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III:Results

IV:Conclusions

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the appendices

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References:

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

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

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REVIEW

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Dermatomal Distributed Skin Diseases: A Systematic Review

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ABSTRACT

Dermatomal distribution of cutaneous lesions is a common pattern that encountered in the field of dermatology. Being familiar with these types of patterns can help evaluating the specifically distributed lesions and may shed a light on the diagnosis. This review summarizes the literature about dermatoses that presents with dermatomal distribution.

Keywords: Blaschko, Dermatology, Dermatome, Herpes zoster, Lichen planus, Melanoma, Metastasis, Psoriasis

Introduction

Recognition of patterns is essential assessing the skin diseases. The skin presents a distinct anatomical pattern due to distribution of sensory nerve fibers originate from a single spinal nerve [1]. An area of skin supplied by a single nerve root is called a dermatome. It can be considered as communicating sensation from skin to the brain. Dermatomes are located horizontally on the trunk and this horizontal pattern contrasts with the pattern of the extremities where it is typically longitudinal. Dermatomes can overlap and an individual's exact pattern of dermatome is unique [2].

A zosteriform pattern describes a unilateral belt like or girdle like presentation of a dermatosis on the area of skin that innervated by sensory branch of a spinal nerve [3-5].

While herpes zoster (HZ) is first to remember between zosteriform dermatoses, a large variety of inflammatory, infectious, neoplastic diseases may also present as zosteriform lesions [6].

There are 8 pairs of cervical, 12 pairs of thoracic, 5 pairs lumbar, 5 pairs of sacral and a pair of coccygeal nerves. There are 30 different dermatomes, despite the fact there are 31 pairs of spinal nerves. This results from the fact that C1 spinal nerve typically doesn't have sensory fibers. As a result, dermatomes start from spinal nerve C2. Even though skin mostly innervated by spinal nerves, the facial skin innervated by cranial nerve V which known as trigeminal nerve [6].

Pathogenesis

Cutaneous diseases that present itself with dermatomal distributed lesions reflects mainly 2 mechanisms.

The isotopic mechanism;

Isotopic response defined as a dermatosis that located and remains restricted to a site; which is the same area that other previously healed skin disease has placed [7-9].

The archetype of this phenomenon is a dermatosis that occurring on the same site of recovered previous HZ.

Although the precise mechanism of isotopic response needs to be enlighten it may be related to varicella zoster virus (VZV) induced modifications of the cutaneous immune system [10].

The neural mechanism;

Neural pathway results from reactivation of latent VZV of neural cells and the cells of dorsal root ganglia. Newly synthesized viral particles transferred to the skin via microtubular system of the axons [11].

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Lines of Blaschko

During embryogenesis, precursor cells start to proliferate on the midline and grow in transversal direction from this line. As the growth progresses these cells set up in S shape in the back and V shape on anterolateral trunk. These lines illustrate ectodermal development patterns. This distribution pattern, especially on the trunk, is frequently hard to distinguish from dermatomes [12].

Herpes Zoster

VZV infection is an important medical entity that concerns many specialties besides dermatology such as infectious diseases and neurology. It can effect variety of individuals from childhood to elderly. Its treatment also requires proficiency in pain management. Varicella generates from acute viremia. HZ appears in later life due to the dormant viral infection. When it is re-activated and virus spreads orthodromically to the target tissue. Generally, one dermatome is involved, however two or three adjoining dermatomes can be effected. The lesions commonly located unilaterally and do not intersect the midline (Figure 1, 2) [13].

If the zosteriform eruption is recent (<10-14 days) HZ is the most plausible diagnosis. However, zosteriform HSV infections are experienced in nearly 25% of the cases diagnosed as HZ at first [14-26]. The differantiation between HSV and VZV can quickly be performed on a Tzanck smear [4]. This difference is important in terms of dosing regimen which is differing from one another [4].

Zosteriform Cutaneous Metastases

Cutaneous skin metastasis results from tumor cells spreading directly and through hematogenous or lymphatics. It is comorbid in 0.7-10% of patients with cancer and composes 2% of cutaneous malignancies. Zosteriform pattern is a rarely seen subtype and there have been less than a hundred case reported [27].

Figure 1. Multiple millimetric papulovesicular eruption on an erythematous basis unilaterally distributed on left side of the trunk

Diagnosis of dermatomal distributed cutaneous metastasis can be tough. It can also prompt untoward investigations, delayed diagnosis and inaccurate treatment.

This sort of distribution pattern has been reported with digestive, respiratory tumors, breast cancer and lymphomas and squamous cell carcinomas (SCC). And the most common sites of metastases were chest and abdominal wall.

Besides the similar location and distribution pattern, patients also reported concomitant pain and that sort of presentation usually leads the physician to HZ and results in administration of antivirals in many cases [28].

Zosteriform cutaneous metastases generating from internal malignancies have also reported. Most frequently in the older patients, lesions with abnormally long duration as well as in patients with a history of cancer.

Cutaneous metastases of breast cancer are the most frequently observed, presumably due to its primary location on the thoracic dermatomes [29-53]. These zosteriform cutaneous metastases may often be initially misdiagnosed as HZ [34,54,55] or as contact eczema [56]. And they are frequently a sign of a poor prognosis and cutaneous metastases have been reported in 0.7-9% of the cancer patients [57]. Although zosteriform distribution of metastases are rare and less known there are few cases reported in the literature.

Figure 2. Multiple millimetric papulovesicular-pustular eruption on an erythematous basis unilaterally distributed on right scapula and upper extremity

Zosteriform Skin Cancers

If the eruption is more long established (more than 14 days), zosteriform distributed primary skin cancers should be considered, predominantly SCC but also angiosarcoma, Kaposi's sarcoma, primary cutaneous B-cell lymphoma and primary cutaneous T-cell lymphoma should be suspected [58-66].

Multiple Eccrine Spiradenomas (ES)

ES is a benign, dermal tumor originating from eccrine sweat glands. It typically presents as a solitary painful lesion, but rarely presents as multiple ES. Multiple ES is estimated to involve less than 2% of total number of cases. And it has increased incidence in females. The etiology of multiple ES is unknown. This diagnosis is aligned with an increased risk of a malignant transformation. Multiple ES can present in a segmental, linear, blaschkoid, or zosteriform pattern [67].

Mycosis Fungoides (MF)

MF presents itself with patches and plaques in the sun protected areas. Variety of clinical forms have been reported including granulomatous MF, hypopigmented MF, folliculotropic MF, pagetoid reticulosis.

Williams et al. [68] reported a case of MF mimicking HZ but immunophenotyping was not performed. In 2017 Rieger et al. [69] reported immunophenotypically and molecularly confirmed zosteriform MF.

Lichen Planus

Lichen planus is an inflammtory mucocutaneous disorder which is characterized by lichenoid, pruritic, shiny, flat papules. In addition to the classical appearance, there are varieties of clinical forms described such as zosteriform lesions. This type of lesions may present zosteriform distribution spontaneously or as Wolf's isotopic response [70-73]. Due to its distribution pattern, it can be also named as linear lichen planus in the literature. Although this rare pattern usually seen as a single dermatomal involvement, occasionally it may represent a multiple dermatomal involvement [74,75].

Melanoma

Zosteriform metastasis is usually painful or pruritic, and is frequently located on a single dermatome, leaving an open door for a potential misdiagnosis [76].

There are six relevant cases reported about recurrence of melanoma in a zosteriform distribution after treatment with chemotherapy [76-81].

Psoriasis

Psoriasis is common, chronic relapsing and remitting inflammatory disease with an overall prevalence of 2% to 3% of the world's population. Koebner phenomenon (KP), also called as isomorphic response, is referred to the occurance of psoriasiform lesions after trauma on healthy skin sites in psoriatic patients. About 25% of the psoriasis patients develop KP after various traumatic injuries. KP lesions are always located at the site of pre-existed HZ eruption with a latent period of approximately one week to four months from the occurrence of HZ [82]. There are one cases reported in literature each resulting from KP and Wolf isotopic response [82,83].

Other Skin Diseases

Additional skin diseases that may appear as zosteriform pattern include zosteriform perforating collagenosis, unilateral nevoid telangiectasia, zosteriform nevus spilus with melanoma, transient acantholytic dermatosis, progressive cribriform and zosteriform hyperpigmentation, Spitz nevi, epitheloid hemangioma, porokeratosis zosteriform nevus spilus, arterio-venous malformations, and segmental vitiligo may also present with a zosteriform pattern [84-98]. Although there is another publication about segmental vitiligo being a misnomer and rather than a dermatomal distributed disease it may be results from cutaneous mosaism [99].

Zosteriform inflammatory lesions may appear as drug reactions to levofloxacin [100]. Uncommon cases are accounted for zosteriform morphea [101]. Incidental cases of zosteriform leishmaniosis have been described [102-105].

Conclusion

Dermatomal distribution instantly reminds physicians about HZ. Considering the patients age, competence of their immune system, history of previous dermatoses located in the same area and other relevant diseases such as cancer should be taken into account in order to avoid unnecessary use of antivirals and incorrect diagnoses. Zosteriform cutaneous metastases are not frequent but they are being reported in the literature as a consequence of large variety of cancers.

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Spider Bites Might Present as Cellulitis Like in Early Cases and Pyoderma Gangrenosum Like in Late Cases

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ABSTRACT

Background: Spiders are blamed for all kinds of things that turn out to be simple infections or some other bugs faults as most are harmless bite except two spiders, the black widow and brown recluse that might cause reaction locally as ulcers and systemic beyond the bite like abdominal pain, cramps or respiratory problems.

Materials and Methods: Twenty-four patients with history of spider bite were recorded during the period from May 2012 to March 2020, their ages ranged from 25-35 years five females and 19 males. All cases were seen three-15 days after biting and no one examined at the time of bite. On careful questioning of patients, many had seen brown-black spider while others had felt a bite only.

Results: On careful examination, the lesional bites could be divided into early and late presentations. Regarding the early presentation in six cases were observed and all had cellulitis like picture with small black necrosis at the center while the late cases showed gangrenous well defined ulcer that simulate pyoderma gangrenosum in (18) patients and these ulcers were characteristically polygonal in shapes at their margins. The sites of these bites were as follow: 14 (58.3%) thighs including groins, 3 (12.5%) legs, 3 (12.5%) fingers, 3 (12.5%) male genitalia and one (4.16%) was left axilla. Medical management including topical antiseptic together with topical and oral antibiotic cover with oral antihistamine and oral prednisolone. The duration of therapy depending on the size of ulcer but generally it took from two weeks to two months. No surgical debridement was carried out.

Conclusion: Spider bites are commonly seen adult males and could be presented as early cellulitis like and late polygonal pyoderma gangrenosum like. The commonest sites affected were lower limbs, most commonly thighs and groins. Healing might take few weeks to few months depending on the size of necrotic ulcer. Wound debridement was not carried out but skin grafting might be suggested for large ulcer as to reduce the time of morbidity and recovery.

Keywords: Spider bite, Pyoderma gangrenosum, Ulcer

Introduction

Spiders are carnivorous members of the animal kingdom that use webs and venom to capture and kill prey. Within the united states, 3 genera contain species whose bites are toxic to man: (a) Latrodectus (b), Loxosceles, and (c) Tegenaria [1].

Latrodectus: Latrodectus genus, or widow spiders, are frequently black in color and own a red, hourglass shaped marking on their abdomen. Females are larger than males. It is the most substantial venomous spider in North America and Australia [2,3]. Its venom is alpha-latrotoxin which results in the exocytosis of synaptic vesicles from parasympathetic endings due to the excitation of

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calcium-dependent mechanisms, releasing acetylcholine and catecholamines [4].

The symptoms that caused by the bite of this spider are called latrodectism. The pain from its bite is same of a pinprick and the skin reaction is similar to the target lesion that can be observed in the site of biting [5]. Latrodectism starts within few minutes with the development of pain throughout the whole body and symptoms such as emesis, respiratory failure, delirium, partial paralysis of limbs, abdominal muscle cramps, hypertension, pyrexia, fasciculation and muscle spasm are developed within a few hours [6]. Symptoms may be misdiagnosed as acute abdomen. Mortality result from biting is less than 1%. Bites commonly occur during warm seasons [7].

Until 2012 there was no any study mentioned the presence of black widow spider in Iraq, after that Al-Iraqi and Nayef, 2012 recorded two species of black widow spiders for the first time in Mosul city (Iraq) during the summer of 2012 and 2013 [8]. Also two females of the red-back spider, Latrodectus scelio Thorell, 1870 were first recorded in Baghdad (Iraq) in 2012 [9].

These spiders weren't existing in the Iraqi environment prior the American occupation to Iraq but they may be introduced unintentionally to Iraq with equipments, goods, and containers that occupation forces fetched with them to Iraq [8].

Loxosceles: Loxosceles spiders are found throughout the world. The brown recluse spider (L reclusa) is tan to brown and has a violin-shaped mark on its back. It has long legs, short body hair, and three couples of eyes [10]. It favors dry, filthy, undisturbed places with good cover such as lofts and storage areas indoors and cowsheds and woodpiles outdoors. Females are more common, are slightly bigger, and inject more venom when they bite [11]. This type of spider was not reported in Iraq but their presence was recorded after 2012 through web sites but not through a study [12].

The venom contains alkaline phosphatase [13], 5' ribonucleotide, hyaluronidase, esterase [14], sphingomyelinase D2, which is the most important one [15]. Hyaluronidase possibly the cause for gravity-dependent lesional spread [16]. Stomach enzymes comprising protease, lipase and hydrolase may go with venom. Lipase is responsible for depressed scarring of lesions, conspicuous above fatty sites [17].

There are two important clinical types of loxoscelism: necrotic cutaneous and viscerocutaneous loxoscelism [18].

The clinical manifestations depend on the age and general health of the patient, the quantity of venom introduced and the location of the bite-fatty areas such as the proximal thigh and the buttocks show further cutaneous reaction and broad involvement of the whole subcutaneous layer [18].

In necrotic cutaneous loxoscelism, there is local damage to the skin and subcutaneous tissues, but systemic symptoms are mild. The bite of the spider is usually relatively painless. However, after a period of minutes or hours, intense pain occurs at the site, accompanied by erythema, oedema and a central vesicle or bulla. In severe envenomation, a 'target' lesion develops - within 12 to 24 hours the lesion may become hemorrhagic, and the characteristic "red, white, and blue sign," consisting of erythema, ischemia, and thrombosis is seen. After three or four days, the central area becomes necrotic, and an eschar develops. The eschar is finally shed, leaving an ulcer, which may take an abundant time to heal [18]. Eventually deep ulcers develop. The bite reaction may cause an ulcer resemble pyoderma gangrenosum [1].

In viscerocutaneous or systemic loxoscelism, general symptoms of fever, malaise, restlessness and headache are noticeable. Within 24 h of the onset of general symptoms, ecchymoses, jaundice, haematuria and haemoglobinuria suggest great intravascular haemolysis, which may lead to acute renal failure and death [1].

Most cases of recluse spider bites are recorded in the hot months when the spider becomes very active; it ordinarily prone to bite when the patient is either sleeping or wear clothes. These spiders appear to have a preference to bite on the trunk, thigh or arms, and the thigh is the commonest site [19,20]. In rare occasions, bites from brown recluse spiders can cause clinically important dermal necrosis and subsequent scarring [21]. Wound chronicity and pyoderma gangrenosum occur rarely this may be due to an unusually severe allergic reaction [22]. Slow healing inflammatory Loxosceles spider bite ulcers may become pyoderma gangrenosum due to sever immunologic abnormalities or *Chlamydia pneumoniae* infection [23].

Tegenaria: Tegenaria agrestis, the hobo spider, is the main cause of necrotic arachnidism in the Pacific Northwest of United States and can be found in a region extending from Alkasa to Utah. The local cutaneous effects after hobo spider, which can ranged from mild to serious, are similar to those produced by the brown recluse [1].

Armadeiras (Armed Spiders): They have long arms. As they usually hide in banana boxes, they are known as banana bunch spiders by locals. Its bite result in intense pain which is noticed in about 96% of patients [24]. The bite of this spider may cause respiratory failure and death [4].

Tarantula: Tarantulas are large hairy spiders common in the southwestern US, and kindred species are presented throughout the world. Tarantula is characterized by its hairy 3-inch brown or black colored body. Itching at the site of urticating hair penetration is the most common skin manifestation and may last for several weeks after exposure [4].

In Iraq, these cases of spider bites are not reported among people but after 2012, patients were seen with picture similar to rash that induced by brown recluse spider. Also, there was no report of presence of both brown recluse and black widow spiders in Iraq and neighboring countries like Iran and Turkey [25] but after 2012, cases were reported from now and then.

So the objective of present work is to report these spider bites for the first time and to do full clinical description of spider bites that had been seen during the period from 2012-2020.

Materials and Methods

Twenty-four patients with history of spider bites were seen during the period from May 2012 to March 2020, their ages ranged from 25-35 years with a mean of 27 year, with five (20.83%) females and 19 (79%) males.

The diagnosis was supported by history and clinical appearance and confirmed if the patient fetched the spider. All cases were seen around three to 15 days after biting.

Satisfying history was taken from each patient included: age, sex, duration of the bites, associated sign and symptoms and past medical history.

Clinical examination was done including the site and clinical appearance of the bite.

A full investigations were carried out included: complete blood count, blood urea and serum creatinine.

No systemic manifestations like nausea, vomiting and hypertension were mentioned by patients at the time of spider bite.

This study followed the Declaration of Helsinki Principles and permission was taken from each patient before photograph. Also, no intervention was done for any patient.

Treatment of the bite and ulcer was conservative using medical therapy and surgical debridement was not advised.

Statistical Analysis

Data were statistically described in terms of rang, mean, frequencies (no. of cases), disease duration and male to female ratio. All statistical calculation were done using Statistical Package for the Social Sciences version 20.

Results

On careful examination, the lesional bites could be divided into early and late presentations. Regarding the early presentation six (25%) cases were observed during 3-15 days after bite and all had cellulitis like picture seen as erythematous plaques with small central necrosis at the center (Figures 1, 2). While the late cases seen in 18 (75%) patients in around 10 days after biting and showed gangrenous well defined ulcers of variable in size and simulated pyoderma gangrenosum. These ulcers were characteristically polygonal at their margins with well-defined in shapes and covered by thick black eschar which was difficult to be removed by forceps. The sites of these bites were as follow: 14 (58.3%) thighs including groins (Figures 3, 4), three (12.5%) legs, three fingers (12.5%) and three (12.5%) male genitalia (Figure 5) and one (4.16%) was left axilla.

The results of all investigations done by patients were normal.

Medical management including topical antiseptic together with topical and oral antibiotic cover with oral antihistamine and oral prednisolone. The duration of therapy depending on the size of ulcer but generally it took from two weeks to two months. No surgical debridement was carried in any patient.

Discussion

There are two spiders that have been reported to cause skin manifestation as results of their bites. These are brown recluse and black widow spiders which are seen all over the world but most common in United States and Australia [1].

These two spiders were not reported in Iraq and neighboring countries like Iran and Turkey [25] but after American occupation of Iraq in 2003, these spiders were suspected to be present as results of seeing of strange cases of skin bites and these were increased in their frequency after 2013. Since then these spiders where documented to be present in Iraq both the black and brown spider [8,9,12]. And as all reported cases presented with spider bites rather than with systemic manifestations, we can assume that this skin problem is caused by brown rather than black spiders. This in agreement with other study where the causative spider is rarely seen for identification [26].

Figure 1. Twenty-six year old male with early lesion as a cellulitis like spider bite after four days affecting the inner aspect of right thigh showing small central necrotic area on the top of well-defined erythematous plaques and cellulitis like picture

Hence this is the first study documenting the skin manifestation of spider bites in Iraq. The present work showed that the thigh with groin was the most common site (58.3%) involved by spider bites, similar to other researchs [19,20,26] followed, three (12.5%) legs, three fingers (12.5) and three (12.5%) male genitalia and one (4.16%) was left axilla. Regarding male genitalia involvement by spider bites, an unusual finding of the present work where there is necrotic ulcer with black eschar affecting the glans penis which is not reported by previous studies.

These bites were commonly seen among males (79%) as seen in the present work and this could be due to pastoral setting and wearing opened clothes so called (Dishdasha) and also happening of spider bites in summer time.

The most important features that differentiate spider bite ulcer from ordinary pyoderma gangrenosum:

(a) The presence of black eschar which resulted from gangrenous tissue caused by spider toxin.

(b) Polygonal border due to uneven distribution of toxin and its effect on the tissues and as venom spread gravitationally.

(c) Sex and site: in the present work most cases were among males and areas of predilection were upper thigh, groin and genitalia.

The presence of black gangrenous area at the center of cellulitis like lesion due to spider bite which is most important diagnostic feature to differentiate cellulitis like due to spider bite from ordinary bacterial cellulitis.

Medical therapy as a conservative regime was applied in the present work and this in agreement with other study as they found that surgical and debridement was not carried out mainly as controlled trials have found that early surgical intervention should not be carried out [27] as surgery increases local inflammation and potentiating toxin effects,in addition, wound chronicity, repeated graft rejection, and pyoderma gangrenosum may result [22,27].

Although spider bites are rare but should be always remembered whenever we see red plaque with central necrosis or polygonal ulcer that covered with black eschar to avoid wrong diagnosis and mismanagement.

To the best of our knowledge this is the first clinical study describing spider bites in such clinical details.

Study Limitations

Histopathology was not carried out for any patient, as biopsy was refused by patients. In addition, the biopsy may exacerbate the acute condition of the spider bite ulcer.

Figure 2. Twenty-five year male patient with spider bite affecting the border of left axilla and showing cellulitis like erythematous plaque with small central necrotic area

Figure 3. Thirty year old female pyoderma gangenosum like spider ulcer affecting the right thigh and showing a well-defined deep ulcer with polygonal irregular margin

Figure 4. Thirty-one year old male with spider showing pyoderma gangrenosum like after ten days (a) and after three weeks (b) following therapy

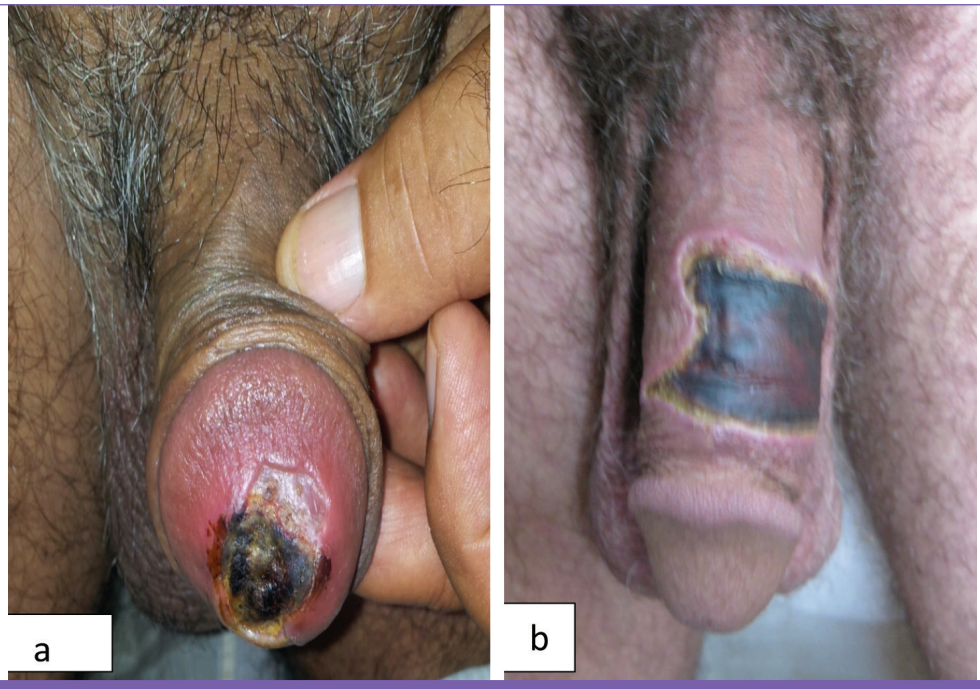

Figure 5. a, b) Spider bites in two males showing pyoderma gangrenosum like ulcers of penis with polygonal margin with thick eschars

Conclusion

Spider bites might be presented as early cellulitis like and late pyoderma gangrenosum like. The commonest sites affected were lower limbs, most commonly thighs and male genitalia. Healing might take several weeks to several months depending on the size of necrotic ulcer.

Wound debridement was not carried out as surgery increases local inflammation and potentiating toxin effects, wound chronicity, repeated graft rejection, and pyoderma gangrenosum may result. Skin grafting might be suggested for large ulcer as to dcrease the time of morbidity and recovery.

Ethics

Ethics Committee Approval: As this study was carried out since the last nine years and it is mainly case series descriptive study rather than therapeutic, hence we do not think to have ethical approval.

Informed Consent: Written permission was taken from each patient before photograph and after explaining to the patient about the nature of the disease and aim of the study.

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.

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An Investigation Into the Frequency of Use of Traditional and Complementary Medicine in Patients Presenting to the Dermatology Clinic: A Survey Study

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ABSTRACT

Background: Although interest in traditional and complementary medicine (TCM) methods has grown, patients are still reluctant to inform physicians that they employ these. Reasons for the increase in the frequency of TCM methods include interventional procedures being performed less or not at all, and the perception that topical treatment is harmless. The great majority of people who use TCM methods acquire the relevant information from the internet and those around them. Physicians therefore need to be aware of such trends and to protect patients against incorrect use by informing them accordingly. The purpose of this study was to investigate the frequency of the use of TCM methods among patients presenting to the dermatology clinic.

Materials and Methods: Patients presenting to the dermatology clinic between June 2018-April 2019, aged over 15, and with symptoms persisting for longer than six weeks was included in the study. Disoriented or uncooperative patients were excluded. Patients agreeing to participate read and signed informed consent forms, after which a question and answer type questionnaire was administered to collect data about TCM applications.

Results: Six hundred fifty-one patients, 56.9% of whom were women, took part, and 13.3% had used TCM. Herbal remedies were the most frequently employed method at 67.8%, followed by cupping at 16%, leeches at 13.7%, and moxibustion at 2.2%. Frequency of use was 48.2% among women and 51.8% among men, while in terms of age the frequency was highest in the 45-55 age range, and in terms of education use was highest among university graduates.

Conclusion: Patients attending for examination should be given information to protect against misuse of TCM methods by inquiring into their attitudes toward them, especially those failing to benefit from the treatment administered or with recurring symptoms. Physicians must be aware of such tendencies on the part of patients and must inform patients about these methods when necessary.

Keywords: Traditional treatment, Complementary treatment, Dermatology

Introduction

Modern/conventional medicine was born from Hippocrates' (460-356 BC) idea of investigating the cause and effect relationship during diagnosis, treatment, and prognosis through accumulated experiences. Freed from being a combination of religious faith, magic, and methods based on empirical treatment applied by priest-physicians, the foundations were laid for it to become a true science [1]. When assistant methods are applied in addition to modern medicine, this is known as 'complementary medicine,' while the use of such techniques instead of modern medicine is known as ''alternative medicine.' Based on World Health Organization definitions, the term 'traditional and complementary medicine (TCM)' decision that from there is no alternative to

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medicine, only to treatment could be an alternative [2]. TCM refers to the totality of skills and practices, explicable or otherwise, based on theories, beliefs, and experiences specific to different cultures in the preservation of health in addition to protecting against, diagnosing, and healing or treating physical and mental diseases [3]. Fifteen forms of TCM are currently approved by the Turkish Ministry of Health - phytotherapy, mesotherapy, larval therapy, prolotherapy, cupping, music therapy, hypnotherapy, homeopathy, leech therapy, ozone therapy, osteopathy, reflexology, acupuncture, apitherapy, and chiropractic [2]. Diseases have been present throughout human history, and there has been a constant search for treatments. The search for a solution outside evidence-based medicine on the part of the patient or relative, the knowledge that the disease in question may persist for a lifetime, recurrence of symptoms after treatment, and the belief that natural compounds have no side-effects all encourage the use of TCM [4]. Reasons for use vary among countries depending on their level of development. In developing countries, TCM is used to meet the basic health needs of communities, while in developed countries it is more used in diseases to which conventional medicine fails to find a solution [5]. Previous studies have investigated the use of TCM among patients presenting to dermatology clinics in countries with very different sociocultural characteristics, such as Singapore [6], the USA [7], the United Kingdom [8], Taiwan [9], Saudi Arabia [10], and Iran [11]. The common finding of these studies is that TCM is commonly employed among patients presenting to dermatology clinics, that patients are reluctant to report this, and that dermatologists therefore need to raise their awareness on the subject of TCM. However, the number of studies from Turkey investigating the frequency of use of TCM in the field of dermatology, the methods employed, and the frequency of their side-effects and effectiveness, is insufficient.

The purpose of this study was to investigate the use of TCM among patients with dermatological symptoms persisting for longer than six weeks presenting to a dermatology clinic in Turkey.

Materials and Methods

Patients presenting to the dermatology clinic between June 2018 and April 2019, aged over 15, and with symptoms persisting for longer than six weeks, and patients attending routine clinical follow-ups were included in the study. Disoriented or uncooperative patients were excluded. All patients meeting the inclusion/exclusion criteria were invited to take part. Patients agreeing to participate read and signed informed consent forms, after which a question and answer type structured questionnaire (Appendix 1) was administered to collect data about TCM applications.

Approval for the study was granted by the Duzce University Ethical Committee (no: 2019/109).

Statistical Analysis

Statistical analysis was performed on Statistical Package for the Social Sciences Software (Windows 20.0; SPSS Inc., IL, USA). Descriptive statistics were calculated as frequency and percentage for categorical variables.

Results

Demographic data for the patients in the study are shown in Table 1, and distributions of TCM use among patients using TCM are shown by age, sex, and education level in Table 2.

In Table 3, TCM was employed by 13.3% of the patients in the study. The most popular TCM method, at 67.8%, was herbal products. Cupping was used by 16% of patients, leech therapy by 13.7%, and moxibustion by 2.2%.

Table 1. Demographic data

Sex	Male	280
	Female	371
Age	15-25	146
	25-35	160
	35-45	142
	45-55	128
	55 and over	75
Education	Illiterate	22
	Literate	31
	Elementary school	113
	Middle school	63
	High school	210
	University	212

Table 2. Rates of traditional-complementary medicine use by sex, age and education level

Sex	Female	42 (48.2%)
	Male	45 (51.8%)
Age	15-25 years	12 (8.2%)
	25-35 years	20 (12.5%)
	35-45 years	14 (9.8%)
	45-55 years	28 (31.1%)
	55 or over	13 (14.9%)
Education	Illiterate	3 (13.6%)
	Literate	2 (6.4%)
	Elementary school	16 (14.1%)
	Middle school	10 (15.8%)
	High school	18 (8.5%)
	University	38 (17.9%)

Table 3. Traditional-complementary medicine questionnaire results		
TCM	Using	87 (13.3%)
	Thinking of using	27
Diagnosis	Erythematous-squamous diseases	27
	Chronic pruritus- chronic urticaria	7
	Zona zoster-related pain	5
	Chronic eczema	36
	Stasis ulcer-chronic wounds	4
	Other	8
Duration of disease	<5 years	449
	5-10 years	124
	>10 years	78
Additional chronic disease	Yes	205
	No	446
TCM method(s) used	Herbal products (as ointment)	59
	Herbal products (for eating or drinking)	-----
	Acupuncture	-----
	Cupping	14
	Leech therapy	12
	Moxibustion	2
	Other	-----
Aims behind TCM use	Support	85
	Treatment	2
	Protection against attacks	----
Benefit obtained from TCM methods	Yes	2
	No	85
	Worsening of symptoms	12
Prior receipt of information about TCM	Yes	72
	No	15
Did the information you obtained come from the internet?	Yes	40
	No	15
Did you have your TCM method applied in a hospital setting?	Yes	20
	No	67
Did any side-effects arise from the TCM method?	Yes	14
	No	63
If you used TCM, would you use it again?	Twenty-four out of 87 patients stated they might use it again	

TCM: Traditional-complementary medicine

Three of the seven patients with psoriasis used leech therapy, and four used cupping.

The seven patients with chronic pruritus and chronic urticaria applied cupping.

Two of the patients with zona zoster-related post-herpetic neuralgia employed cupping, one employed leech therapy, and two used moxibustion.

Two patients with acne rosacea employed leech therapy, but reported an increase in their symptoms. Three out of four patients with androgenic alopecia used leech therapy, and one employed cupping.

Three patients with venous ulcer employed leech therapy, with healing accelerating in one of these, and other reporting partial improvement. Fifty-nine patients with existing diagnoses of chronic

eczema and psoriasis reported employing creams made from various herbal compounds.

In terms of side-effects, cupping-related scarring was determined in one patient, worsening of lesions after cupping in three patients, allergic contact dermatitis associated with creams applied in two patients, cheloid in leech bite points in one patient, and allergic reaction after leech therapy in three patients in Table 3.

Discussion

As in the rest of the world, procedures described as TCM began being increasingly employed in Turkey after the 1990s. However, 60-80% of patients using TCM methods are reported to conceal this from their physicians [12]. Reported TCM use rates among patients presenting to dermatology clinics are 25.7% in Singapore [6], 45% in the United Kingdom [8], 41% in Taiwan [9], 40% in Saudi Arabia [10], and 31.3% in Ireland [11].

In their study of 1.610 patients from eastern Turkey, Bilgili et al. [13] determined that 43.7% used at least one TCM method, particularly henna, cologne, prayer, and herbal remedies. Can et al. [14] reported TCM use among 26.1% of pediatric patients, most commonly herbal remedies, and that the father being a university graduate increased the use rate. In a study of 217 patients, Sivamani et al. [15] found that 13.4% used TCM, the most common method again being herbal remedies. A review of 58 studies from 19 countries reported that TCM use rates ranged between 8% and 48.5%, and concluded that homeopathy was more common in Germany, the United Kingdom, and Canada, while the use of herbal remedies was more frequent in Germany, Turkey and Brazil [16].

The TCM use rate in the present study was 13.3%, the most commonly employed method being herbal remedies at 67.8%. The highest rate of use was among university graduates at 17.9% (n=38). No patients in this study used acupuncture for dermatological diseases.

The second most commonly applied TCM method after herbal remedies was cupping, at 16%. Patients with psoriasis, chronic pruritus, chronic urticaria, post-herpetic neuralgia, and androgenic alopecia had cupping performed. Cupping is a traditional therapy that has been performed for thousands of years across the world [17]. There are two forms of cupping - dry and wet. It is defined as eliminating 'stagnant blood' from the body [5]. Studies have investigated its use in various medical conditions, including dermatological applications. Despite the absence of high-quality clinical studies evaluating the effectiveness of cupping therapy, it is widely employed worldwide [17]. Several studies have discussed inappropriate applications resulting in various complications [18]. A review of 12 randomized controlled studies involving 842 patients with urticia reported that wet cupping might be capable of enhancing the efficacy of antihistaminic therapy. However, that review also reported that the need for attention in the results of studies regarding cupping since they might be poor quality [19]. A meta-analysis of studies involving the application of cupping in patients with psoriasis concluded that it was not effective in treating the [20]. Paradoxically, there are numerous cases in the literature of the Koebner phenomenon developing in association with cupping [21,22]. Tian et al. [23] found that wet cupping exhibited its effect by reducing substance P levels in patients with post-herpetic neuralgia. Another study also reported that cupping was effective in shingles-related post-herpetic neuralgia [24]. The most commonly encountered side-effects of cupping include anemia due to excessive bleeding [25,26] and herpes virus infection [27]. Later changes include scarring in the incision site and hyperpigmentation [28]. Histories revealed exacerbation of lesions occurred following cupping in patients diagnosed with psoriasis in this study, partial improvement in one patient with chronic pruritus and post-herpetic neuralgia, and to no therapeutic effectiveness in other patients taking part.

Leech therapy was employed by 13.7% of the patients in this study. The treatment of medical problems using medical leeches is known as hirudotherapy. Leeches feed on the blood of the organism to which they attach themselves. Anesthetic substances in leech secretions reduce pain, while their anticoagulant properties prevent clotting. The effects of leech therapy are thought to be due to the secretions containing hirudin, hyaluronidase, kaline, destabilase, aspirase, eglin, bdellin, dekorsin, guamerin, piguamerin, gelin, gamma-glutamyl transpeptidase, platelet-activating factor antagonist, ornithine-rich plasma, and other active biomolecules [29]. The US Food and Drug Administration approved the use of medical leeches in the healing of graft tissue and problems associated with venous congestion in 2004 [30]. Cases have been reported of successful use of leech application in healing chronic wounds [30,31] and venous congestion [32]. In an analysis of case reports and case series collected from 67 different article, Whitaker et al. [33] reported that leech application assisted flap rescue in 216 patients undergoing flap surgery. In addition to the proven efficacy of leech therapy, Aktaş and Hamidi [34] reported a different case, of a patient treated on an outpatient basis for warts recalcitrant to treatment persisting for seven years. Those authors reported that shrinkage occurred followed leech therapy applied by the patient. Two patients with rosea in this study underwent leech therapy, but reported a worsening in their symptoms. Three patients with venous ulcers had leech therapy performed, with one reporting accelerated healing and another partial improvement. Patients with existing psoriasis reported no effectiveness of leech therapy, and one reported increased pruritus as a side-effect. The most commonly reported side-effect of leech application is infection, at a rate of 21.8%. Infections arise from the leech's microbiota

[33]. Bauters et al. [35] determined an infection rate of 27.5% and recommended the prophylactic use of levofloxacin. One rare side-effect is pseudolymphoma [36,37,38]. Another side-effect that may be seen is allergic reaction [39]. Hemoglobin should be monitored due to continuous blood loss for several hours during and after leech therapy, and transfusion must be performed if necessary [33]. Three patients presented to our clinic due to development of allergy (Figure 1) following leech therapy. One patient also presented due to cheloid after leech therapy. A patient with existing venous congestion and chronic venous ulcer reported benefitting after leech application. Leech applications can be employed for wound healing due to their prophylactic and palliative effects. However, standard procedures and scientific parameters need to be developed if the effectiveness of leech application is to be proved in a rational manner.

Herbal remedies were the most commonly used TCM method in this study. These have been used in the treatment of dermatological diseases for hundreds of years [40]. The use of natural herbal compounds has become increasingly popular in recent years [41]. Recent research from the USA has determined use of a herbal product among 20-60% of adolescents and in 70% of individuals between 30 and 40. Men frequently use these for therapeutic purposes, while women more often employ them for cosmetic reasons [41]. In a study from Iran, Dastgheib et al. [11] reported that 31.3% (n=188) of 600 patients used TCM. The great majority of these patients, 89.9%, favored herbal products. The majority of patients using herbal remedies were also in the eczema group. According to the World Health Organization, some 35,000-70,000 plants worldwide are used for therapeutic purposes, of which only 5.000 have been subjected to medical analysis [42]. These products, generally inaccurately described as herbal medicines, are propagated by physicians and non-physicians based on reports with no supporting scientific evidence, and are sold in places where they are easily accessible to all. Although patients are reluctant to admit to using these products, they employ them in an uncontrolled manner out of the belief that 'natural products are harmless.' Worsening of lesions was observed in a patient receiving biological therapy and under follow-up by ourselves. When asked about this, the patient stated that she had purchased a product containing seaweed online, had rubbed it on her body and left it there for six h, and that the symptoms had subsequently worsened within one week.

Figure 1. Erythematous papules in leech biting areas

Study Limitation

The number of patients is limited in terms of survey study.

Conclusion

TCM enjoys a wider range of use than physicians may expect. Patients are largely advised to use TCM by non-professionals. They are also reluctant to consult physicians to obtain information about the applications they are considering using. They use the internet, the media, and friends and relatives as sources of information, for which reason TCM usage rates are rising. Patients should be asked about the use of TCM when an otherwise unexplained worsening in lesions is detected. At the same time, it should always be remembered that the TCM methods employed may interact with conventional medications.

Ethics

Ethics Committee Approval: The study was conducted in the light of the declaration of Helsinki and followed a protocol approved by Duzce University Ethical Committee (approval number: 2019/109).

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

Peer-review: Internally peer-reviewed.

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Appendix 1. Traditional and complementary medicine method use questionnaire for patients with chronic dermatological diseases

Age: .....

Sex:

☐ Male ☐ Female

Education:

☐ Illiterate ☐ Literate ☐ Elementary school ☐ Middle school ☐ High school University and above

Diagnosis: .....

Duration of disease:

☐ 5 years ☐ 5-10 years ☐ > 10 years

Additional chronic disease:

☐ Yes ☐ No

Use of TCM:

☐ Yes ☐ No

Which TCM methods do you use?:

☐ Herbal products (as ointment) ☐ Aromatherapy (oils) ☐ Acupuncture ☐ Cupping ☐ Leech therapy ☐ Moxibustion ☐ Other

Reason for use of TCM methods:

☐ Relief ☐ Support ☐ Treatment ☐ Protection against attacks

Symptoms requiring use of TCM methods:

☐ Itching ☐ Rash ☐ Pain ☐ Dissatisfaction with external appearance

Benefit obtained from TCM methods?

☐ Yes ☐ No

If benefit was achieved, which symptoms improved?

☐ Itching ☐ Rash ☐ Pain Dissatisfaction with external appearance

Did you receive treatment alongside TCM?

☐ Yes ☐ No

Receipt of information about the TCM method concerned prior to application?

☐ Yes ☐ No

Was information requested from a physician?

☐ Yes ☐ No

Did you obtain information from the internet?

☐ Yes ☐ No

Did the TCM method cause any side-effects?

☐ Yes, if so which .....

☐ No

If you employed TCM, would you use it again?

☐ Yes ☐ No

TCM: Traditional-complementary medicine

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Demographic Characteristics of Lichen Simplex Chronicus and Prurigo Nodularis Patients: 5-Year Policlinic Evaluation

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ABSTRACT

Background: Lichen simplex chronicus (LSC) and prurigo nodularis (PN) are two similar diseases of the psychocutaneous dermatoses group. Several factors play a role in the pathogenesis of these two diseases. The aim of our study was to evaluate the demographic characteristics of LSC and PN.

Materials and Methods: We investigated the cases of LSC and PN in 63,206 patients who applied to the outpatient clinic of the Dermatology Department of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine between 01.11.2007 and 01.12.2011. The data was recorded in a computer data entry program based on the International Statistical Classification of Diseases and Related Health Problems diagnostic code system and were retrospectively reviewed.

Results: In LSC, the distribution of the disease by age was found to be statistically significant with the highest frequency was the 50-59 age group. PN was found to be most frequent in the third decade in our clinic patients. In both diseases, women were more effected than men. We also found that the frequency of both diseases varied seasonally.

Conclusion: In this retrospective study, we evaluated the LSC and PN patients that applied to our outpatient clinic; the parameters were the disease frequency, average age, age distribution, sex distribution, month and season of application and the frequency of applying to the outpatient clinic. The frquency of LSC was 1.94% and PN was 0.14%. The average age of LSC parients was 46.37±16 and that of PN patients was 45.22±19. These data are in compliance with previous literature. In terms of gender distribution, both of the diseases affect women more frequently. LSC has a 71% women and 29% male prevenance. PN has a 64% women and 36% male prevelance. The results are in compliance with previous literature. Age based gender distribution was statistically insignificant. LSC is seen more frequently during winter and PN is seen more frequently during autumn. This difference was statistically significant for LSC but insignificant for PN. The yearly average of out-patient clinic application for both diseases was 1.2. The results were based upon the retrospective evaluation of the patients that applied to the outpatient clinic of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine Dermatology Department. Further multicenter studies with longer follow up intervals and greater sample sizes are needed in order to reach nation-based conclusions.

Keywords: Lichen simplex chronicus, Prurigo nodularis, Age, Gender, Demographic

Introduction

Lichen simplex chronicus (LSC) and prurigo nodularis (PN) are two similar diseases of the psychocutaneous dermatoses group. Approximately one-third of the dermatological diseases are associated with psychiatric or psychosocial problems. Stress affects both health and longevity negatively, especially when it gets chronic. Several factors play a role in the pathogenesis of these two diseases. In general, it is very difficult to define the interaction between

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mental factors and the diseases. However due this type of skin diseases are visible and are accompanied by a very uncomfortable itch, individuals have a difficulty in accepting the disease and its persistant and repetitive features.

Materials and Methods

In this study, we investigated the cases of LSC and PN in 63206 patients who applied to the outpatient clinic of the Dermatology Department of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine between 01.11.2007 and 01.12.2011. The informed consent of the patients were taken beforehand. Approval of the Cerrahpasa Medical Faculty Ethics Commitee was taken (13.03.2012-B.30.2.IST.0.30.11.06/108).

In patients with LSC or PN; frequency, age, gender and the distribution of the disease according to months of application were taken into account.

Statistical Analysis

The data were recorded in a computer data entry program based on the International Statistical Classification of Diseases and Related Health Problems (ICD) diagnostic code system and were retrospectively reviewed. The data were evaluated by statistical study.

Statistical analyzes were performed using Statistical Package for the Social Sciences V.15 and Number Cruncher Statistical System 2007 programs. $P<0.05$ was considered statistically significant. Chi-square test was applied in the analyzes and frequency tables and descriptive statistics were used.

Results

In this section, the findings were evaluated separately for LSC and PN.

Lichen Simplex Chronicus

A total of 63,206 patients who admitted to Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine of Dermatology between 01.11.2007-31.12.2011, 1.225 (1.94%) of them were diagnosed with LSC. The mean age of the patients was 46.37±16.4 (0-88 years) years. These patients with the diagnosis of LSC were divided into nine groups according to their age. The age group with the highest frequency was the 50-59 age group and second most frequent was the 40-49 age group. The distribution of the disease by age was found to be statistically significant ($p<0.05$). Of the 1,225 patients diagnosed, 361 (29%) were male and 864 (71%) were female. The ratio of female patients bearing the disease was significantly higher than the male patients ($p<0.05$).

Gender distribution among the patients were analysed and it was determined that the number of women in all age groups was higher than the number of men. The difference between the gender distribution of this disease in terms of age groups between men and women ($p=0.205$) was found to be statistically insignificant. Gender distribution by age groups in LSC is shown in Table 1.

The patients were also evaluated according to their application months. Between 01.11.2007-31.12.2011, the patients were admitted to our outpatient clinic mostly in December, January and February. It was found that the frequency of the disease varied seasonally ($p<0.05$). The distribution of patients according to the months and seasons is shown in Figure 1.

A total of 1,225 patients entered the outpatient clinic 1,476 times. The average frequency of a patient with LSC applying to our outpatient clinic is 1.2 times a year.

Prurigo Nodularis

Between the dates of 01.11.2007-31.12.2011, out of 63,206 patients who applied to Cerrahpasa Medical Faculty Department of Dermatology, 90 were diagnosed as PN (0.14%). The mean age of the patients diagnosed with PN was 45.22±19 years.

PN was found to be most frequent in the third decade, and second most frequent in the fifth decade. The distribution of disease by age was found to be statistically significant ($p<0.05$).

Of the 90 patients diagnosed, 32 (36%) were male and 58 (64%) were female. The ratio of female patients in the disease was significantly higher than the male patients ($p<0.05$).

Gender distribution was also evaluated separately among the patients according to age groups. We found that the number of women in the 30-39 and 50-59, 60-69 age groups were higher compared to the number of men. There was no statistically significant difference between the sex distribution of this disease and the age groups among women and men ($p=0.475$). Gender distribution by age groups is shown in Table 2.

The patients with PN were examined according to their application months and seasons. We found that more patients applied to our clinic in autumn compared to other seasons. However, seasonal distribution of the disease was not statistically significant ($p=0.107$). The distribution of patients by application months is shown in Figure 2.

The patients with PN were examined in the period between 01.11.2007-31.12.2011; it was found that a total of 90 patients entered the clinic 111 times. On average, a patient with PN was admitted to our outpatient clinic 1.2 times a year.

Discussion

LSC is a disease characterized by hyperpigmented and depigmented plaques due to chronic pruritus and friction. It is grouped under

Table 1. Gender and age distribution of the patients with lichen simplex chronicus

			Gender		Total
			Male	Female	
Age	0-9	Frequency	0	6	6
		%	0%	7%	5%
	10-19	Frequency	19	32	51
		%	5.3%	3.7%	4.2%
	20-29	Frequency	42	119	161
		%	11.6%	13.8%	13.1%
	30-39	Frequency	56	159	215
		%	15.5%	18.4%	17.6%
	40-49	Frequency	81	183	264
		%	22.4%	21.2%	21.6%
	50-59	Frequency	75	195	270
		%	20.8%	22.6%	22.0%
	60-69	Frequency	51	104	155
		%	14.1%	12.0%	12.7%
	70-79	Frequency	29	46	75
		%	8.0%	5.3%	6.1%
	80-89	Frequency	8	20	28
		%	2.2%	2.3%	2.3%
Total		Frequency	361	864	1225
%		100.0%	100.0%	100.0%	

Table 2. Gender and age distribution of the patients with prurigo nodularis

			Gender		Total
			Male	Female	
Age	0-9	Frequency	1	1	2
		%	3.1%	1.7%	2.2%
	10-19	Frequency	2	1	3
		%	6.3%	1.7%	3.3%
	20-29	Frequency	3	11	14
		%	9.4%	19.0%	15.6%
	30-39	Frequency	6	14	20
		%	18.8%	24.1%	22.2%
	40-49	Frequency	6	8	14
		%	18.8%	13.8%	15.6%
	50-59	Frequency	6	12	18
		%	18.8%	20.7%	20.0%
	60-69	Frequency	1	6	7
		%	3.1%	10.3%	7.8%
	70-79	Frequency	5	3	8
		%	15.6%	5.2%	8.9%
	80-89	Frequency	2	2	4
		%	6.3%	3.4%	4.4%
Total		Frequency	32	58	90
%		100.0%	100.0%	100.0%	

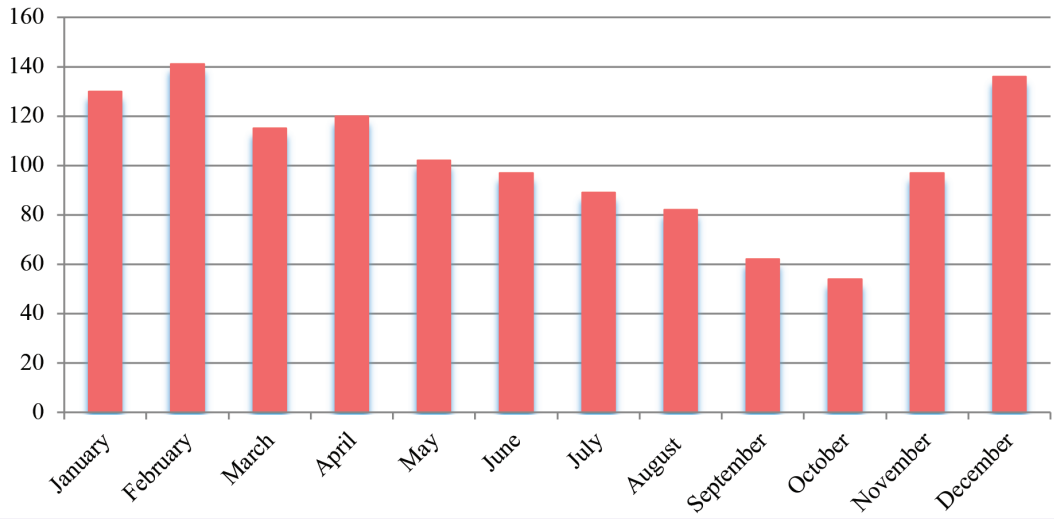

Figure 1. The distribution of lichen simplex chronicus patients according to the months

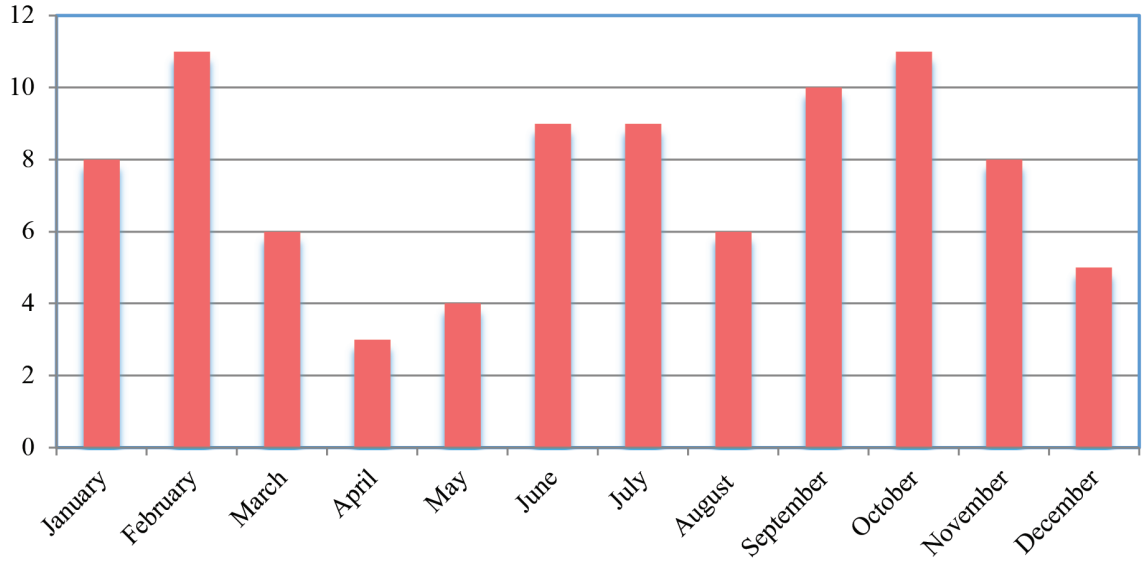

Figure 2. The distribution of prurigo nodularis patients according to the months

psychocutaneous dermatoses. The disease usually starts insidiously and slowly, the main symptom is paroxysmal pruritus. A strong feeling of itching and a sense of relief as it scratches are the most common symptoms. Since there is no definite cure for the disease, patients suffer from LSC for a long time [1,2,3,4].

PN is a chronic skin disease that manifests itself with severely pruritic papules and nodules. The lesions may be located at any part of the body; however there is a predeliction for extensor aspects of extremities, face and trunk. Psychogenic factors such as stress, depression and anxiety are common etiologic factors for both LSC and PN [5,6,7,8].

Literature was reviewed for both of the diseases in English and in Turkish; however an epidemiologic study and source was not found. In this retrospective study, we evaluated the LSC and PN patients that applied to our outpatient clinic; the parameters were the disease frequency, average age, age distribution, sex distribution, month and season of application and the frequency of applying to the outpatient clinic. A total of 63,206 patients with the matching ICD codes were included in this study. Of these patients, 1.225 were diagnosed with LSC and 90 were diagnosed with PN.

Among the total number of patients that applied to our outpatient clinic 1.94% were diagnosed with LSC and 0.14% were diagnosed with PN. LSC is considered to be a common disease according to the

previous literature, although a definite prevelance and incidence was not calculated. Compared to LSC, PN is a rarer disease [1,5,6,9]. However, in our opinion, the prevelance that was calculated in this study is an underestimation; it projects the prevelance among the outpatients clinic but not the general population.

The average age of LSC patients is 46.37±16 (0-88) and the average age of PN patients is 45.22±19 (0-90). Although a definite age range was not described in literature, most of the studies show that the diseases are seen in the middle age population [1,10]. Our study showed similar results. LSC is seen most commonly in the range of 50-59 years, second most commonly in 40-49. PN is seen most commonly in the range of 30-39, second most commonly in 50-59. The age distribution was statsitically significant. The disease is seen more frequently after the age of 40. This might be due to the increased stress due to increasing responsibilities.

In terms of gender differences, women are affected more both in LSC and PN. LSC has a prevelance of 71% in women and 29% in men. PN has a prevelance of 64% in women and 36% in men. These findings are similar to literature [1,2,5,7,9,11]. Both of the diseases are seen more frequently in female patients. Stress and anxiety are common etiologic factors in both of the diseases [12,13,14,15]. We believe that this relationship might be due to the male dominant and supressive enviroment against women in Turkey. Stress, if unexplored, may lead to somatisation. Due to the supressive enviroment, women may not be able to show their stress and thus somatisize subconsciously. On the other hand, men are more expressive and have less somatizising symptoms. Furthermore, women have a greater tendency to apply to the outpatient clinics.

In terms of age groups, from 0 to 90 years of age, LSC is seen more commonly in women than in men, in every age group. PN is also seen more frequently in women in every age group from 0 to 90. There is no statistical difference in age related gender differences since the diseases are seen more frequently in women in every age group.

In terms of seasonal differences, LSC patients apply to the outpatient clinics more frequently in december, january and february, i.e. during winter. On the other hand, PN patients apply to the clinic more frequently during autumn. Seasonal differences were found to be statistically significant for LSC patients; however, there is no such difference in PN patients, whşch might be related to the smaller sample size. Again, there is no study about the seasonal differences in literature. During wintertime, humidity decreases and wind increases; this leads to xerosis cutis, which in turns lead to the itch and scratch cycle and thus increased LSC lesions [15,16]. Furthermore, social isolation increases during wintertime and this leads to decreased experession of stress and increased somatization. On the contrary, during summertime, sress is relatively decrased and the prevelance of the diseases decreases. In short, both LSC and PN are seen more frequently during wintertime; however, a definite distinction can not be made since both of the diseases are chronic.

Overall, the yearly average of outpatient clinic applications for both of the diseases was 1.2 times, according to the five years data.

In epidemiologic studies, it is important to describe if the study is clinic based or population based. Our study was based on the outpatient clinic applicants and thus is clinic based. Further more, as our clinic is a university hospital, we are a referral center. Additionally, it is important to specify the age distribution of the applicants. Our patients are usually adults and thus children are under-represented in this patient group. Our study was a retrospective study based upon the definitive diagnosis of these two diseases by dermatologists. Even though this study incorporated a long time interval and many patients, prospective studies on this topic would lead to more population-based results.

Study Limitations

The results were based upon the retrospective evaluation of the patients that applied to the outpatient clinic of Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine Dermatology Deparment. Further multicenter studies with longer follow up intervals and greater sample sizes are needed in order to reach nation-based conclusions.

Conclusion

In this retrospective study, we evaluated the LSC and PN patients that applied to our outpatient clinic; the parameters were the disease frequency, average age, age distribution, sex distribution, month and season of application and the frequency of applying to the outpatient clinic.

The frquency of LSC was 1.94% and PN was 0.14%. The average age of LSC parients was 46.37±16 and that of PN patients was 45.22±19. These data are in compliance with previous literature.

In terms of gender distribution, both of the diseases affect women more frequently. LSC has a 71% women and 29% male prevenance. PN has a 64% women and 36% male prevelance. The results are in compliance with previous literature. Age based gender distribution was statistically insignificant.

LSC is seen more frequently during winter and PN is seen more frequently during autumn. This difference was statistically significant for LSC but insignificant for PN.

The yearly average of out-patient clinic application for both diseases was 1.2.

Ethics

Ethics Committee Approval: Approval of the Cerrahpasa Medical Faculty Ethics Commitee was taken (13.03.2012-B.30.2.IST.0.30.11.06/108).

Informed Consent: The informed consent of the patients were taken beforehand.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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Juvenile Xanthogranuloma on the Auricle: Unusual Case Report and Clinico-Dermoscopic Correlation

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ABSTRACT

Juvenile xanthogranuloma (JXG) is a rare and benign proliferative disease, which is the most common form of the non-Langerhans group of histiocytic disorders. We describe a case of JXG with a rather unusual clinical presentation and highlight the importance of using dermoscopy (a "setting sun" pattern) as a non-invasive adjuvant tool in the diagnosis of JXG in a female patient presenting with an eight-month history of multiple auricular nodules. Due to it being a self-regressing disorder, accurate diagnosis of JXG by dermoscopy is crucial and confers advantages by avoiding unnecessary invasive procedures and aggressive treatment for children.

Keywords: Juvenile xanthogranuloma, Dermoscopy, "Setting sun" Pattern

Introduction

Juvenile xanthogranuloma (JXG) is a rare and benign proliferative disease, which is the most common form of the non-Langerhans group of histiocytic disorders [1,2]. It was first described by Adamson [3] in 1905, who presented a child that developed numerous yellow-white papules on the body in the first two weeks of life. However, widespread recognition of an entity resembling JXG occurred in 1954 with Helwig and Hackney [4]. JXG appears predominantly in the childhood period, especially in the first two years of life, despite there being adult cases. It is usually characterized by one or multiple yellow-pink cutaneous nodules and less often additional lesions can involve extracutaneous tissues.

The etiopathogenesis of xanthogranuloma is not exactly known, but the disease is believed to be a reactive granulomatous process against undetermined physical or infectious stimuli rather than neoplasia. The prognosis of patients with cutaneous involvement is excellent, with spontaneous regression, but in some cases atrophic residual hyperpigmented scars may remain. The diagnosis of JXG is clinically based and supported by histopathology. The dermoscopic examination also provides clues and allows distinguishing from other possible diseases.

We describe a case of JXG with a rather unusual clinical presentation and highlight the importance of using dermoscopy (a "setting sun" pattern) as a non-invasive adjuvant tool in the diagnosis of JXG in a female patient presenting with an eight-month history of multiple auricular nodules. Due to it being a self-regressing disorder, accurate diagnosis of JXG by dermoscopy is crucial and confers advantages by avoiding unnecessary invasive procedures and aggressive treatment for children.

Case Report

We report the case of a seven-year-old female patient, presenting with non-tender, mobile yellowish-red multiple nodules over the

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helical rim of her left ear for eight months (Figure 1). Her personal and family histories revealed no relevant findings. In addition, she had no history of any trauma or infection. On dermatological examination, the left ear was remarkable for three well-defined yellow-red nodules, including the largest one 10 mm x 5 mm over the helical rim. The nodules were shiny, with some evidence of telangiectasia and scaling located centrally. There was no ulceration of the overlying skin, it did not appear to be fixed and no enlarged lymph nodes were palpated.

On dermoscopy, we observed a red-yellow structureless center with a pale erythematous halo, characterizing the "setting sun" pattern, as well as linear and branched telangiectasias, which are characteristic features of JXG (Figure 2). Although these were typical dermoscopic findings for JXG, due to clinical features of the lesions, the case was compatible with angiolymphoid hyperplasia with eosinophilia. Therefore, we performed a punch biopsy. Histopathologic examination revealed mild hyperkeratosis and acanthosis in the epidermis and histiocytic infiltrate in the dermis, as well as an eosinophilic infiltrate with a few lymphocytes mixed with multinucleated Touton giant cells. Touton giant cells were scattered throughout the lesion in association with moderate numbers of lymphocytes and histiocytes with a foamy cytoplasm (Figures 3, 4). There was no malignant appearance, such as nuclear atypia, an increased number of nucleoli or necrosis.

In the immunohistochemical analysis of the lesional cells, they were positive for CD68, but negative for S100, CD1a, and langerin. Based on clinical examination, dermoscopic and histological findings, a diagnosis of JXG was made. Complete blood count and biochemical parameters were investigated for possible systemic involvement. An ophthalmic exam was also conducted for ocular JXG since this is the most common type of extracutaneous JXG. Finally, all blood tests were in the normal range and there was no ocular involvement. The patient was followed up due to the self-healing nature of JXG.

Discussion

The term "histiocyte" refers to large white blood cells resident in tissues, including Langerhans cells, monocytes-macrophages and dendritic cells. This group of diseases has generally been divided into Langerhans cell histiocytosis (LCH) and non-Langerhans

Figure 1. Non-tender, mobile yellowish-red multiple nodules over the helical rim

Figure 2. A red-yellow structureless center with a pale erythematous halo and linear and branched telangiectasias

histiocytosis (non-LCH). Langerhans cells are specialized dendritic cells found in the skin and mucosa. In contrast, non-LCH is thought to be derived from the monocyte-macrophage lineage. In LCH there is a predominance of CD1a, langerin, and S100 positive cells. Positivity of histiocytic markers such as CD68, and negativity for CD1a, langerin, and S-100 protein indicate the origin of non-Langerhans cells. JXG is the most common form of non-LCH.

The pathogenesis of JXG remains unclear. It is most likely a reactive granulomatous reaction of histiocytes to unidentified stimuli rather than a neoplastic process. It has been reported that JXG as a disease in which the macrophage response may occur from a non-specific injury [5,6,7,8]. It has been reported that JXG represents 0.5% of all pediatric tumors [2]. The disease usually appears in the first two years of life: 5 to 17% are present at birth and 40 to 70% appear during the first year [5,6]. Despite the term "juvenile", 10% of cases manifest in adulthood [6].

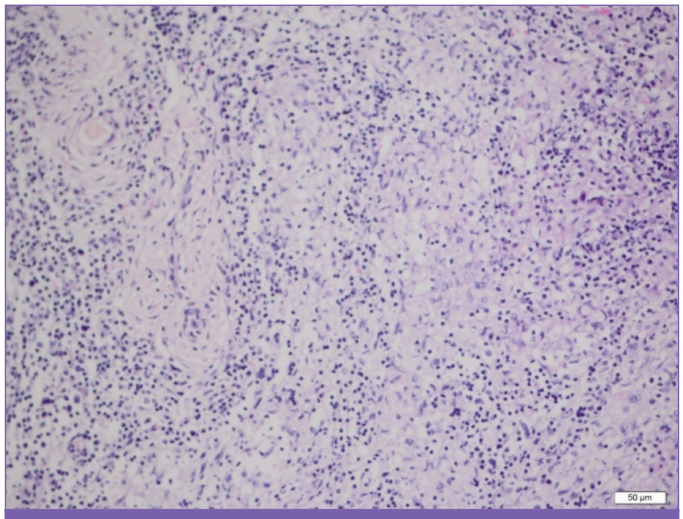

Figure 3. Epitheloid and foamy histiocytes in groups of polymorphic mature lymphocytes in the dermis (hematoxylin and eosin, x100)

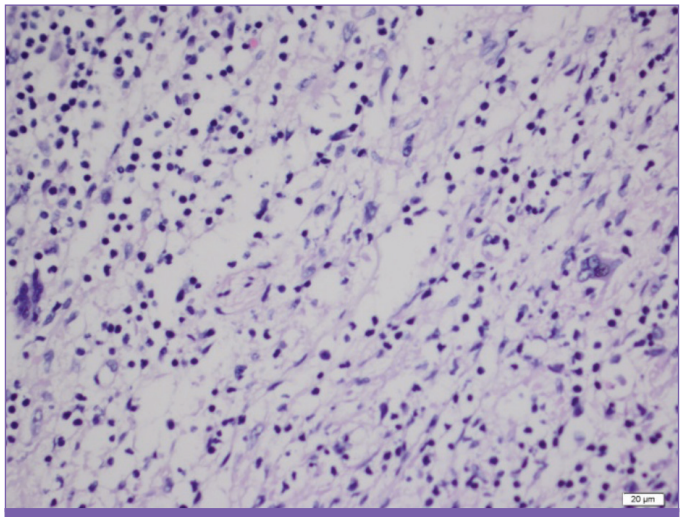

Figure 4. Touton type and foreign body type multinuclear giant cells (hematoxylin and eosin, x200)

JXG is characterized by one or multiple 2 to 7 mm firm, elastic, rounded papules or nodules that initially start as pink-brown and evolve to a xanthomatous yellowish appearance with erythematous halos. Superficial telangiectasias or brownish color may be visible in later stages [1,6,9]. Although JXG mostly occurs as a solitary lesion, multiple JXG may occur in 7 to 10% of the cases, specifically in infants and males [2,6,7]. Skin is the most commonly involved organ for JXG and less often additional lesions may be seen in the deeper soft tissue and visceral organs. Cutaneous JXG mostly occurs in the head and neck, followed by the trunk, limbs and palmoplantar region [6,7,8]. Clinical differential diagnosis of JXG includes LCH, mastocytoma, angiolymphoid hyperplasia with eosinophilia, Spitz nevus, and other xanthomatous conditions (papular and tuberous xanthoma, xanthoma disseminatum and eruptive xanthomas).

Dermoscopy has an important role in the non-invasive diagnosis of JXG. Under polarized dermoscopy, the four most commonly dermoscopic features of JXG include a setting sun pattern; clouds of pale yellow globules; a whitish streak; and branched and/or linear vessels [9,10]. Moreover, clouds of pale yellowish globules represent lipid-laden xanthomatous histiocytic infiltration in the upper dermis, while a discrete pigment network and whitish streaks indicate areas of fibrosis. The pattern described as setting sun is characterized by a yellow-orange central area, which may show areas of white-yellow clouds and an erythematous halo. JXG has three stages: (i) early evolutionary stage, (ii) fully developed stage, and (iii) late regressive stage. The main observed dermoscopic feature of JXG is the setting sun appearance and surrounding linear or branched vessels, which can be appreciated in the three stages with the whitish streak becoming more prominent and surrounding erythema decreases in the late regressive stage. Clouds of pale yellow globules become more evident in the advanced stages due to the transformation of vacuolated cells to xanthomatous cells, becoming more yellowish across the three stages [11].

Conclusion

We describe a case of JXG with a rather unusual clinical presentation and highlight the importance of considering this entity in the differential diagnosis of benign soft tissue tumors of the ear. There are only occasional case reports of xanthogranuloma involving the auricle. Due to the self-regressing and benign nature of the disease, and in order to avoid unnecessary surgical procedures, dermoscopy is a useful noninvasive diagnostic technique for clinicians. In addition, follow-up with dermoscopy may prevent invasive procedures due to self-regression and the benign nature of the disease.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: I.G.İ., Ö.K., Design: I.G.İ., Ö.K., Data Collection or Processing: P.C., Analysis or Interpretation I.G.İ., Ö.K., F.E.T., İ.B., P.C., H.M.E., Literature Search: I.G.İ., F.E.T., İ.B., Writing: I.G.İ.

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Treatment of Psoriasis After Initiation of Nivolumab Therapy for Metastatic Malignant Melanoma: An Ancient Drug Revisited

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Dear Editor,

Checkpoint inhibition can cause various immune-related adverse events in any organ but skin toxicity occurs most frequently [1]. We report *de novo* development of psoriasis vulgaris in a patient receiving nivolumab for treatment of metastatic melanoma which was controlled with sulfasalazine (SSZ).

A 69-year-old male was initiated with nivolumab 3 mg/kg every two weeks for metastatic BRAF-negative melanoma of the back. The patient's medical history was notable for arterial hypertension and dyslipidemia for which he has been medically treated. There was no personal or family history of psoriasis. One week after the fourth cycle of nivolumab, asymptomatic, sharply bordered, erythematous and scaly plaques were seen on the the anterolateral aspects of shins, dorsa of hands, feet, scalp, and trunk (Figure 1a). A skin biopsy revealed psoriasiform epidermal hyperplasia with prominent orthohyperkeratosis, and mounds of parakeratosis, containing neutrophils. The suprapapillary epidermis was thinned, and there were collections of neutrophils in the spinous layers which were consistent with psoriasis (Figure 1b, 1c). The patient had psoriasis area and severity index score of 12. He did not have psoriatic arthritis. The patient's melanoma improved with nivolumab therapy but the skin lesions increased. As the patient was refractory to topical therapies, he was switched to acitretin but experienced severe side effects (hyperlipidemia), so therapy

Figure 1. a) Psoriatic lesions on the hands

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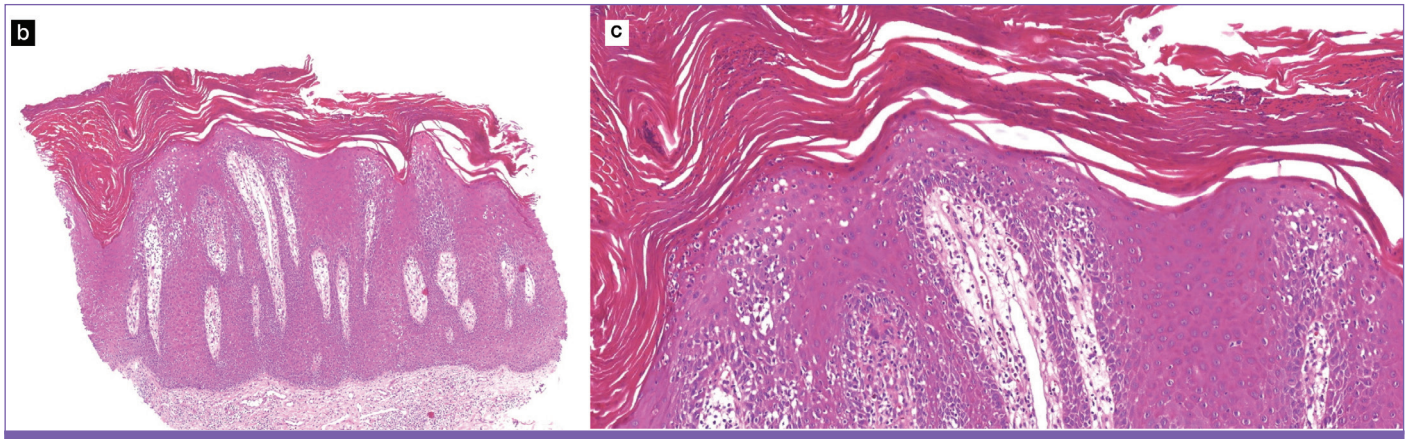

Figure 1. b, c) Psoriasiform epidermal hyperplasia with mounds of parakeratosis and collections of neutrophils in the upper spinous layers (hematoxylin and eosin Å~40; hematoxylin and eosin Å~200)

was discontinued at the end of two months. Methotrexate was initiated, but led to liver toxicity a short period of time. Due to numerous drug failures and the high cost of biologic therapies, we decided to start SSZ (2 gr/day). SSZ therapy controlled the psoriatic lesions with no side effects. Currently, the patient is in remission and his skin lesions are under control.

Nivolumab can give rise to a variety of cutaneous side effects that may influence decisions about the therapy. In our patient psoriatic lesions developed nine weeks after nivolumab therapy with no prior history of psoriasis. Increased Th1 and Th17 responses induced by nivolumab are important for its' an antitumor effect but may unmask a psoriatic reaction in a predisposed individual [2].

SSZ induces few side effects and has been used to treat of psoriasis and psoriatic arthritis with variable success. SSZ has been shown to decrease cytokine release, including tumor necrosis factor-alpha (TNF-α) [3]. Blocking TNF-α has been demonstrated to prevent checkpoint inhibitor induced colitis in a genetically susceptible animal model [4]. This is consistent with human observations inflammatory arthritis [5] induced by immune checkpoint inhibitors that was treated successfully with TNF-α inhibitors. In the genetically susceptible animal model, not only did blocking TNF-α reduce colitis but it also increased the anti-tumor activity of anti-cytotoxic T lymphocyte-associated antigen-4 and PD-1 antibodies. Therefore, if moderate or severe psoriatic lesions develop during nivolumab therapy, SSZ therapy cannot only treat the skin lesions but may also increase nivolumab's anti-tumor effect.

If dermatologic side effects occuring in patients receiving checkpoint inhibitor therapy that are not severe, therapy should not be stopped. For the treatment of moderate and severe psoriatic conditions during nivolumab therapy, we recommend SSZ, as it induces minimal side effects and may allow doses of nivolumab to be safely increased.

Ethics

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

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Authorship Contributions

Surgical and Medical Practices: G.O., K.N.P., C.D., Concept: G.O., K.N.P., C.D., Design: G.O., K.N.P., C.D., Data Collection or Processing: G.O., K.N.P., C.D., Analysis or Interpretation: G.O., K.N.P., C.D., Literature Search: G.O., K.N.P., C.D., Writing: G.O., K.N.P., C.D.

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