intense pruritus, which leads to secondary excoriations [3]. The oral disease has a more chronic course; it presents with a lace-like white

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reticulation most commonly symmetrically located on the buccal mucosa. Erosions and ulcerations may occur [2]. The disease may involve the hair follicles, as lichen pilanopilaris, and the nail unit as well [4].

As the cutaneous disease has a benign course, treatment depends on the location of the lesions; and the severity of the symptoms such as itching and hyperpigmentation. The mucosal disease, instead, has a more chronic course and should be treated due to the risk of squamous cell cancer arising within it. The first line treatment modality for cutaneous lesions is high potency topical corticosteroids [2]. Other treatment modalities used for cutaneous LP, especially for more wide-spread disease, are systemic corticosteroids, acitretine, sulfasalazine, griseofulvin, hydroxychloroquine and narrow-band ultraviolet-B (nbUVB) [5,6]. The treatment of mucosal lesions is beyond the scope of this article.

nbUVB is a phototherapy modality in which a light of 310 to 315 nm wavelength is emitted from a light source; the most commonly used wavelength being 312 nm. The nbUVB has inhibitory effects on the Langerhans cells along with inducing anti-inflammatory effects via Intracellular Adhesion Molecule 1 suppression. nbUVB is unique for its selective wavelength and fewer side effects; and it can even be used safely in children and in pregnant women [7]. nbUVB has been proven to be efficacious in the treatment of cutaneous LP. The previously used treatment protocols had an average energy of 9-17 J/cm^2 and nbUVB was applied three to four times weekly [7,8,9,10,11]. The total number of treatment sessions needed was found to be independent of age and disease duration [9,11]. This study aims at determining the correlation between the patient's age and the total number of treatment sessions needed to achieve remission; and between the disease duration and the total number of treatment sessions needed to achieve remission, in a larger study group.

Patients and Methods

This is a retrospective study evaluating the relationship between total number of nbUVB treatment sessions needed to achieve remission, with the disease duration and the age of the patient, in cutaneous LP patients. The patient files of the cutaneous LP patients who received nbUVB treatment at the Phototherapy Outpatient Unit of our department between the January 2018 and January 2020, were analyzed. Only the patients who have achieved complete remission were included in this study: a total of 49 patients. The following parameters were noted from the files: age at the time of treatment (in years), the disease duration (in months) and the total number of sessions needed to achieve remission. The nbUVB treatment protocol for all patients was as follows: a starting dose of 0.30 J with a 15% dose increment every 2 sessions, three sessions per week. The patients wore protective gear for the ocular and genital areas.The nbUVB device that was used is Waldmann W- UV 7002. Topical mouisturizers and topical medium-potency corticosteroids were offered to the patients. Relapse and recurrence rates were not analyzed in this study. The approval of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine Ethics Committee was obtained before the study was initiated. Patient consent was taken from all patients before the phototherapy.

Statistical Analysis

SPSS was used for statistical analysis. Non-parametric tests were performed since the data did not show a normal distribution. Spearman correlation coefficient was calculated.

Results

A total of 49 patients were included in this study. The mean age of the patients was 46 years with a standard deviation of 13.6; the oldest patient was 71 years old and the youngest patient was 9 years old. The mean disease duration was 43.27 months with a standard deviation of 75.4 months; the shortest disease duration was 1 month and the longest was 300 months. The mean number of nbUVB sessions needed to achieve remission was 27.5 sessions with a standard deviation of 9.6; the minimum number of sessions was 12 and the maximum was 63. The data did not show a normal distribution pattern. The descriptives of the data is summarized in Table 1.

The Spearman correlation coefficient between the age of the patient and the number of sessions to achieve remission was calculated as -0.158. The Spearman correlation coefficient between the disease duration and the number of sessions needed to achieve remission was -0.270. Both of the relationships were statistically insignificant. Thus, there is no correlation between the number of sessions needed to achieve remission and the patient's age or disease duration.

Table 1. Descriptives of the data

	Mean	Standard deviation	Minimum	Maximum
Age (years)	46	13.6	71	9
Disease duration (months)	43.37	75.4	1	300
Number of sessions needed to achieve remission	27.5	9.6	12	63

Discussion

Epidermal cell destruction orchestrated by T-lymphocytes is the underlying pathogenetic mechanism for LP [10]. nbUVB has various cutaneous immunosuppressive effects, which makes it a potentially good treatment modality for cutaneous LP that is an immune-driven disease. nbUVB decreases the number of Langerhans cells in the epidermis; increases the production of anti-inflammatory cytokines, prostanoids and neuropeptides from the keratinocytes: interleukin-10, alpha-melanocyte stimulating hormone and prostaglandin E2; increases the expression of interleukin-1 receptor-2; suppresses the neurophils and decreases Intracellular Adhesion Molecule 1 [12].

Taneja and Taylor [10] were the first to report the efficacy of nbUVB treatment in cutaneous LP patients. A year later, Saricaoğlu et al. [8] studied the efficacy of nbUVB in 10 cutaneous LP patients. In their study, 50% of the patients achieved remission at the end of the 30th treatment session; and 80% achieved remission by the end of the study. They also concluded that nbUVB was effective in the treatment of cutaneous LP; and that nbUVB was safer than psoralen-UVA treatment and the cumulative UV dose was lower in nbUVB.

Iraji et al. [7] compared the efficacy of nbUVB in disseminated cutaneous LP to systemic corticosteroids. A total of 46 patients, who had at least 20% body surface area involvement and had pruritus resistant to oral anti-histaminic drugs, were divided into two groups: the first group received nbUVB three times weekly for 6 weeks at a maximum dose of 9 J/cm^2; and the second group received oral prednisolone 0.3 mg/kg/day for 6 weeks. nbUVB was found to be more effective than systemic corticosteroids in the treatment of disseminated cutaneous LP. Furthermore, it serves a good treatment alternative in patients for whom systemic corticosteroids or other immunosuppressive drugs are contraindicated.

There are two previous studies in the literature which have studied the parameters that might affect the treatment response of LP to nbUVB. Habib et al. [11] conducted a study on twenty patients. They found that the average number of sessions required for remission was 30; which is close to our result of 27.5. They also concluded that the required session number was independent of patient's gender, skin phototype, disease duration and patient's age. Pavlotsky et al. [9] investigated the effect of gender, age, phototype, disease duration, previously used treatment modalities and comorbid diseases on the treatment response and the cumulative exposure dose in 43 cutaneous LP patients who were treated with nbUVB. They concluded that the complete response rate and the cumulative exposure dose, thus the total number of treatment sessions required to achieve remission, were independent of all the parameters that were mentioned above. Similar to Habib et al. [11] and Pavlotsky et al. [9], we also report that the total number of treatment sessions required to achieve remission is independent of the patient's age and the disease duration. Moreover, our sample size (49) was greater than Habib et al. [11] and Pavlotsky et al. [9] (Table 2).

Conclusion

nbUVB treatment is a safe and effective treatment modality in cutaneous LP patients. This study evaluated the effect of patient's age and disease duration on the total number of treatment sessions needed for complete remission. The number of sessions needed is independent of the patient's age and disease duration.

Ethics

Ethics Committee Approval: The approval of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine Ethics Committee was obtained before the study was initiated.

Informed Consent: Patient consent was taken from all patients before the phototherapy.

Peer-review: Internally peer-reviewed.

Table 2. Efficacy of narrow-band UVB in lichen planus

Authors	Year	Number of patients	Maximum dose (J/cm^2)	Conclusions
Taneja and Taylor [10]	2002	5	Not mentioned	nbUVB is a treatment alternative for generalized cutaneous LP
Saricaoğlu et al. [8]	2003	10	17	nbUVB is a treatment alternative for generalized cutaneous LP
Habib et al. [11]	2005	20	Not mentioned	nbUVB is efficacious in the treatment of generalized cutaneous LP; skin phototype, gender, age and disease duration do not influence the treatment response
Pavlotsky et al. [9]	2007	43	11	The treatment response of generalized cutaneous LP is independent of gender, age, skin phototype, disease duration, previous treatment modalities and comorbid diseases
Iraji et al. [7]	2011	46	9	nbUVB is more efficacious than systemic corticosteroids in the treatment of generalized cutaneous LP (p=0.008)

LP: Lichen planus, nbUVB: Narrow-band ultraviolet-B

Authorship Contributions

Surgical and Medical Practices: T.K.Ü.U., D.Ö., Ö.A., B.E., Concept: T.K.Ü.U., Ö.A., Design: T.K.Ü.U., Ö.A., B.E., Data Collection or Processing: T.K.Ü.U., D.Ö., Ö.A., B.E., Analysis or Interpretation: T.K.Ü.U., Ö.A., B.E., Literature Search: T.K.Ü.U., D.Ö., Writing: T.K.Ü.U., D.Ö.

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ORIGINAL ARTICLE

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Epidemiology and Comorbidities of Bullous Pemphigoid: A Retrospective Study

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ABSTRACT

Background: Bullous pemphigoid is the most common autoimmune subepidermal bullous dermatosis which is most commonly seen in the elderly population. Bullous pemphigoid was confirmed to be associated with neurologic and psychiatric disorders; however, it is not associated with malignancies.

Materials and Methods: The aim of this study is to determine the female-to-male ratio and the mean ages of diagnoses; disease durations and comorbidities separately in the female and male Turkish patient groups. In this descriptive study, the patient files of bullous pemphigoid patients who applied to the Istanbul University-Cerrahpasa Faculty of Medicine, Department of Dermatology Blistering Diseases Outpatient Clinic between the years 1999 and 2019 were evaluated retrospectively. The gender, the age at the time of diagnosis, the disease duration and comorbid diseases of each patient were noted.

Results: For the 58 patients included in this study the female-to-male ratio was 1.42. The average age of diagnosis was 73.79 years (15-103 years). The average disease duration was 104.9 months (1-264 months). As for the comorbidities, the most commonly observed ones were, in decreasing frequency, hypertension, diabetes mellitus, coronary artery diseases, chronic kidney disease and osteoporosis.

Conclusion: Bullous pemphigoid has a female predominance and is usually diagnosed during the seventh decade. This study showed an association between bullous pemphigoid and cardiac diseases or diabetes mellitus. However, the results failed to show an association with neurologic or psychiatric diseases. Bullous pemphigoid is not associated with malignancies; similarly, this study did not find a significant prevalence of history of malignant neoplasms in bullous pemphigoid patients.

Keywords: Bullous, Comorbidities, Epidemiology, Pemphigoid

Introduction

Bullous pemphigoid is an autoimmune subepidermal blistering disease that is most commonly seen in the elderly population [1]. It is the most commonly diagnosed autoimmune blistering disease overall. The rise in the incidence of bullous pemphigoid can be explained by three factors: the aging population, the increase in drug-induced cases and the ameliorated diagnosis of the non-bullous forms [2]. Dipeptidyl peptidase-4 inhibitors, a novel drug used in the treatment of diabetes mellitus, are frequent culprits for drug induces cases [3]. Diuretics, antipsychotics and check-point inhibitors used in the treatment of malignancies are also responsible for drug induced cases [2].

Bullous pemphigoid has a wide spectrum of disease presentation. In the non-bullous phase of the disease, the patient complains of generalized pruritus, erythema or urticaria-like lesions. Thebullous phase, presents with tense vesicles or bullae on

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erythematous or healthy skin appearing symmetrically on the lower trunk, flexor aspect of the extremities and the abdomen [4]. The diagnosis of bullous pemphigoid is confirmed by biopsy from the lesions, perilesional direct immunofluorescence, indirect immunofluorescence from the patient's sera and immunoblotting [5].

In the past, the mortality rate of bullous pemphigoid has been reported up to 25% [6]. The first line treatment modalities are systemic and topical corticosteroids. Doxycycline, dapsone, methotrexate, azathioprine, mycophenolic acid, intravenous immunoglobulin, rituximab and omalizumab may be used in patients who cannot tolerate corticosteroids or in refractory cases [2,3,7]. The association of bullous pemphigoid with malignancies has been questioned a lot and it was concluded that the disease is not associated with malignancies overall; however, there is a possible association with hematologic malignancies that has not been confirmed yet [8]. On the other hand, bullous pemphigoid was confirmed to be associated with neurologic and psychiatric disorders [1].

Previous studies have shown an overall female predominance of the disease with mean ages of diagnoses ranging from the 6th decade to 8th decade [1]. The aim of this study is to determine the female-to-male ratio and the mean ages of diagnoses; disease durations and comorbidities separately in the female and male Turkish patient groups.

Materials and Methods

In this descriptive study, the patient files of bullous pemphigoid patients who applied to the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Dermatology Department Blistering Diseases Outpatient Clinic between the years 1999 and 2019 were evaluated retrospectively. The gender, the age at the time of diagnosis, the disease duration and comorbid diseases of each patient were noted. Only the patients whose diagnosis was confirmed with biopsy and direct immunofluorescence were included in this study. Patients with cutaneous and/or mucosal lesions were included in the patient group. A total of fifty-eight patients met the inclusion criteria.

The approval of Istanbul University-Cerrahpasa Medical Faculty Ethics Committee was obtained before the study was initiated (06/12/2019-186949).

Statistical Analysis

Data analysis was performed with SPSS program. The female-to-male ratio and the mean ages of diagnoses; disease durations and comorbidities overall and separately in the female and male patient groups were determined. The comorbidities were analyzed separately for both genders.

Results

A total of 58 patients were included in this study. There were 34 female patients and 24 male patients. The female-to-male ratio was 1.42. The average age of diagnosis was 73.79 years (15-103 years). The average disease duration was 104.9 months (1-264 months) As for the comorbidities, the most commonly observed ones were, in decreasing frequency, hypertension, diabetes mellitus, coronary artery diseases, chronic kidney disease and osteoporosis. Tables 1 and 2 show the comorbid diseases observed in the female patient group and male patient group respectively.

Table 1. Comorbid diseases observed in female patients

Disease	Number of patients
Hypertension	15
Diabetes mellitus	7
Osteoporosis	3
Alzheimer's diseases	3
Hypothyroidsm	2
Coronary artery disease	2
Valvular diseases	2
Chronic kidney disease	1
Hyperlipidemia	1
Uterine myoma	1
Ovarian cysts	1
Pulmonary hypertension	1
Parkinson's disease	1
Schizophrenia	1
Cerebrovascular accident	1
Hodgkin's disease	1
Gastritis	1
Hemoroids	1

Table 2. Comorbid diseases observed in male patients

Disease	Number of patients
Hypertension	11
Diabetes mellitus	7
Chronic kidney disease	3
Coronary artery disease	2
Arrythmia	1
Osteoporosis	1
Parkinson's disease	1
Seizure disorder	1
Hyperlipidemia	1
Glaucoma	1
Rectum cancer	1
Asthma	1

Thirty-four female patients were included in this study. The average age of diagnosis was 74.94; the oldest patient was 103 years old and the youngest patient was 15 years old. The average disease duration was 105.7 months for females; 264 months the longest and 1 month the shortest. The most commonly observed comorbidities in female patients were hypertension, diabetes mellitus, Alzheimer's disease, osteoporosis, hypothyroidism, coronary artery diseases and heart valve diseases, in decreasing frequency. Eight of the female patients had no comorbid disease.

Twenty-four of the patients were males. The average age of diagnosis for male patients was 72.17 years; 92 years the oldest and 52 years the youngest. The average disease duration for male patients was 97.04 months; 240 months the longest and 9 months the shortest. The most common comorbid diseases were hypertension, diabetes mellitus, chronic kidney disease and coronary artery diseases, again in decreasing frequency. Seven of the male patients had no comorbid disease.

When the female and male patients are compared, the age of diagnosis for male patients is younger than the female patients; and the disease duration is longer in the female patients. Hypertension, diabetes mellitus and coronary artery diseases are common in both genders. On the other hand, Alzheimer's disease, osteoporosis and hypothyroidism are observed more frequently in female patients; and chronic kidney disease is observed more frequently in male patients.

Discussion

This study revealed similar results to the previous studies. In this study the female-to-male ratio was calculated as 1.42. A similar ratio was reported in many studies previously. Kridin and Bergman [9] reported a ratio of 1.41; Cozzani et al. [10] of 1.46; Bernard et al. [11] of 1.48; Gudi et al. [12] and Joly et al. [13] of 1.5; and Langan et al. [14] of 1.59. In alliance with the previous studies, this study has also shown that bullous pemphigoid has a female predominance similar to other autoimmune diseases in general.

Bullous pemphigoid is a disease of the elderly and it was previously reported that the prevalence of bullous pemphigoid in the 9th decade is 300-fold that of the 6th decade. Thus, the incidence increases with age [4]. The average age of diagnosis was found to be 73.79 years for both genders. This result is similar to those reported in the previous literature. Zillikens et al. [15] reported that the average age of diagnosis was 73.7 years. Cozzani et al. [10] reported the average age of diagnosis as 74 years; Bertram et al. [16] as 74.6 years; and Brick et al. [17] as 75 years. Previously, there were only two studies which determined the average age of diagnosis according to genders [18,19]. This study showed that the average age of diagnosis was 74.94 years for female patients and 72.17 for male patients. Serwin et al. [18] reported that the average age of diagnosis was 68.9 years in female patients and 67.3 years in male patients. Similar to Serwin et al. [18], we have also found that the average age of diagnosis was younger in male patients. However, the averages of the diagnosis age in both genders were younger in Serwin et al.'s [18] study. Jung et al. [19] reported that the average age of diagnosis was 73.7 in female patients and 76.1 in male patients. The fact that Jung et al. [19] showed the age of diagnosis was younger in female patients contrasts to our result even though the age averages are closer to our results than that of Serwin et al. [18].

The most commonly observed comorbidities in bullous pemphigoid patients were hypertension in 26 patients (45%), diabetes mellitus in 14 patients (24%), coronary artery diseases in 6 patients (1%), chronic kidney disease in 4 patients (0.7%) and osteoporosis in 4 patients (0.7%). A study that evaluated a Finnish cohort of bullous pemphigoid patients with an average age of 77 years also reported that the most commonly observed comorbidities in bullous pemphigoid patients were hypertension (44%), diabetes mellitus (34%) and ischemic heart diseases (26%). A significant association between bullous pemphigoid and a history of malignancies, diabetes mellitus and chronic obstructive pulmonary disease was found in the Finnish cohort. Furthermore, 46% of the patients had neurologic comorbidities [20]. Only two of the patients in this study had a past medical history of malignancy: one patients had rectum cancer and the other patient had Hodgkin's disease; both of the malignancies were cured at the time of bullous pemphigoid diagnosis. Previously, Atzmony et al. [8] reported that there was no significant association of bullous pemphigoid with malignancies; but a possible association might have existed between hematologic malignancies and bullous pemphigoid. Similarly, we also report that a history of malignancy is insignificant for bullous pemphigoid. Cardiovascular diseases, including hypertension and coronary artery diseases, were reported to co-exist with bullous pemphigoid ranging from 38% up to 70% in several previous studies [21]. The prevalence of cardiovascular comorbidities is 70% in our study as well, in alignment with the previous literature. Another study investigating the comorbidities of bullous pemphigoid patients reported 55.8% of the patients had a neurologic comorbidity, which was significantly more than the control group [22]. The most commonly observed neurologic comorbidities were stroke, seizure disorder, dementia (including Alzheimer's and Parkinson's disease) and multiple sclerosis [1,22]. Three patients in our patient population had Alzheimer's disease, 2 patients had Parkinson's disease, 1 patient had seizure disorder and 1 patient had a history of stroke. Overall, only 1% of our patients had a neurologic comorbidity, which contrasts the literature. Psychiatric comorbidities are also reported to be frequent in bullous pemphigoid patients: most common diseases are schizophrenia, bipolar disorder and personality disorders [1]. Only one patient

had a psychiatric disorder, namely schizophrenia, in our patient population, which again differs from the previous literature.

Conclusion

Bullous pemphigoid is an autoimmune blistering disease with a female predominance which is usually diagnosed during the seventh decade; according to the previous literature and this study. Previous studies have shown that bullous pemphigoid was associated with cardiac diseases, diabetes mellitus, neurologic and psychiatric diseases. Similar to the literature, this study has also shown an association between bullous pemphigoid and cardiac diseases or diabetes mellitus. However, the results failed to show an association with neurologic or psychiatric diseases. Bullous pemphigoid was reported to be not associated with malignancies; similarly, this study did not find a significant prevalence of history of malignant neoplasms in bullous pemphigoid patients.

Ethics

Ethics Committee Approval: The approval of Istanbul University-Cerrahpasa Medical Faculty Ethics Committee was obtained before the study was initiated (06/12/2019-186949).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Concept: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Design: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Data Collection or Processing: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Analysis or Interpretation: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Literature Search: Ö.A., D.K., T.K.Ü.U., C.M., Z.K., Writing: Ö.A., D.K., T.K.Ü.U., C.M., Z.K.

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CASE REPORT

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A Case of Living Donor Liver Transplantation due to Hepatic Failure Cause of Isotretinoin Therapy

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ABSTRACT

Observation: Isotretinoin is a widely used in acne treatment. It has been some side effects. This drug may rarely cause severe liver failure. Thirty-five year old woman, liver function tests significantly increased 25 days after start to using isotretionin. Other reasons that cause acute liver failure was investigated and there was not found any other reason. During follow-up period in our hospital, the bilirubin and international normalized ratio levels was not decreased. The liver biopsy showed that widespread necrosis. Finally, the patient underwent living donor liver transplantation. Isotretionin treatment may not be innocent. We recommend that the medicine be used only in well-selected patients and by monitoring.

Keywords: Hepatic failure, Isotretionin, Liver transplantation

Introduction

Isotretinoin is a widely used agent for the treatment of severe persistent nodular acne when topical treatment is unresponsive. It is known that this agent which is good in acne treatment is teratogenic; in addition side effects such as cheilitis, dryness on skin and mucosal membranes, increased risk of cutaneous staphylococcus auerus infection, myalgia, hyperlipidemia and increased liver function tests can be seen. This case report has been published with the written consent of the patient.

Case Report

Thirty-five years old female patient with no previously known disease history has begun using isotretinoin therapy for approximately 45 days. Complaints of abdominal pain, nausea and vomiting started 20 days ago. Liver function tests was found to be high in examinations. Patients who detected negative viral markers were referred to our center because of increased bilirubin and international normalized ratio (INR) values that may require liver transplantation. At the first examination of the patient at our center; aspartate aminotransferase (AST): 848 U/L, alanine aminotransferase (ALT): 593 U/L, total bilirubin: 21 mg/dL, direct bilirubin: 16 mg/dL, creatinine (Cr): 0.6 mg/dL, albumin: 4.1 g/dL, INR: 2.4, C-reactive protein: 3, white blood cells: 9160/µL, platelet: 203 000/µL, ammonia: 190 was detected. N-acetyl cysteine infusion and ursodeoxycholic acid treatment were started. The viral and autoimmune markers were negative. Immunoglobulin G, seruloplasmin and alpha-1-antitrypsin were found to be normal. The patient had triphasic computed tomography scan; no evidence of chronic liver disease, and vascular structures were evident. On the 6th day of

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hospitalization, liver-tru-cut biopsy was performed cause of poor response to medical treatment. The histopathological findings were sentinelobuler, bridging, panasinine necrosis areas as active acute hepatitis. In this process, the patient who had prepared live donor, bilirubin and INR values were not regressed on the follow-up and living donor liver transplantation was performed on the 15th day of hospitalization. Histopathologic evaluation of explant liver revealed diffuse centrilobular and panasyner necrosis, mild portal inflammation.

Discussion

Although isotretinoin is known to have side effects, it is often used because of its good efficacy in acne treatment and rarely can cause life-threatening side effects [1]. For this reason, monitoring of some tests is generally recommended during the use of the drug. The frequency with which monitoring should be done is still controversial. Some authors have defined liver enzymes and lipid profile control as weekly or biweekly until the time when the relevant response is received after the onset of the drug, which is usually defined as a 4-week period; some sources suggest baseline and monthly monitoring of blood count, lipid profile, and liver function tests [2,3].

With the treatment of ISO, elevation in liver function tests is detected in 15-20% of patients. When interrupted for drug use, they usually fall within normal limits and are usually insignificant [4,5,6]. In fact, some authors state that the risk of developing liver disease is low, if the liver function tests are normal before the treatment [5]. In our patient, the liver function tests had been elevetaed 25 days after begun the treatment.

In the study of Hansen et al. [7], which included 515 patients using ISO cause of acne, investigated the frequency, timing and severity of side effects. High ALT level was found 19 (3.3%) of patients and the most severe case was found to be 264 U/dL in the second month (after vitamin replacement); in another case ALTX4 NUS increased in the first month. The mean time to detect elevation in ALT was 61.9 days. Therefore, it is recommended that patients with normal baseline liver function tests before treatment, take a two-month follow-up of control tests and if they are normal, they should not be controlled again. It is emphasized that blood count monitoring is not necessary in the same study.

In Lee et al.'s [8] systematic review and meta-analysis, it is suggested that less frequent laboratory monitoring is safe for most patients, laboratory anomalies are likely to occur according to the patient's clinical and additional disease status (preexisting liver disease, additional hepatotoxic drug use, Metabolic syndrome) it is stated that more frequent control can be made in patients, in summary monitorisation can be individualized.

Ataseven et al.'s [9] in retrospective analysis of 110 patients included, there was statistically significant increase in total cholesterol, triglyceride and AST values, no significant increase in low-density lipoprotein-cholesterol, no increase in high-density lipoprotein-cholesterol, Cr and ALT values when baseline-to-third-month laboratory tests were evaluated.

Ucak et al.'s [10] study that evaluated 40 patients, a statistically significant increase was detected in AST and no significant increase was detected in ALT. The increase in AST value was also reported to be correlated with the dose and a significant difference was found between baseline and 3rd month values at >0.51 mg/kg/day.

It has been stated that ISO therapy may be associated with hepatitis, but in some studies there is no relationship between ISO and chronic liver toxicity [6]. If the liver function tests were normal during two months after the treatment started, it was observed that they stayed in the normal limits in the later period [11].

Conclusion

From a liver perspective, ISO treatment may not be innocent, as stated in the literature. It is recommended that the medicine be used only in well-selected patients and by monitoring. Patients with serious hepatitis should be directed to the transplant center in time.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.A., Ş.Y., A.K., R.D., S.A., K.Y.P., Ç.A., M.A., Concept: Ş.A., M.A., Design: Ş.A., M.A., Data Collection or Processing: Ş.A., M.A., Analysis or Interpretation: Ş.A., M.A., Literature Search: Ş.A., Ç.A., M.A., Writing: Ş.A., M.A.

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CASE REPORT

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Touraine Solente Gole Syndrome (Pachydermoperiostosis): Case Report and Brief Review

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ABSTRACT

Observation: Hypertrophic osteoarthropathy (HOA) is systemic disease characterized by periostosis, digital clubbing and arthritis. Touraine Solente Gole syndrome (TSGS), or pachydermoperiostosis - clinical variant of primary HOA, involving skeleton, soft tissues and cutis. The patents with TSGS may develop complications due to excessive growth in the soft tissues and bone tissues or develop serious associated diseases such as malignancies. Therefore, timely diagnosis of HOA and TSGS as a rare variant of it is important in aspect of prevention or early viewing of associated disease ad complications.

Keywords: Hypertrophic osteoarthropathy, Touraine Solente Gole syndrome, Pachydermoperiostosis, Malignancies

Introduction

Hypertrophic osteoarthropathy (HOA) is systemic disease characterized by periostosis, digital clubbing and arthritis. There are two variants of HOA: primary (idiopathic) and secondary (approximately 35% of cases) [1]. Touraine Solente Gole syndrome (TSGS), or pachydermoperiostosis (PDP). TSGS, or PDP - clinical variant of primary HOA - is rare inherited or idiopathic disease predominantly involving skeleton, soft tissues and cutis. In classical presentation the syndrome characterized by periosteal disorders, soft tissue hypertrophy and pachydermia (*cutis verticis gyrata*) most commonly involving the scalp and face. Facies leonina can develop in cases facial involvement.

Primary HOA was first described by Fredreich [2] in 1868 as a familial case of HOA. In 1830, Pierre Marie described it as "*osteoarthropathie hypertrophiante pneumique*" [3]. Touraine et al. [4] described TSGS as a form of primary HOA.

TSGS may be idiopathic or inherited. Although, an autosomal dominant inheritance with incomplete penetrance and variable expression has been confirmed, both autosomal recessive and X-linked inheritance has been suggested [5].

Case Report

We present the case of 13 years old white Caucasian male complained of skin thickening in the scalp (Figure 1A) and forehead (Figure 1B), digital clubbing, hypertrophy of soft tissues of digits and hyperhydrosis (Figure 2), manifestation of total hyperhidrosis (Figure 3), arthralgia, that had persisted nearly for four years.

Physical examination revealed skin thickening and folds formation in the face and forehead area, between the eyes, deep nasolabial folds, sebaceous gland hyperplasia, eyelids hypertrophy resulting in mechanical ptosis. This clinical feature resembled so-called *facies leonine*. Scalp examination revealed appearance consisting cutis

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verticis gyrata with deep folds in cerebriform distribution. Anomaly of fourth toe of both feet is also detected.

Body temperature of 36.6 ºC. PR: 70/min. BP: 120/60 mmHg. In other the physical examination revealed no pathologic signs.

Symptoms gradually progressed and there is no complete remission. Patient received treatment for different diagnosis of systemic rheumatic diseases such as rheumatoid arthritis, acute rheumatic fever etc with no or short term benefits: the symptoms recurred as soon as the treatment has been discontinued. Then the patient was referred to Department of Dermatology and Venerology of Azerbaijan Medical University by the rheumatologist due to skin changes.

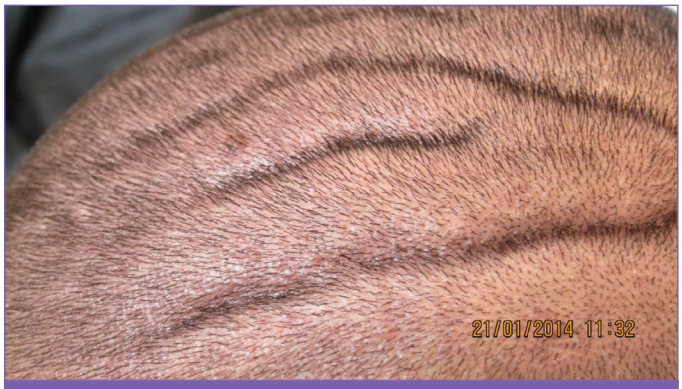

Figure 1A. Skin thickening and cutis verticis gyrata with deep folds in cerebriform distribution on scalp

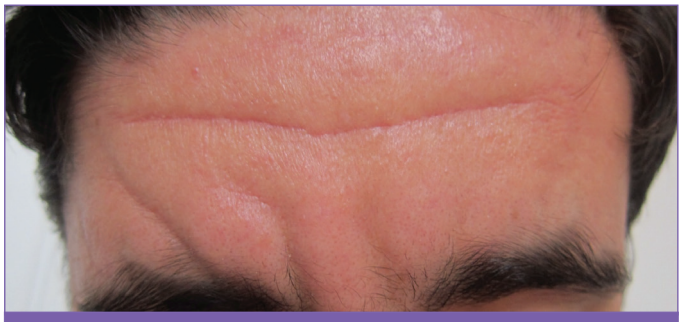

Figure 1B. Skin thickening and furrowing on the face and forehead

A blood work up including a hemoglobin, hematocrit, red blood cell, white blood cell and blood biochemistry resulted (glucose, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, serum creatinine, urea) in the normal ranges. An acute phase markers slightly elevated: erythrocyte sedimentation rate (ESR): 30 mm/h and C-reactive protein (CRP): 20 mg/L. P-ANCA, C-ANCA, ANA, RF, cryoglobulins were all negative. A serology for sexually transmitted diseases, viral hepatitis (VDRL, TPHA, HBsAg, anti-HIV, anti-hepatitis C virus), TORCH, antibodies against streptococcus, Epstein-Barr virus and Write test for brucellosis was negative. A urinalysis revealed no changes. Abdominal ultrasound and chest X-ray examination revealed no pathology. Electrocardiogram and electrocochleaography revealed no heart pathology.

The patient's medical history is remarkable for four surgical interventions for femoral bone fracture four years ago.

His parents are consanguineous. The patient has a brother. Al the family members are healthy. No history of TSGS present in father's or mother's relatives, but there is a history of anomaly of fourth toe of both feet.

Diagnosis of TSGS (PDP) was made basing on clinical, radiological and laboratory data.

Therapy with isotretinoin 20 mg/day, nimesulid 100 mg b.i.d. was started with mild clinical efficacy: arthralgia resolved, skin folds became less prominent.

Discussion

TSGS is related to mutations of the gene encoding for 15-hydroxyprostaglandin dehydrogenase [6]. TSGS patients have

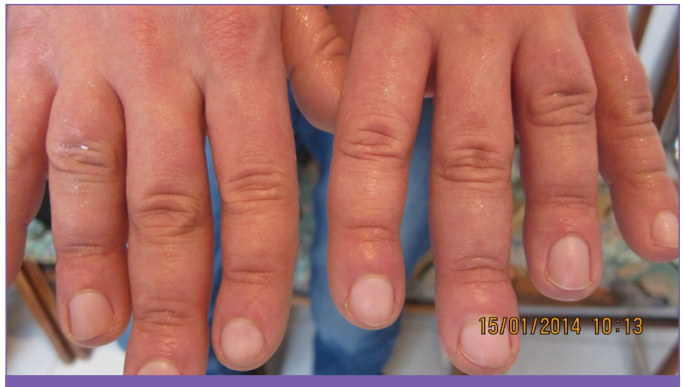

Figure 2. Skin thickening on hands, digital clubbing, hypertrophy of soft tissues of digits and hyperhydrosis

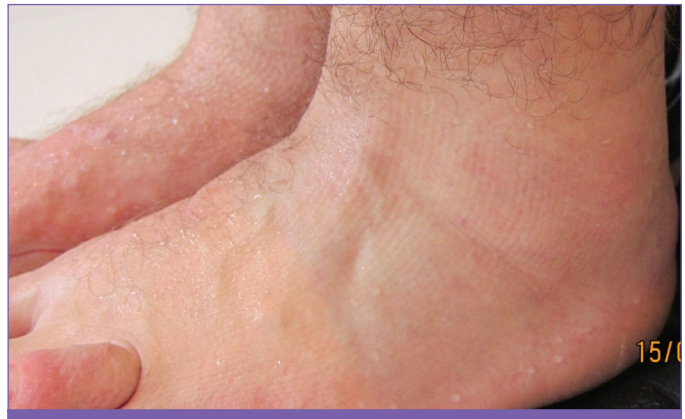

Figure 3. Skin thickening on foots and marked hyperhydrosis

high levels of PGE2 and decreased levels of PGE-M (the metabolite of PGE2). PGE2 can mimic the activity of osteoblasts and osteoclasts, which may be responsible for the acro-osteolysis and periosteal bone formation [7]. PGE2 also has vasodilatory effects, which may be responsible for prolonged local vasodilation resulting in digital clubbing [7].

TSGS as a form of primary HOA has been described by Touraine et al. [4] in 1935 in their paper entitled: *Un syndrome osteo-dermopathique: La pachydermia plicaturee avec pachyperiostose des extremites.* HOA characterized by *triad* of symptom including digital clubbing, periostitis and swollen limbs. TSGS accounts for only 3-5% cases of HOA0020 [8]. Touraine et al. [4] distinguish *three* clinical forms of TSGS: *complete* (pachydermia, clubbing and periostosis), *fruste* (pachydermia with minimal skeletal changes) and *incomplete* (skeletal changes with no pachydermia) TSGS.

Diagnostic criteria TSGS include *major* (pachidermia, periostosis, finger clubbing) and *minor* (hyperhidrosis, arthralgia, gastric ulcer, cutis verticis gyrate, blepharoptosis, joint effusion, column-like legs, edema, seborrhea, acne, hyperhidrosis, flushing) one.

The clinical diagnosis of TSGS may be easily confirmed by radiography of the long bones viewing characteristic periosteal changes and absence of any underlying pulmonary or cardiac disease, which must be carefully ruled out.

As in our case report the symptoms of TSGS often begin at the adulthood, progress during several years and become stable. According to Kerimovic-Morina and Mladenovic [9] family history exists in about a 25-38% of the cases and so it is important to consider close relatives.

TSGS is more common in men with men-to-women ratio 9:1 [1,10].

There is no racial predisposition.

Patients with PDP may present to multiple clinical specialist like orthopedist, rheumatologist, endocrinologist and dermatologist. The general physician is very occasionally confronted with such a case in a lifetime. Such cases are intriguing, challenging to diagnose and difficult to treat [2].

A diagnosis of primary HOA can be made only after carefully exclusion of secondary PDP with rapid bone changes and painful clubbing which may occur as a manifestation of severe pulmonary diseases such as adenocarcinoma of bronchus, pleural mesothelioma, bronchiectasis, gastric carcinoma or cyanotic heart diseases [11], because TSGS accounts for only in minority of cases of HOA.

The presence of nonspecific arthralgia or arthritis sometimes erroneously suggests systemic connective tissue diseases such as rheumatoid arthritis, or systemic infectious diseases (acute or chronic) - brucellosis, Lyme disease, viral hepatitis etc. Nevertheless, it is advisable to check for these diseases as comorbidities.

Other differential diagnoses include - acromegaly, thyroid acropachy, rhematoid arthritis etc. Patients with predominantly cutaneous manifestations may also have to be differentiated from the rare hyperelasticity disorders such as Ehler Danlos syndrome, cutis laxa, Meretoga's syndrome, Marfan's syndrome and pseudoxanthoma elasticum, which may cause forehead furrows [3].

Osteonecrosis of the femoral head [12], carpal and Tarsal Tunnel syndrome [13] are the *complications* of TSGS occurring with different rate.

No specific laboratory findings of TSGS available in routine clinical practice. Nevertheless, Zhang et al. [10] state elevated ESR and CRP with synovitis might be found in patients with PDP, yet it is fairly rare to note a two-fold elevation of ESR and a 10-fold elevation of CRP.

Non-steroidal anti-inflammatory drugs, pamidronate, isotretinoin for skin disorders. Surgical treatment may be required in some cases of prominent skin changes.

Finally, it needs to be underlined that patients with primary HOA require regular monitoring as, in the long term, they may develop malignancies and complications due to excessive growth in the soft tissues and bone tissues [1]. Therefore, timely diagnosis of HOA and TSGS as a rare variant of it is important in aspect of prevention or early viewing of associated disease ad complications. It is also important to check for malignancies at the time of diagnosis.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B., Concept: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B., Design: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B., Data Collection or Processing: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B., Analysis or Interpretation: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B., Literature Search: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B., Writing: Z.H.F., I.A.A., I.Z.B., N.Z.V., P.Z.B., H.Z.B.

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