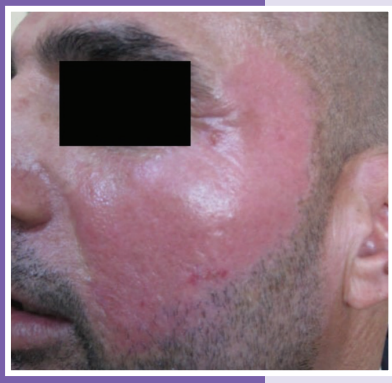
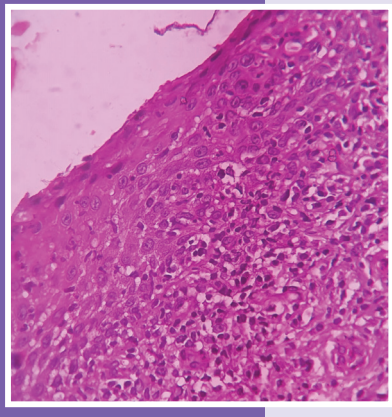
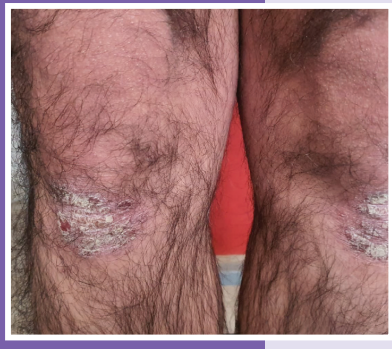
E-ISSN: 1307-394X

Journal of the Turkish Academy of Dermatology

Volume: 15 | Issue: 1 | March 2021







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Online Publishing Date: March 2021
E-ISSN: 1307-394X
International scientific journal published quarterly.

Journal of the Turkish Academy of Dermatology

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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

Book: - Monsel G, Delaunay P, Chosidow O. Arthropods. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology, 9th ed. Singapore: Blackwell Science; 2016. p. 32-34.

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REVIEW

DOI: 10.4274/jtad.galenos.2021.02486
J Turk Acad Dermatol 2021;15(1):1-7

Medical Complications of Tattoos

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ABSTRACT

Decorative tattooing involves the process of inserting external pigments and/or dyes into the dermis to create a permanent design. Tattooing is an application that has been widely practiced worldwide since ancient times. The popularity of permanent decorative skin tattooing has increased over the past thirty years. It will increase in patients with tattoo complications who apply to dermatologists due to the increase tattooing. Although tattooing is mostly for entertainment purposes, it can also be used for aesthetic and medical purposes. Although complications have decreased in modern, professional tattoos, these tattoing procedures may be associated with a wide variety of cutaneous and extracutaneous complications. Herein, we review the complications that can occur after tattooing, based on a comprehensive review of the literature. This review ensures an overview of the current aspects of medical complications associated with permanent tattooing based on previous reviews, studies, case series and related case reports.

Keywords: Tattoo, Complication, Adverse reaction, Pigment, Cancer

Introduction

Decorative tattooing involves the process of inserting external pigments and/or dyes into the dermis to create a permanent design [1]. Tattooing is an application that has been widely practiced worldwide since ancient times. The popularity of permanent decorative skin tattooing has increased over the past thirty years. In Western countries, 10% of the general population has skin tattoos, while 25% between the ages of 18-50 have tattoos [1]. It will increase in patients with tattoo complications who apply to dermatologists due to the increase tattooing.

Although tattooing is mostly for entertainment purposes, it can also be used for cosmetic purposes (permanent eyebrows in alopecia areata, etc.). Some tattoo applications for aesthetic and therapeutic purposes (medical) are given in Table 1. Tattooing is done by inserting pigments and dyes into the dermis [2]. Tattoo inks have changed in recent years, with metal salts that were previously used frequently, replaced by azo pigments, an industrial pigment [3]. Azo pigments are preferred because of their more vivid colors and longevity. Although cutaneous reaction is less common in azo pigments, the long-term safety of these pigments is largely unknown. Møller and Wallin [4] evaluated azo pigments as genotoxic and carcinogenic.

The modern professional permanent tattoo process typically involves repeated injection of ink into the dermis using an electrically powered tattoo machine that can pierce the skin 3,000 times per minute. In professional tattoo parlors, items that come into contact with customers and potentially contaminate are usually disposable or autoclaved before each use [3]. Although complications have decreased in modern, professional tattoos, these tattooing procedures may be associated with a wide variety of cutaneous and extracutaneous complications [5].

In this review, we examined the cutaneous and systemic complications of tattooing (although they may intertwine from time to time, for example malignant melanoma (MM) can be classified as both a cutaneous and systemic complication) separately.

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Received: 06.08.2020 Accepted: 04.01.2021

1. Cutaneous Complications of Tattooing

The frequency of cutaneous complications related to tattooing is not clearly known. There are studies reporting the prevalence of complications between 2% and 43% [6,7,8]. In a survey conducted with tattooed people, it was found that 42.6% complained about their tattoos. The three most common of these complaints are; wax and waning swelling (57%), transient itching (45.7%) and swelling after sun exposure (23%) [8]. However, it may not be the right approach to evaluate all these complaints as pathological. We think the same that this type of cutaneous complaints should not be considered as a complication since it is an expected side effect in many tattoos.

There is no single classification of post-tattoo cutaneous complications and they have been classified in various ways in the literature. For example, they can be classified according to their clinical pathology (infection, hypersensitivity, etc.) as well as acute and chronic reactions [1]. In this review, we tried to classify cutaneous reactions according to their clinical types. In Table 2, we classified all post-tattoo cutaneous reactions in the literature.

Pyogenic Cutaneous Infections

Local disinfectants are generally not applied during tattooing, so failure to follow asepsis rules during or after the tattoo session increases the risk of infection [1]. After tattooing, acute superficial and deep pyogenic infections (folliculitis, acne varioliformis, impetigo, furunculosis, ecthyma, erysipelas, cellulitis, etc.) may occur [9]. Cutaneous pyogenic infections generally develop in association with *Staphylococcus aureus, Streptococcus pyogenes, Corynebacterium, Pseudomonas, Clostridium* and *Klebsiella* can be detected as causative agents. Such complications can be reduced with hygiene measures and modern aseptic tattooing techniques. However, tattooing procedures that do not comply with hygiene and asepsis rules can lead to dramatic consequences that can progress to deep cutaneous abscesses and necrotizing fasciitis [9]. Cutaneous pyogenic infections usually develop within days to weeks after the tattooing procedure. The management of post-tattoo pyogenic infections is not different from any other pyogenic infections.

Although serious and deep cutaneous infections have decreased significantly with modern tattooing methods, several serious cases of polybacterial cellulitis, necrotizing fasciitis and septicemia have recently been reported from New Zealand [10]. It is observed that such serious infections are generally not complied with the acepsis conditions and especially in traditional tattooing. Immunosuppressive patients are more inclined to such serious cutaneous infections. Tendas et al. [11] reported the fatal case of a 26-year-old man with a history of acute myeloid leukemia developing a large skin ulcer after tattooing. Before the tattooing procedure, the medical and drug history of the patients must be questioned.

Viral Cutaneous Infections

Viral contamination during tattooing is thought to be due to the presence of viral pathogens in the tattoo ink and tattoo needle [12]. Cutaneous viral infections due to human papilloma virus, herpes simplex virus and pox virus (molloscum contaginosum etc.) have been reported association with tattooing [2,12].

Fungal Cutaneous Infections

Fungal contamination during tattooing is thought to be due to the presence of fungal pathogens in the tattoo needle. Cases of superficial tinea infection infected with trichophyton rubrum and epidermophyton floccosum have been reported association with tattooing [2,13]. It has also been defined as a tattoo complication in a case of zygomycosis, which is a rare mycotic infection [14].

Table 1. Tattoo applications for aesthetic and therapeutic purposes (medical)

Medical situations	The purpose of tattoo usage
Patients receiving cancer radiotherapy	It can be used to properly align the radiotherapy treatment areas
Patients undergoing endoscopic surgery	It can be used to mark surgical intervention areas in patients before endoscopic gastrointestinal surgery
Tattooing for medical alert purposes	- Diabetic patients using insulin - Patients with allergies and anaphylaxis - Patients with Alzheimer's disease
Patients with corneal pathology	It can be used for monitoring corneal pathology
Patients with reconstructive breast surgery	It can be used three-dimensional tattooing of the areola and nipple after surgery
Patients with alopecia	It can be used to camouflage the areas with hair loss (especially eyebrows)
Patients with vitiligo	It can be used to camouflage areas with pigment loss
Patients with hemangioma, Klippel-trenaunay or weber syndrome	It can be used to camouflage areas with vascular pathology

Mycobacterial Cutaneous Infections

Mycobacterial agents are common in nature and are highly resistant to disinfection methods [15]. Tattoo ink is a usual suspect in terms of growth and contamination of mycobacterial infectious agents [3]. Cases of cutaneous tuberculosis (tuberculosis verrucosa cutis, primary inoculation tuberculosis, lupus vulgaris, scrofuloderma), atypical mycobacterial infections and leprosy have been reported association with tattooing in the literature [3,15,16,17,18].

Table 2. The post-tattoo cutaneous complications

Cutaneous infections	**Pyogenic infections** - Impetigo contagiosa - Acne varioliformis - Ecthyma - Erysipelas - Cellulitis **Viral infections** - Verruca vulgaris - Herpes simplex virus infections - Molluscumcontagiosum **Fungal infections** - Superficial tinea infections - Zygomycosis **Mycobacterial infections** - Tuberculosis verrucosa cutis - Atypical mycobacterial infections - Primary inoculation tuberculosis - Leprosy
Allergic disorders	Allergic dermatitis Urticaria Photoallergic reaction
Granulomas	Sarcoid granulomas Allergic granulomatous reactions Keloid scars Foreign body granulomas
Skin disease localized in tattooed area	Psoriasis Vitiligo Lichen planus, lichen planus pemphigoides Pseudolymphoma Atopic dermatitis Pyoderma gangrenosum Darier's disease Perforating dermatosis Eruptive xanthomas Granuloma annulare Necrobiosis lipoidica Miliums Epidermoid cysts Lichen sclerosus Morphea Discoid lupus erythematosus
Neoplasms	Basal cell carcinoma Squamous cell carcinoma Melanoma Dermatofibroma Dermatofibrosarcoma protuberans Pseudoepitheliomatous hyperplasia

Allergic Disorders

Hypersensitivity reactions (or allergies) to tattoo inks are the most common complications after tattooing. In addition, it is often not possible to predict and prevent these complications [5]. The biggest fear of permanent tattooing is these unpredictable allergic reactions.

Allergic Dermatitis

After tattooing, the type 1 allergic reactions and anaphylaxis are very rare [19]. Usually a type 4 (delayed type) allergic reaction develops [20]. In post-tattoo care, moisturizers and dexpanthenol are often used, such as wound care [21]. Any topical agent used in post-tattoo care can cause allergic contact dermatitis [22]. Localized hypertrichosis has also been observed in some cases following this contact dermatitis in the literature [23].

Urticaria

Urticarial reactions can be triggered, especially by rubbing the blue-black tattooed areas [24]. Isolated urticaria and urticaria-angioedema cases after tattoo have been reported in the literature [25,26].

Photoallergic Reaction

Tattoos with yellow pigment containing cadmium sulfide are blamed for photodermatoses. In addition, cadmium sulfide can be found in minimal amounts in tattoos containing red color [2].

Granulomas

Like other exogenous materials injected into the skin, tattoo pigments can be perceived as foreign bodies for the body and cause granulomatous reactions [27]. Foreign body and sarcoid type granulomatous tattoo reactions constitute the majority of cases [3]. A definitive diagnosis by punch skin biopsy and histopathological examination is important. Because, any granulomatous reaction can be indicative of the underlying idiopathic sarcoidosis [6].

Sarcoid Granulomas

Sarcoidosis is an autoinflammatory condition of unknown cause, characterized by non-caseating epithelioid granulomas that can involve the skin and internal organs [28]. Sarcoidal granulomas that can develop from scars (scar sarcoid) and can also arise secondary to foreign matter, including tattoos, have often been reported in the literature [27,29]. The relationship of sarcoidal reactions to tattoos is unique, with tattoo reactions typically presenting as papules, nodules or plaques that are usually confined to tattooed area [30]. The onset of skin lesions may develop weeks or even decades after tattooing, the red pigment being responsible most often [31]. Patients with pre-existing sarcoidosis should be advised to avoid tattooing.

Allergic Granulomatous Reactions

Allergic granulomatosis responses are difficult to treat reactions to the dye pigment of the tattoo. The most risky color pigment for this reaction is red, while the safest color pigment is black [6].

Keloid Scars

Mild fibrosis is usually seen as a result of the trauma of the tattoo needle. Hypertrophic scar or keloid scar development may occur in individuals susceptible to tattoos. It is very difficult to predict this complication. This risk increases in areas such as the chest, shoulders and upper arms, and in tattoos with damaged needles or poor quality needles [32]. Nevertheless, this complication can occur in any application and any localization.

Foreign Body Granulomas

Foreign body granulomas are relatively common after tattooing and are characterized by pigment-laden foreign body-type giant cells. The first-line approach is a trial of superpotent topical steroids or intralesional corticosteroids. In most cases, the reaction can regress over time [33].

Skin Disease Localized in Tattooed Area

Dermatoses that can develop after tattooing are quite common [34]. In many skin diseases known to develop Koebner phenomenon (e.g. psoriasis, vitiligo and lichen planus etc.), post-tattoo activation and active disease development in the tattoo area can be observed [35]. Also, skin diseases with skin trauma in the etiology (e.g. pseudolymphoma, pyoderma gangrenosum, granuloma annulare, milium and epidermoid cyst etc.) can also develop after tattooing.

In the literature, psoriasis, vitiligo, lichen planus, pseudolymphoma, atopic dermatitis, pyoderma gangrenosum, Darier's disease, perforating dermatosis, eruptive xanthoma, granuloma annulare, necrobiosis lipoidica, milium, epidermoid cyst, lichen sclerosus, morphea and discoid lupus erythematosus has been reported as post-tattto skin diseases [2,5,6,34,35,36,37,38]. Patients with a history of skin disease in their medical and family history should be informed that their illness may flare before getting the tattooing. Management of skin diseases on tattoos does not differ from non-tattoo skin.

Laser epilation on tattooed areas requires special attention. Much more laser burns and keloids may develop in laser hair removal procedures performed on tattooed skin than normal skin [6].

Neoplasms

The relationship between tattoo and skin malignancies is controversy. Some authors argue that this relationship is accidental, while others draw attention to the potential carcinogenic effect of tattoo ink and argue that this relationship is not accidental [3]. When the literature is reviewed, there are many patient reports developing post-tattoo basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and MM [2,3,4,5,6]. Again in reports; while BCC and MM have been reported to develop more frequently in black, dark blue or dark tattoos; SCC, keratoacanthoma and benign pseudoepitheliomatous hyperplasia have been reported to develop more frequently in red tattoos [2,3,5,6,39].

The relationship between tattoo and MM is of particular importance due to the mixing of pigmented lesions. MM cases occurring after tattooing have been reported in many times. In addition, tattooing causes difficulties in the diagnosis and treatment of MM. Tattooing complicates the clinical and dermatoscopic examination of melanocytic nevi [40]. Patients with multiple melanocytic lesions should be advised to avoid tattooing, especially patients with melanoma risk factors. Tattoo artists should be informed about patients with multiple nevi, and these patients should definitely meet with their dermatologists before tattooing.

In addition to all these negativities in melanocytic nevi, tattoos can also cause negativities in patients who have already developed melanoma. Pigment-loaded macrophages caused by tattoo pigment can be confused with metastatic melanoma in the evaluation of sentinel lymph nodes and cause unnecessary radical lymph node dissection [41].

2. Systemic Complications of Tattooing

It is not always possible to divide tattoo complications into cutaneous and systemic with a sharp margin [6]. Some complications may start cutaneous and become systemic. In the literature, all systemic complications reported after tattooing are shown in Table 3. In this

Table 3. The post-tattoo systemic complications

Systemic infections	Syphilis Leprosy Tetanus Tuberculosis Leishmaniasis Endocarditis Sepsis Hepatitis B, C AIDS
Psychosocial complications	Depression Internalized stigma Dissatisfaction
Neoplasms	Basal cell carsinoma Squamous cell carcinoma Melanoma Lymphoma
Other rare complications	Uveitis Vasculitis Burning after magnetic resonance imaging

part, we will only evaluate isolated systemic complications (we will not repeat what we have examined in cutaneous complications here).

In the literature, there are reported cases syphilis, leprosy, tuberculosis, leishmaniasis, endocarditis, sepsis, hepatitis C, hepatitis B and AIDS (HIV) after tattooing [2,3,5,6,42]. These systemic infections are most frequently observed in conditions where asepsis rules are not followed, such as traditional tattoos. Today, if the rules of hygiene and asepsis are followed, the material is sterilized and needles are not shared between customers, the risk of developing these infections is considered to be absent [43]. Nevertheless, cases have been reported in which these infections can develop more easily and are fatal in immunocompromised individuals despite all these antisepsis rules [42].

Tattooing is more common among adolescents and psychological fluctuations are common in this period [44]. In some tattooed people, regret due to getting a tattoo can go up to internal stigma and depression over time [45]. In recent years, the interest of researchers in the psychogenic effects of tattoos has increased [46,47,48].

Clinically detectable lymphadenopathies can be seen due to the migration of tattoo pigments to lymph nodes and is an expected side effect. However, due to the carcinogenic effects of tattoo inks, their contribution to the development of systemic lymphoma is controversial [49]. Prospective controlled clinical trials are required to enlighten the issue in terms of post-tattoo BCC, SCC, MM and systemic lymphoma development. Although these devastating side effects can often be controlled with treatment, they may require excision of the tattooed area and serious immunosuppressive treatments from time to time.

Rare complications such as uveitis and vasculitis have been reported after tattooing in the literature [50]. Although such systemic side effects are thought to be the result of sarcoidosis triggered after tattooing, it has been reported in the literature in cases who developed uveitis without sarcoidosis.

Also, complaints of burn in the tattoo areas have been reported in tattooed patients after magnetic resonance imaging (MRI) examination [6]. This situation is caused by the tattoo pigments being affected by the magnetic field. This risk is higher in large and dark pigment tattoos. In such risky patients, non-MRI imaging methods should be preferred, if possible.

Conclusion

Tattoos can be complicated by a diversity of infectious, inflammatory or neoplastic conditions. Over the years, complications have changed course with the development of dyes and methods used in tattooing. Cutaneous reactions are significantly reduced with the use of azo dyes in tattoo pigments instead of metal salts and the attention of tattoo artists to hygiene procedures. Hypersensitivity reactions (or allergies) to tattoo pigments are currently the most common complications in the tattooing. Unfortunately, it is not possible to predict and prevent these reactions. Again, the potential carcinogenic effects of azo dyes are not clearly known today. More clinical studies are needed to further clarify the complications of tattooing and to increase the knowledge.

It is important to raise more public awareness of tattooing and its complications. Especially tattoo artists need to be aware of tattoo complications and contraindications. Even the knowledge of which patient to refer to the clinician before tattooing can be vital for many complications. Patients with known skin diseases should definitely consult their dermatologist and get information about tattoo complications before tattooing. Patients with chronic conditions and/or impaired immunity should discuss with their physician about the complications of tattooing.

The management of tattoo complications must be done by a dermatologist. Treatment of tattoo-related complications is a specialized and experienced field that may include local destructive measures (dermabrasion, chemical destruction, cryotherapy, electro-surgery, ablative laser destruction), surgical excision, and thermolysis of the pigment using Q-switched laser therapy [51].

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.T., E.Ö., Concept: E.Ö., S.A.T., Design: E.Ö., S.A.T., Data Collection or Processing: S.A.T., E.Ö., Analysis or Interpretation: S.A.T., E.Ö., Literature Search: S.A.T., E.Ö., Writing: S.A.T., E.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

DOI: 10.4274/jtad.galenos.2020.87487
J Turk Acad Dermatol 2021;15(1):8-13

Assessment of Acute and Chronic Radiodermatitis of Female Patients with Breast Cancer: The Impact of Radiotherapy and Patient Related Factors

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ABSTRACT

Background: Radiotherapy used after breast-conserving surgery may cause acute and chronic side effects on skin. In our study, we aimed to investigate skin adverse effects caused by both personal factors and factors about radiotherapy.

Materials and Methods: Female patients with breast cancer aged more than 18 were recruited into this study. Clinical and laboratory data including age, hight, weight, body mass index (BMI), smoking status, educational status, adjuvant chemotherapy and/or hormono therapy, skin phototype, using of any skin care cream, analyze aspartate aminotransferase, alanine aminotransferase, fasting plasma glucose, fasting plasma insulin, homeostatic model assessment-insulin resistance (HOMA-IR) and creatinine, type of surgery, radiotherapy technical details. We examined the area of skin receiving radiotherapy at the end of the first month (early side effects) and the third month (late side effects) of radiotherapy for breast.

Results: We reached 78 patients but 56 of 78 patients came to dermatology outpatient clinic for their second controls and 34 of 78 patients came for their third controls. We determined significant relationships between BMI and acute radiodermatitis (p=0.021). In addition, there were significant relationships between smoking, BMI, fasting plasma insulin, HOMA-IR and chronic radiodermatitis (p=0.01, p=0.049, p=0.012, p=0.025 respectively).

Conclusion: According to our study, smoking, BMI, fasting plasma insulin, HOMA-IR are significantly effective on radiodermatitis. Nevertheless, further studies conducted with more extensive patient series are needed to validate our findings and assess their clinical importance.

Keywords: Radiodermatitis, Breast cancer, Radiotherapy

Introduction

Radiotherapy is a treatment method that's used after breast-conserving surgery, with this method locoregional recurrence of breast cancer is tried to be prevented [1]. Irradiation of the breast may cause acute and chronic side effects on skin. There are different factors that are effective on skin side effects, such as total delivered dose, dose per fraction, location and volume of the treated area, radiating energy, concomitant chemotherapy [2,3,4,5]. According to the literature individual variations depending on age, chronic diseases, skin phototypes, genetic predisposition, skin damage from the previous are important on occuring early and late skin damages. Skin reactions vary from mild erythema to necrosis [6]. In our study, we aimed to investigate skin adverse effects caused by both personal factors and factors about radiotherapy.

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Received: 21.12.2020 **Accepted:** 22.12.2020

Materials and Methods

Study Design

This study was designed as a prospective single-center study, and it was conducted under the ethical principles reported in the Declaration of Helsinki. It was approved by the University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethical Review Committee (protocol number: 2019/13-31, date: 11.09.2019). Female patients with breast cancer aged more than 18 who presented to the radiation oncology outpatient clinic of Izmir Tepecik Training and Research Hospital between September 2019 and October 2020 were recruited into this study. Dermatologic examinations of patients were always made by the same dermatologist of the same hospital. Both verbal and written informed consents were obtained from study participants. Clinical data including age, hight, weight, body mass index (BMI), smoking status, educational status, adjuvant chemotherapy and/or hormono therapy, skin phototype. All study patients were asked to give blood samples to analyze aspartate aminotransferase, alanine aminotransferase, fasting plasma glucose, fasting plasma insulin, homeostatic model assessment-insulin resistance (HOMA-IR) and creatinine. We examined the area of skin receiving radiotherapy at the end of the first month (early side effects) and the third month (late side effects) of radiotherapy for breast. We used Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer radiation toxicity grading system for acute and chronic skin side effects [7,8].

Radiation Therapy

In our clinic, adjuvant radiotherapy is applied to all patients who underwent breast-conserving surgery and to all patients who underwent mastectomy with T3-4, N (+) in accordance with our hospital protocol. In patients undergoing breast conserving surgery, was applied to the whole breast radiotherapy and then an additional dose (boost) to the tumor bed. In those who undergo mastectomy, radiotherapy was applied to the chest wall. Boost was given to the incision scar in patients with skin involvement and positive surgical margins. In both groups, patients with positive lymph nodes were applied to peripheral lymph nodes irradiation.

A total of 50 Gy was given to the whole breast or chest wall, and boost to the tumor bed or incision scar with 2 Gy fraction dose in 5 days. If the surgical margin is positive or there is skin involvement, the boost dose is increased to 66 Gy.

Eclips version 15.5 is used for all plans by using the field in field technique with two conformal tangential fields has also been done including tomograpy based planning, simulation, verification&quality assurance. 110% the maximum dose (Dmax) was allowed in the plans. Two tangential fields are planned with single or combined photon energy and boost is planned by using electron or photon. Treatment was given in the Varian Vital Beam linear accelerator.

In the light of clinical information and planning data, which breast of the patients is irradiated, it's stage according to the "American Joint Committee on Cancer" Cancer Staging Manual 8th Edition, type of surgery, radiotherapy technical details (energy, presence of bolus, mean-Dmax) were recorded.

In their first concultation, patients are advised to take a warm shower and not to use abrasive cleaning products and cosmetic products during the therapy. Patients come to the polyclinic once a week during the treatment process. Epithelizing cream is recommended to patients about two weeks when acute side effects begin. Additional medication is recommended if increased side effects are observed.

Statistical Analysis

Statistical power analysis was made with G-Power 3.1.9.4 programme and we determined that our study had 85.8% power. Statistical analysis was performed with Statistical Package for the Social Sciences version 17.0 statistic software package. Different variables were investigated with analytical methods if they were suitable for normal distribution (Kolmogorov-Smirnov/Shapiro-Wilk tests). In descriptive analysis, parameters were written as frecuency, percent, mean, standard deviation. Chi-squared test and Spearman test were used in comparing categorical data. P values of less than 0.05 were regarded as statistically significant.

Results

We reached 78 patients but 56 of 78 patients came to dermatology outpatient clinic for their second controls and 34 of 78 patients came for their third controls. Therefore we recorded the datas of 56 patients, excluded 22 patients who never came to controls because of Coronavirus disease-2019 pandemic. All datas of patients were presented in tables (Tables 1, 2, 3, 4, 5). None of the patients stopped treatment due to the side effects. The mean radiotherapy dose (Dmean) was 55.45±4.37 Gy (minimum 50, maximum 62) and the Dmax was 62.04±4.33 Gy (minimum 53, maximum 74). When we investigate only the patients who came to their third dermatology controls, we determined that Dmean was 55.97±4.68 Gy (minimum 50, maximum 62) and Dmax was 61.65±3.96 Gy (minimum 53, maximum 66). We determined significant relationships between BMI and acute radiodermatitis (p=0.021) (Table 6). In addition, there were significant relationships between smoking, BMI, fasting plasma insulin, HOMA-IR and chronic radiodermatitis (p=0.01, p=0.049, p=0.012, p=0.025 respectively) (Tables 5, 6). There were no correlations between features about radiotherapy and acute and chronic radiodermatitis (Table 7).

Discussion

The most common adverse effect of breast cancer radiotherapy is radiodermatitis. The pathogenesis of radiodermatitis is complex. A combination of radiation tissue injury occurs after an inflammatory reaction. Vascular permeability and vasodilation increase and consequently an erythematous skin reaction happens and then an inflammatory response occurs. Keratinocytes, fibroblasts, and endothelial cells take part in this inflammatory reaction with the cytokines and chemokines they produce and acute and chronic radiodermatitis can occur as an adverse effect [9].

Table 1. Parameters that may be effective on skin damage during radiotherapy

Parameters	Patients (n/%)
Smoking	
- Yes	12/21.4
- No	44/78.6
Adjuvant chemotherapy	
- Yes	28/50
- No	28/50
Adjuvant hormono therapy	
- Yes	7/12.5
- No	49/87.5
Educational status	
- Illiterate	8/14.3
- Literate	2/3.6
- Primary school	29/51.8
- Middle school	0/0
- High school	9/16.1
- University	8/14.3
Skin phototype (Fitzpatrick)	
- 1	4/7.1
- 2	37/66.1
- 3	14/25
- 4	1/1.8
Skin care cream	
- Yes	15/26.8
- No	41/73.2
Type of skin care cream	
- None	41/73.2
- Calendula cream	1/1.8
- Any barrier cream	2/3.6
- St. John's wort oil	4/7.1
- Radiocare	6/10.7
- Urea	2/3.6
Total	56/100

The impact of smoking is uncertain. Some researchs found significant relationships between smoking and radiodermatitis [10,11], some studies couldn't find any significant relationships [12,13,14]. In contrary to the findings of the studies of Back et al. [12] and Borm et al. [14] our results suggest that smoking is associated with chronic radiodermatitis. We think smoking is a risk factor for chronic radiodermatitis not for acute radiodermatitis.

Age is mentioned in the extrinsic factors of radiodermatitis [11]. According to the study of Back et al. [12] and Borm et al. [14] age isn't effective on occuring of radiodermatitis. We reached the same result in our study therefore we think that age isn't an effective factor of radiodermatitis.

Adjuvant chemotherapy and hormono therapy can be effective factors on occuring of radiodermatitis [11]. According to the study of Iwakawa et al. [11] and Borm et al. [14], it wasn't be found any statistically significant relationship between adjuvant chemotherapy and hormono therapy and radiodermatitis. Our findings are in line with Iwakawa et al. [11] and Borm et al. [14]. We think that adjuvant chemotherapy and hormono therapy aren't effective factors for radiodermatitis.

Skin phototype classifications were initially developed by Fitzpatrick [13]. According to the study of Yamazaki et al. [13], self-reported skin phototype can be potentially a good predictor determining skin sensitivity to radiation exposure during the process of clinical screening. In our study, incompatible with the study of Yamazaki et al. [13], analysis of the relationships between skin phototype and radiodermatitis revealed that radiodermatitis couldn't be associated with skin phototype. Additionally, in the study of Yamazaki et al. [13], researchers found that the "suntan" skin phototype predicted higher pigmentation in radiation dermatitis. We think that skin phototype isn't an effective factor for radiodermatitis.

Non-comedogenic emollient creams are recommended for the care of skin that receives radiotherapy [15]. According to the study of

Table 2. Laboratuary findings of patients with breast cancer

Parameters (normal range)	Patients (mean±standard deviation)
Age	53.02±12.12
BMI (18.5-24.9 kg/m^2)	27.6±4.84
AST (0-35 U/L)	19.83±5.62
ALT (0-35 U/L)	20.6±6.54
Creatinine (0.6-1.1 mg/dL)	0.73±0.1
Fasting plasma glucose (74-106 mg/dL)	108.91±27.92
Fasting plasma insulin (1.9-23 mU/L)	9.54±6.29
HOMA-IR (0-2.5)	2.66±2.31

BMI: Body mass index, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HOMA-IR: Homeostatic model assessment-insulin resistance

Yamazaki et al. [15], daily dermocosmetic use is useful from the beginning of radiotherapy to prevent acute radiodermatitis. In our study, we determined that 15 cases were using any dermatologic care cream (antibacterial creams, creams including zinc-urea, radiocare etc.) in addition of epithelizing cream. Nevertheless, we didn't found any significant relationship between using extra skin care cream and radiodermatitis. If we could include more cases, maybe the results could change in favor of skin care creams. According to another study, Calendula officinalis can prevent radiodermatitis and the studies were not conclusive, either due to systematic driving errors or results without statistical significance [6].

Our investigation regarding the relationship between educational status and radiodermatitis revealed that educational status isn't an

Table 3. Findings about radiotherapy

Parameters	Patients (n/%)
Breast	
- Right	23/41.1
- Left	31/55.4
- Both right and left	2/3.6
Type of surgery	
- BCS	43/76.8
- Total mastectomy	13/23.2
Pathology	
- DCIS	2/3.6
- IDC	54/96.4
Boost	
- Yes	45/80.4
- No	11/19.6
Bolus	
- Yes	2/3.6
- No	54/96.4
Boost energy type	
- Photon	35/62.5
- Electron	21/37.5
Acute damage of skin	
- No damage	2/3.6
- Grade 1	15/26.8
- Grade 2	14/25
- Grade 3	25/44.6
Chronic damage of skin (for 34 patients)	
- No damage	8/14.3
- Grade 1	5/8.9
- Grade 2	21/37.5
- Total	34/60.7
Energy used on primary area	
- 6 mvx	11/19.6
- 6-10 mvx	4/7.1
- 6-15 mvx	41/73.2
Total	56/100

BCS: Breast conserving surgery, DCIS: Ductal carcinoma in situ, IDC: Invasive ductal carcinoma

Table 4. Stage of breast cancer of patients according to the American Joint Committee on Cancer stagining system

Phases	Patients (n/%)
Stage 0 (TisN0M0)	2/3.6
Stage 1	11/19.6
Stage 2	31/55.4
Stage 3	9/16.2
Stage 4	-

Table 5. Correlations between personel factors of patients and acute and chronic radiodermatitis

p	Acute radiodermatitis	Chronic radiodermatitis
Age	0.98	0.63
Smoking	0.84	0.01*
Adjuvant chemotherapy	0.79	0.95
Adjuvant hormono therapy	0.89	0.8
Educational status	0.49	0.51
Skin phototype (Fitzpatrick)	0.22	0.65
Using care cream for skin	0.36	0.22

*p≤0.05

Table 6. Correlations between laboratory findings of patients and acute and chronic radiodermatitis

p	Acute radiodermatitis	Chronic radiodermatitis
BMI	0.021*	0.049*
Fasting plasma glucose	0.15	0.68
Fasting plasma insulin	0.78	0.012*
HOMA-IR	0.63	0.025*

BMI: Body mass index, HOMA-IR: Homeostatic model assessment-insulin resistance, *p≤0.05

Table 7. Correlations between features about radiotherapy and acute and chronic radiodermatitis

p	Acute radiodermatitis	Chronic radiodermatitis
Boost	0.082	0.49
Energy type	0.22	0.2
Type of surgery	0.059	0.46
Dmean skin (Gy)	0.48	0.29
Dmax skin (Gy)	0.36	0.26
Energy used on primary area	0.62	0.58

Dmean: the mean radiotherapy dose, Dmax: the maximum radiotherapy dose, *p≤0.05

effective factor on occuring acute or chronic radiodermatitis. We didn't found any literature that mentioned relationships between educational status and radiodermatitis.

BMI can be thought an effective factor for occuring radiodermatits. In the study of Yamazaki et al. [15] BMI was found to be a simple and effective tool for examining radiation dermatitis. In our study, compatible with the research of Yamazaki et al. [15], we found that there was a significant relationship between BMI and acute and chronic radiodermatitis. According to our study patients with normal BMI are less likely to have acute and chronic radiodermatitis.

Diabetes mellitus has been cited as one of the causes of radiodermatitis [16]. We determined in our study that there were significant relationships between fasting plasma insulin, HOMA-IR and chronic radiodermatitis. We observed that these two factors weren't effective on acute radiodermatitis. In the literature we didn't find any other studies that were similar to our work about the effects of fasting plasma glucose, fasting plasma insulin and HOMA-IR on radiodermatitis.

In our study, we observed that boost, energy type, type of surgery, Dmean, Dmax used on primary area weren't effective on occuring of acute and chronic radiodermatitis. In Borm et al.'s [14] study with 255 cases, researchers investigated acute radiodermatitis in modern adjuvant 3D conformal radiotherapy for breast cancer and used for scoring of radiodermatitis Common Terminology Criteria for Adverse Events V.4.0. The researchers observed that boost wasn't significantly effective on occuring of acute radiodermatitis. In this study, 92.2% of all cases received boost. In our research, the percentage of cases who got boost was 80.4%. In the same study, researchers didn't find any significant relationships between Dmax and Dmean and radiodermatitis. According to our research, we think parameters about radiotherapy technics weren't significantly effective on acute and chronic radiodermatitis. That is because of using high conformal techniqeu and also close clinical follow up.

Study Limitations

Our study has some limitations which need to be considered while evaluating its findings. First, it is a single-center study. Second, although radiation oncologist was always working in the same part of hospital, dermatologist was working in the three different parts of the hospital during the process of research, therefore patients who had skin damage because of radiotherapy, couldn't be sometimes examined by dermatologist. Somestimes, cases forgot their second and third visits for dermatology outpatient clinic. If dermatologist and radiation oncologist always worked in the same part of hospital, the number of patients would be higher.

Conclusion

In conclusion, during breast cancer radiotherapy, nearly all patients will experience radiodermatitis. Different factors can be effective on occuring radiodermatitis. According to our study, smoking, BMI, fasting plasma insulin, HOMA-IR are significantly effective on radiodermatitis. Our study was the first to evaluate the relationship between radiodermatitis and different, numerous factors to the best of our knowledge. Nevertheless, further studies conducted with more extensive patient series are needed to validate our findings and assess their clinical importance.

Ethics

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethical Review Committee (protocol number: 2019/13-31, date: 11.09.2019).

Informed Consent: Both verbal and written informed consents were obtained from study participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., Z.G., Concept: M.G., Z.G., Design: M.G., Z.G., Data Collection or Processing: M.G., Z.G., Analysis or Interpretation: M.G., Z.G., Literature Search: M.G., Z.G., Writing: M.G., Z.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

DOI: 10.4274/jtad.galenos.2021.46220
J Turk Acad Dermatol 2021;15(1):14-18

Immunoglobulin E and Serum Interleukin-4 in Patients with Alopecia Areata and Its Correlation to the Severity of the Disease

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ABSTRACT

Background: Alopecia areata (AA) is a common form of non-scarring hair loss. The eatio-pathogenesis AA is unknown. To assess serum level of immunoglobulin E (IgE) and interleukin-4 (IL-4) and in patients with AA and its correlation to severity of the disease.

Materials and Methods: Fifty-seven patients with AA [38 (66.6%) females and 19 (33.3%) males]; and 17 normal volunteer enrolled in the study. Serum level IgE and IL-4 assessed by enzyme-linked immunosorbent assay and severity of AA assessed with Severity of Alopecia Tool.

Results: The study included 57 patients with AA [38 (66.6%) females and 19 (33.3%) males]; among them, there were 28 patients (49.1%) with LAA, 10 (17.5%) with AT, and 19 (33.4%) with AU. The difference of IgE and IL-4 levels between different age groups was statistically significant among both cases and controls ($p \leq 0.05$). The difference between IgE and IL-4 levels and severity of AA was statistically highly significant ($p \leq 0.05$).

Conclusion: IgE and IL-4 levels are elevated in patients with AA. The elevation of IgE and IL-4 is positively correlated the increasing severity of disease. This suggests a shift from a T-helper1 response in early AA to chronic Th2 immune profile.

Keywords: Alopecia areata, IgE, IL-4, Pathogenesis, SALT

Introduction

Alopecia areata (AA) is an unpredictable, medical condition in which there is nonscarring hair loss from some or all hair-bearing areas of the body, usually from the scalp [1,2]. According to the hair loss extension, AA classified into localized or patchy AA (LAA), complete loss scalp hair or alopecia totalis, and total body hair loss with alopecia universalis (AU) [3]. The pathogenesis is complex and involve the interplay of multiple factors, as immunological, environmental, psychological, and genetic factors; however, the exact factors are unknown [4].

Role of cellular immunity and T-helper1 (Th1) cytokines as interferon-γ (IFN-γ) and interleukin-2 (IL-2) in AA was reported [5], humeral immunity and Th2 cytokines as (IL-4, IL-5 and IL-13) are also incriminated in the pathogenesis of AA [6,7]. IL-4 and IL-13 stimulate the transcription of IgE in B-cells through Ig constant region genes [8,9]. Unfortunately, the mechanism in which IL-4 and IgE may interact in the pathogenesis of AA is unknown [6,10,11].

Therefore, the aim of this study was to assess serum IL-4 and IgE levels of in Egyptian patients with different clinical forms of AA without atopic background and healthy subjects. Also to investigate the relation between these levels to the severity of AA using Severity of Alopecia Tool (SALT).

This study conducted to assess the level of IL-4 and IgE in patients with AA and its correlation to severity of the disease.

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Received: 01.02.2021 Accepted: 05.02.2021

Materials and Methods

This pilot, parallel group and randomized controlled trial conducted over 12 months. It received an approval from the Institutional Research Review Board Ethical Committee of the Suez Canal University, Faculty of Medicine, Ismailia, Egypt. It conducted in accordance with the guidelines of the Helsinki Declaration and performed after obtaining the informed consent from all participants.

Inclusion criteria for this study included non-atopic AA with no evidence of any systemic autoimmune diseases (as Hashimoto's thyroiditis) or dermatologic disease as (atopic dermatitis or vitiligo). Exclusion criteria included pregnant women, lactating women, and patients who were receiving treatment for AA, sessions of PUVA, for at least six months before this study. Sixty-three patients were eligible for participation, and 57 completed the study. Complete medical history obtained from each patient, and underwent a general physical examination, stool analysis to exclude parasitic infestation, skin prick test to a panel of allergens, complete blood count to determine the number of eosinophils, and assessment of serum levels of anti-thyroid peroxidase antibodies in those had clinically suggestion of Hashimoto's thyroiditis. In addition to clinical assessment of AA SALT, a formalized mathematical approach for the determination of hair loss and hair regrowth. Briefly, the % of scalp hair loss in each of the sides, back and top of the scalp were determined independently, each was multiplied by the % scalp covered in that area of the scalp and the products of each section summed for a final total % hair loss designed as SALT score [12].

Both patients and controls were subjected to determination of serum IL-4 levels using enzyme-linked immunosorbent assay (ELISA) technique and IgE levels using microparticle enzyme immunoassay technique AviBion Human IL4 ELISA Kit. FINLAND for IL4 and Monobind Inc. USA for IgE. The assay performed blindly on coded samples by a blinded investigator, after the collection of all samples had been completed. In healthy, non-allergic adults, reference range of IgE in children and adult was up to 60 IU/mL and less than 120 IU/mL respectively.

Statistical Analysis

Statistical analysis carried out using computer program Statistical Package for the Social Science (SPSS) version 16 (SPSS; Inc., Chicago, IL, USA). A probability value (p value) <0.05 considered statistically significant. Qualitative data were analyzed using chi-square test while quantitative data analyzed by Kruskal-Wallis and Mann-Whitney test. Pearson correlation coefficient was for IgE and IL-4. The probability of error at 0.05 considered significant, while at 0.01 is highly significant.

Results

The study included 57 patients with AA [38 (66.6%) females and 19 (33.3%) males]; among them, there were 28 patients (49.1%) with LAA, 10 (17.5%) with AT, and 19 (33.4%) with AU. The mean age of enrolled patients was 28±7.8 years, ranging from six to 47 years. The duration of AA ranged from two weeks to 13 years with a mean of 21.4 months. There were 24 patients (42.1%) with positive family history of AA. Thirty-seven patients (64.9%) showed a relation between the onset of their disease and a preceding period of stress, while 20 (35.1%) stated no relation to stress (Table 1). SALT score according to patients showed in Table 2.

The difference of IgE and IL-4 levels between different age groups was statistically significant among both cases and controls (p≤0.05) (Table 3). The difference between IgE and IL-4 levels and severity of AA was statistically highly significant (Table 4). In addition, there were strong significant positive correlation between these levels and duration of disease and SALT score (severity of disease) (p value <0.05), but not with age or gender (p value >0.05) (Table 5).

Discussion

Many mouse and human data revealed that the initiation phase of AA is heavily Th1- based immune response, while the maintenance of hair follicle destruction by cytotoxic cells is due to shift from Th1 response to more chronic Th-2 immune response [13]. Although

Table 1. Disease characteristics among cases

Age	
Mean±SD	28±7.8
Range	6-47
Family history	
Present n (%)	24 (42.1%)
Absent n (%)	33 (57.9%)
Duration in months	
Mean±SD	21.4±38.5
Range	0.5-676
Major life events	
Present n (%)	37 (64.9%)
Absent n (%)	20 (35.1%)

SD: Standard deviation

Table 2. Severity of Alopecia Tool score of study cases

Score	No.	%
S1 (<25%)	15	26.3
S2 (25-49%)	8	14
S3 (50-74%)	7	12.3
S4 (75-99%)	8	14
S5 (100%)	19	33.4

Table 3. IgE E and IL-4 levels among different age groups of study subjects

Age group	Number of patients		IgE level		IL-4 level	
	Cases	Controls	Cases (n=57) Mean±SD	Controls (n=17) Mean±SD	Cases (n=57) Mean±SD	Controls (n=17) Mean±SD
0-<15 yrs	14	4	31.7±18.4	21.9±5.9	25.4±6.5	50.7±8.7
15-<30 yrs	18	5	103±23.6	13.7±8.4	55.1±1.1	40±5.2
30-<45 yrs	11	4	125.9±28.8	18.5±3	48.8±12.7	55.6±6.5
>45 yrs	14	4	69.8±32.8	105±7	56.2±13.8	52±1.4
t test value			10.23#	6.65#	11.48#	3#
p value*			0.01*	0.08	0.02*	0.11

*Significant at p value <0.05
#Kruskal-Wallis test was used.
Yrs: Years, IgE: Immunoglobulin E, IL-4: Interleukin-4, SD: Standard deviation

Table 4. Comparison between IgE and IL-4 levels in different clinical forms of alopecia areata using Kruskal-Wallis test

Type of alopecia	IgE (IU/mL) Mean±SD	IL-4 (Pg/mL) Mean±SD
AU	164.41±31.45	57.11±21.1
AT	102.41±33.12	33.31±51.9
LAA	72.41±11.25	5.46±23.3
Kruskal-Wallis	29.16	27.81
p value	<0.01**	<0.01**

AU: Alopecia universalis, AT: Alopecia totalis, IgE: Immunoglobulin E, IL-4: Interleukin-4, SD: Standard deviation

Table 5. Correlation coefficients (r) of age, gender, disease duration, and SALT score and with IgE and IL-4 levels

Variable	IgE		IL-4	
	Correlation coefficient (r#)	p value	Correlation coefficient (r#)	p value
Age	0.34	0.052	0.30	0.08
Gender	0.25	0.06	0.13	0.47
Duration of disease	1.16	0.04*	1.25	0.02*
SALT score	1.41	0.02*	1.42	0.01*

*Significant at p value <0.05.
#Spearman correlation was used.
SALT: Severity of Alopecia Tool, IgE: Immunoglobulin E, IL-4: Interleukin-4

increased levels of Th1 cytokines (IFN-γ and IL-2) in lesional skin have been reported [14]. Th2 immune response is incriminated also in the eatio-pathogenesis of AA [11]. Cytokines derived from Th2-cells (IL-4 and IL-13) can stimulate the transcription of IgE in B-cells through Ig constant region genes [10].

In human B-cells, the induction of IgE synthesis requires three types of signals. The first signal is delivered through the B-cell antigen receptor. The second signal is provided primarily by cytokines derived from Th2-cells, e.g. IL-4 and IL-13 that stimulate the transcription of IgE through the Ig constant region genes. Finally, the third signal is provided via the interaction between the constitutively expressed CD40 molecule on B-lymphocytes and CD154 (CD40 ligand), a molecule expressed on T-lymphocytes following activation [9,10]. IL-4 and IL-13 induced STAT6 signaling has been shown to play an important role in the differentiation of Th2-cells, B-cell induced expression of Ig-G and IgE and the cell surface display of MHC class II and CD23 [15].

The present study designed to investigate the role of IL-4 and IgE in the immuno-pathogenesis of AA and its correlation to its severity in patients with AA after exclusion of those with possible atopic disease. This in order to evaluate the role of immune signals to induce IgE; in AA patients, irrespective of atopic immune mechanisms. This study included 57 AA patients and other 17 healthy volunteers.

In 1977 O'Loughlin et al. [16], pointed to the association of serum IgE levels and AA. Later on, in 1986 Przybilla et al. [17], found elevated IgE in 19.7% in patients with AA. In the present study, the IgE and IL-4 levels were significantly higher in cases versus controls. Our result agreed with other studies [18,19,20,21,22]. On the other hand, other studies disagree with ours and showed non-significant difference [17,23,24,25].

Cytokines IL-4, 6, 7, 9, 13 enhance IgE production, but IFN-γ and IL-10 inhibit the production [26]. So, high IL-4 and IgE levels may due to lower IL-10 [14], IFN-γ, and transforming growth factor-ß1 [11].

On the other hand, serum levels of IFN-γ were significantly elevated in patients with extensive AA [27]. This may reflect the state of inflammation, especially in the extensive forms of the disease [28]. Therefore, the measurement of serum IFN-γ could be a prognostic indicator to predict AU.

Tumor necrosis factor-α (TNF-α) is synthesized in epidermal keratinocytes and is known to play a key role in the pathogenesis of AA [29]. It is a very potent inhibitor of proliferation [30] and creates a micro-environment rich in the Th2 cytokines, IL-4 and IL-13, enhancing IgE class switching [31].

In addition, the sera of patients with AA contain extremely high levels of B-cell activating factor (BAFF), which belongs to the TNF-α family [32]. BAFF is stimulated by IFN-γ and increased in severe AA [33,34].

Over expression of CD40 considered as another possible mechanism of IgE elevation in patients with AA [35]. It is suggested that CD40 stimulation alone could enhance IL-4 and IgE production [36]. As it present in the hair structures and dermal papilla of AA lesions pointing to its role in serum IL-4 and IgE elevation in patients with AA [37].

Regarding the relation of serum levels of both IL-4, IgE and the SALT score (for assessment of AA severity) and types of AA, we found that there was a strong positive correlation between each of IL-4, IgE and the severity of the disease assessed by SALT score. By comparing these results with previous studies, it comes in agreement with Attia et al. [19], 2010 as they found significant elevated serum IL-4 and IgE in patients with AA, particularly AU, irrespective of the presence of atopy. In contrast of our results, Teraki et al. [27], 1996 found significant elevated serum levels of IL-1α and IL-4 in patients with the LAA, while there was significant elevated serum levels of IFN-γ and IL-2 in patients with extensive forms. Katagiri et al. [11], 2007, suggested the same result, who found that the levels of IFN-γ tended to increase while the levels of IL-4 tended to decrease in severe cases of alopecia. This could be explained by the fact that previous studies did not exclude patients with atopy and did not relate cytokine profile to disease chronicity.

This study revealed that psychic trauma precedes the onset of AA in 37 (64.9%). This coincided with Güleç et al. [38], 2004, who reported that anxiety and depression play a major role in the etiopathogenesis of AA, and stressful life events may act as a trigger in the onset and/or exacerbation of the disease. Also the same finding was found by Manolache and Benea [39], 2007 who suggested that stress playes an important role in the onset and aggravation of both vitiligo and AA, often with one stressful event before disease onset.

The study showed a strong positive correlation between duration of the disease and IL-4 and IgE level. This was in agreement with Attia et al. [19], 2010 and Zuel Fakkar et al. [20], 2010 who found that the longer the disease duration was the higher the level of IL-4 and IgE was present.

Conclusion

Finally, IL-4 and IgE levels are elevated in patients with AA. Positive correlation of this elevation to the increasing severity of disease, suggests a shift from a Th1 response in early AA to a more chronic Th2 immune profile, with secondary B-cell stimulation and possible IgE class switching.

Ethics

Ethics Committee Approval: It received an approval from the Institutional Research Review Board Ethical Committee of the Suez Canal University, Faculty of Medicine, Ismailia, Egypt.

Informed Consent: It conducted in accordance with the guidelines of the Helsinki Declaration and performed after obtaining the informed consent from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A.El-L., G.F.M., F.A., M.E., Concept: R.A.El-L., G.F.M., F.A., M.E., Design: R.A.El-L., G.F.M., F.A., M.E., Data Collection or Processing: R.A.El-L., G.F.M., F.A., M.E., Analysis or Interpretation: R.A.El-L., G.F.M., F.A., M.E., Literature Search: R.A.El-L., G.F.M., F.A., M.E., Writing: R.A.El-L., G.F.M., F.A., M.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

DOI: 10.4274/jtad.galenos.2021.03511
J Turk Acad Dermatol 2021;15(1):19-23

Innovative Cosmetic Therapy of Wrinkles by Heat Dermabrasion with Longstanding Outcomes

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ABSTRACT

Background: Wrinkling is a major health problem following excessive sunlight exposure and aging that gives a bad cosmetic appearance and premature aging. These wrinkles will interfere with job selection and social activities.

Materials and Methods: This is a surgical cosmetic interventional trial where four patients shared in this new procedure, their ages ranged from 35-70 years with three males and one female. After local anesthesia, a direct diathermy heated needle was applied on wrinkles (two males, one with crow's feet and one with frown lines). While in other two patients, one male and one female, this procedure was carried out for the whole face wrinkles and other aging changes, followed directly by 35% trichloroacetic acid peel. Patients were given topical and systemic antibiotics to be seen after 2 weeks. Then, the patients were given mild topical corticosteroids and avoiding sunlight exposure. Follow up was done after 1, 2, 4 months and four years. Reduction score of wrinkling was assessed as follow: mild (1-25%), moderate (>25-50%), marked (>50-75%) and excellent (>75-100%).

Results: There was marked to excellent reduction of wrinkles with general healthy youthful looking of the face and these cosmetic changes continued even many years after the procedure. No complications were seen apart from temporary pigmentation that was observed during the first month and gone overtime.

Conclusion: Heat dermabrasion of moderate to severe wrinkling gave marked to excellent results in reduction of wrinkles and gave more youthful healthy appearance to the face.

Keywords: Wrinkles, Crow's feet, Heat dermabrasion, Diathermy, Rejuvenation

Introduction

Skin aging is characterized by cutaneous signs such as wrinkles and increased skin laxity [1]. Cosmetically the face is an important area, as the face is prone to wrinkling, subjects are more concerned with facial wrinkles than those of any other area [2].

During the aging processes, the skin goes through extrinsic and intrinsic changes simultaneously. Extrinsic aging process is caused by exposure to ultraviolet light, trauma, and diverse skin diseases, whereas the intrinsic aging process is the deterioration of the regeneration ability of the skin due to aging itself [3,4,5]. The aging process changes both the structure and mechanical properties of the skin, mainly through changes of the elastic and collagen fibers in the dermis [6]. These fibers become thin and fractionated, and the skin commonly loses elasticity [7]. As a result of skin aging, the skin gets more wrinkles [8]. Microscopically, the fine mesh of skin surface declines and each wrinkle becomes obvious, as its height and width grows with age [9,10].

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Received: 19.02.2021 Accepted: 24.02.2021

Various treatment modalities have been used to improve skin wrinkling and laxity, starting from topical anti-aging products passing through chemical peels, botox injection, injectable fillers, and laser treatment reaching to facelift surgery [11,12,13,14,15].

A novel and safe technique called heat dermabrasion using a needle of diathermy has been introduced by Sharquie [16] in the treatment of different types of acne scaring and nose volumeplasty for bulky nose under local anesthesia in one session with minimal or no adverse effects [17,18,19,20]. In this study heat dermabrasion is applied to removed wrinkles on the face.

So the aim of this work is to search for new cosmetic ways and procedures that give longstanding correction of moderate and severe wrinkling with minimal or no complications.

Materials and Methods

This is a surgical, cosmetic, interventional trial took place from July 2016 to October 2020.

Four patients (three males and one female) with deep facial wrinkles were enrolled in this study, their ages ranged from 35-70 years with a mean of 49.75 years and Fitzpatrick's skin type 3 and 4. The study was approved by the Ethics Committee of Fallujah Teaching Hospital (number: 725, date: 11.02.2021). This study followed the Declaration of Helsinki Principles and written formal consent was taken from patients before starting treatment and the need for before and after treatment photographs. All patients received a complete facial examination at the initial visit which is focused mainly on the wrinkles and standardized photographs were taken before treatment, at the end of the session, and each visit during follow-up.

The treated area was cleaned with spirit and povidone-iodine then in two male patients one with crow's feet and the second with frown lines, and under local anesthesia, direct diathermy heated needle was applied on wrinkles and two passings were done, superficial and deep until a smooth erythematous surface was reached. While in other two patients, one male and one female, this procedure was carried out for the whole face aging and wrinkling, followed directly by 35% trichloroacetic acid (TCA) peel. Patients were given topical and systemic antibiotics to be seen after two weeks. Then after patients were given mild topical corticosteroids and avoiding sunlight exposure. Follow up was done after one, two, four months and four years. Any complications or occurrence of adverse effects were recorded at each post-session visit. One session only was carried for all patients.

Table 1. To assess the reduction rate in facial wrinkles

Parameter	Reduction rate (%)	Score
No change	0	0
Mild reduction	1-25	1
Moderate reduction	>25-50	2
Marked reduction	>50-75	3
Excellent reduction	>75-100	4

The degree of improvement in the appearance of facial wrinkles after a single session of heat dermabrasion alone or heat dermabrasion followed by 35% TCA was assessed using a reduction score of wrinkling (Table 1).

Two dermatologists compared the digital pictures of cases before and after intervention besides the clinical evaluation using the same score in Table 1.

Patient's satisfaction to response to the treatment was assessed as follow:

1) Full satisfaction.

2) Partial satisfaction.

3) No satisfaction.

Statistical Analysis

Data have been analyzed using Statistical Package for the Social Science version 22. These data were statistically described in terms of frequencies (no. of cases), mean, range, percentage (%), and male to female ratio.

Results

During the study period, 4 subjects were included in the study. All subjects displayed marked to an excellent reduction of facial wrinkles Table 2.

Skin resurfacing of the whole face with heat dermabrasion followed by 35% TCA induces marked skin retraction and improvement of wrinkles in these patients, providing further cosmetic advantage.

There was marked to an excellent reduction of wrinkles with general healthy looking of the face and these cosmetic changes continued even many years after the procedure. On the other hand, there was significant improvement in skin texture after heat dermabrasion procedure alone or heat dermabrasion followed by 35% TCA.

Table 2. Showing the sex, treated sites, type of intervention, and reduction rate following one session of heat dermabrasion

Case no.	Sex	Treated site	Type of intervention	Reduction
1	Male	Frown lines	Heat dermabrasion	Marked
2	Male	Crow's	Heat dermabrasion	Marked
3	Female	Whole face	Heat dermabrasion followed by TCA	Excellent
4	Male	Whole face	Heat dermabrasion followed by TCA	Excellent

TCA: Trichloroacetic acid

For the most treated sites, healing was rapid, pain was minimal, erythema was disappeared within 15-30 days, and temporary pigmentation that observed during the first month and gone overtime.

Pictures of the subjects before treatment and during follow up period were shown in Figures 1, 2, 3.

In one patient (Figure 3), after we did heat one sessions of heat dermabrasion for crow's feet area only, but this surprisingly was followed by sudden lifting of the whole face sides that continued for several years. This patient refused full face dermabrasion.

Full satisfaction with the result outcome was achieved in all patients.

Discussion

Wrinkles on the face are the most important marker for human aging. Wrinkles are cutaneous folds created by the structural and mechanical properties of the skin [9,21].

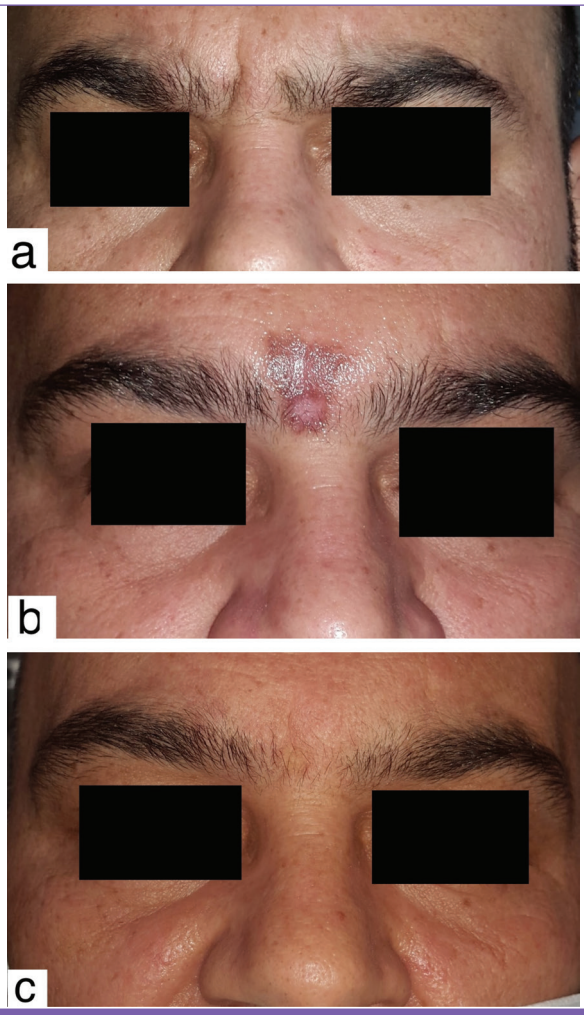

Figure 1. Thirty-five years old male with frown lines. Before treatment (a), two weeks after treatment with heat dermabrasion (b) and after four years (c)

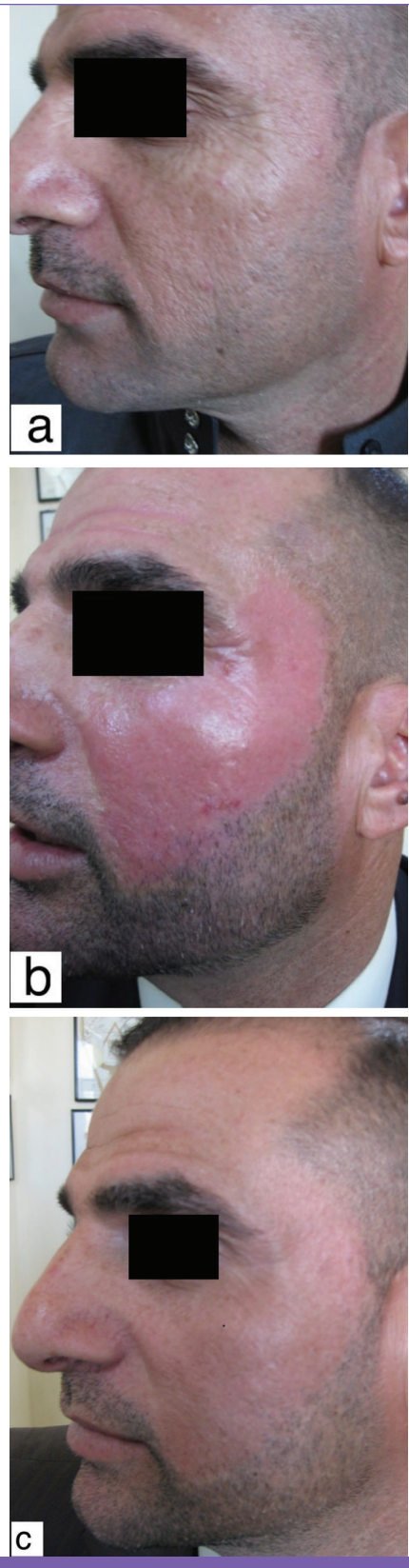

Figure 2. Forty years old male with different types of facial wrinkles. Before treatment (a), two weeks after treatment with heat dermabrasion combined with trichloroacetic acid peeling (b) and after four years (c)

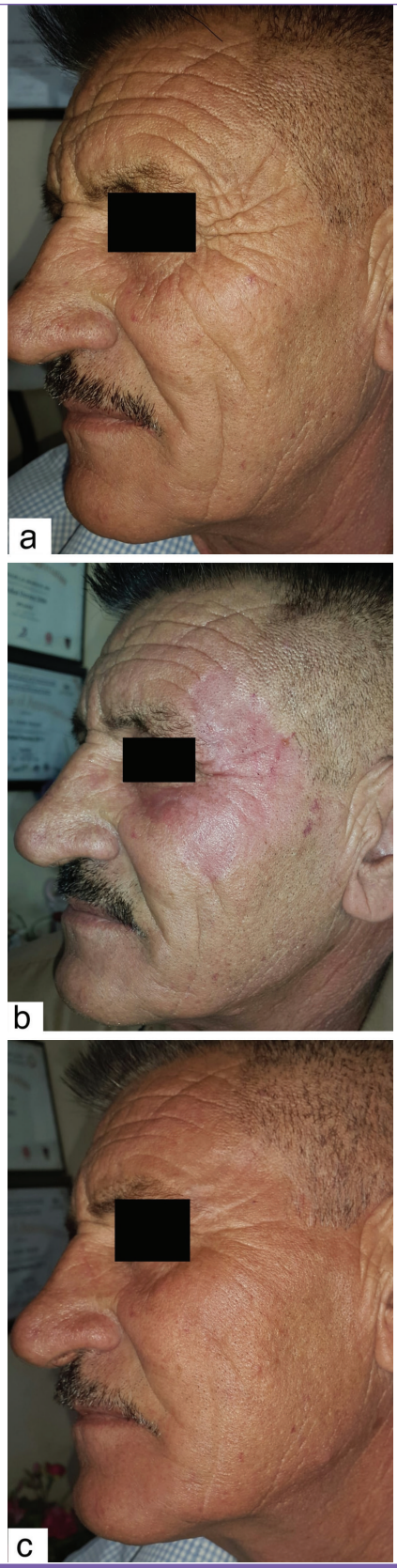

Figure 3. Seventy years old male with deep crow's feet wrinkles. Before treatment (a), two weeks after treatment with heat dermabrasion (b) and after four years (c)

To our knowledge, this is a unique clinical trial that highlights the using of heat dermabrasion for the treatment of facial wrinkles.

In this study, we tested the ability of single session of heat dermabrasion on rejuvenating the general appearance of the face and correcting facial wrinkles for long period of time.

One of the patients refused to do heat dermabrasion for the whole face and he wanted to do it only around the eyes so called crow's feet wrinkles but it is very surprising, this gave marked improvement for wrinkles with obvious lifting for the whole face sides and for unknown reason so this site may be considered very critical area in facial lifting and rejuvenation.

There are numerous existing methods and techniques for treating facial wrinkles.The earliest and oldest technique is classical dermabrasion. This technique may be effective but often needs general anesthesia. Also, this procedure is messy and bloody as using a brush that might cause blood contamination to the surroundings, even causing the transmission of infection from patients to the medical staff. Besides, it is a costly procedure and may generate complications [22,23,24].

Botox has been used in the treatment of facial wrinkles but still, many patients refused to use it as it gives short standing results (3-6 months) so it needs repeated injections, costly, associated with some unwanted effects such as ptosis, diplopia, or others [25,26].

Lasers both ablative and non-ablative have also been used as methods for skin rejuvenation. This is, however, a risky procedure, as lasers require protection for the doctor's and patient's eyes, require significant experience, are costly, may cause postinflammatory hyperpigmentation, and may require multiple sessions to achieve the final cosmetically acceptable outcome [27,28,29].

The outcome of this study shows that heat dermabrasion is an effective technique for decreasing facial wrinkles, and also, improvement in the skin texture. This procedure can produce marked to excellent results if the technique is carried out by a well-trained dermatologist on an appropriate subject. The key of the success of heat dermabrasion is related to the experience and the appropriate know-how of the dermatologist on the principles to produce the accurate resurfacing at the accurate depth to prevent unwanted scar formation. On the other hand, heat dermabrasion using a needle of diathermy removes the epidermis and papillary dermis, creating a partial thickness wound to heal by second intention and this enhances a new collagen fibers formation during the healing process which is important for skin rejuvenation.

This technique had been already applied in treatment of scars including acne scarring and bulky nose and has many benefits include relatively quick and easy, cost effectiveness, relatively simple equipment requirements, used on an outpatient basis, long standing results, and safe, effective results with no significant complications [16,17,19,20].

Study Limitations

The major limitation of this study was a small sample size.

Conclusion

Heat dermabrasion of moderate to severe wrinkling gave marked to excellent results in reduction of wrinkles and gave more youthful healthy appearance to the face. This novel technique was characterized by long standing outcome and no significant complications, with fully satisfaction aesthetic results, and was used with success for improving the skin texture. It is an easy, clean, and non-costly procedure that may be used on an outpatient basis.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Fallujah Teaching Hospital (number: 725, date: 11.02.2021).

Informed Consent: This study followed the Declaration of Helsinki Principles and written formal consent was taken from patients before starting treatment and the need for before and after treatment photographs.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.E.S., R.I.J., Concept: K.E.S., R.I.J., Design: K.E.S., R.I.J., Data Collection or Processing: K.E.S., R.I.J., Analysis or Interpretation: K.E.S., R.I.J., Literature Search: K.E.S., R.I.J., Writing: K.E.S., R.I.J.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/jtad.galenos.2021.41636
J Turk Acad Dermatol 2021;15(1):24-26

Corymbose and Annular Pattern in Secondary Syphilis with Concomitant Chancre on Penis: Can it Be a Manifestation of Early Latent Syphilis

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ABSTRACT

Secondary syphilis (SS) usually involves skin, mucous membrane, lymphnodes, eyes, bones. A rare but characteristic manifestation of SS is corymbose pattern where is a large central papule and a few small ones at the periphery. The papules may be present in annular configuration. Here we present a case who has only few corymbose and annular lesions of SS over face with no lesions in other areas of body, with concomitant chancre over penis.

Keywords: Secondary syphilis, Corymbose and annular pattern, Early latent

Introduction

Secondary syphilis (SS) is a sexually transmitted infection caused by the spirochete *Treponema pallidum*, subspecies pallidum. It can manifest as macular, papular, pustular syphilide. Papular form can manifest as annular, corymbose pattern which is characteristics of SS. Physicians unaware of its protean manifestations may easily overlook its atypical presentation. After healing of SS lesions, patient enters in phase of latency, but relapses occur in 25% cases during latent phase among untreated syphilitics [1]. Clinical relapses conform to a picture of SS, though the disease is less extensive. Occasional occurrence of a relapsing lesion resembling a primary chance at the site of initial primary chancre has been referred as 'chancre redux. Here we report a case who has only few corymbose and annular lesions of SS over face with no lesions in other areas of body, with concomitant chancre redux over penis.

Case Report

A 27-year-old, unmarried male patient presented with asymptomatic annular lesions over chin (Figure 1) and left sided cheek (Figure 2) and a penile lesion (Figure 3) for last six weeks. He had history of unprotected sexual intercourse with an unknown male. He had no history of similar lesions over his body in past. But he gave history of painless penile lesions eight months back which was started after four weeks of unprotected sexual intercourse. On clinical examination, the papular lesions were arranged in annular configuration, there was a one central large papule which was surrounded by multiple small satellite papules resembling corymbose lesion. The lesions were painless, non-pruritic. There was whitish to slightly reddish non tendered, non-pruritic plaques and ulcers over glans penis and undersurface of prepuce. Mucosa, lymph node and systemic examination were normal. No other cutaneous lesions were present. Venereal disease research laboratory was positive at 1:64 and *Treponema pallidum* hemagglutination assay was positive. He

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Received: 24.12.2020 Accepted: 11.01.2021

was negative for HIV 1 and 2. Biopsy from facial lesions revealed aggregate of lymphocytes with few epithelioid cells and plenty of plasma cells in upper dermis (Figures 4, 5).

Discussion

Atypical cutaneous manifestations of the SS rash may be more common than generally assumed and include (but are not limited to) annular, nodular, pustular, psoriasiform, circinate, bullous, rupioid, framboesiform, nodular-ulcerative, ulceronecrotic, granulomatous, vesicular, follicular, pigmentary (leukoderma syphiliticum and pigmentary syphilide), and corymbose lesions [2]. A corymbose (or corymbiform) arrangement (from the Greek kórymbos, cluster of fruits or flowers) comprises a central greater papule surrounded by smaller satellite lesions. Corymbose syphilis may present as single lesion [3] or several lesions [4]. Adamson reported in the early twentieth century that corymbose syphilis was a well-known though somewhat rare type of syphilide [5]. After many years of syphilology practice, Fournier considered syphilide papuleuse en corymbe a rare and bizarre presentation of SS that was "very significant due to its singularity" [6].

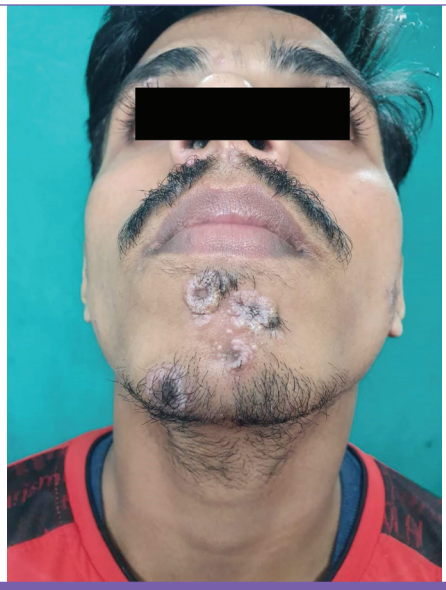

Figure 1. The papular lesions were arranged in annular configuration and in corymbose pattern over chin

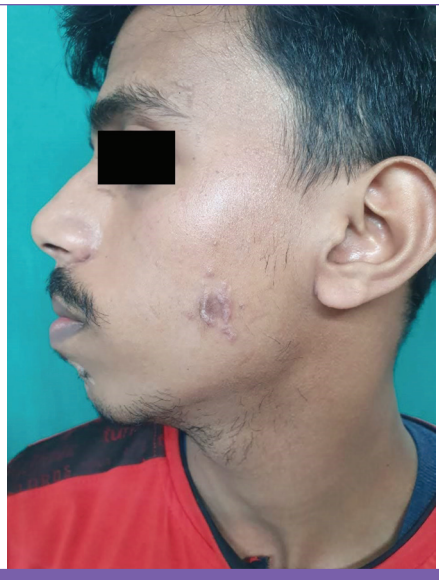

Figure 2. Papular lesions were arranged in annular configuration over left sided cheek

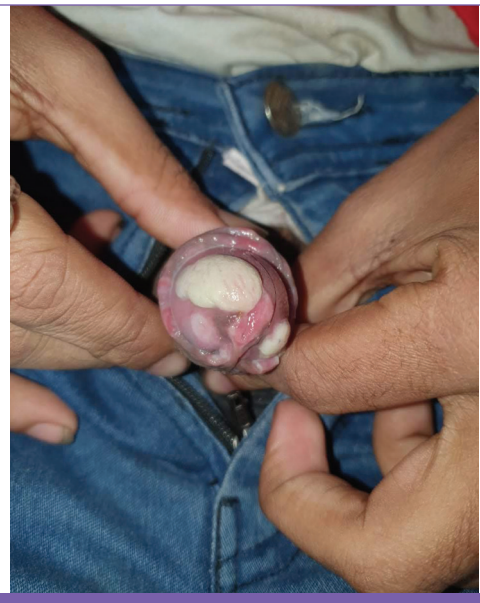

Figure 3. Chancre redux

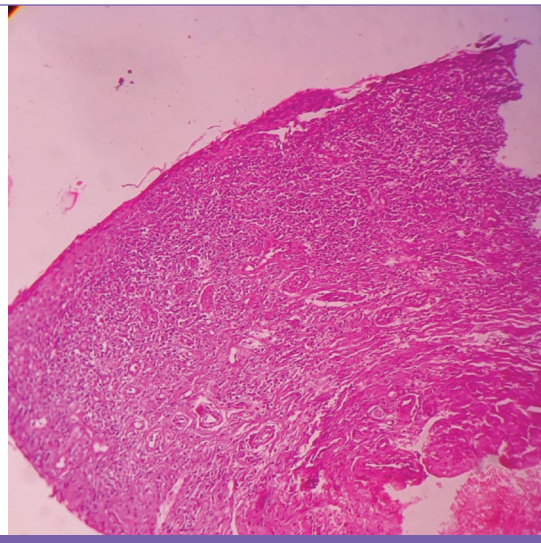

Figure 4. Biopsy from facial lesions revealed aggregate of lymphocytes with few epithelioid cells and plenty of plasma cells in upper dermis under low power in hematoxylin and eosin stain

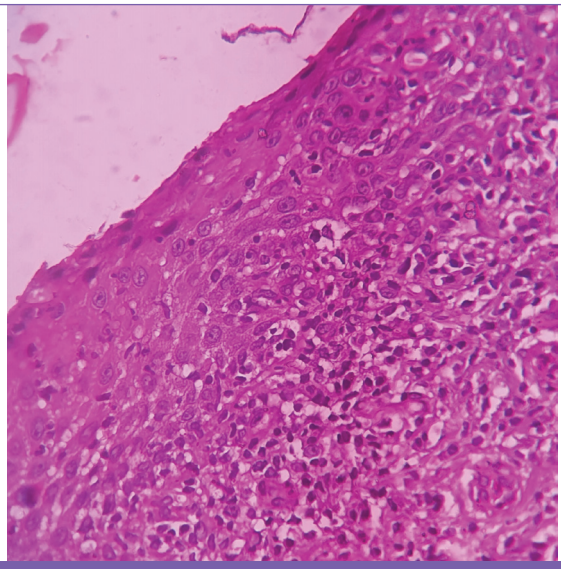

Figure 5. Biopsy from facial lesions revealed aggregate of lymphocytes with few epithelioid cells and plenty of plasma cells in upper dermis under high power in hematoxylin and eosin stain

Our case is important because our case has only few reports of corymbose pattern in literature and our patient has also concomitant chancre redux on penis which could indicate an early latent syphilis. Failure to recognize and appropriately treat syphilitic lesions may have ominous consequences, since the lesions will undergo spontaneous remission, entering into a latent stage, and life-threatening complications may eventually ensue.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B., S.M., O.R., P.N., A.M., A.P., Concept: S.B., S.M., P.N., A.M., A.P., Design: S.B., S.M., P.N., A.P., Data Collection or Processing: S.B., S.M., O.R., P.N., A.M., A.P., Analysis or Interpretation: S.B., S.M., O.R., P.N., A.M., A.P., Literature Search: S.B., S.M., O.R., P.N., A.M., A.P., Writing: S.B., S.M., A.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/jtad.galenos.2020.46855
J Turk Acad Dermatol 2021;15(1):27-29

Two Patients with Psoriasis and Hepatitis B Treated with Secukinumab During COVID-19 Pandemic

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ABSTRACT

Secukinumab may be a safety option for patients with psoriasis and hepatitis B virus (HBV) infection because of its treatment mechanism. Two patients with chronic HBV who had used tenofovir disoproxil 245 mg per day were suffering from psoriasis. For one, on July 31, 2019 treatment with standard dose secukinumab was started and for another on January 20, 2020. Although on March 11, 2020 Coronavirus disease-2019 (COVID-19) pandemic started in Turkey, we didn't stop secukinumab treatments of our patients. Based on the start of treatment of secukinumab of our 50-year-old patient, after eight weeks Psoriasis Area Severity Index (PASI) 90 response and after 15 weeks PASI 100 response was reached and PASI 90 response was obtained in our 35-year-old patient after five weeks and PASI 100 response was reached after 18 weeks after starting secukinumab. Secukinumab treatments of our patients are going on. Further long-term studies and case reports are needed to validate the safety and efficacy of secukinumab in patients with HBV. Our cases were deemed worthy of presentation because they were the first reported cases with psoriasis and HBV infection used secukinumab and tenofovir disoproxil in COVID-19 pandemic.

Keywords: Psoriasis, Secukinumab, Hepatitis B virus, Coronavirus disease-2019

Introduction

Using biologic therapies for immune diseases, such as psoriasis, is controversial when hepatitis B virus (HBV) infection is active in the patient because this status has been associated with reports of HBV reactivation [1]. Food and Drug Administration is suggesting that patients with HBV should not be treated with biologics targeting tumor necrosis factor (TNF) [2]. Secukinumab is an anti-interleukin (IL) 17A monoclonal antibody produced by T-helper 17 (Th17) cells [1]. IL-17 has been shown to mediate host defence mechanisms in response to various infective agents including viruses and plays an important role in HBV activity [1,3]. Increased serum levels of IL-17 and frequency levels of Th17 can be used as indicators for HBV infection and progression according to various studies [1].

Safety data for secukinumab in patients with psoriasis and viral hepatitis are lacking in the literature. Here we present two male patients with chronic plaque psoriasis and chronic viral HBV infection who achieved Psoriasis Area Severity Index (PASI) 100 response with the treatment of secukinumab.

Case Report

A 50 year-old male with chronic plaque psoriasis and chronic HBV applied to dermatology outpatient clinic of Izmir Tepecik Training and Research Hospital. The patient suffering from psoriasis for 30 years didn't have any joint involvement. His PASI was 18 (Figure 1). He had used tenofovir disoproxil 245 mg per day. On July 31, 2019 his hepatitis B surface antigen (HBsAg) was 4853.47 S/CO (positive), immunoglobulin M (IgM) antibody to hepatitis B core antigen (anti-HBc IgM) and anti-hepatitis Be (anti-HBe) were negative, immunoglobulin G (IgG) antibody to anti-HBc IgG was positive, hepatitis B surface antibody (anti-HBs) was 0.48 mIU/mL (negative),

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Received: 20.11.2020 Accepted: 23.11.2020

anti-hepatitis C virus (anti-HCV), anti human immunodeficiency virus (anti-HIV) and quantiFERON-TB Gold (QFT) test were negative. On the same day, treatment with standard dose secukinumab (300 mg sc at week 0, 2, 4, 6, 8 and then 300 mg sc every one month) was started. On August 8, 2019 HBV-DNA was 370000.0 IU/mL (normal level <10 IU/mL) and HBsAg increased to 5631 S/CO. On March 9, 2020 his HBsAg was 5631 S/CO (positive) and anti-HBs was negative. Although on March 11, 2020 Coronavirus disease-2019 (COVID-19) pandemic started in Turkey, we didn't stop secukinumab treatment of our patient. We telled to him all necessary warnings and suggestions during pandemic period. Based on the start of treatment of secukinumab, after eight weeks PASI 90 response and after 15 weeks PASI 100 response was reached (Figure 2). Our patient was at the 34th week of treatment and PASI 100 response is going on (on May 26, 2020). He is still in remission. Our other 35-year-old male patient suffering from plaque psoriasis for 13 years applied to our dermatology outpatient clinic on September 12, 2019. PASI was 14.6 (Figure 3). He had used tenofovir disoproxil 245 mg per day because he was chronic HBV. On September 12, 2019 according to his laboratory findings HBsAg (2150.28 S/CO), anti-HBc IgG (10.38 S/CO) and anti-HBe (0.01 S/CO) were positive. Anti-HBs and anti-HBc IgM were negative. HBV-DNA was 117000.0 IU/mL and after three months HBV-DNA was measured as 370000.0 IU/mL, on January 20, 2020 HBV-DNA was 4.4E IU/mL. Anti-HCV, anti-HIV and QFT tests were negative.On the same day treatment with standard dose secukinumab (300 mg sc at week 0, 2, 4, 6, 8 and then 300 mg sc every one month) was started. After five weeks, PASI 90 response and after 18 weeks PASI 100 response were obtained (Figure 4). He is still in remisson. No adverse effects developed. Both verbal and written informed consents have been provided from the cases.

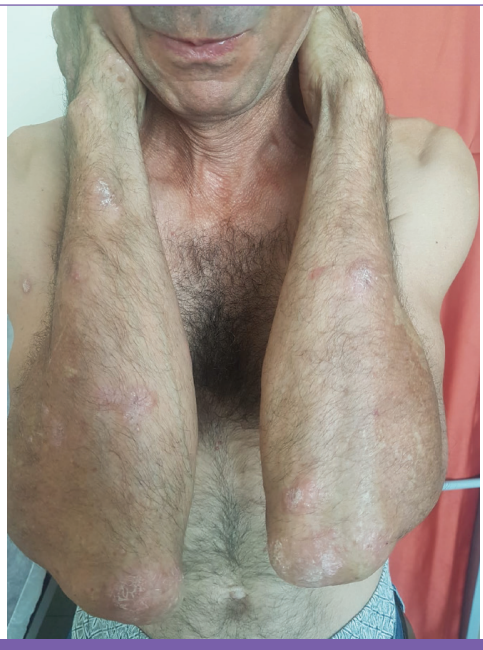

Figure 1. Elbows

Discussion

Biologic agents can change the balance between the degree of virus replication and host immune control, which may thereby cause virus reactivation [3]. HBV, a DNA virus, persists latently in hepatocellular nuclei and proliferates when the immunity of the host is suppressed by immunosuppressive drugs or biological agents. The reactivation rate of HBV by anti-TNF therapy varies from 33 to 62%, by anti-IL-12/23 antibodies reaches 29% [4].

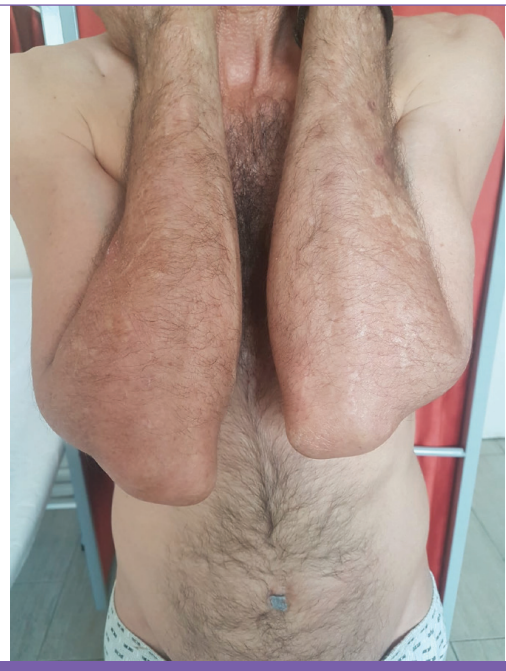

Figure 2. Elbows

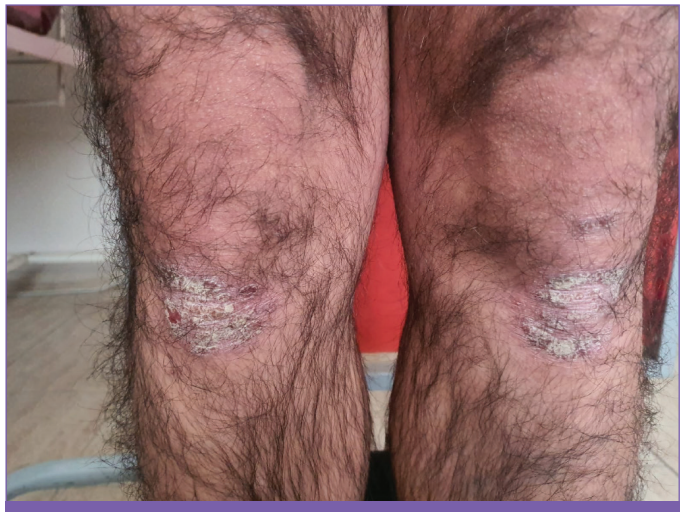

Figure 3. Knees

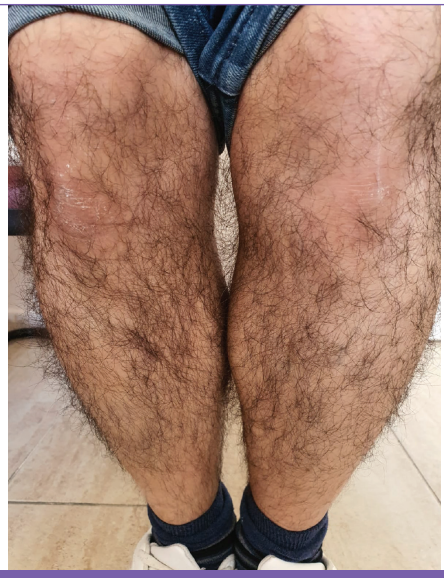

Figure 4. Knees

Secukinumab, may be a much-needed treatment for moderate-to-severe psoriasis in HBV patients experiencing suboptimal disease control with other therapies [3,4,5,6]. The data available for patients with psoriasis with concomitant HBV infection treated with systemic therapies are limited to case studies and small groups [7]. Feaster et al. [1] presented a 48-year-old case with psoriasis, psoriatic arthritis who is a carrier of congenital HBV. This case was treated successfully with secucinumab whitout reactivation of HBV. Yanagihara et al. [4] presented another case study of a 66-year-old man with HBV, he was successfully treated with a combination therapy of secukinumab and entecavir, with no reactivation of HBV over nine months of follow-up. In Chiu et al.'s [3] study, twenty-five of the 49 patients with HBV infection had chronic HBV infection, 13 had resolved HBV infection and the other 11 were infected with occult HBV at the time of recruitment. Four of 49 patients used concomitant immunosuppressants or immunomodulators in addition to secukinumab. Three patients with HBV infection (HBsAg positive and HBsAb negative) received antiviral prophylaxis, in the form of 600 mg telbivudine or 0.5 mg entecavir daily. HBV reactivation wasn't occured in these three patients. However, six patients of 22 with HBV (HBsAg positive and HBsAb negative) who did not receive antiviral prophylaxis developed HBV reactivation after 3.4±2.8 months. None of these patients adjusted or discontinued the secukinumab therapy [3]. Furthermore, in a multicenter study of 324 patients with moderate to severe PsO treated with secukinumab including six patients with HBV, secukinumab was effective and safe, with no reports of HBV reactivation [8].

Further long-term studies and case reports are needed to validate the safety and efficacy of secukinumab in patients with HBV. Our cases were deemed worthy of presentation because they were the first reported cases with psoriasis and HBV infection used secukinumab and tenofovir disoproxil in COVID-19 pandemic. Our patients continue secukinumab treatments without any side effects and remain self-isolated at home.

Ethics

Informed Consent: Both verbal and written informed consents have been provided from the cases.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., D.D.B., Concept: M.G., D.D.B., Design: M.G., D.D.B., Data Collection or Processing: M.G., D.D.B., Analysis or Interpretation: M.G., D.D.B., Literature Search: M.G., D.D.B., Writing: M.G., D.D.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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