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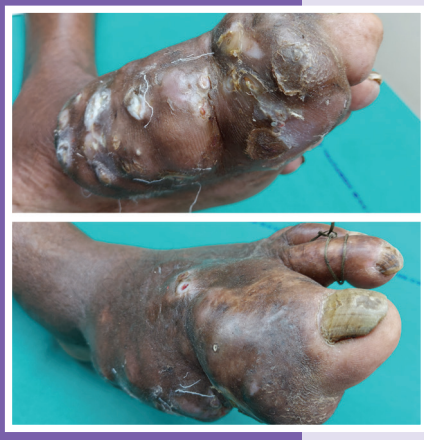

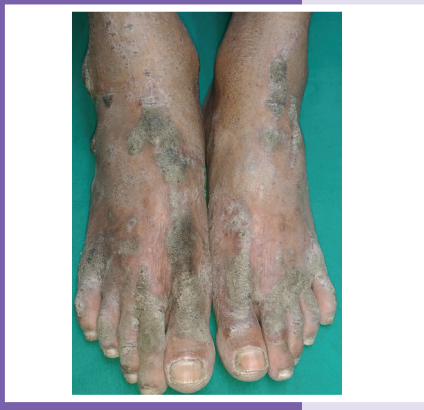

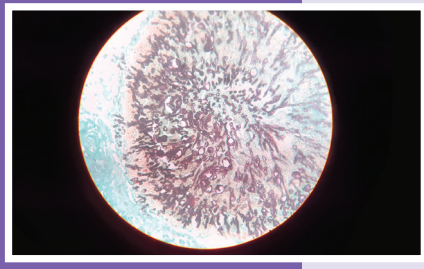

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Mareledwane NG. A randomized, open-label, comparative study of oral doxycycline 100 mg vs. 5% topical benzoyl peroxide in the treatment of mild to moderate acne vulgaris. Int J Dermatol 2006; 45: 1438-1439. PMID: 17184250

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REVIEW

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Microbiota and Dermatology

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ABSTRACT

Barrier structure and function of skin are essential to human health. Skin represents the primary interface between the host and the environment; it is colonized by microorganisms, most of which are harmless or even beneficial to their host. Colonization is driven by the ecology of the skin surface, which is highly variable depending on topographical location, host factors and environmental factors. In recent years, investigations have shown that the microbiome has a major impact on physiological functions including protection against infections, reaction patterns in the immune system, and disposition for inflammation-mediated diseases. An enhanced understanding of the skin microbiome is necessary to gain insight into microbial involvement in human skin disorders and to enable novel therapeutic approaches for their treatment.

Keywords: Microbiota, Microbial interaction, Skin, Immunity, Skin diseases

Introduction

Microbiota is a term that describes the microorganisms found on all anatomical sites and includes bacteria, viruses and funghi. Microbiome refers to the collection of these microorganisms containing genome [1]. It has been estimated that there are ten times more microbial cells than body cells in humans [2]. We can imagine these microorganisms to be a kind of a microbial organ. Until recently the studies have been focused on microorganisms as agents of disease, but now they are recognized as regulators of the immune system and therefore important factor for the human health [3].

Primary function of the skin, which is the largest organ of the human body, is to act as a barrier against endogenous and exogenous factors. The skin is in direct contact with the external environment and therefore providing a home to various microorganisms.

These microorganisms have a symbiotic relationship with the skin and help maintaining the homeostasis of the skin by regulating the immune system. Disruption of this relationship can lead to various dermatological diseases.

The aim of this review is to evaluate the skin microbiome and it's role in dermatological diseases.

History

The research of human microbiota in dermatology began with Kligman in 1950 using cell culture method [4]. In 2000 Nobel laureate Joshua Lederberg suggested using the term human microbiome to describe the collective genome of microorganisms colonizing the human body [5]. The International Human Microbiome Consortium launched in 2008 with the mission of generating resources that would enable the characterization of the human microbiome and analysis of its role in human health and disease [6].

Microbiota Development

Development of microbiota begins with the first day of pregnancy. 'The first 1000 days" refers to the child's life from conception to the end of the 2nd year of life. This time is the most important period for microbiota development. Factors like pregnancy, delivery mode, intrapartum antibiotic use, lactation and maternal dietary

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factors cause temporary or permanent changes on composition of microbiota [7].

Pregnancy is the first step on the development of baby's microbiota. Sequencing analysis of unculturable microorganisms has been used to define microbial composition of placental membranes, amniotic fluid, umblical cords and meconium. The placental microbiota composition has been found similar to the maternal oral microbiota and it's been considered that it can influence the fetal immune tolerance [8]. Maternal dietary factors, maternal body mass index, intrapartum antibiotic use and stress during pregnancy affect maternal microbiota composition. That, in turn, has an effect on the babies microbiota composition and immune system [8,9].

Delivery mode is one of the key factors on the development of microbiota. During vaginal delivery newborn's skin is colonised with the maternal vaginal flora. Skin flora in newborns delivered by Cesarean section (C-section) resembled that of the mother's skin. A study by Dominguez-Bello in 2010 has shown that microbiota compositions of newborns differ between vaginal delivery and C-section. Vaginal delivered infants acquired bacterial communities resembling maternal vaginal microbiota, dominated by *Lactobacillus* and followed by *Atopobium*, *Prevotella*, or *Sneathia*. *Lactobacillus* has not been found dominant in C-section delivered infants, on the contrary, their microbiota were dominated by *Staphylococcus* similar to skin flora [10].

An another research by Martin et al. [11] has shown that in vaginally born infants receiving breast milk, *Bifidobacterium* dominance occurs in 20 days in contradistinction to six months in C-section delivered infants. In a systematic review, Rutayisire et al. [12] reported that *Bifidobacterium*, *Enterobacteriaceae*, *Bacteroides* and *Lactobacillus genera* were to be significantly more frequent in vaginally delivered infants compared with CS delivered. *Haemophilius*, *Veillonella*, *Clostridiaceae* ve *Klebsiella* genera were more frequent in CS delivered infants. *Clostridiaceae* dominance in microbiota continued to the end of the 2nd month, on the other hand Bifidobacterium and *Bacteroides* became prominent only after 3rd month.

Another key factor for the early-life development of microbiota is the breastfeeding (8). Studies on breastfeeding have shown that a diverse population of bacteria is present in breast milk (ranging from 100 to 10^5 CFU per mL depending on the study) and this population differs with the delivery mode and gestational age [13,14]. Streptococcus, *Staphylococcus*, *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Propionibacterium* were most common but other short-chain fatty acid producing bacteria such as *Veillonella*, *Propionibacterium*, and *Faecalibacterium* have also been isolated from breast milk [15]. Breastfeeding may influence development of immune-mediated diseases through several mechanisms including shaping gut microbiota and thus impacts on immune system [8].

Skin Microbiome

The skin microbiota conceived of as two microbial groups; permanent residents and transient microorganisms (temporary residents) which arise from the environment and persist for hours to days [16]. Grice and Segre [17] reported that *Actinobacteria*, *Firmicutes*, *Bacteroidetes* and *Proteobacteria* were dominant in skin microbiota.

Skin microbiota and microbial colonization are dependent on the anatomical and physiology of the skin site [17,18]. Human skin consists of 4 microenvironments: dry, moist, sebaceous and other (sweat glands, hair follicles, dermal layers) [19]. Each microenviroment has a distinct microbiota. *Corynebacteria*, *Proteobacteria*, *Flavobacteriales* are dominant on dry areas like forearm and buttock; *Corynebacteria*, *Proteobacteria*, *Staphylococcus* are dominant on moist areas like axillary vault, antecubital and popliteal fossa. Sebaceous microenviroment like face and upper body contains mainly *Cutibacterium* and *Staphylococcus* [20]. In addition, a specific microbiome profile has been found not only on the skin surface but also in the deep layers of the epidermis, dermis and dermal fat tissue [21].

The skin microbiome consists not only of bacteria, but also of microorganisms such as fungi, arthropods, viruses (22). Most common fungal species *Malassezia* spp. are especially prevalent on most of the body and scalp. The Demodex mites, which are microscopic arthropods, are lipophilic. *Demodex folliculorum* are located in hair follicles; *Demodex brevis* are located in sebaceous glands and meibomian glands which line the margin of the eyelids [23].

Skin microbiome may differ from person to person. This differences can be divided as intrinsic and extrinsic factors. Intrinsic factors are age, genotype, body temperature and pH and host immune system. Extrinsic factors are climate, humidity, antibiotic use, clothing choices, detergent and emollient use, surface contact factors such as antiperspirant and frequency of hygiene [24,25,26,27,28,29,30,31].

Skin Microbiota and Immune System

The skin consists of two layers called "epidermis" and "dermis". The first cells that take an active role in the immune response in the skin are "keratinocytes" in the epidermis. These cells recognize structures of pathogens with pattern recognition receptors (PRR), and produce anti-microbial peptides and cytokines. "Langerhans cells", a special subgroup of dendritic cells, are also located in the epidermis. Dermis contains dendritic cells, macrophages, mast cells, T-cells, plasma cells, natural killer cells, natural lymphoid cells [32].

The main function of these cells is to identify pathogens entering the skin and to balance the host and skin microbiome [33].

Skin microbiota affects the innate immune responses in the skin by triggering the production of antimicrobial peptides (AMPs), complement system elements and interleukin-1 (IL-1). IL-1 production triggers the production of IL-17 and interferon-gamma from T-cells (34).

The skin has the capacity to distinguish between commensal microorganisms that form microbiota and pathogenic microorganisms. Although its mechanism is not known exactly, it has been thought to be achieved by dendritic cell modulation [33]. How commensal microorganism antigens are continuously recognized by the immune system is not yet known. It is thought to be possible with dendritic cell extensions, direct uptake by keratinocyte or antigen presenting cells, or by passive epidermal diffusion [34].

T-cell responses are important in interaction with the microbiota. In healthy skin, gamma-delta (γδ) T lymphocytes and alpha-beta T lymphocytes are found in both epidermal and dermal layers. Apart from these, there are resident memory T-cells (Resident memory T: TRM), which have a strong and long-lasting effect, and Foxp3 + memory regulator T (Treg) cells located around the hair follicles. CD8+ TRM cells are found in the epidermis, CD4+ TRM cells are found in the dermiş [35]. Langerhans cells are normally involved in the formation of regulatory T-cells against self-antigens and microbiota and take part in providing tolerance [36].

In the neonatal period, the formation of Foxp3 + Tregs as a result of encountering commensal bacteria such as *S. epidermidis* is critical in the development of commensal-specific tolerance [37,38]. Some substances produced by *S. epidermidis* selectively inhibit *S. aureus* and group A streptococci [33]. Lipoteichoic acid, a product of *S. epidermidis*, inhibits TLR3 signaling by binding to toll-like receptor-2 (TLR2), one of the natural immune system receptors, during tissue damage; and thus reduces inflammation, promotes wound healing, and triggers IL-17A+ CD8+ T-cells to settle in the epidermis [39]. In addition, *S. epidermidis* colonization has been shown to be sufficient to trigger protective immunity against pathogenic Leishmania major infection [40]. It has been shown that Treg cells accumulate in the skin of mice treated with *Vitreoscilla* filiformis lysate, which is a gram negative bacterium, and IL-10 production is triggered [40].

Dectin-1, located in the stratum corneum, is a non-TLR beta-(β)-glucan PRR and is the most important PRR in antifungal immunity [41]. It triggers Th1 response against *Candida albicans* in the pathogenic form of pseudohyphae. It has been shown that IL-17A-producing dermally located γδ T-cells decrease and commensal bacterial colonization increases in germ-free mice skin [42,43]. These cells provide IL-17A production in the early stage and it's important in protecting against *S. aureus* and *C. albicans* infections.

The skin microbiome is mostly controlled by AMPs and proteins induced by cytokines such as IL-17A and IL-22, produced by T-cells in the skin. The presence of CD1a restricted T-cells that produce high levels of IL-22, recognize natural autoantigens and respond to intrinsic lipids has been demonstrated in the skin. This suggests that microbiome-derived lipids may also be effective in the establishment and maintenance of T-cells in the skin [44].

The deterioration of the balance of the microbiota for any reason is called "dysbiosis" and this can lead to the emergence of some inflammatory and systemic autoimmune diseases. The activation status of the host, its genetic predisposition, the localization of a certain microbe and its association with other microbial members are effective in triggering the disease [45].

Microbiata and Dermatological Diseases

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by itching, xerosis and eczema attacks. Pathophysiology of AD involves elements of fillagrin gene mutation, epidermal barrier dysfunction, changes in cellular immune response and environmental factors.

The "hygiene hypothesis", which shows that the development of allergy increases with the decrease of microbial contact in early childhood, has turned into the "biodiversity hypothesis" with the detection that the microbiome is much more diverse than is known [46]. The rapid decline of environmental biodiversity associated with development has been associated with the increase in the prevalence of inflammatory and especially allergic diseases. Microbiota diversity and immunomodulatory capacity decrease due to decrease in natural environmental biodiversity [47]. The long-term protective effect of early exposure to microbial agents may be due to epigenetic regulation of the epithelium or long-term effects on T and B cell programming [48].

Staphylococcal colonization of the skin has been found to be high in children with atopic dermatitis. *S. aureus* activates protease receptors to disrupt the epidermal barrier of AD patients. It releases endotoxins and enterotoxins that stimulate mast cells and cause inflammation and dysregulation of keratinocytes. It also upregulates the production of type 2 cytokines such as thymic stromal lymphopoietin, IL-4 and IL-13 [49]. High IL-4 and IL-13 consume AMPs produced by keratinocytes needed to control pathogenic organisms [50]. Thus, TLR2-mediated detection of *S. aureus* in Langerhans cells is impaired, causing a keratinocyte dysregulation and disruption of the skin microbiome [51].

In healthy skin, *Staphylococcus epidermidis* activates TLR2, which induces keratinocyte-induced AMP secretion. In addition, coagulase negative bacteria such as *S. epidermidis*, *S. hominis*, and *S. lugdunensis* secrete antimicrobials that limit *S. aureus* overgrowth and biofilm formation. This protective process is impaired when *S. aureus* is the dominant species in the skin. According to the studies *S. aureus* colonization was found to be more intense in the disease involvement areas and was found to be associated with exacerbations in the disease [52].

Apart from the skin microbiome, the gut microbiota is also important in the disease [46]. Decreasing diversity of the gut microbiome has also been reported to cause the development of atopic dermatitis [53]. It has been shown that in patients with atopic dermatitis, the number of *Bifidobacteria* leading a commensal life in the gut flora is lower [54]. It has been reported that the risk of developing atopic dermatitis is increased in patients with increased antibiotic use in the first two years of life [46].

In contrast to atopic individuals, it has been shown that the density of *Acinetobacter* species from the *Gammaproteobacteria* class and IL-10 production in peripheral mononuclear cells increase in direct proportion to healthy individuals. TLR2 activation by non-pathogenic bacteria has been shown to trigger the formation of tolerogenic dendritic cells and regulatory Tr1 cells and reduce atopic inflammation [39].

Due to the strong relationship between AD and microbiome, it is aimed to increase commensal microorganisms in treatment. In the study by Nakatsuji et al. [55], it was found that autologous microbiome transplantation of *S. hominis* and *S. epidermidis* was effective in controlling *S. aureus* overgrowth. In the study of Myles et al. [56], the addition of topical *Roseomonas mucosa* and *Vitreoscilla filiformis* bacterial lysate improved the inflammation and severity of eczema.

Psoriasis

Psoriasis is an inflammatory skin disease characterized by erythematous scaly plaques. Recent studies on psoriasis and microbiome have found differences in both skin and gut microbiome of psoriasis patients. In 2008, Gao et al. [57] reported an increase in the number of *Firmicutes* and a decrease in the number of *Proteobacteria* and *Acinetobacter* in psoriatic plaques when compared to non-lesional skin. In a study by Alekseyenko et al. [58] in 2013, an increase in the number of *Staphylococci* and a decrease in *Proteobacteria* (*Cupriavidus* spp., *Schlegelella* spp., *Methylobacterium* spp.) and *Bacteroidetes* (*Flavisolibacter* spp.) were found in psoriasis patients. Many studies have reported an increase in the number of *Staphylococci*, *Streptococci* and a decrease in the number of *Cutibacteria* in psoriatic lesions. In a similar study, an increase in the number of *Corynebacterium*, *Cutibacterium*, *Staphylococcus* and *Streptococcus* and a decrease in the number of Firmicutes and Actinobacteria were found in lesional and non-lesional skin of psoriasis patients. It has been reported that there is a decrease in the variety of bacteria in both lesional and non-lesional skin of psoriasis patients compared to healthy controls [59]. In a study, Chang et al. [60] compared psoriasis patients with healthy controls and found that *S. aureus* colonization was increased in both lesional and non-lesional skin in psoriasis patients. In the same study, it was found that mice colonized with *S. aureus* stimulate the Th17 response more than mice colonized with *S. epidermidis*. They suggested that *S. aureus* increased proinflammatory cytokine release and inflammatory response in psoriasis patients. This suggests that the irregularity of the skin microbiome in psoriasis patients is not limited to lesioned skin, but affects the entire skin microbiome.

In addition, it has been determined that psoriasis patients differ not only in skin microbiome but also in gut microbiome. In a study comparing psoriasis and psoriatic arthritis patients with healthy controls, it was found that the colonization of *Coprococcus genus*, *Akkermansia* and *Ruminococcus* genera decreased [61]. In a study by Scher et al. [62], they found a decrease in the diversity of bacteria in the gut of patients with psoriatic arthritis and psoriasis. They found a decrease in *Actinobacterium* colonization in both groups compared to healthy controls. In the group of psoriasis patients, they reported that the high *Firmicutes/Bacteroidetes* ratio showed a positive correlation with the Psoriasis Area Severity Index score intralesional and topical, to C. acnes-induced lesions suppressed.

Although it has been suggested that psoriasis may be related to the changes in the composition of the skin-gut bacteria and that changes in the microbiome may trigger psoriasis, the different results obtained with different methods do not provide a definite evidence on psoriasis-microbiome relationship. For this reason, it has been suggested that psoriasis is not only due to changes in the microbiome, but also a combination of genetic and environmental factors.

Acne

The acne microbiome started in 1960 with culture-based studies and continues to gain momentum today. As a result of sequencing with metagenomic analyzes, *Cutibacterium acnes* was found to be dominant in the pilosebaceous units of both patients with acne and healthy individuals [63]. *Cutibacterium*, *Staphylococcus* and *Malassezia* species were isolated by PCR examination of acne follicles and a correlation was found with the number of *Malassezia* species on the skin surface and the number of inflammatory acne [64]. *C. acnes* causes tissue destruction by secreting lipase, porphyrins and proteases. There is a correlation between the amount of porphyrin in the hair follicle and the severity of acne. It has been shown that acne-associated type IA-2 strains produce more porphyrin and that porphyrin synthesis of these strains is increased with vitamin B12

intake [65]. In *C. acnes* species in healthy skin, a gene (deoR) has been identified which suppresses porphyrin biosynthesis. These findings suggest that methods targeting the porphyrin biosynthesis pathway and the probiotic use of *C. acnes* species associated with healthy skin may be the new possible acne treatment options. In addition, in an *in vitro* study, it has been shown that skin microorganisms, especially *S. epidermidis*, have an inhibitory effect on the growth of *C. acnes* by making glycerol fermentation. The researchers later demonstrated in vivo that administration of succinic acid, both intralesional and topical, to *C. acnes*-induced lesions suppressed *C. acnes*-mediated inflammation [66].

Rosacea

Rosacea is a skin disease characterized by facial erythema, telangiectasia and/or inflammatory papules and pustules. Abnormal neurovascular activation, irregular release of inflammatory molecules and proliferation of microorganisms in the skin are blamed in the etiopathogenesis [67]. Although Demodex folliculorum is a mite that lives on healthy skin, an increase has been detected in patients with rosacea. It has been hypothesized that this mite's exoskeleton stimulates the release of pathogenic inflammatory mediators [68]. *Helicobacter pylori* is the most accused agent in the relationship between rosacea and gut microbiota [69]. Although the exact pathway between H. pylori infection and rosacea has not been fully elucidated, studies suggest that it may act via proinflammatory virulence peptides, especially in those with gastrointestinal symptoms [70]. However, the relationship to *H. pylori* and rosacea remains controversial, as other studies have failed to find a correlation between the two entities [71,72,73,74]. Whether dysbiosis occurs in response to rosacea or is a cause is still debated [75].

Hidradenitis Suppurativa

Although hidradenitis suppurativa (HS) is stated to be sterile at the beginning of the disease process, it is suggested that the microbiome of preclinical HS is also different due to the detection of less bacteria and biofilms in the nonlesional axillary skin of the patients compared to healthy individuals. Therefore, it has been suggested that HS should be considered in the spectrum of bacterial biofilm-based disorders [76].

Conclusion

Commensal microorganisms on the skin protect the skin from external factors like a shield with a symbiotic relationship. Disruption of this relationship plays a key role in the pathogenesis of different skin diseases. Today many studies on the roles of microbiota in etiopathogenesis of systemic and dermatological diseases ar ongoing, and attetion is drawn to its importance in protecting human health. As a result of these studies, the emergence of different microbiota-related treatment options is an evidence that demonstrates the importance of the issue on human health.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.D., E.E., Concept: E.E., İ.Z., Design: E.E., Data Collection or Processing: E.E., Analysis or Interpretation: D.D., E.E., İ.Z., Literature Search: D.D., Writing: E.E.

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ORIGINAL ARTICLE

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Investigating Dermatologic Side Effects of Anti-Cancer Chemotherapeutic Agents

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ABSTRACT

Background: Various chemotherapeutic agents are used in cancer treatment. The side effects they create on skin are sometimes the same and sometimes different. We purposed to investigate skin, skin appendages and mucosa adverse effects of anti-cancer chemotherapeutic agents with literature in our study.

Materials and Methods: Age, gender, type of cancer, used anti-cancer chemotherapeutic agents, number of cycles of patients were noted. Skin, skin appendages and mucosa adverse effects of anti-cancer chemotherapeutic agents were recorded.

Results: Forty-eight patients were included in our study, 12 of them (25%) were male and 36 of them (75%) were female. We observed different skin, skin appendages and mucosa adverse effects of anti-cancer chemotherapeutic agents and presented them in tables.

Conclusion: Chemotherapeutics can have beneficial effects as well as damaging effects on various organs. We compared dermatologic side effects of chemotherapeutic agents in the light of literature in our study. We also mentioned dermatologic side effects that haven't been mentioned in the literature yet. We believe that our research will contribute to the literature with all these aspects.

Keywords: Anti-cancer chemotherapeutic agent, Skin, Skin appendage, Mucosa, Dermatologic side effects

Introduction

Cancer is a complex disease that occurs with the uncontrolled division and proliferation of cells and consists of genetic and environmental conditions. There are various treatment methods for cancer, one of them is chemotherapy. The main purpose of chemotherapy is to kill cancer cells using chemotherapeutic agents and cytotoxic anti-neoplastic agents play the leading role in this type of therapy [1]. Conventional anticancer treatments target cells that can divide rapidly. Their side effects are observed more common in tissues containing proliferative cells, in addition, their systemic side effects are more prominent than their side effects on skin. The frequency of skin side effects of the targeted anticancer treatments is gradually increasing and their skin side effects are more prominent than their systemic side effects [2,3]. In our study, we aimed to evaluate the skin side effects of anticancer drugs in the light of the current literature.

Materials and Methods

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. Patients aged more than 18 who presented to the Oncology Outpatient Clinic of Izmir Tepecik Training and Research Hospital between September 2019 and March 2020 recruited into this study. Both verbal and written informed consents were

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obtained from study participants. The patients included in the study were those who were currently receiving chemotherapy for their own diseases. The patients who were followed up in the oncology clinic of our hospital and had side effects on the skin, mucosa and skin appendages because of their chemotherapy, were included for the research. We noted the age, gender, cancer type, chemotherapy drug, number of cycles, examination findings about side effects of chemotherapy on skin-mucosa-skin appendages of the patients. Dermatological regions with side effects were examined under six sub-units in terms of localizations: hair, scalp, nail, oral mucosa, genital mucosa, conjunctiva, skin.

Statistical Analysis

Statistical analyzes were performed using Statistical Package for Social Sciences (SPSS v.17.0, IBM Corporation, Armonk, NY, US) software. The results were evaluated with descriptive analysis.

Results

During the study period, 48 patients were included to our study (12 male, 25%; 36 female, 75%). The mean age of all patients was 55.46±12.5 (minimum: 23, maximum: 82). We determined the mean age of female patients as 54.53±12.56 (minimum: 37, maximum: 82) and of male patients as 58.25±12.51 (minimum: 23, maximum: 75). Cancer types of the patients, types of chemotherapy and the side effects of these chemotherapies are shown in the tables (Table 1, 2).

Discussion

Various chemotherapeutic agents have been used for cancer treatment over the past 20 years. These drugs are divided into some subgroups according to their mechanisms; signal transduction inhibitors [epidermal growth factor receptor (EBFR) antagonists, multikinase inhibitors], proteasome inhibitors, spindle inhibitors (taxanes, vinca alkaloids), antimetabolites (purine analogs, primidine analogs), genotoxic agents. These chemotherapeıtics may have various dermatological side effects [4].

Tablo 1. Cancer types of patients

Types of cancer	Number (gender)	Percent (%)
Lung	1 (male)	2.1
Brain	1 (male)	2.1
Kidney	1 (male)	2.1
Endometrium leiomyosarcoma	1 (female)	2.1
Liver	1 (male)	2.1
Colon	4 (3 female, 1 male)	8.3
Larynx	2 (male)	4.2
Breast	28 (female)	58.3
Stomach	1 (female)	2.1
Osteosarcoma	1 (female)	2.1
Ovary	2 (female)	4.2
Prostate	1 (male)	2.1
Rectum	2 (male)	4.2
Testis	2 (male)	4.2

In our study, it is thought that the papulopustular rash is mostly due to cetuximab if we compare the dual use of 5-fluoroucil (5-FU) and cetuximab with the triple use of 5-FU, oxaliplatin and cetuximab. Oxaliplatin didn't cause any additional skin findings in these two drugs combinations. Cetuximab had caused only herpes zoster in its single use. The most common side effect of cetuximab, an EBFR inhibitor, is papulopustular rash seen in 60% to 80% of patients [5]. According to the data of our study, this side effect can be brought to the fore even in combination therapies. In the work of Yazganoğlu and Baykal [6], papulopustular rash on the face of a female patient 62-year-old, had been observed in the dual use of 5-FU and cetuximab, too. Interestingly, the triple use of 5-FU, cetuximab and carboplatin caused seborrheic dermatitis and xerosis as dermatological side effects. Platins are in the cytotoxic cancer treatment category and their most common side effect is alopecia [7]. In the combination therapies using oxaliplatin and carboplatin, alopecia didn't occur. We thought that other agents in the combination could prevent the occurrence of alopecia. In the triple use of 5-FU, irinotecan, cetuximab, oral mucosa pigmentaiton and eczema on the hands were observed, these are rare side effects. We determined oral aphthaes and desquamation on hands and feet in the triple use of 5-FU, irinotecan and aflibersept in our study, papulopustular rash didn't occur. Aflibersept has inhibitory effects on vascular endothelial growth factor (VEGF), can lead to thrombotic events [8]. We thought the cause of oral aphthae of our case was aflibersept. In addition, there were publications in the literature that aflibersept caused ulcers in the abdominal wound scar and around the stoma [8,9]. According to tha data of our study, carboplatin and oxaliplatin could occur side effects more quickly. It could be observed that 5-FU, cetuximab, irinotecan and aflibersept were slow to cause dermatologic side effects.

Bevacizumab is a VEGF inhibitor and papulopustular rash because of it has been reported in a small number of cases [6]. It is known that irinotecan causes papulopustular rash. In our research, in the dual use of bevacizumab and irinotecan, the occurence of telangiectasia contradicts the mechanism of bevacizumab, this suggests that irinotecan may be more dominant in the formation of telangiectasia. Additional studies are needed in this topic. We observed that dominant side effect was erythema on face and neck in the triple use of capecitabine, oxaliplatin, bevacizumab. Capecitabine is the prodrug of 5-FU. We thought that capecitabine was responsible for this erythema because the

dominant dermatologic side effect of oxaliplatin was alopecia and of bevacizumab was ulcer on skin. Photosensitive lichenoid skin reaction had been reported in a female patient 73-year-old because of capecitabine in the literature [10]. According to our study, side effects of paclitaxel were observed until the 12th cycle and in the dual use of paclitaxel and carboplatin dermatologic side effects occured earlier and less amount. Dominant side effects of taxans (dosetaxel, paclitaxel) are reversible alopecia, dorsal hand foot syndrome, edema, flexural and intertriginous rash, onycholysis, mucositis. It was reported that hand foot syndrome was caused

Tablo 2. Chemotherapies and side effects on skin-mucosa-skin appendages

Chemotherapy (type of cancer)	Number (%)	Cycle number	Side effects
5flouracil+oxaliplatin+cetuximab (colon)	1 (2.1)	5	Papulopustular rash on face, front of body and back
5flouracil+irinotecan+aflibersept (colon)	1 (2.1)	10	Oral aphthae, desquamation on hands and feet
5flouracil+setuximab (liver)	1 (2.1)	17	Papulopustular rash on scalp, neck, front of body and back
5flouracil+carboplatin+setuximab (larynx)	1 (2.1)	3	Seborrheic dermatitis on scalp, xerosis on body, arms and legs
Bevacizumab+irinotecan (brain)	1 (2.1)	4	Hair loss, telangiectasia on front of body
Bleomycin+etoposide+cisplatin (testis)	2 (4.2)	3 and 4	Hair loss, onychomadesis and onychogrifosis on thumb nail, onychogrifosis, oral aphthae, acne on shoulders, ecchymosis on front of body and back
Carboplatin+paklitaxel (ovary)	2 (4.2)	6	Hair loss, eczema on soles of feet, telangiectasia on legs
Doxorubicin+cyclophosphamide (breast cancer in 7 patients, endometrium leiomyosarcoma in 1 patient)	8 (16.8)	2-4	Hair loss, alopecia totalis, seborrheic dermatitis on scalp, oral aphthae, swelling of the palate, melanonychia striata on the nails, hyperpigmented macules on hands, seborrheic keratosis on armpits, ulcer and seborrheic dermatitis on front of body, eczema on legs
Docetaxel (prostate)	1 (2.1)	3	Hair loss, eczema on legs
Docetaxel+transtuzumab+pertuzumab (breast)	4 (8.4)	3, 7, 8	Hair loss, eyebrow loss, oral aphthae, folluculitis on genital mucosa, papulopustular rash on front of body, inflamation on thumbs, thickening of nails and melanonychia striata on nails, erythema on armpits, groins and soles of feet, xerosis
Docetaxel+cyclophosphamide (breast)	2 (4.2)	1 and 2	Hair loss, papulopustular rash on scalp, excoriation on front of body and back, desquamation on finger tips
Epirubicin+docetaxel (breast)	1 (2.1)	1	Hair loss, oral aphthae, tinea corporis on front of body
5flouracil+irinotecan+setuximab (rectum)	1 (2.1)	4	Acne on scalp and face, pigmentation on oral mucosa, eczema on hands
Capecitabin (colon)	1 (2.1)	6	Desquamation on hands and feet
Capecitabin+oxaliplatin+bevacizumab (colon)	1 (2.1)	2	Erythema on face and neck
Carboplatin+ifosfamide+etoposide (osteosarcoma)	1 (2.1)	3	Hyperpigmentation on face
Nivolumab (kidney)	1 (2.1)	4	Seborrheic dermatitis on face and scalp
Oxaliplatin+capecitabine (rectum and stomach)	2 (4.2)	4	Seborrheic dermatitis on scalp, thickening on thumb nails, papulopustular rash on neck, front of body and back
Paclitaxel (breast)	10 (21)	2-12	Hair loss, alopecia totalis, xerosis of hair, hair whitening, onychomadesis, melanonychia striata and leukonychia on nails, easy breakage in nails, oral aphthae, erythematous plaque on genital mucosa, inflamation on thumb, xerosis cutis, dorsal hand foot syndrome, geografic tongue, pruritus
Paclitaxel+transtuzumab (breast)	2 (4.2)	3 and 6	Hair and eyebrow loss, xerosis cutis
Setuximab (larynx)	1 (2.1)	11	Herpes zoster
Cisplatin+pemetrexed (lung)	1 (2.1)	1	Papulopustular rash on front of body and back
Transtuzumab (breast)	1 (2.1)	16	Melanonychia striata, herpes zoster

by especially docetaxel [11]. In our research, we observed that this syndrome could be caused by paclitaxel although rare. These dominant side effects were in line with the results of our study. The side effects of transtuzumab are mild on the skin. In the study of Adachi et al. [12], skin side effects in 25 patients, nail side effects in 14 patients and both skin and nail side effects in 12 patients were observed. Eruptions on face and body, thinning of skin of hands and feet, pruritus, xerosis cutis, softening and thinning of nails, paronychia, discoloration were determined. In our study, in the single use of transtuzumab, melanonychia striata and herpes zoster occured. To sum up, we thought that carboplatin and transtuzumab could decrease the side effects of paclitaxel in the combination treatments.

The most side effects of capecitabine are edema on hands and feet, feeling of tightness and pain [13]. In our study we observed desquamation on hands and feet, probably, we thought that there was edema firstly and desquamation developed as the skin healed.

In the research of Prussick et al. [14], in the triple use of carboplatin, ifosfamide and etoposide, periorbital erythema, mucositis, erythema on face and groin occured in eight patients. In addition there are publications that reported hyperpigmentation because of ifosfamide in the literature [15]. These results were consistent with our study.

In the study of Swain et al. [16], alopecia, rash on body, pruritus and xerosis cutis occured in the triple use of pertezumab, transtuzumab and dosetaxel. Baselga et al. [17] detemined alopecia, rash on body, peripheral edema, xerosis cutis in their research. In the research of Nakatsukasa et al. [18], peripheral edema and rash on body occured in the dual use of cyclophosphamide and dosetaxel in 48 female patients. Nitz et al. [19] determined hand and foot syndrome and mucositis/stomatitis in 198 patients. These all results were consistent with our research.

In the study of Petrioli et al. [20] stomatitis was observed in 10 patients of those using epirubicin only, in five patients of those using dosetaxel only. Hand and foot syndrome was determined in six cases of those using epirubicin only and in three cases of those using dosetaxel only. Accoding to these results, epirubicin has a higher potential to cause side effects on skin and its appendages than docetaxel. We observed in our study that hair loss, oral aphthae, tinea corporis on front of body could occur in the dual use of epirubicin and dosetaxel.

Nivolumab is a chemotherapeutic agent from the programmed cell death inhibitor 1 group. It causes lichenoid reactions, eczema, vitiligo and pruritus especially [21]. Incompatible with this study we observed that nivolumab could cause seborrheic dermatitis on face and scalp.

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 oncologist was always working in the same part of hospital, dermatologists were working in the three different parts of the hospital during the process of research, therefore patients who had skin damage because of anticancer drugs, couldn't be sometimes examined by dermatologists. If dermatologists and oncologist always worked in the same part of hospital, the number of patients would be higher.

Conclusion

In conclusion, chemotherapeutics can have beneficial effects as well as damaging effects on various organs. We compared dermatologic side effects of chemotherapeutic agents in the light of literature in our study. We also mentioned dermatologic side effects that haven't been mentioned in the literature yet. We believe that our research will contribute to the literature with all these aspects.

Ethics

Ethics Committee Approval: It was approved by the University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethical Review Committee (protocol number: 2019/13-30, date: 11/09/2019).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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The Effect of Stromal Vascular Fraction for Patients with Androgenetic Alopecia

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ABSTRACT

Background: Androgenetic alopecia (AGA) is a dermatological disease that can be seen in both men and women and can cause problems in one's self-perception. Stem cell is an increasingly popular treatment method in the treatment of various diseases in recent medicine. Stromal vascular fraction (SVF) is a specimen that contains high levels of stem cells and very easy to be obtained from fat. In our study, we investigated the effectiveness of SVF treatment in AGA patients.

Materials and Methods: Twenty patients were included in the study. Fourteen (70%) of the patients were male and 6 (30%) were female. The age of the patients was minumum-maximum 21-41 years. In the 3rd month of the study, the hair density and increase in thickness of hair of patients were evaluated with both macroscopic and trichoscopic examination.

Results: An increase in both hair density and hair thickness was detected in the 3rd month.

Conclusion: It was concluded that SVF is an effective and safe treatment option in AGA.

Keywords: Androgenetic alopecia, Stromal vascular fraction, Stem cell

Introduction

Androgenetic alopecia (AGA) is an androgen-dependent progressive disease that causes hair loss in women and men with genetic predisposition [1]. AGA is the most common type of alopecia and by the age of 60, it affects 80 percent of men and 50 percent of women [2,3]. It is categorized as a nonscarring patterned form of alopecia and is characterized by bitemporal recession, a progressive loss of hair in the frontoparietal region in men, and a diffuse hair thinning with preservation of frontal hairline in women [2]. In women, it can be seen as female pattern hair loss and also it may seen with hyperandrogenemic hormone changes and findings [4,5]. It is believed that a high concentration of dihydrotestosterone against androgen-sensitive hair follicles lead to thinning of the dermal papillae and shortening of the anagen phase is the underlying mechanism [6,7]. Diagnosis of AGA is mostly made with a history and physical examination without any laboratory examination [4]. Current acknowledged treatment modalities concentrates on various mechanisms: androgenic effects on hair follicles are reduced by using 5a-reductase inhibitors, hair growth is stimulated by minoxidil, moving androgen in dependent hair to the affected scalp is done by hair transplantation [8,9,10].

Stem cells differ from mature cells by some features they possess and have a very important potential in clinical applications. These features are the trophic effect they have, immune system modulation, heading to the injury site (homing) and tissue differentiation [11,12]. Stem cells show their trophic effect through

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their growth factors, cytokines, extracellular matrix elements, extracellular matrix proteases, hormones and lipid mediators in the region or micro-environment in that they are applied. In particular, vascular endothelial growth factor, hepatocyte growth factor and transforming growth factor-beta increase angiogenesis and wound healing, as well as stimulating new tissue formation and growth [13]. With the studies carried out in the early 2000s on the adipose tissue, it has been revealed that the human body is a very important source for stem cells [14]. Compared to bone marrow, which is the most important source of stem cells known to date, interest in adipose tissue and mesenchymal stem cells derived from adipose tissue [adipose-derived stem cells (ADSC)] has increased rapidly in recent years due to its easier access and potential to obtain more cells [15].

Stromal vascular fraction (SVF) is a heterogeneous cell cocktail that is obtained by the enzymatic destruction of surgically acquired fat tissue (either through excision or lipoaspiration), it is known to be rich in stem cells, containing preadipocyte, endothelial cells, hematopoietic serial cells, fibroblasts as well as ADSCs and pericides located around the vessels [16,17].

Underlying inflammation is spotted in various degrees in many scarring and nonscarring forms of alopecia. In patients with AGA, mild perifollicular fibrosis and infiltrates are also detected [18]. By enhancing antioxidative and anti-inflammatory mechanisms, ADSCs can prevent further inflammation and potential damage to hair follicles. Their anti-inflammatory and immunomodulatory properties are reflected in their potential to prevent the maturation and production of cytokines and to disrupt the cytotoxic potential of natural killer cells and T lymphocytes [19].

When injected into an area that is affected by hair loss, adipose tissue may show an antiandrogen effect without causing systemic effects [20].

We planned to use both the anti-inflammatory and antiandrogenic effects of SVF and to work with the idea that cytokines released from SVF will correct neovascularization, an important pathological problem in AGA.

Materials and Methods

Twenty patients diagnosed with AGA between 2018 and 2020 were included in the study after obtaining their consent. Before the study started, approval was obtained from the Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine with the number 236.

Inclusion criteria for the study:

- Male and female patients with AGA,

- To be 15 years old or older,

- Active hair loss within last six months,

- Hamilton score 3 to 4 in male patients and Ludwig score 1-3 in female patients.

Exclusion criteria for the study:

- Patients with inflammation, infection, malignancy, allergic disease, autoimmune disease, pregnancy, and on current anticoagulant therapy,

- Patients on chemotherapy during the last 5 years.

- Having received oral, topical or intradermal hair loss treatment in the last 6 months,

For the svf preparation management, the following operations are carried out in order on a beautycell device from bitorend company.

- Patients are prepared for the procedure under local anesthesia. 50 mL of fat is taken from the belly area through liposuction method. The fat tissue aspirated by liposaction is transferred into 50 mL falcon tubes as 25 mL each and is completed with Ringer lactate/SF solution up to 50 mL.

- It is centrifuged at 100 g for 3 minutes.

- The red blood cell part of the centrifuged fat tissue is separated from the bottom of the falcon tube with the help of a 10 mL pipette.

- Adipose tissue purification is performed.

- 25 mL of adipose tissue, which has been purified, is completed with 25 mL of Ringer's lactate/SF solution to 50 mL.

- 0.5 mL enzyme solution is added.

- It is taken to the incubator which has a temperature of 37 ºC and is incubated for 30 minutes at 200 rpm shaking speed.

- After incubation, adipose tissue is centrifuged at 800 g for 5 minutes.

- After centrifugation, the fat tissue on the top is discarded with a 25 mL pipette.

- The concentration in the Falcon tube is discarded by pulling downwards with a pipette until it remains 5 mL at the bottom.

- The 5 mL cell suspension isolated from adipose tissue is completed to 50 mL with Ringer lactate/SF solution.

- It is centrifuged at 300 g for 3 minutes.

- After centrifugation, the top part is discarded with a pipette, leaving 5 mL of liquid in the bottom.

- The enzyme is removed from the cell suspension, by repeating this washing process 3 or 4 times.

- The cell suspension, which has been washed, is passed through a filter (cell strainer 100 µm) placed in a sterile falcon tube.

- SVF cell suspension is obtained at the bottom of the falcon tube.

5 mL SVF was applied to the scalp of the patient with 30 g-4 mm

needle by intradermal injection technique. After a total of 25 injections of 0.2 mL in each area, the process was completed by applying 2 mm dermapen. The most important point to be considered here is that the obtained SVF was used without waiting for the procedure. The procedure was applied for once. Patients were able to return to work after the procedure. All patients were told that they should not wash their hair for 24 hours, and avoid some works such as 3 hours of heavy exercise, and do not have a sun bath for 1 week. Before the procedure, macroscopic images of all patients were recorded and bitemporal and vertex photographs were taken with "fotofinder medicam 800 hd" trichoscope camera.

Statistical Analysis

After 12 weeks, patients were called for control and changes in the same regions were re-evaluated with visual analog scale and changes in the data which are entered in SPSS 23 were recorded as %.

Results

Of the patients included in the study, 14 (70%) were male and 6 (30%) were female. The age of the patients was minimum-maximum 21-41 years. Two (14.28%) of the male patients were stage 1, 4 (28.6%) were stage 2, 6 (42.9%) were stage 3, and 2 (14.28%) were stage 4. Two (33.3%) of the female patients were evaluated as stage 1, 2 (33.3%) as stage 2, and 2 (33.3%) as stage 3. When looking at the density of hair in the temporo-parietal region in the 3rd month in male patients, 25% of the patients did not change, while 25% increased by 10% and 50% increased by 20%. In vertex, there was a 10% increase in hair density in 75% of patients, while there was a 20% increase in 25% of patients.

In terms of hair thickness: In the temporo-parietal region, in all patients, the hair thickness has increased by 25%. In vertex, there was no change in 50%, while in 25%, hair thickness increased by 10% and in the remaining 25% it is increased by 30% (Figures 1, 2).

In female patients, an increase of 10% was observed in 50% of the patients, while an increase of 20% was observed in 50% of the patients. In vertex, only 10% increase was observed in all patients. There was no change in hair thickness.

Discussion

In our study, it was concluded that the application of SVF on a single session in patients with AGA, which is difficult to treat, provides a significant increase in the number and thickness of hair, especially in the bitemporal region.

Adipose tissue has an important place in both tissue engineering and regenerative medicine applications as a biological active complex. Adipose tissue can be used either directly as SVF or as stem cell separated from SVF [21]. In our study, we used SVF, which contains stem cell, directly. SVF is considered to be a very useful method as it becomes usable within approximately 2 hours after it is obtained from adipose tissue. There are very few studies evaluating the outcome of SVF treatment for hair loss. The studies were mostly done with cultured adipose tissue stem cell and blood derived stem cell [22,23].

Anderi et al. [24] reported that treatment with SVF is an effective and safe method in 20 patients with alopecia areata. Cohen et al. [25] reported in 2010 that the fat enriched with SVF was injected into the scalp of a woman with alopecia and it resulted in a "significant improvement in hair growth" after nine months of follow-up. Perez-Meza et al. [26] injected SVF-enriched autologous fat into five patients who are aged 18 to 55 years in another study. The liposuction and the application of the SVF solution were done on the same day and patients were followed up with for up to 24 weeks postoperatively.

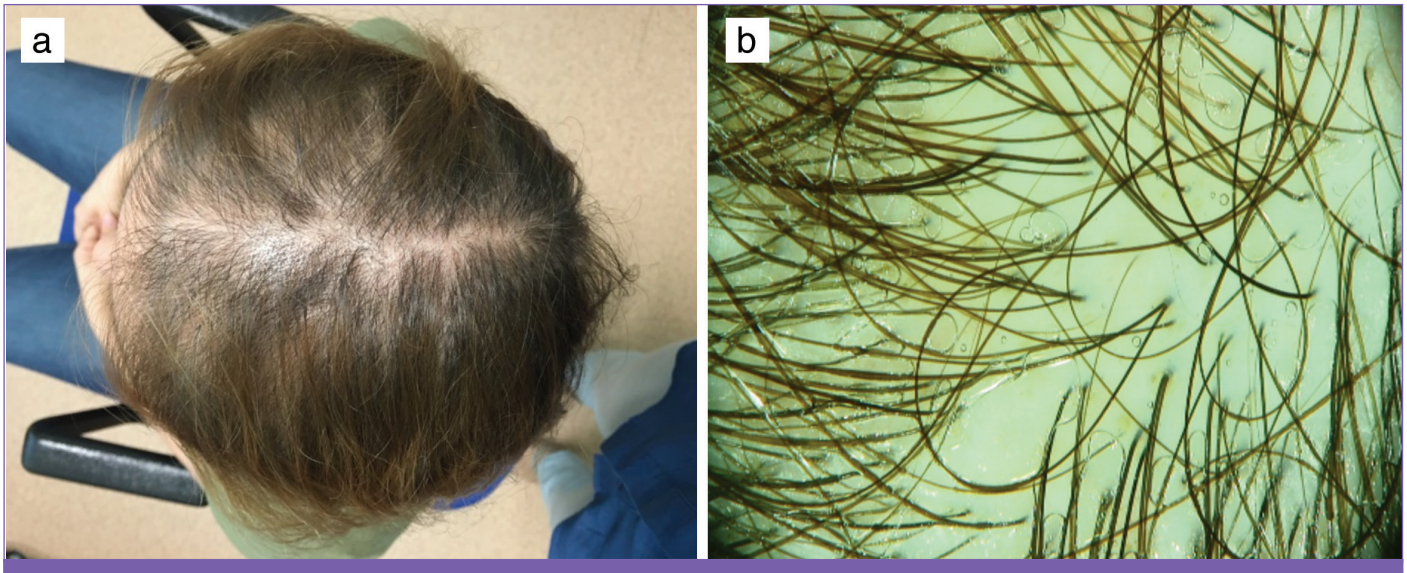

Figure 1. a) Pretreatment, b) pretreatment

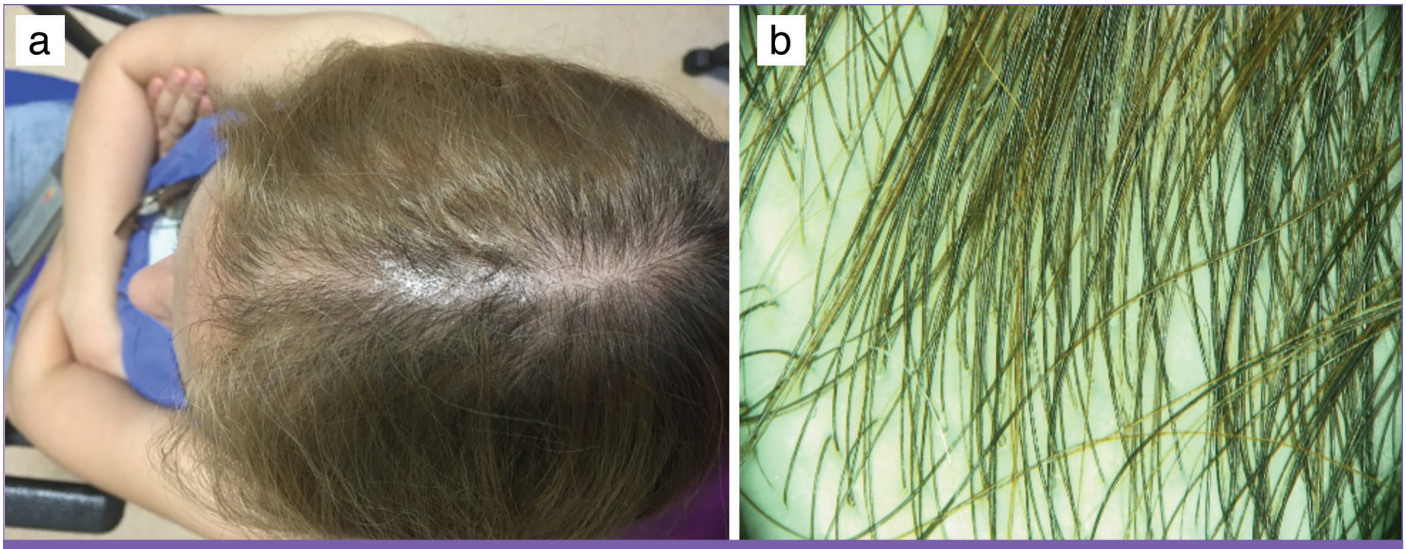

Figure 2. a) Posttreatment, b) posttreatment

On average, 23% increase in hair count and 24.2% increase in hair thickness were reported with an increase of 93% in the amount of anagen hairs and decrease of 35% in the amount of telogen hairs. Aronowitz et al. [27] showed a significant 14% increase in hair count at six months after the autologous fat enriched with SVF was applied to the scalp of eight men and a woman with hair loss. In addition, the number of anagen phase hair has been increased by 34 percent.

In our study, unlike other studies, the dermapen process was added to increase the regional blood supply and through the increased blood supply it was aimed to make growth factors that provide wound healing come to the area that was treated. Thus, additional contribution was made to the paracrine effect, antiandrogen effect and anti-inflammatory effect of SVF.

Study Limitations

The low number of patients is the limitation of our study.

Conclusion

As a result, SVF along with dermapen administration can be an effective and safe treatment method in AGA.

Ethics

Ethics Committee Approval: It was approved by the Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (protocol number: 236).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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The Evaluation of Narrowband Ultraviolet B Therapy in Neurodermatitis and Idiopathic Pruritus Patients

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ABSTRACT

Background: Pruritus and neurodermatitis are very frequent diseases that usually require muitiple treatment approaches. Narrowband ultraviolet B (UVB) therapy is one of the effective and safe treatment option for pruritus and neurodermatitis that are resistant to topical treatment. This study aims to evaluate treatment responses of narrowband UVB phototherapy in patients diagnosed with neurodermatitis and idiopathic pruritus.

Materials and Methods: Twenty-two patients diagnosed with idiopathic pruritus and 16 patients diagnosed with neurodermatitis at the Department of Dermatology in Cerrahpasa Faculty of Medicine were included in this study. Patients were evaluated at the end of phototherapy sessions.

Results: The mean age of patients diagnosed with idiopathic pruritus and neurodermatitis were 58.6 and 50.6 respectively. The mean decrement in pruritus score following narrowband UVB therapy was 53.5% in idiopathic pruritus patients and 65% in neurodermatitis patients. There were no significant relation between phototherapy response and age, gender, duration of disease and number of therapy sessions in both groups.

Conclusion: The narrowband UVB is safe and effective treatment option both in pruritus and neurodermatitis patients.

Keywords: Narrowband ultraviolet B, Neurodermatitis, Idiopathic pruritus

Introduction

Pruritus is a very frequently seen dermatological condition which usually has no underlying reason. Pruritus can be seen secondary to the dermatological or systemic conditions. Phototherapy is one of the treatment options especially in widespread pruritus cases. Pruritus is generated by signals carried to spinal cord via cutenous receptors. Ultraviolet (UV) light modifies signaling of cutenous receptors so that sensation of pruritus decreases [1]. Neurodermatitis is dermatologic condition that results from psychogenic factors. It is mostly seen in female patients [2]. It usually has sudden onset and severity increases gradually overtime. The pruritus due to neurodermatitis usually increases at night and excoriations due to scratching are visible at reachable sites of body. Narrowband UVB therapy is also among treatment options in widespread neurodermatitis cases. Previous studies showed that narrowband UVB is effective, tolerable and safe treatment method. Narrowband UVB is preferred more than UVA treatment since it lacks side effects of psoralen usage, can be used in children, pregnant patients and patients with liver and/or kidney failure. This study aims to evaluate narrowband UVB treatment response in patients diagnosed with idiopathic pruritus and neurodermatitis.

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Materials and Methods

Thirty-eight patients diagnosed with neurodermatitis and idiopathic pruritus between 01.09.2018 and 01.05.2020 at our clinic were included in the study. These patients received 2-3 session narrowband UVB treatment per week. Demographical features of patients, duration of disease, decrement in pruritus scores of patients were all evaluated. Approval of the Cerrahpasa Faculty of Medicine Ethics Committee (IUC date and no.: 11/09/2020-118656) and informed consents of all participants were obtained before the study.

Statistical Analysis

Pearson correlation test and independent t-test were used for comparison. P values less than 0.05 were considered statistically significant.

Results

The data of the patients participated in the study are listed in Table 1 and 2. The study involved 22 patients diagnosed with idiopathic pruritus, 11 being females and 11 males, and 16 patients diagnosed with neurodermatitis, 11 being females and five males. The mean age of diagnosis of the patients with idiopathic pruritus was 58.6±15.2 and that of the patients with neurodermatitis was 50.6±16.8. The average narrowband UVB phototherapy session number of the patients with idiopathic pruritus was 22.5±4 whereas that of the patients with neurodermatitis was 24.5±5.3. As for the percentage drop in the complaints of the patients with idiopathic pruritus after the UVB phototherapy, there was recorded a decrease of 53.5±25.7%. That decrease was 65.1±22% for the patients with neurodermatitis. There was no significant correlation between the phototherapy response and the disease duration, gender, age and session number of the patients diagnosed with idiopathic pruritus. Similarly, no significant correlation was recorded between the phototherapy response and the disease duration, gender, age and session number of the patients diagnosed with neurodermatitis.

Table 1. Characteristics of 22 patients with idiopathic pruritus

Age, years, mean (min-max)	58.6 (25-82)
Number of NB-UVB therapy sessions, mean (min-max)	22 (16.0-32.0)
Sex, %	
Female	11 (50%)
Male	11 (50%)
Duration of disease, years, mean (min-max)	6.5 (1.0-32.0)
Decrement in pruritus score, %, mean (min-max)	53 (20-100)

NB-UVB: Narrowband ultraviolet B, min: Minimum, max: Maximum

Discussion

Neurodermatitis is a dermatological disease more frequently seen in females after puberty. Though such triggering factors as trauma can play a role in the etiology, the patients generally report an insidious onset. Idiopathic pruritus indicates the somatic itchings initiated by psychogenic factors which can not be related to organic causes. Narrowband UVB therapy is one of the options which can be preferred fort he treatment of patients diagnosed with neurodermatitis and pruritus. The initial dosage in the treatment and the dosage increments are determined according to the either Fitzpatrick skin phototype or the minimal dosage that induces erythema [3]. There exists no standart protocol as yet regarding the initial dosage, treatment frequency, and dosage increments. The treatment is generally applied twice or three times a week. Whereas the duration of the treatment may vary based on its severity, 20 to 30 sessions will frequently suffice. In our clinic the average session numbers for the patients diagnosed with pruritus and neurodermatitis were 22 and 24, respectively.

Whereas the ratio of female to male patients diagnosed with idiopathic pruritus was 1, the female patients diagnosed with neurodermatitis constituted the majority of the patients as was reported in the literature [4]. The mean diagnosis age of the patients with idiopathic pruritus in our study was 58.6 whereas Seckin et al. [5] and the co-workers recorded a mean diagnosis age of 51 in their study. Moreover, the mean age of diagnosis of the patients with neurodermatitis was 50.6 in our study while mean age of diagnosis of neurodermatitis patients was 46.3 in the study conducted by Askin et al. [4]. In our study, following narrowband UVB therapy, a 53% decrement was observed in the pruritus score of idiopathic pruritus patients. Likewise, after the narrowband UVB treatments, Seckin et al. [5] also reported drops of 52.4% and 54.0% in the pruritus scores of the patients diagnosed with idiopathic pruritus and uremic pruritus, respectively. On the other hand, another study by Ada et al. [6] which involved 20 patients diagnosed with uremic pruritus yielded a drop of 69.3% in the pruritus score following narrowband UVB therapy.

Table 2. Characteristics of 16 patients with neurodermatitis

Age, years, mean (min-max)	50.6 (26-76)
Number of NB-UVB therapy sessions, mean (min-max)	24 (15.0-30.0)
Sex, %	
Female	11 (69%)
Male	5 (31%)
Duration of disease, years, mean (min-max)	11.3 (2.0-40.0)
Decrement in pruritus score, %, mean (min-max)	65 (20-100)

NB-UVB: Narrowband ultraviolet B, min: Minimum, max: Maximum

In another research, Esen Salman et al. [7] studied a total of 176 patients 26 of whom were diagnosed with neurodermatitis. The patients were undergone on average 29-session narrowband UVB treatment. Middle-to-high degree disease controls were attained in 73.8% of the patients after the treatment. Likewise, we also observed a 65% decrement in the pruritus scores of the patients diagnosed with neurodermatitis following a treatment of an average 24-session narrowband UVB.

Study Limitations

The number of patients were limited in this study.

Conclusion

Narrowband UVB treatment is a reliable treatment option for patients who are diagnosed with neurodermatitis and idiopathic pruritus, especially for those who display resistance to topical treatments.

Ethics

Ethics Committee Approval: Approval of the Cerrahpasa Faculty of Medicine Ethics Committee (IUC date and no.: 11/09/2020-118656).

Informed Consent: Informed consents of all participants were obtained before the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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CASE REPORT

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A Case of Localized Psoriasis Following Treatment with Iodine^{131} for Hyperthyroidism: A Rare Entity

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ABSTRACT

Psoriasis is a T-cell mediated inflammatory skin disease, characterized by circumscribed erythematous plaques, covered by silvery micaceous scales. It is known to be triggered by a number of factors including drugs. Drugs may either cause de novo psoriasis or responsible for aggravating preexisting psoriasis. The morphological types can vary from localized or generalized plaque psoriasis to pustular psoriasis and even erythroderma. In this work, we report the case of a 45-year-old male patient who developed localized psoriasis following treatment with iodine^{131} for hyperthyroidism. Based on history, clinical pictures, localized examination and histopathological findings with psoriasiform changes favoured the diagnosis. He was treated with topical steroid with clobetasol propionate (0.05%) and salicylic acid (6%) combination for 1 month following which lesions resolved. We suspected that the mechanism behind this is due to activation of dihydrofolate reductase by radioactive iodine. Further study about the folic acid pathway in psoriasis and the connection between radioactive iodine with psoriasis may be necessary.

Keywords: Localized psoriasis, Radioactive iodine^{131}, Hyperthyroidism

Introduction

Psoriasis is a T-cell mediated inflammatory skin disease, characterized by circumscribed, erythematous well-defined plaques covered by silvery micaceous scales. Radioactive iodine (I^{131}) is an important isotope used in hyperthyroidism (Graves' disease, Toxic multinodular goiter and autonomously functioning thyroid nodule). The most significant cutaneous adverse effect of I^{131} is iododerma. Here we report a case of localized psoriasis following treatment with radioactive iodine for hyperthyroidism.

Case Report

A 45 years old male shopkeeper by occupation attended skin OPD with itchy plaque over dorsum of feet which was gradually increasing for last 1 month. He is a known case of thyrotoxicosis for which he was on oral carbimazole for last 6 years and not responding and recently treated with 9.2 mili curie of oral radioiodine^{131}. He developed erythematous papular eruption over dorsum of both feet after 20 days of I^{131} therapy and it is slowly increasing in size. On examination symmetrical hyperkeratotic plaque was present over dorsum of both feet (Figure 1). Auspitz's sign was positive. Oral radioiodine therapy had been stopped. No others cutaneous or mucosal sites were involved. He had no history of similar episode in the past. General, systemic and routine blood examinations were unremarkable other than thyroid profile. Histopathology showed hyperkeratosis, parakeratosis acanthosis, suprapapillary thinning, club shaped rete ridges and collection of neutrophils in stratum corneum (Munro's microabscess) and in dermis there was dilated blood vessels and perivascular lymphocytic infiltrates in papillary dermis (Figures 2, 3). A final diagnosis of I^{131} induced localized plaque psoriasis was made. Patients was treated with topical steroid with clobetasol propionate (0.05%) and salicylic acid (6%)

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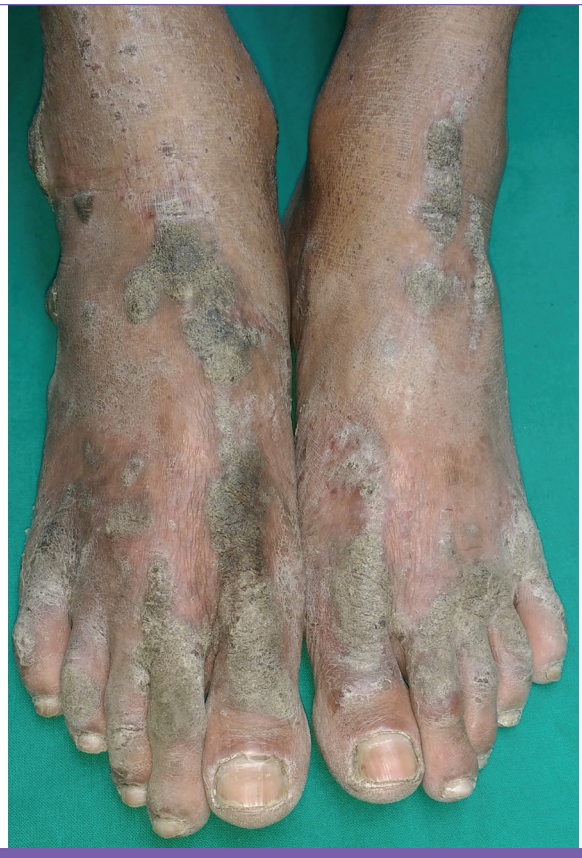

Figure 1. Symmetrical hyperkeratotic plaque was present over dorsum of both feet

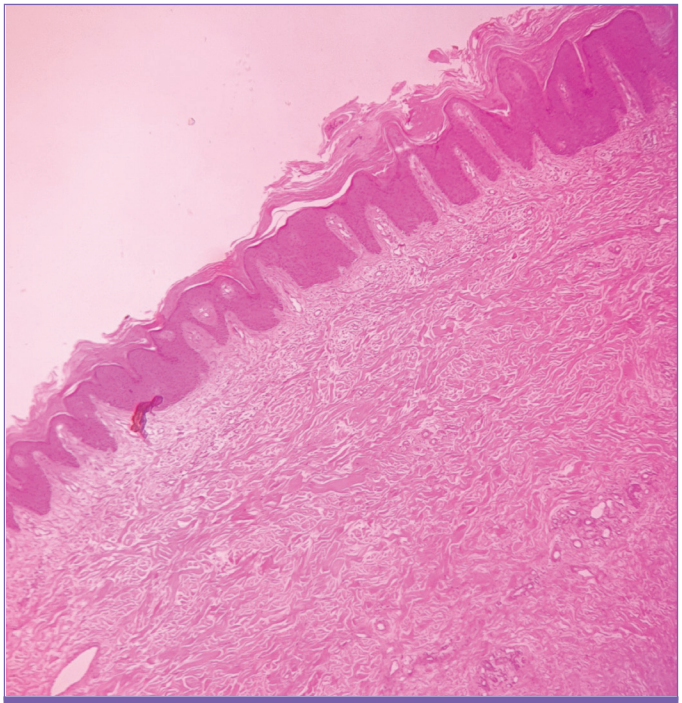

Figure 2. Hyperkeratosis, parakeratosis acanthosis, suprapapillary thinning, club shaped rete ridges (hematoxylin and eosin stain under 4x)

combination for 1 month following which lesions resolved and there was only hyper pigmentation (Figure 4). Radioiodine therapy had not been restarted and he had been started on oral methimazole. Informed consent has been taken from the patient.

Discussion

Psoriasis is a T-cell mediated common, chronic and recurrent inflammatory skin disease, characterized by circumscribed, erythematous sharply demarcated papules and plaques covered by silvery micaceous scales. Many factors contribute its pathogenesis like genetic, immunological and environmental factors. Several other factors like trauma, stress, infections and medications might exacerbate psoriasis [1]. Radioactive I^{131} is an important isotope used in hyperthyroidism (Graves' disease, Toxic multinodular goiter and autonomously functioning thyroid nodule). Cutaneous adverse effect of I^{131} include iododerma, which is characterized by acneiform eruption with inflammatory follicular pustules, or may present as urticaria or bullous lesion with ulceration and crust. Iododerma may occurs in the face, neck, extremities and trunk [2]. There have been many drugs documented to directly trigger the eruption of psoriasis (antibiotics, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, interferon, amiodarone,

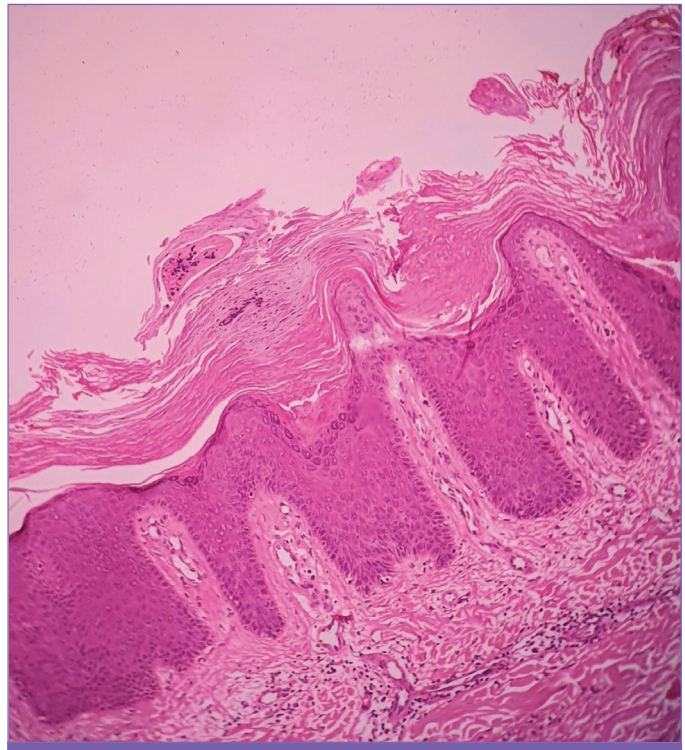

Figure 3. Hyperkeratosis, parakeratosis acanthosis, suprapapillary thinning, club shaped rete ridges and collection of neutrophils in stratum corneum (Munro's microabscess) and in dermis there was dilated blood vessels and perivascular lymphocytic infiltrates in papillary dermis (hematoxylin and eosin stain under 10x)

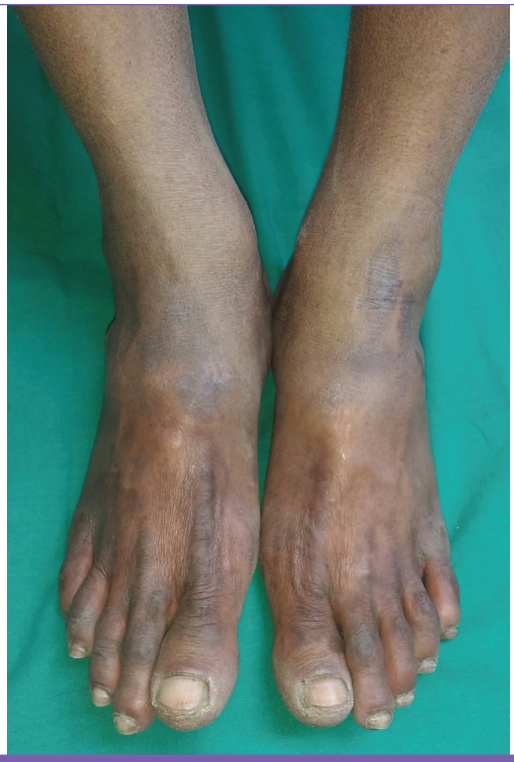

Figure 4. Lesions resolved with residual hyperpigmentation

terbinafine, benzodiazepines, digoxin, clonidine, quinidine, gold, potassium iodide, imiquimod etc.) and many others exacerbate the existing psoriasis (acetazolamide, aminoglutethimide, amiodarone, antibiotics, terbinafine, diltiazem, hydroxychloroquine, lithium, potassium iodide, propanol etc.) [3,4]. It is very difficult to explain the exact mechanism, they may affect the psoriatic process at different stages but with same results. It has been seen that iodine/iodides specifically activate the enzyme dihydrofolate reductase and Kang and Kim [5] reported a case of psoriasis exacerbated by radioactive iodine therapy. We suspected that the mechanism behind this, is due to activation of dihydrofolate reductase through radioactive iodine as there is no other significant drug history. Further study about the folic acid pathway in psoriasis and the connection between radioactive iodine with psoriasis may be necessary. This article has been presented to highlight the rarity of such condition.

Ethics

Informed Consent: Informed consent has been taken from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M., P.N., S.B., S.M., O.R., Concept: A.M., P.N., S.B., S.M., O.R., Design: A.M., P.N., S.B., S.M., O.R., Data Collection or Processing: A.M., P.N., S.B., S.M., O.R., Analysis or Interpretation: A.M., P.N., S.B., S.M., O.R., Literature Search: A.M., P.N., S.B., S.M., O.R., Writing: S.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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Painless Swelling of the Forefoot with Multiple Sinuses and Discharging Granules: Eumycetoma a Neglected Tropical Disease

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Keywords: Eumycetoma, Black grains, Discharging sinus

Dear Editor,

Mycetoma is a chronic infectious disease caused by fungus and bacteria, characterized by formation of tumor like swelling with multiple sinuses discharging grains. The infection evolves from a small subcutaneous nodule but patients usually presents late with advancing disease including destruction of soft tissue and adjacent bony structure with limb deformity. It commonly affects the male between 20 to 40 years, living in rural areas and frequently reported in farmers, shepherds and workers of low socioeconomic status. The most common site of affection is forefoot, however it can affect the other parts of the body.

A 48-year-old male, farmer by occupation, came to Dermatology Outpatient Department with six years history of painless swelling of left foot which was progressive in nature. He had history of working barefoot in the field. Cutaneous examination revealed 8 cm x 6 cm sized nontendered swelling with multiple sinuses discharging serosanguinous fluid and black granules (Figure 1). The black granules were soft in consistency and their shape and size were variable (Figure 2). Webspaces of left foot was normal. There was no regional lymphadenopathy. No other abnormalities were found in left foot. Rest of the cutaneous examinations were normal. General and systemic examination were unremarkable. Standard X-ray of his foot showed no bony involvement. Laboratory tests revealed no abnormalities in hemogram.

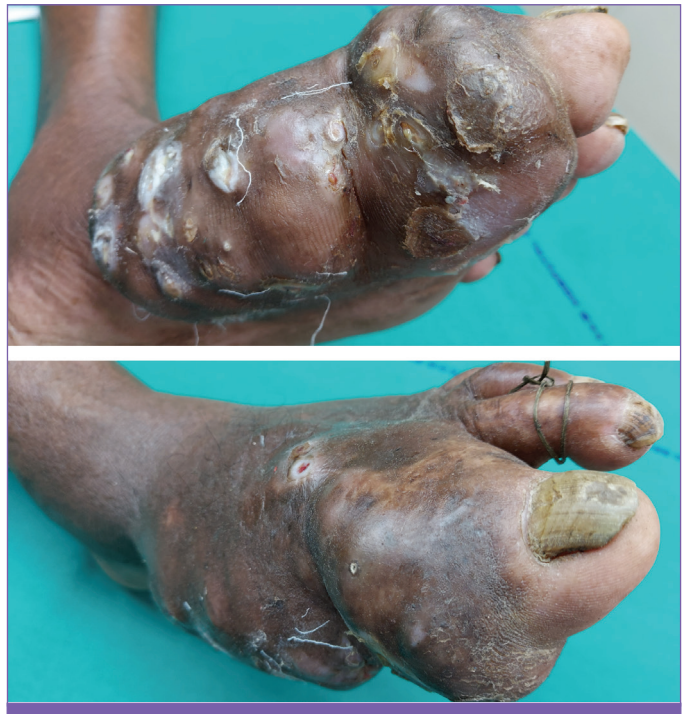

Figure 1. 8 cm x 6 cm sized nontendered swelling with multiple sinuses discharging

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Information and Communications Technology Council report was negative. KOH mount preparation was done and black grains were found. Gram stain and Ziehl-Neelsen stain findings were insignificant. Histopathology revealed inflammatory infiltrate with sulfur graunules in a purulent area of granulation tissue. Special stain with Gomori Methenamine Silver was done and it clearly visualized the sulfur granules composed of septate hyphae, chlamydospores in deep dermis and subcutaneous tissue (Figures 3, 4) Patient was given Itraconazole 200 twice daily following histopathological report and currently patient is under treatment.

Eumycetoma is a chronic granulomatous disease caused by fungus presents with tumorous swelling, multiple discharging sinuses and black grains. Tropical eumycetoma is frequently is caused by the fungus *Madurella mycetomatis*. It is responsible for most cases of black grain eumycetoma in dry arid region. In Eastern India, black grain mycetoma is caused by *Madurella grisea* whereas in South *Madurella mycetomatis* is either the dominant pathogen or the 2nd largest group [1]. The clinical lesions, typical grains, special stain with histopathological examination are characteristic for diagnosis [2]. Most of the patients of eumycetoma were living in rural areas and involved in agricultural activities [3]. The colour of the grains are important for actinomycotic and eumycetomic differentiation. Black colour are specific to eumycetoma whereas white or yellow colour granules both in action and eumycetoma. Red grains are found in actinomadura pelletieri [4]. Radiological examination with X-ray, ultrasonography and magnetic resonance imaging are usefull to determine the extent of involvement of soft tissue and bones [5]. Diagnosis and treatment at an early stage are necessary to prevent complication [6]. For treatment of eumycetoma, high dose of oral itraconazole (400 mg once daily) is necessary [7]. Newer antifungals like voriconazole, posaconazole are indicated for resistance cases [8]. Surgercial options like local excision to amputation are indicated for resistance cases of mycetoma or not responding to conventional therapy [9]. The triad of painless swelling, macroscopically visible dark grains and patient from endemic country as well as histological demonstration of fungal hyphae and chlamydospores raised our suspicion of eumycetoma.

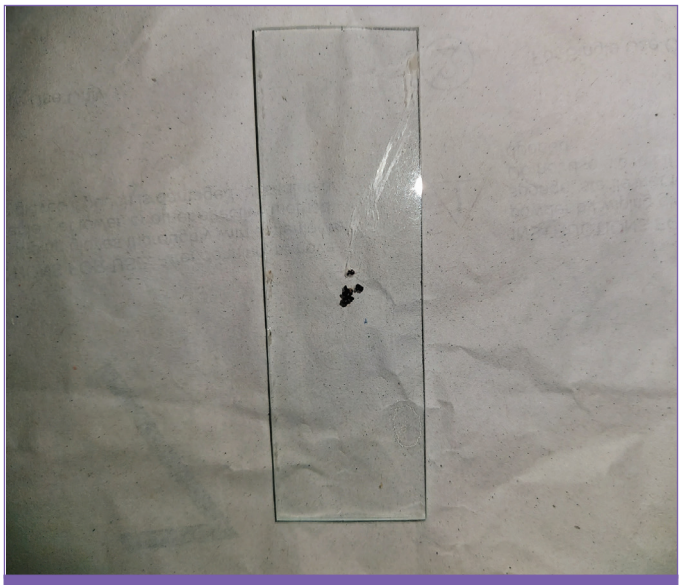

Figure 2. Black grains of various sizes and shapes

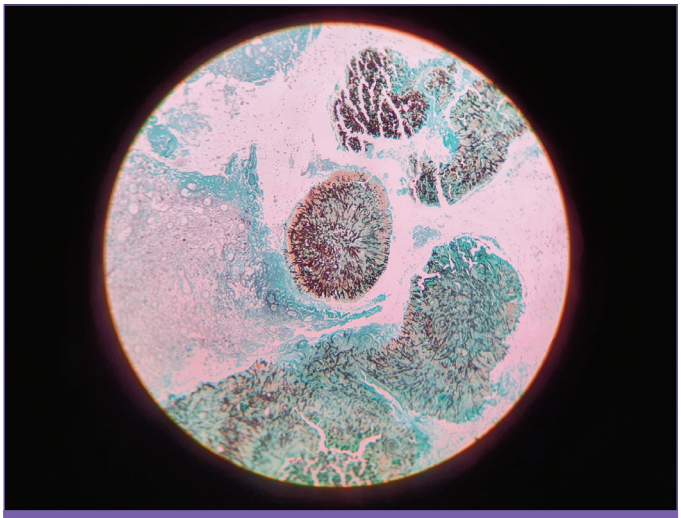

Figure 3. Gomori methenamine silver stain shows the sulfur granules at low power view (10x)

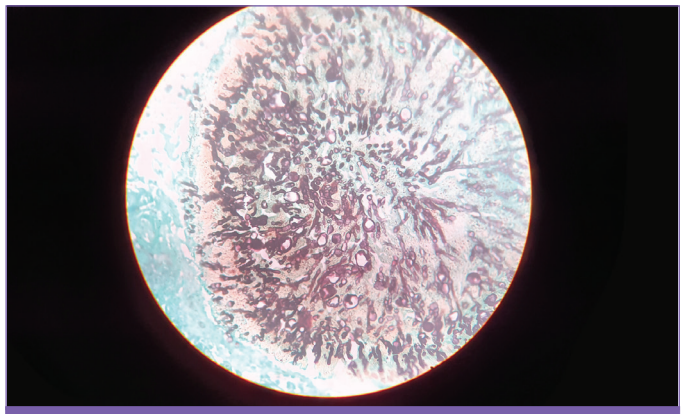

Figure 4. Gomori methenamine silver stain shows the sulfur granules composed of septate hyphae, chlamydospores at high power view (40x)

Ethics

Informed Consent: Informed consents of all participants were obtained before the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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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2020 Referee Index

Algün Polat Ekinci

Arzu Kılıç

Ayşe Serap Karadağ

Demet Kartal

Didem Didar Balcı

Fatma Pelin Cengiz

Kenan Aydoğan

Nazan Emiroğlu

Necmettin Akdeniz

Özge Aşkın

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Serap Güneş Bilgili

Tuğba Kevser Üstünbaş Uzunçakmak

Ümit Türsen

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