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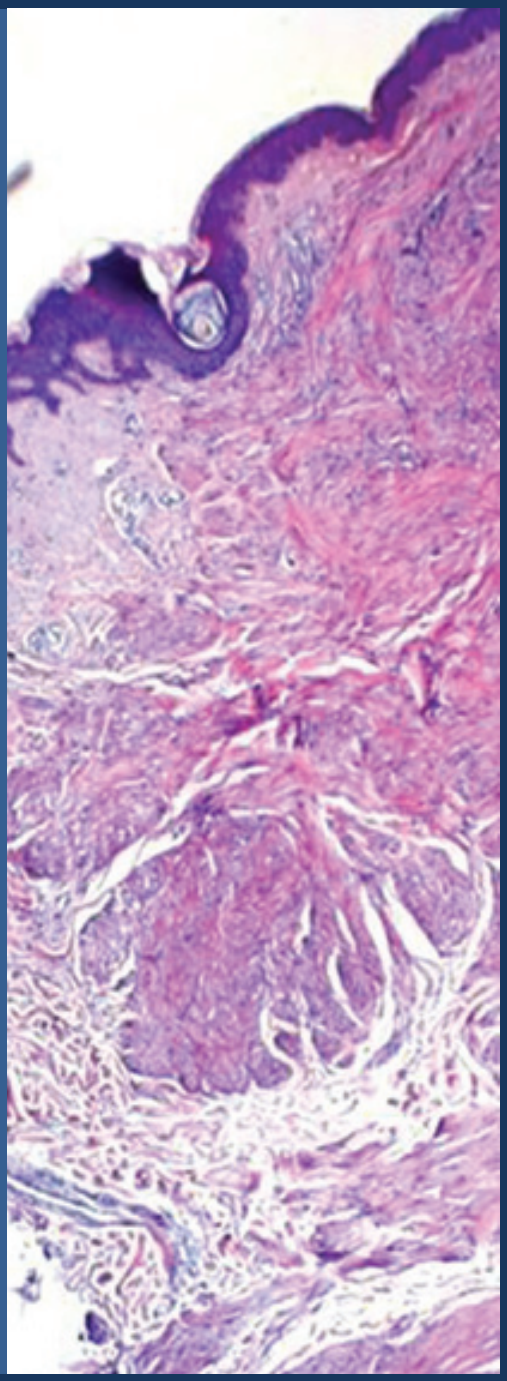

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CASE REPORTS

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Autoimplantation – An Immunological Treatment For Multiple Warts

Abhineetha HOSTHOTA[1], Bindushree REDAPPA[1], Savita KOREGOL[2]

[1]Department of Dermatology, The Oxford Medical College, Hospital & Research Centre, Bangalore, India
[2]Department of Dermatology, Al Ameen Medical College and Hospital, Bijapur, Karnataka, India

Correspondence: Abhineetha Hosthota, E-mail: abhineethahosthota@yahoo.com

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Abstract

Introduction. Warts are benign epithelial lesions that involve skin and mucosa. Successful management depends on the patient's immunity, site and type of wart. In spite of huge therapeutic armory available, no treatment has been found to be effective so far. **Objective.** To evaluate the effectiveness of autoimplantation in the management of multiple warts. **Material and Methods.** This is a hospital based prospective study of forty patients with multiple warts. A prospective, hospital-based study included forty cases of multiple warts for autoimplantation. Resolution of warts within three months was taken as complete clearance; the follow up of any recurrence lasted six months. **Results.** The majority of patients were males (69.7%), belonging to 21–30 years age group (57.6%). Complete resolution was observed in 25 patients, partial response was achieved in 5 patients and there was no response in 3 patients. The majority of patients did not have any complication or recurrence **Conclusion.** Autoimplantation is a simple, daycare, effective procedure. It provides resistance by inducing cell mediated immunity and also prevents recurrence to a great extent.

Key words: Warts; Transplantation, Autologous; Skin Transplantation; Recurrence; Treatment Outcome; Immunotherapy

Introduction

Viral warts are benign lesions involving epithelium of skin and mucus membrane caused by different strains of Human Papilloma Virus (HPV) (1). The clinical presentation of warts is variable and depends on HPV strain, site of infection and immunity of the patient. The most common clinical presentations are verruca vulgaris, verruca plana, palmoplantar warts and genital warts (condyloma acuminata). This is a common dermatologic complaint, which spreads by direct skin-to-skin contact, fomites or autoinoculation (2).

The virus enters through abrasions on the skin surface and remains latent in the basal cell layer of the epidermis cell for 1 to 8 months (3). The process of virus replication produces proliferation of prickle cells which alters the character of the epidermis, resulting in the visible warty appearance of the verrucae. However, unlike many viruses, HPV infection spreads through shedding of infected epithelial cells from the surface of the skin. So, there is limited release of viral proteins to the circulating dendritic cells, causing inadequate antigen presentation to the immune system. Furthermore, HPV proteins also encode specific functions to inhibit immune responses by inducing specific anti-inflammatory mechanisms by activating T suppressor cells (3, 4). Due to the above pathomechanism warts are usually multiple and recalcitrant causing psychological distress to the patients and a therapeutic challenge for the dermatologists (5).

Previous literature has stated that warts resolve spontaneously in 40% of cases and others need medical or surgical intervention (5). Multiple treatment modalities are available for treating warts which destroy conspicuous infected tissue but there is no one such treatment which targets inconspicuous infected lesions to ward off further recurrence. Majority of treatments are direct, such as cryotherapy by liquid nitrogen, electrosurgery, lasers and photodynamic therapy. Numerous modes have been used to activate the immunological response such as oral levamisole, topical imiquimod and 5-FU, and intralesional immunotherapy with tuberculin antigen, MMR vaccine, BCG vaccine (6).

Rapid proliferation of wart in HIV-infected patients, solid organ transplant recipients and

epidermodysplasia verruciformis is due to low T-lymphocyte cell count. Significant epidermal and dermal influx of CD4+ lymphocytes is seen in a spontaneously regressing wart. The above observations suggest that wart proliferation is controlled by cell-mediated immunity (7, 8). As the immune system seems to play an important role in the control of wart, there is a new inclination towards the use of immunotherapy. The current study was conducted to find autoimplantation as an effective immunotherapeutic approach in the treatment of multiple viral warts.

Material and Methods

This was a prospective, hospital-based study conducted at Dermatology Outpatient Department, The Oxford Medical College, Hospital & Research Center (Bangalore, India), over a period of six months. The analysis included forty consecutive cases of warts in the patients (whose age ranged from 20 to 50 years) who did not have any other skin disease and who gave their consent to participate in this study. Patients with multiple (> five warts), verruca vulgaris, verruca plana and palmoplantar warts were enrolled. Pregnant, lactating mothers, immunocompromised individuals were excluded from the study. The patients were assessed monthly; resolution of all warts within 3 months was taken as complete clearance. The patients were followed up for six months after clearance of lesions for any recurrence. Institutional ethical clearance was granted.

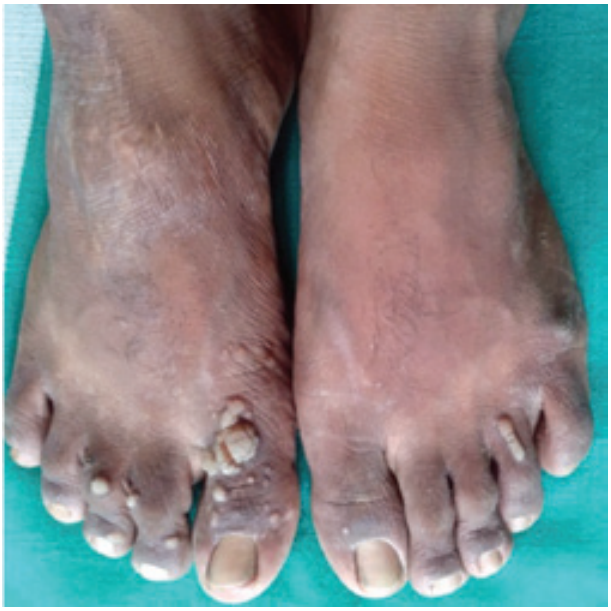


Figure 1. Before autoimplantation

Autoimplantation Methodology

The enrolled patients were prepared after testing for lignocaine 2% sensitivity. The wart of at least 5 mm size was cleansed with povidine iodine solution and excised under local anaesthesia (2% lignocaine). The wound was then cauterized at borders and sealed with Povidine iodine ointment. The excised wart tissue was immersed in normal saline for 5 minutes, minced into tiny pieces. A small incision (1 cm) was made in the anterior aspect of mid thigh under local anaesthesia. A dermal pocket was created with an artery forceps and the minced wart tissue was placed and pushed under the skin, away from the incision site. The incision was then sutured using Prolene and dressed. Tablet Azithromycin 500 mg was given for 5 days and the suture was removed on the 10th day. The patients were reviewed every four weeks for 3 months. Every follow up visit was aimed at observing the regression in size and number of warts every month, complete resolution of warts in 12 weeks, any recurrence of lesions during 6 months all in order to analyze the efficacy of autoimplantation.

Results

Out of 40 enrolled cases, 7 were lost for follow-up and 33 patients were available for procedure and evaluation **(Flow chart).** Majority of the subjects were males (69.7%), mostly belonging to the age group of 21–30 years (57.6%). Mean duration of disease was 14.72±4.12 months and number of lesions was 17.6±5.6 on average. Majority of study subjects were illiterate from low socioeconomic strata with rural background **(Table 1)**. All of them had multiple wart lesions **(Figure 1)**, 20 had verruca vulgaris, 8 had verruca plana and 5 with palmoplantar warts **(Pie Chart)**.

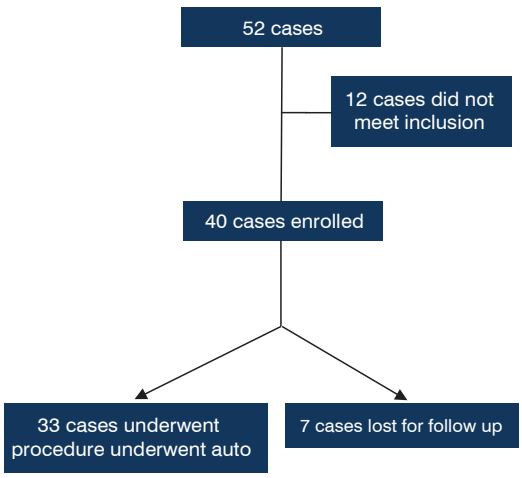
After 4 weeks of autoimplantation, 5 cases (15.1%) achieved complete resolution of lesions at the earliest and partial improvement was observed in 11 patients (33.3%). Complete resolution of warts within 12 weeks was observed in 25 cases (75.7%) **(Figure 2).** However, 5 patients had partial response and

Table 1. Sociodemographic profile of patients

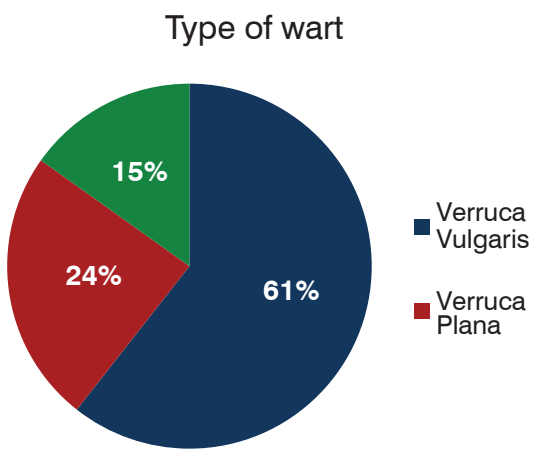
Variables		n = 33	%
Age (years)	Mean	21.10±4.35	57.6
	21–30	19	24.2
	31–40	08	18.2
	41–50	06	00.0
	>50	00	
Gender	Male	23	69.7
	Female	10	30.3
Place	Rural	28	84.8
	Urban	05	15.2
Socioeconomic status	Low	16	48.5
	Middle	13	39.4
	High	04	12.1
Education	Illiterate	21	63.6
	Literate	11	33.3
Occupation	Factory	13	39.4
	Agriculture	17	51.5
	Student	05	15.1
	Homemaker	08	24.2
Family history	Present	02	6.0
	Absent	31	93.9

Table 2. Follow up Visit

Clinical response	4 weeks	%	8 weeks	%	12 weeks	%
No response	11	33.3	07	21.2	03	9.1
Partial response	17	51.5	19	57.6	05	15.1
Complete response	05	15.1	07	21.2	25	75.7



Flow chart



Pie Chart

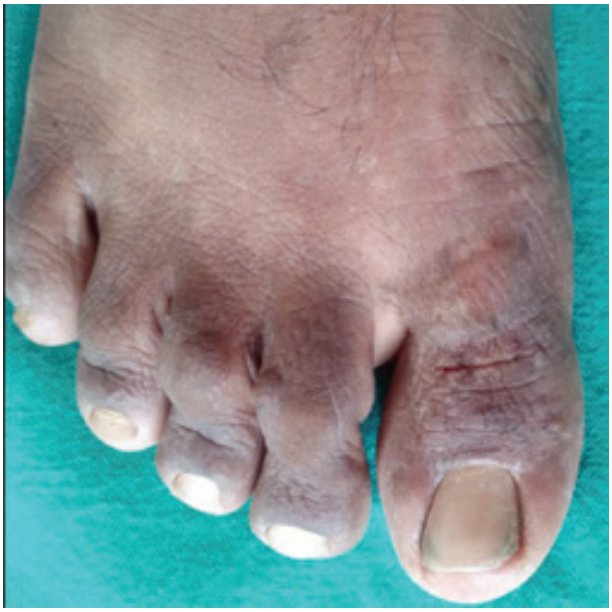


Figure 2. After autoimplantation

3 did not show any response at the end of 12 weeks **(Table 2).** During 6 months of observation we noticed 3 patients with recurrence of lesions at different sites.

Majority of patients did not have any complication. One patient noticed pus discharge at the site of implantation which was later treated with systemic antibiotics. Hyperpigmentation at the site of resolution of warts was noted in 3 patients.

Discussion

Management of warts is still a challenge and there is a dearth of ubiquitous consensus about therapeutic modalities in the literature. Warts have been exasperating for patients and clinicians for ages. They can greatly affect a patient's quality of life by causing embarrassment, fear of negative appraisal by others and frustration due to persistence or recurrence (9). One of the most challenging issues in the treatment of warts is the high recurrence rates (up to 30% or more), as the existing modalities of treatment do not eradicate the viral reservoir present in the adjacent tissues (10).

Common incidence of warts with its clinical significance, absence of specific antiviral therapy against HPV, variable efficacy of the available therapeutic modalities, high incidence of adverse effects and recurrence rates, particularly with the use of destructive approaches are the few factors which has paved the way for immunological therapeutics against HPV (10). Autoimplantation has a focused effect on immune response to HPV which has drawn interest but the progress has been slow over a decade.

In our study, males outnumbered females with mean age of presentation being 21.10±4.35 years which is in concordance with previous studies (11, 12). Mean duration of illness was 14.72±4.12 months that being congruent with Lal et al, whereas Das et al. observed that the majority (47%) presented with warts within one year of appearance of lesions (12, 13). In the current study, the subjects had multiple warts; the majority of them had verruca vulgaris (61%) followed by verruca plana and a few had plamoplantar warts. Similarly Swaroop et al. and Lal et al. observed verruca vulgaris, palmoplantar warts and periungual warts in their study (11, 12).

There is vast armamentarium for management of warts depending on the site, size and number of warts and side effects are the factors to determine the appropriate treatment which includes ablative or immunomodulatory modalities. Although 50% of warts resolve spontaneously within 1 year and 66% will resolve within 2 years, it can persist for years causing physical discomfort and psychological trauma (14). The treatment modalities available for recalcitrant warts are cryotherapy, lasers, intralesional bleomycin and 5% imiquimod. Systemic retinoids, photodynamic therapy and topical sensitizers such as dinitriochlorobenzene (DNCB), squaric acid dibutylester (SADBE) and diphencyprone are reported to be effective for multiple lesions (15). In multiple warts on the palms and soles, destructive procedures are inappropriate and impractical (16). Studies have reported that intralesional immunotherapy has cleared distant warts without scarring, lower rate of recurrence and a high safety profile (17, 18). Combinations of treatment modalities have been tried with an average of 60.70% clearance in 3 months (5). Currently available destructive modalities may be painful, ineffective, expensive, associated with disfiguring scars and high recurrence rates (19).

Most of the treatments destroy affected tissues, either by cytotoxic or physically ablative mode of action. However, tissue damage alone may not be enough to produce the rel-

evant cytokines to destroy latent virus in the adjacent cells. Thus the absence or reduction of a cellular response may explain many unsuccessful treatments even in immune-competent individuals (4, 20). The possibility of spreading to the close contacts and other sites demands a permanent cure. The ideal treatment for warts should avoid recurrence/persistence /reinfection, induce lifelong immunity to human papilloma viruses (5). This can be achieved by exposing viral antigens to immune mediators thus producing local as well as systemic immunity against HPV. Immunotherapy helps clinicians to target remote warts, multiple warts and warts at inaccessible sites. The best way to combat HPV infection would be by developing specific immune response targeted against early viral proteins. One way of achieving this would be by autoimplantation, which leads to better presentation of viral antigens.

We observed complete clearance of warts in 75.7% of cases in 12 weeks. Previous studies on autoimplantation have reported clearance rates from 62.5% to 74.1% (11, 12, 15, 21). The lowest cure rates of 34.69% was reported by Gugle et al. (16). Partial clearance was noted in 15.1% of patients at the end of 12 weeks, a similar observation was made by Nischal et al. and Swaroop et al. (11, 21). In a study conducted by Gugle et al. 53.06% the patients had partial clearance of warts which is much higher than our observation (16). In our study 9.1% of patients did not show any response to autoimplantation. This may be due to the presence of different type of warts in the same patients. However, we had the lowest failure rate compared to previous studies (11–30%) (16). We did not find any significant association between duration, number/ site of warts at presentation and the outcome as reported by Lal et al. (12).

Autoinoculation leads to delayed hypersensitivity reaction to HPV antigens. There will be an alteration in cytokine profile, predominantly Th1 type, decreasing Th2 response. Th1 cytokines like TNF-α and IL-1 down regulate transcription of HPV genes whereas INF-γ and IL-2 stimulate cytotoxic T cells and natural killer cells to eradicate HPV infected cells. Thus CMI enables the body to recognize antigens, stimulates production of memory T cells against HPV and intensifies response mechanism to prevent recurrence (10).

Adverse effects noted in this study are purulent discharge and hyperpigmentation at the site of implantation was found in few patients. Erythematous nodule with discharge, keloids and hypopigmentation at the implantation site are the adverse events noted in previous literature (11, 12, 15). Of the patients who had complete clearance, three came with recurrence within 6 months follow-up period. This may be due to the presence of periungual warts in them. As in this technique, it is more likely that immunity against the same serotype is elicited (16). Das et al. reported 3.33% of recurrence after one year of autoimplantation (13). This is in contrast to findings of previous investigators who did not report any recurrence during follow-up (2, 12, 21).

Currently autoimplantation is not extensively practiced, which may be due to the lack of published research, and because clinicians prefer to utilize established treatment modalities such as cautery and cryotherapy. Autoimplantation has potential advantages such as treating distant, multiple warts in single sitting, difficult to treat areas like around eyes and periungual area. It is a simple, daycare procedure with promising efficacy and safety profile compared to other traditional therapies. The limitations of our study are short follow up period, and the fact that specific HPV type was not determined and immunity levels of cases before and after treatment were not assessed. There is scope for clinical groundwork to recommend standardized procedure with its efficacy and adverse effects.

Conclusion

Autoimplantation is an easy, day care, minimally invasive procedure which induces an immune response to aid in resolution of both treated and untreated warts. Every new trial on immune modification edges us closer to an effective and safe modality treatment of HPV. This is a promising modality of immunotherapy to be considered worthwhile to generate more randomized control trials data.

Abbreviations

HPV– Human Papilloma Virus
HIV – human immunodeficiency virus
DNCB – dinitriochlorobenzene
SADBE – squaric acid dibutylester

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Autoimplantacija – imunološki tretman za multiple *verrucae vulgares*

Sažetak

Uvod. Bradavice ili veruke su benigne epitelne lezije koje zahvataju kožu i sluznicu. Uspešno lečenje zavisi od imunskog odgovora pacijenta, lokalizacije i tipa bradavica. Uprkos mnogim terapijskim metodama, nijedan tretman do danas nije u potpunosti efikasan u sprečavanju recidiva. **Cilj.** Proceniti efikasnost autoimplantacije u lečenju multiplih veruka. **Materijal i metode.** Prospektivna, bolnička studija obuhvatila je četrdeset pacijenata sa multiplim bradavicama kojima je urađena autoimplantacija. Rezolucija veruka u toku od tri meseca smatrana je kao kompletan odgovor na terapiju. Pacijenti su praćeni tokom šest meseci u cilju registrovanja recidiva. **Rezultati.** Većina pacijenata bili su muškarci (69,7%), koji su pripadali starosnoj grupi 21–30 godina (57,6%). Potpuna rezolucija uočena je kod 25 pacijenata, delimičan terapijski odgovor kod pet, odsustvo efekta kod tri pacijenta, a sedam je izgubljeno iz praćenja. Većina nije imala komplikacije ili recidive. **Zaključak.** Autoimplantacija je jednostavan, efikasan postupak koji se sprovodi ambulantno. Obezbeđuje otpornost prema HPV virusima indukujući imunski odgovor posredovan ćelijama i u velikoj meri sprečava recidiv.

Ključne reči: Bradavice; Autologna transplantacija; Transplantacija kože; Recidiv; Ishod terapije; Imunoterapija

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Necrotizing Fasciitis: a Clinical Case and a Review of the Literature

Ivanka Danchova TEMELKOVA[1], Yordan Stoyanov MILEV[2], Zhasmina Krasimirova GARKOVA[1], Tsveta Ivanova KALINOVA[3], Zhenya Krasimirova DIMITROVA[3], Bogdana Dimitrova IVANOVA[1], Jana Stoyanova KAZANDJIEVA[4], Sonya Stoyanova MÁRINA[1]

[1]Department of Skin and Venereal Diseases, Medical Institute of the Ministry of Internal Affairs
[2]Department of Purulent-Septic Surgery, University Multi-Profile Hospital for Active Treatment and Emergency Medicine "N. I. Pirogov"
[3]Department of Infectious Diseases, Parasitology and Dermatovenereology, Medical University, Varna
[4]Department of Dermatology and Venereology, Medical University, Sofia

Correspondence: E-mail: Sonia Marina, E-mail: soniamarina1@yahoo.com

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Abstract

Necrotizing fasciitis is a soft tissue, life-threatening infection with a fulminant and often fatal course. Early diagnosis is usually delayed as the onset of the disease is often masked in the form of erysipelas or cellulite. The condition is characterized by necrosis of the skin, subcutaneous tissue and underlying fascia. We describe a case of a 42-year-old man with a complaint of erythema, fever and severe pain in his right leg 4 days before hospitalization. The patient was admitted and treated with a diagnosis of erysipelas. A few hours after admission, in connection with a drastic deterioration in the general condition and dermatological status, he was transferred to a purulent-septic ward with a fulminant picture of necrotizing fasciitis. Debridement and fasciotomy were performed successfully and timely. Good prognosis and survival in patients with NF correlate directly with the complex of measures. Appropriate antibiotics and intensive general support avoid massive systemic diffusion. Early and adequate surgical debridement and fasciotomy are associated with improved survival.

Key words: Fasciitis, Necrotizing; Soft Tissue Infections; Diagnosis; Signs and Symptoms; Debridement; Fasciotomy; Treatment Outcome; Antibacterial Agents

Introduction

Necrotizing fasciitis (NF) is an aggressive infection of the skin and soft tissues (SSTI) (1). It is also known as "flesh-eating disease" as it results in necrosis of muscle fascia and subcutaneous tissue (1, 2). The condition is life-threatening with a high mortality rate of nearly 70% (3). It most often affects the limbs, perineum and genitals (Fournier gangrene), and less often the chest or abdomen (2). No age or gender predilection has been observed (2). It is caused by toxin-producing, virulent bacteria (2, 3). NF usually progresses rapidly, within hours, and it is often associated with severe systemic toxicity to sepsis (4). The high death rate in patients with NF requires immediate assessment, antibiotic treatment, and surgical intervention (5, 6).

Case Report

A 42-year-old man was admitted to the University Clinic of Dermatology and Venereology complaining of severe pain in the area of the toes of the right foot. The complaints date back to four days before the admission with the appearance of fever, redness and difficulty in movement of the affected limb. Having been examined by a surgeon, the patient was given the treatment with oral antibiotic, compresses with ethacridine lactate, alcohol and ice was applied - without a satisfactory effect. Gradual deterioration occurred with increasing temperature and progressive redness of the foot and right lower leg. The patient was admitted in an impaired general condition and temperature of 37-37.5°C. He was hospitalized with the suspicion of erysip-

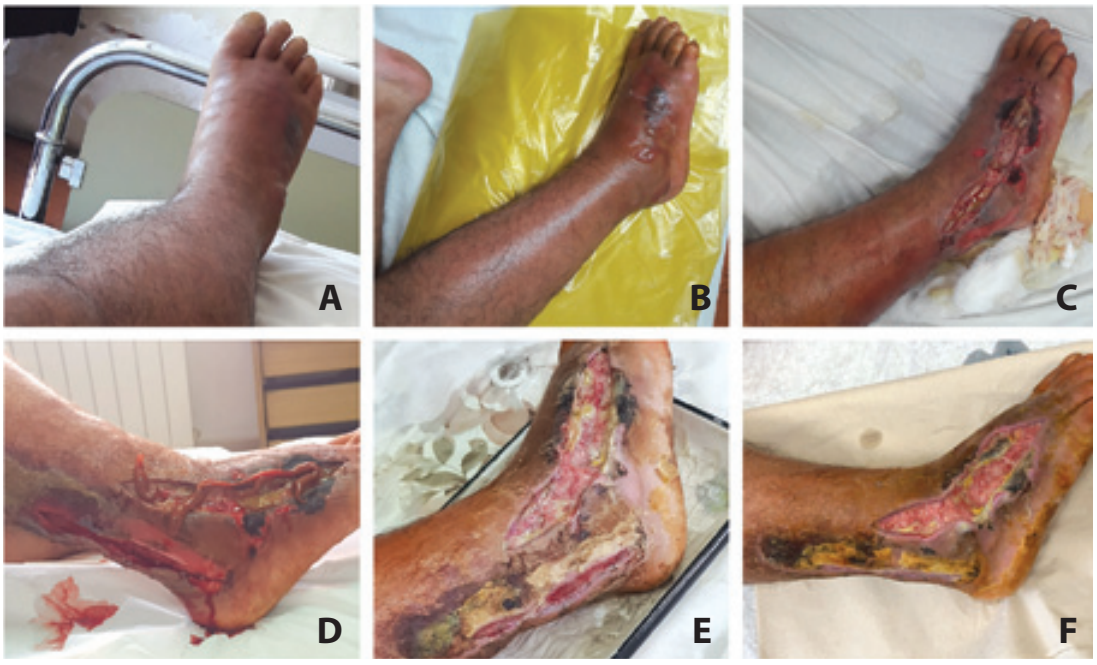

Figure 1. (A) Initial picture: tense hemorrhagic bulla on a shiny swollen erythemo-infiltrative plaque. **(B)** A necrotic area is established on the back of the right foot as the edema extends beyond the boundaries of the erythematous zones. **(C)** 12 hours after admission to the surgical ward: hyperemia of the right lower leg, extensive necrotic fields on the back of the foot and purulent exudate in the area of the right talocrural joint. **(D–F)** Postoperative status after fasciotomy and initial epithelialization of the wound

elas. The initial examination of the right limb revealed a tense hemorrhagic bulla, on a shiny swollen erythematous-infiltrative plaque and an increased local temperature **(Figure 1a).** Slightly enlarged inguinal lymph nodes on the right were found.

Initial blood investigation revealed C-reactive protein (CRP) 456 mg/dL, white blood cell count (WBC) 18.2 per mm^3, Hgb 126 g/dL, Serum sodium 140 mmol/L, Serum creatinine 82 μmol/l, Serum glucose 11 mmol/L.

The microbiological examination of the culture content, after rupture of the bulla, revealed Gram (+) group B streptococci. No anaerobic microorganisms were detected. The patient was initiated on dual systemic antibiotic therapy with Ceftriaxone 3 g/daily i.v. and Gentamicin 2x80 mg/daily i.v. Topical therapy included fusidic acid cream and compresses with potassium permanganate. Water-salt rehydration was performed with a bank of saline.

Within a few hours after hospitalization, the patient's condition deteriorated and he developed an acute inflammatory reaction with rapid breathing, fever - 38.8°C, erythema along the lymph vessels and complaints of pain in the right inguinal fold. A necrotic area appeared on the back of the right foot, as the edema extended beyond the boundaries of the erythematous areas **(Figure 1b)**.

On the second day of hospitalization in the dermatology ward, the patient was discharged and transferred to the clinic of purulent-septic surgery with suspicion for necrotizing fasciitis. Within 12 hours after admission to the surgical ward, hyperemia of the right lower leg, extensive necrotic fields on the back of the foot and purulent exudate in the area of the right talocrural joint were observed **(Figure 1c)**. The therapy was modified by infusion of Amoxicillin/clavulanic acid 3 x 1.2 g /i.v., Penicillin 4x5 million UI /i.v., NaCl solution 0.9%. Anticoagulant therapy with enoxaparin sodium 0.6/s.c. and analgesia with Dexketoprofen 1 amp./i.v. was initiated. Under general anesthesia, an incision of the skin and subcutaneous tissue was performed, as well as a fasciotomy on the dorsal part of the right foot and the lateral part of the right lower leg

with evacuation of a large amount of purulent exudate. The wound was treated with oxygenated water, a gauze tamponade was made with brown salt and a sterile dressing. On the 5th postoperative day, the patient was discharged from hospital in good general condition with guidelines for daily cleaning of the wound by a surgeon until its full epithelization **(Figure 1d-1f).**

Discussion

Necrotizing fasciitis belongs to the group of the so-called Necrotizing soft tissue infections (NSTIs). It was first described in the 5th century by Hippocrates as a complication of acute streptococcal infection (3). The term NF was first introduced by Wilson 1952, and it is still used (7).

Although rare, this disease is often a fatal soft tissue infection due to rapidly progressing necrosis of subcutaneous fat and fascia (8). The incidence for Western Europe is 1 case per 100,000 inhabitants and mainly affects adult patients (3). For ages over 80 incidence increases progressively, reaching 12 per 100,000 (3).

The main risk groups include immunocompromised patients, patients with diabetes mellitus, underlying malignancy, kidney impairment, obesity, malnutrition, peripheral vascular disease, alcohol use, and varicella infections (for pediatric patients) (5). Caution is given to groups of patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) (2, 5). NSAIDs may suppress any signs and symptoms of inflammation and may be associated with a worsened clinical course leading to alterations in the immune response (2, 5). Animal and insect bites (honey bee sting) are considered to be predisposing factors (9, 10), as well as childbirth, burns, soft tissue infections, minor invasive procedures, traumatic injury, visceral-cutaneous fistulas, percutaneous catheter insertion, and gastrointestinal perforation (5). Fournier gangrene or NSTIs of the perineum and genitalia can occur due to trauma, urinary tract infections or stones, Bartholin's gland abscesses, and surgery or other instrumentation (2).

First described by Giuliano et al., the classification divides Necrotizing fasciitis into three types according to bacteriologic classes (11).

Type I NSTIs

Type I infections are classically polymicrobial (2). They are the most common subtype (55–80%) and are usually a mixture of aerobic and anaerobic organisms (2, 3). The main causative agents in this group are:

– Gram-positive cocci, such as *S. aureus, S. pyogenes, and Enterococci;*

– Gram-negative rods such as *E. coli and P. Aeruginosa*;

– Anaerobes like *Bacteroides or Clostridium species - Clostridium perfringens, C. septicum, and C. Sordellii, Proteus, Klebsiella, Peptostreptococcus*

Type I predominantly affects the trunk and the perineum (2). The main risk groups are older immunocompromised patients, with more medical comorbidities such as diabetes, chronic renal failure and others. Usually, there is no evidence of previous trauma in this subtype.

Type II NSTIs

Type II (20% of cases) is a monomicrobial infection or also called group A β-hemolytic streptococci (GAS) necrotizing fasciitis (8). The most common location is the limbs. It can also be combined with infection from staphylococcal species. The predominant group is healthy young immunocompetent hosts, with a history of recent trauma, surgery, or IV drug-abuse (12). GAS infections have a high potential for aggressive local spread, including toxic shock syndrome (13).

Type III NSTIs

The infections caused by Vibrio species (*V. vulnificus*). It occurs along warm-water coastal regions in the southeastern United States, Central and South America, and Asia. Infection can occur via exposure through an open wound or other break in the skin (contact with seawater) or via ingestion of raw seafood (Aeromonas, a bacterium found in fresh and brackish water) (5, 14). *Vibrio vulnificus* is a fatal, rapidly progressive soft-tissue infection with early evidence of significant systemic toxicity (14). All age groups are affected, and multisystem organ failure and cardiovascular collapse without any localized cutaneous evidence of infection may be observed (2).

Some authors have described ***type IV of NF***, caused by fungal pathogens, such as *Candida albicans* (15). Eleven cases of Candida species necrotizing fasciitis have been described, as the major risk factors include trauma, gunshot wounds, diabetes and immunocompromised individuals (15).

Clinical Presentation

Early signs and symptoms of NSTI often mislead to a diagnosis since they resemble cellulites, abscesses or erysipelas (2). NF is divided into two main clinical subtypes - hyperacute and sub-acute variants (16). Initial complaints include intense pain, erythema, swelling, and fever (4, 5). Necrotizing fasciitis typically presents without a defined margin or lymphangitis (12). There is a fast progression to tense edema, grayish-brown discharge, and vesicles (3, 17). Several "hard" clinical signs are more suggestive of NSTI: (1) the presence of bullae, (2) skin ecchymosis that precedes skin necrosis, (3) presence of gas in the tissues by examination or radiographic evaluation, and (4) cutaneous anesthesia (1–3). Hemorrhagic bullae and crepitus are a sign of underlying fascia and muscle being compromised (18). Crepitus is a later sign, very specific, but found in only 13–31% of patients (3, 19). Less specific clinical signs are pain out of proportion to examination, edema that extends beyond the skin erythema, systemic toxicity, and progression of infection despite antibiotic therapy (4, 12). Hyperacute course presents with sepsis and rapidly progresses to multiorgan failure (12). Complaint of pain range from severe to decreased pain or anesthesia in some group of patients, notably those with diabetic neuropathy (12, 17).

Evaluation

The Laboratory Risk Indicator for Necrotizing Infection (LRINEC) Score is the most common system for assessing the severity of necrotizing fasciitis that was proposed in 2004 by Wong et al. (20). Even clinically early cases of necrotizing fasciitis can be distinguished through it (20). It evaluates abnormalities in six independent variables: C-reactive protein, mg/L, Total white cell count (WBC), cells/mm, Hemoglobin, g/dl, Sodium, mmol/L, Creatinine, mg/dL, Glucose, mg/dL (1). According to Wall and colleagues, white blood cell (WBC) count <15,000 cells/mm^3 and a serum sodium level greater than 135 mmol/L have about 99% negative predictive value, and a 90% sensitivity for detecting NSTIs (21). It should be noted, however, that author teams noted that many other conditions could cause similar laboratory derangements (2).

Histological criteria for diagnosing NF are: 1) extensive superficial fascial necrosis; 2) aggregates of neutrophils; 3) fibrin thrombi with fibrinoid necrosis of arterial and venous walls; 4) clusters of various types of microorganisms within the destroyed fascia and dermis (1, 3).

Plain radiography, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) may be used as diagnostic adjunct.

Treatment

The treatment for NSTI involves different therapeutic modalities (13, 22–25):

– Resuscitation of the patient in shock

– Early and complete debridement and fasciotomy of the necrotic tissue is essential for the treatment of NSTI; debridements should be repeated every 24 to 48 hours until the infection is controlled

– Appropriate broad-spectrum antibiotic coverage (Linezolid, Aminogliycosides, Cephalosporins, Piperacillin/Tazobactam, Clindamycin, Penicillin G, Vancomycin, and Gentamicin, fluoroquinolones – instead of Gentamicin to avoid the nephrotoxicity of aminoglycosides); widely used regimen is the combination of Penicillin G, Clindamycin and Gentamicin

– Hyperbaric oxygen (HBO) therapy - the assumptions are that elevated oxygen levels reduce edema, stimulate fibroblast growth, and increase the killing ability of leukocytes

– Intravenous immunoglobulin (IVIG) therapy - based on the idea that it leads to a limitation of the systemic inflammatory response

– Reconstruction of skin defects either on the extremities and torso, or on the abdominal or chest wall; novel concepts of layer-specific reconstruction include biologic meshes

Mortality in patients with NSTI remains high. Patients with necrotizing fasciitis are at risk for a variety of complications: multiorgan failure, compartment syndrome, acute respiratory distress syndrome, septic shock, toxic shock syndrome, loss of extremity, severe scarring, disseminated intravascular coagula-

tion, rapid advancement of disease resulting in death (26). Early diagnosis and extensive surgical debridement of affected tissue performed within 24 hours are associated with a lower mortality (27).

Abbreviations

NF – necrotizing fasciitis
SSTI – skin and soft tissues
CRP – C-reactive protein
NSTI – necrotizing soft tissue infection
NSAID – nonsteroidal anti-inflammatory drug
GAS – group A β-hemolytic streptococci
LRINEC– Risk Indicator for Necrotizing Infection
WBC – white cell count
CT – computed tomography
MRI – magnetic resonance imaging
HBO – hyperbaric oxygen

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Nekrotizirajući fasciitis – klinički slučaj i pregled literature

Sažetak

Nekrotizirajući fasciitis je infekcija mekog tkiva, opasna po život, sa fulminantnim i često fatalnim tokom. Rano dijagnostikovanje se obično odlaže, jer se početak bolesti često maskira u obliku erizipela ili celulita. Stanje karakteriše nekroza kože, potkožnog tkiva i osnovne fascije. Opisujemo slučaj 42-godišnjaka koji se žalio na eritem, temperaturu i jake bolove u desnoj nozi četiri dana pre hospitalizacije. Pacijent je primljen i lečen pod dijagnozom erizipela. Nekoliko sati nakon prijema, zbog drastičnog pogoršanja opšteg stanja i dermatološkog statusa, prebačen je na infektivno odeljenje sa fulminantnom slikom nekrotizujućeg fasciitisa. Uspešno i blagovremeno su izvedeni debridman i fasciotomija. Dobra prognoza i preživljavanje kod pacijenata sa nekrotizirajućim fasciitisom direktno koreliraju sa kompleksnim terapijskim merama. Odgovarajući antibiotici i intenzivna opšta podrška sprečavaju masovnu sistemsku difuziju. Rano i adekvatno hirurško određivanje i fasciotomija povezani su sa poboljšanim preživljavanjem.

Ključne reči: Nekrotizirajući fascitis; Infekcije mekih tkiva; Dijagnoza; Znaci i simptomi; Hirurški debridman; Fasciotomija; Ishod terapije; Antibakterijski lekovi

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Secondary Tumor Arising in a Nevus Sebaceous

Biljana JEREMIĆ GAJINOV[1, 2], Sonja PRĆIĆ[1, 3], Milana IVKOV SIMIĆ[1, 2], Nada VUČKOVIĆ[1, 4], Milan MATIĆ[1, 2], Zoran GOLUŠIN[1, 2], Ljuba VUJANOVIĆ[1, 2]

[1]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[2]Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia
[3]Pediatric Clinic, Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia
[4]Center for Pathology and Histology, Clinical Center of Vojvodina, Novi Sad, Serbia

Correspondence: Biljana Jeremić Gajinov, E-mail: biljana.jeremic@mf.uns.ac.rs

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Abstract

Introduction. Nevus sebaceous is a rare congenital hamartoma, composed of epidermis, sebaceous glands, sweat glands and hair follicles. It is possible to develop secondary tumors in the area of nevus sebaceous during the lifetime, most often after puberty. Secondary lesions are most often benign, while malignant lesions may occur but significantly less frequently. **Case report.** We present the case of a 21-year-old patient who came for an examination due to the appearance of a nodule in the area of a yellowish lesion on the head. The yellowish lesion was present since birth, and the nodule appeared about a year before. The dermoscopic examination of the lesion was nonspecific. The final diagnosis of eccrine poroma as a secondary lesion in nevus sebaceous was made by pathohistological analysis. **Conclusion.** Every secondary tumor in nevus sebaceous deserves full attention, with either close follow up, or excision with pathohistological analysis.

Key words: Nevus, Sebaceous of Jadassohn; Poroma; Neoplasms, Second Primary; Dermoscopy; Diagnosis

Introduction

Nevus sebaceus (NS) is a rare congenital hamartoma, composed of epidermis, sebaceous glands, sweat glands and hair follicles. It was first described by the German dermatologist Josef Jadassohn in 1895 (1, 2). NS may be present at birth or immediately after birth in 0.3% of newborns (3). During the lifetime, most often after puberty, the development of secondary tumors in the area of NS is possible. Secondary lesions are most often benign in nature, while malignant lesions may occur significantly less frequently, almost always in the adult population (2, 4). Most common benign lesions are trichoblastoma, syringocystadenoma papilliferum, while the most common malignant lesion is basal cell carcinoma (4, 5). Very rarely, eccrine poroma (EP) can occur in NS and mimic other benign and malignant tumors (6). EP is a benign neoplasm arising from the sweat gland ducts. It was first described in 1956 by Goldman and co-workers. It is most often localized on the palms and soles, although it can also be present on other parts of the body where the eccrine sweat glands are found (7). It is rarely described in papers in collision with NS.

Case Report

A 21-year old female presented due to the appearance of a nodule in the area of a yel-

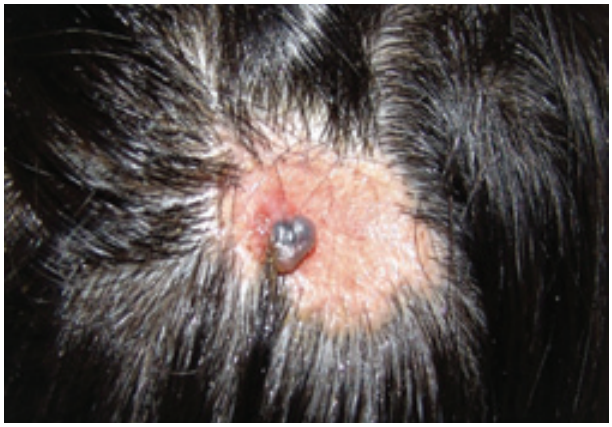

Figure 1. Yellowish slightly verrucous plaque with a reddish-bluish nodule in the area of the right parietal region

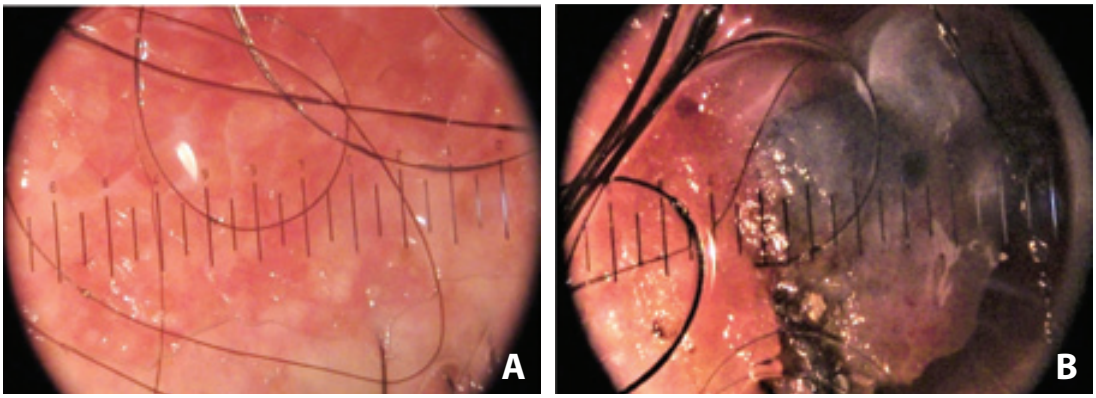

Figure 2. a. Dermoscopy of yellowish verrucous plaque: Yellow-whitish lobular appearance; **b.** Dermoscopy of reddish-bluish nodule: glomerular blood vessels, blue-black sign

lowish lesion on the head. The yellowish lesion was present since birth, and the nodule appeared about a year before. It was painless and the patient denied previous head injuries and other health problems. Clinical examination revealed a reddish-bluish nodule 1 cm in diameter on a yellowish slightly verrucous plaque, 3x2 cm in diameter in the area of the right parietal region **(Figure 1)**. On palpation, the nodule was of soft consistency. Regional lymph nodes were not enlarged. Dermoscopy of verrucous plaque showed a yellow-whitish lobular appearance **(Figure 2a)**. This dermoscopic appearance was on the entire yellowish part without significant asymmetry. On the other hand, the pigmented nodule showed, although not characteristic, a blue-black sign which was present on the proximal two thirds and discrete glomerular blood vessels in the distal part **(Figure 2b)**. Surgical excision of the plaque with a secondary lesion was performed. Pathohistological analysis of the excised lesion showed acanthotic epidermis with multiple, monomorphic cubic cells, which were smaller than keratinocytes, without peripherally formed palisades **(Figure 3a)**. The hair follicle and hair shaft were surrounded with diffuse, dense chronic inflammatory infiltrate **(Figure 3b)**. In the tips of the papillae of the dermis there were hyperplastic sebaceous glands without hair follicles, with an opening directly into the epidermis **(Figures 4 a and b)**. The marginal hair follicles and sebaceous glands were regular. The sweat glands were regularly located and of regular morphology. Based on the clinical and pathohistological findings, the final diagnosis of eccrine poroma arising within nevus sebaceous was made.

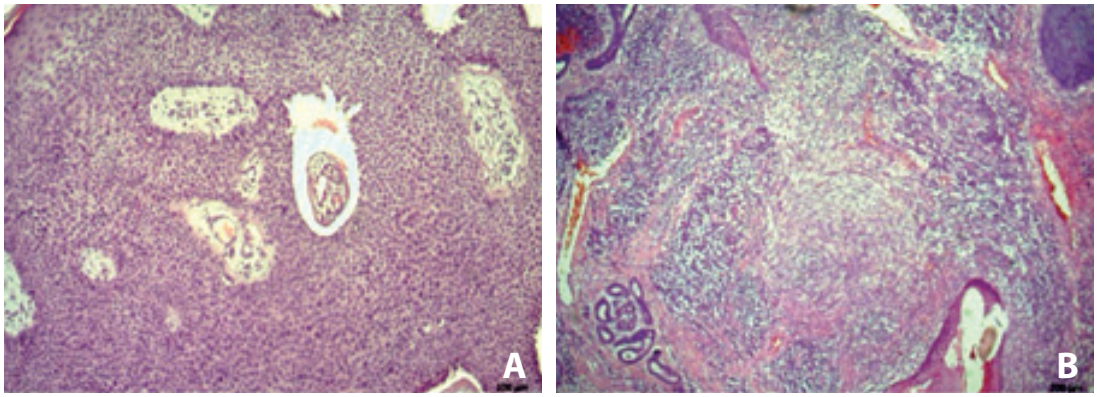

Figure 3. a. Ecrine poroma with acanthotic epidermis with multiple, monomorphic cubic cells, which are smaller than keratinocytes, without peripherally formed palisades (hematoxylin and eosin, x100); **b.** Part of a hair follicle with part of a hair shaft surrounded by a diffuse, dense chronic inflammatory infiltrate (hematoxylin and eosin, x50).

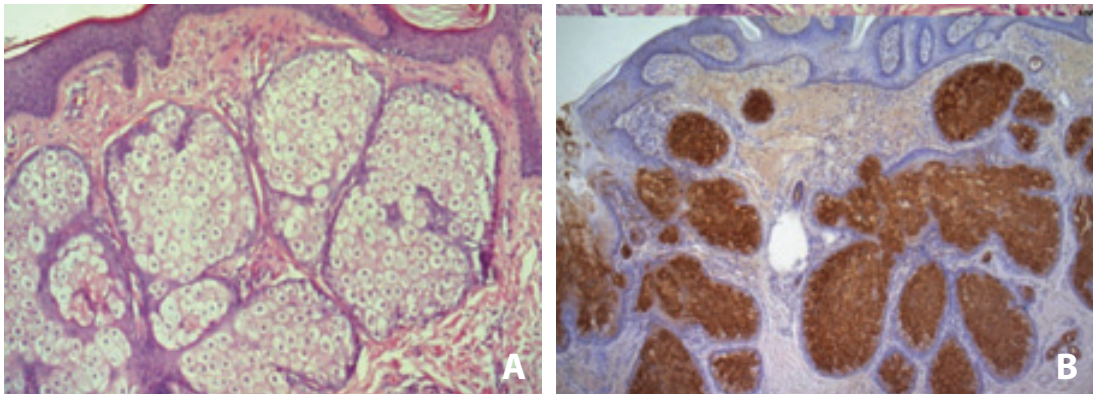

Figure 4. a. Hyperplastic sebaceous gland lobules without hair follicles (hematoxylin and eosin, x100); **b.** Immunohistochemical staining of multiplied sebaceous lobules (EMAx50)

Discussion

NS is a rare congenital hamartoma, composed of the epidermis, sebaceous glands, sweat glands and hair follicles (2). During the lifetime, NS changes its appearance and goes through three stages of development. At birth, clinically it has the appearance of a linear, circular or oval plaque of pink-yellow color, without hair, most often localized in the region of the head and neck. Dermoscopic characteristics of this stage are yellowish globules aggregated in the clusters. In puberty, during the second stage, NS becomes verrucous and dermoscopically is characterized by yellowish-white lobular or yellowish-gray papillary structures, brown globules on a yellow background, or as in the first stage yellowish globules aggregated in clusters. After puberty, in the third stage of NS development, it is possible to develop secondary keratnocyte and adnexal tumors in the NS. At this stage, it is dermoscopically characterized by a homogeneous yellowish-white pattern and blood vessels can be present as linear, irregular, or arborescent (2, 3, 8). In the case of our patient dermoscopy of plaque showed a yellow-whitish lobular appearance, without visible blood vessels.

Secondary lesions that occur in NS are most often benign in nature, while malignant lesions can occur significantly less frequently, almost always in the adult population (2, 4). Histopathology of early lesions shows a transient enlargement of sebaceous glands, acanthosis and mild papillomatosis may be present in the epidermis. In puberty, the development of mature sebaceous glands occurs, which are often located abnormally high in the dermis. Hair follicles remain small and may even disappear completely. The epidermis is more papillomatosus and acanthotic, and the dermis is often thickened. A mild chronic inflammatory cell infiltrate of lymphocytes and plasma cells is often present (9).

A retrospective study conducted by Munir H. Idriss analyzed NS from 1999 to 2012. Of the 707 NS analyzed, secondary lesions were identified in 159 samples (22.5%). Of these, 18.9% (n = 132) were benign lesions, while 2.5% (n = 18) lesions were malignant, and 1.2% (n = 9) contained warts, cysts, and connective tissue nevi. Among secondary benign lesions, the most common were trichoblastoma and syringocystadenoma papilliferum. The most common malignant secondary lesion was basal cell carcinoma (5). In our patient's case the pathohistological analysis showed benign neplasm arising in NS.

Diagnosis of NS can be straightforward based on history, clinical examination and dermoscopic picture (2, 3, 8). It usually does not need to be excised, especially in children. However, there is still no consensus on whether and when the treatment is needed. Some authors point out that surgical excision is unnecessary for prophylactic reasons since secondary lesions on the NS do not occur often. They also state that most secondary lesions are benign in nature. However, other authors suggest that prophylactic excision before puberty is a better therapeutic modality than the long-term follow-up. They believe that secondary tumors occur more often after puberty when the NS is significantly larger and require more surgical intervention than in childhood when a NS is smaller (2, 5).

We prefer clinico-dermoscopic approach as a solution for NS and NS with a secondary tumor.

Compliance with parents is essential in childhood. It is crucial to explain them the behavior of NS in childhood, and potential secondary tumors, most of them being of benign nature, and role of dermoscopy in doubtful situations (5, 8). If a secondary tumor is arising, it is usually benign. Dermoscopy can aid the diagnosis.

In a specific situation like NS and EP, although dermoscopic picture of NS is rather defined on one side, dermoscopic and clinical features of EP can be confusing on the other side. Clinical EP may have the appearance of a papule, verrucous plaque or exophytic skin-colored nodule, somewhat less often the lesion may be pigmented. It is most often localized on the palms and soles (10). The differential diagnosis of EP is very broad. Dermoscopy can be very helpful so that we can differentiate them from other tumors: melanoma, pigmentary basal cell carcinoma, seborrheic keratosis, pyogenic granuloma, dermatofibroma, squamous cell carcinoma, Bowen disease, dermal nevus and angioma (11, 12). In a study conducted by the International Dermoscopy Society dermoscopic characteristics of EP include white interlacing areas around vessels, yellow structureless areas, milky-red globules and branched vessels with rounded endings (11). Pathohistological analysis of EP shows a circumscribed tumor composed of cords and columns of uniform basaloid cells. The cells are smaller than epidermal cells. Melanin pigment may be present. Ducts and small cysts may also be seen within the tumor columns (9).

In our patient's case, pigmentary basal cell carcinoma and melanoma in NS was considered as a differential diagnosis on the basis of clinical and dermoscopic findings. Dermoscopic examination of the lesion was very nonspecific, even bizarre in appearance. As such, it was highly suspicious, and malignancy could not be ruled out without pathohistology. The final diagnosis of EP as a secondary lesion in NS was made by pathohistological analysis.

Conclusion

Every secondary tumor in NS deserves full attention, with either close follow up, or excision with pathohistological analysis.

Abbreviations

NS – Nevus sebaceus
EP – Eccrine poroma

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Pojava sekundarnog tumora u nevusu sebaceusu

Sažetak

Uvod. Nevus sebaceus je redak kongenitalni hamartom, izgrađen od epiderma, sebacealnih žlezda, znojnih žlezda i folikula dlake. Tokom života, najčešće nakon puberteta, moguć je nastanak sekundarnih tumora u predelu nevusa sebaceus. Sekundarne lezije su najčešće benigne prirode, dok se značajno ređe mogu javiti i maligne lezije. **Prikaz slučaja.** Prikazujemo slučaj pacijentkinje starosti 21 godinu, koja je došla na pregled zbog pojave čvorića u predelu žućkaste lezije na poglavini. Žućkasta lezija je bila prisutna od rođenja, dok se čvorić pojavio pre godinu dana. Dermoskopskim pregedom lezija je bila veoma nespecifična. Konačna dijagnoza ekrinog poroma kao sekundarne lezije u nevusu sebaceus postavljena je patohistološkom analizom. **Zaključak.** Svaki sekundarni tumor u nevusu sebaceus zaslužuje pažnju, kratkoročno praćenje ili eksciziju sa patohistološkom analizom.

Ključne reči: Nevus lojnih žlezda Jadasona; Porom; Druga primarna neoplazma; Dermoskopija; Dijagnoza

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Blistering Beetle Dermatitis Mimicking Herpes Zoster Ophthalmicus: a Case Report

Pankaj DAS[1], Sandeep ARORA[1], Gautam Kumar SINGH[1], Amit BAHUGUNA[1], Neelam SINGH[1], Prashant BELLAD[1], Aakansha GUPTA[1]

[1]Department of Dermatology, Base Hospital Delhi Cantt & Army College of Medical Sciences, New Delhi, India

Correspondence: Pankaj Das, E-mail: pankaj3609@gmail.com

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Abstract

Blistering beetle dermatitis is an important dermatological disease of tropical countries. Although the clinical features are classical, little awareness amongst medical practitioners may cause difficulties in the diagnosis of this condition. Further, it may sometimes mimic an unrelated disease which can lead to delay in treatment causing prolonged suffering of the patient. We present a case of blistering beetle dermatitis that was initially misdiagnosed as a case of herpeszoster ophthalmicus. The case is presented to reinforce awareness on this dermatologicaldisease and discuss its atypical presentation and its management.

Key words: Insect Bites and Stings; Dermatitis, Contact; Coleoptera; Blister; Herpes Zoster Ophthalmicus; Diagnosis; Diagnostic Errors

Introduction

Blistering beetle dermatitis is a type of contact dermatitis caused by vesicants such as pederin and cantharidin possessed by beetles in the order *Coleoptera* (1). This disease is seen in most regions of the world but is prevalent in tropical countries (2). Pederin/cantharidin is released on inadvertent crushing of beetle on the skin which is responsible for causing irritant contact dermatitis which usually manifests with characteristic linearly arranged vesicles/bullae (3). Prompt irrigation of the affected part to wash off the toxin and application of topical steroids reduces the inflammation.

Case Report

A 26 years old male presented to dermatology outpatient department with history of painful fluid filled lesions around the right eye of 02 days duration. He was apparently asymptomatic before 02 days when on waking up, he complained of burning sensation associated with redness over the area around his right eye. In the next few hours, he noticed eruption of some fluid-filled lesions over the same area associated with pain. He consulted a general practitioner who diagnosed him as a case of herpes zoster ophthalmicus and started on tab acyclovir 800 mg five times daily but the lesions continued to progress. On second visit to the general practitioner, he was referred to dermatology outpatient department. On detailed history taking, he revealed that while asleep, he felt some insect crawling over his left forearm and tried to remove it with his right hand. He noticed burning sensation and redness followed by eruption of fluid-filled lesions around his right eye, the next morning. Dermatological examination revealed a bulla, numerous tiny vesicles and crusts over erythematous and edematous upper and lower eyelids and the area around medial canthus of the right eye **(Figure 1).** Unaided ophthalmological examination revealed uninvolved cornea and conjunctiva with negative Hutchinson's sign (ophthalmic zoster with nasal tip involvement). There was no photophobia and vision in both eyes were 6/6. Examination of other body sites revealed involvement of right cubital fossa in form of 02 x erythematous crusted lesions suggestive of "kissing lesions" classically described in Blistering Beetle Dermatitis **(Figure 2).** The patient was counseled about the etiology and course of the blistering beetle dermatitis and managed with twice daily normal sa-

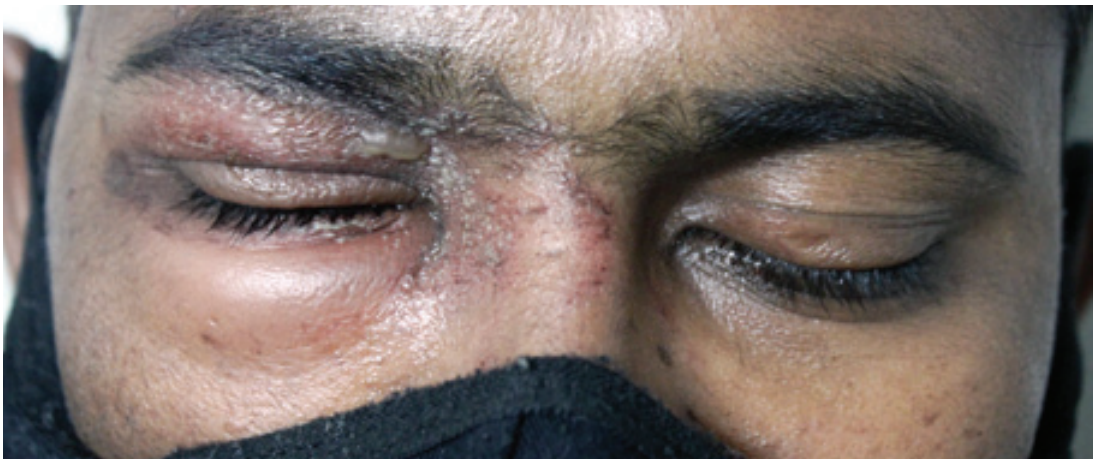

Figure 1. Numerous tiny vesicles, a solitary bulla and crusts over erythematous and edematous upper and lower eyelids and area around medial canthus of the right eye

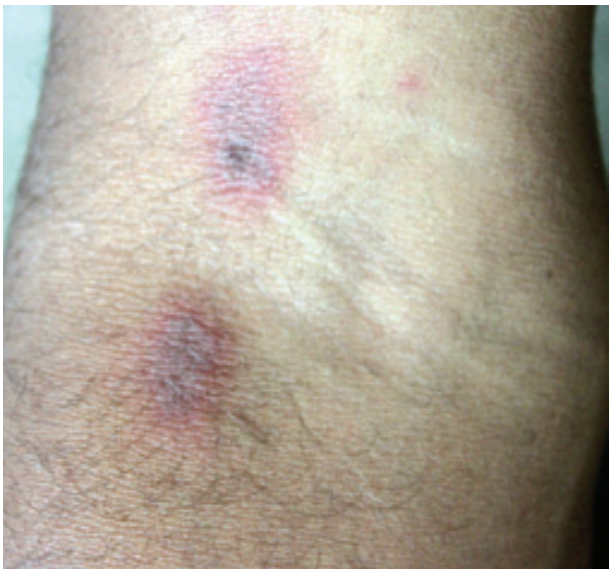

Figure 2. 02 x erythematous crusted lesions on the right cubital fossa suggestive of "kissing lesions" described in blistering beetle dermatitis

line compresses followed by application of mild topical steroid cream without any topical/oral antibiotics, after which the lesions resolved with hyperpigmentation in a week.

Discussion

Blistering beetle dermatitis was first described in medical literature in 1901 (4). It typically manifests as painful erythemato-vesicular rash due to a vesicant (5). Beetles causing this dermatitis belong to 03 families- *Meloidae, Oedemereidae*&*Staphylinidae* under the order *Coleoptera* (6). While cantharidin is the vesicant present in *Meloidae* and *Oedemereidae;* pederin is the chemical responsible for vesiculation in the family *Staphylinidae* (Rove beetles) and the genus *Paederus.* Differences between experimentally induced skin lesions by cantharidin and pederin are mentioned in **Table 1** (7). The beetles belonging to the genus *Paederus* have a slender body-about 7–10 millimeter long and 0.5 millimeter wide with small elytra under which lengthy folded membranous wings are attached (8). The head and posterior one-third of the abdomen are commonly black, the thorax and anterior two-thirds of abdomen are orange or yellow, while the elytra are metallic green or blue, but may differ from species to species **(Figure 3)** (8). *Paederus* beetles prefer moist and shady habitat like soil cracks, rock crevices, decaying vegetable matter, logs and barks as their larval stages

Figure 3. *Paederusfuscipes* (Order: *Coleoptera* Family: *Staphylinidae* Genus: *Paederus* Species: *fuscipes*)

Table 1. Differences between experimentally induced skin lesions by cantharidin and by pederin

Feature	Pederin	Cantharidin
Delay between contact and onset of erythema	36-72 h	18-24 h
Character of erythema	Marked and painful	Mild or symptomless
Character of vesicle	Small or very small; clear fluid, becoming purulent; tendency to coalesce; deep base	Small, rapidly coalescing; clear fluid on a superficial base
Symptoms	Pronounced itching and burning	Almost none
Healing	Formation of a crust	By resorption or by blister bursting
Residual lesion	Marked persistent pigmentation; itching may also be present	May be none; may be light transient pigmentation

are susceptible to desiccation from excessive heat (9). Life cycle consists of at least two larval instar stages between egg and pupa, before emergence of the adult beetle which usually appears during or around conclusion of the damp season (10). Agricultural workers are most affected during the day since exposure occurs while beetles feed on the crops. At night, beetles are attracted to light and may enter houses. The beetles are attracted more to fluorescent than incandescent sources of light so much so that an outbreak of blistering beetle dermatitis in Tanzania was arrested after mercury tube fluorescent lights were replaced with incandescent bulbs (1). History of contact with the beetle may not always be available as exposure to the toxin may occur while asleep. The exposed parts of the body like face, neck, upper and lower extremities are most often affected. It is interesting to note that it is not the beetle, but *Pseudomonas*-an endosymbiotic gram-negative bacteria which synthesizes the toxin instead (11). Female beetles are believed to be the carriers of the endosymbiont bacteria. The larvae-forms acquire it by ingestion of eggshells contaminated with *Pseudomonas* (12). Although pederin constitutes approximately 1% of the body weight of the beetle, it is an extremely potent toxin which completely inhibits cell growth at concentrations as low as 1.5 nanograms per mililitre and has median lethal dose (LD_{50}) of 2 milligram per kilogram for humans (13, 14). At molecular level, pederin induces an apoptotic reaction by inhibiting mitosis and thereby disrupting DNA and protein synthesis which correlates clinically with an acute necrotic reaction (13). Since blister beetles neither sting nor bite, allowing them to roam over the skin does not cause any reaction. However, crushing them against the skin leads to secretion of pederin or cantharidin present in hemolymph which leads to blistering. Apart from causing dermatitis, cantharidin has been used in the treatment of warts and molluscum (15). Pharmaceutical grades of cantharidin available in some countries are: Cantharone and Canthracur PS (0.7% in collodion base); Canthacur PS (1% cantharidin, 30% salicylic acid, 5% podophyllin); and cantharidin crystals with collodion base sold separately (16). Also of interest is oral ingestion of blistering beetles as aphrodisiac and abortifacient but is associated with serious adverse effects like gastrointestinal hemorrhage, hemorrhagic shock, renal and cardiac toxicity and death (17–19). Skin manifestations of contact exposure to toxin presents classically with sudden onset of painful linear erythematous plaques studded with vesicles sometimes coalescing to form bullae which heal with post inflammatory hyperpigmentation over 10-14 days (3). Another classical presentation is “kissing lesions” on the contiguous areas of the skin in close physical contact with each other e.g. axillary area and cubital and popliteal fossae which underlines the fact that smearing of the vesicant fluids to the contiguous surfaces lead to the appearance and spread of the lesions (20). Our case showed classical kissing lesions on the ipsilateral upper limb which might have been caused due to smearing of the vesicant fluid on the adjacent areas in contact with each other. The lesions around the right eye occurred through contamination of finger tips of left hand while attempting to dislodge the beetle crawling on the right forearm. Involvement of eye and periocular area oc-

curs due to contamination by toxin and has been termed as "Nairobi eye" (21, 22). Early lesions show spongiosis comprising of neutrophils, exocytosis, scattered acantholysis and even necrosis (23). Blistering beetle dermatitis mimics different dermatoses like herpes simplex and herpes zoster, impetigo contagiosa, Toxicodendron dermatitis, phytophotodermatitis, millipede dermatitis, liquid burns, dermatitis artefacta and in case of periorbital involvement – periorbital cellulitis (24). Treatment consists of washing of the affected area and application of mild topical steroid cream (25).

Conclusion

Blistering beetle dermatitis classically affects the exposed areas of the body. Our case too presented with lesions on the exposed parts – the right periocular area and right antecubital fossa. This presentation although theoretically classical, may be misdiagnosed as herpes zoster ophthalmicus as pain and burning sensation is the predominant complaint in both the clinical scenarios. However sudden onset of lesions overnight or in hours without a significant prodrome as seen in herpes zoster and presence of "kissing lesions" in some cases further support the diagnosis as blistering beetle dermatitis. Detailed history and clinical examination is essential to diagnose this condition.

Abbreviations

DNA – Deoxyribonucleic acid
PS – Pharmaceutical Services

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Bulozni dermatitis izazvanih ubodom insekata koji liči na *herpes zoster oftalmikus* – prikaz slučaja

Sažetak

Bulozni dermatitis nastao ubodom insekata su važno dermatološko oboljenje u tropskim zemljama. Iako su kliničke karakteristike klasične, nedovoljna svest o ovoj bolesti može izazvati teškoće u dijagnostikovanju. Pored toga, ova vrsta dermatitisa može ponekad da liči na druga oboljenja, što može dovesti do neblagovremenog tretmana i tako produžiti patnju pacijenta. Ovo je prikaz slučaja dermatitisa u obliku plikova izazvanih ubodom insekta koji je prvobitno pogrešno dijagnostikovan kao herpes zoster oftalmikus. Slučaj prezentujemo da bismo podigli svest o ovom dermatološkom oboljenju i prodiskutovali njegovu atipičnu manifestaciju i lečenje.

Ključne reči: Ujedi i ubodi insekata; Kontaktni dermatitis; Koleoptere; Plik; Očni herpes zoster; Dijagnoza; Dijagnostičke greške

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Piloleiomyoma Presented by Multiple Cutaneous Nodules: a Case Report

Lala CAHANGIROVA[1], Jamal MUSAYEV[2]

[1]Department of Dermatology, Modern Hospital, Baku, Azerbaijan
[2]Department of Pathology, Azerbaijan Medical University, Baku, Azerbaijan

Correspondence: Jamal Musayev, E-mail: patolog.jamalmusaev@gmail.com

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Abstract

Introduction. Piloleiomyoma is a rare benign tumor which is caused by erector pili muscle and makes up 5% of all leiomyomas. They can be solitary and multiple. Multiple lesions still pose challenges for clinicians since their treatment option is very limited. **Case report.** We report a case of a 25-year-old male patient who had painful papules and nodules on the neck and chest for three years. Multiple red-brown papules and nodules in the skin of regio mammaria dextra and regio submandibularis on the left were seen on physical examination. Histopathological examination of punch biopsy sample revealed well-circumscribed nodule composed of spindle cells. The case was reported as cutaneous leiomyoma (piloleiomyoma). The patient was given 5 mg/day amlodipin and kept under control. **Conclusion.** The ideal treatment option for piloleiomyoma is surgical excision, but the problem with that treatment is that the lesions have tendency to recur. Medicamentous therapy plays a limited role; however, calcium-channel blockers and α-adrenergic blockers may help in palliating or eliminating associated pain through inhibition of smooth muscle contraction.

Key words: Leiomyoma; Skin Neoplasms; Smooth Muscle Tumor; Biopsy; Calcium Channel Blockers; Adrenergic alpha-Antagonists; Rare Diseases

Introduction

Cutaneous leiomyoma is a rare benign tumor caused by smooth muscle fibers. It was initially described by Virchow in 1854 (1). It is categorized into three groups, depending on the type of the tissue: angioleiomyoma, piloleiomyoma and genital leiomyoma (2). Especially the last two types can be very problematic for the patient due to pain and discomfort. Piloleiomyoma makes up 5% of all leiomyomas (3). In this report, multiple piloleiomyoma case presented with clinical and pathological findings.

Case Report

The authors report a case of a 25-year-old male patient who had painful papules and nodules on the neck and chest for three years. There were not any ulceration and flow on lesions or systematic complaints. There were not any similar complaints in the family or first relatives of the patient. Birth and development of the patient was normal. Multiple red-brown papules and nodules in the skin of regio mammaria dextra **(Figure 1a)** and regio submandibularis on the left **(Figure 1b)** were seen on physical examination. Punch biopsy was taken from the lesions and sent for histopathological examination with initial diagnosis of molluscum contagiosum, piloleiomyoma, pilomatrixoma and sarcoidosis. Histopathological examination revealed well-circumscribed nodule composed of spindle cells in the dermis **(Figures 2 a and b)**. Atypia, mitotic activity and necrosis were not seen in spindle cells. According to histopathological findings the case was reported as cutaneous leiomyoma (piloleiomyoma). The patient was given 5 mg/day amlodipin and kept under control.

Discussion

The classification of cutaneous leiomyomas is based on the type of smooth muscle which develops the lesion. Piloleiomyoma arises from the smooth muscle of the hair (erector pili) while angioleiomyoma stems from smooth muscle of the vessels (4). The

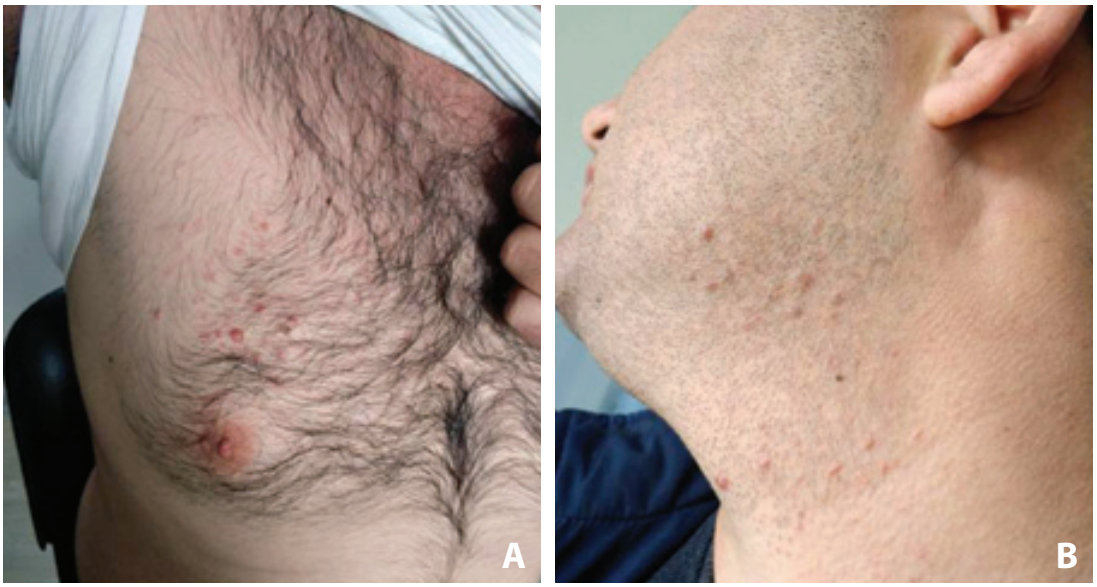

Figure 1. Multiple red-brown papules and nodules in the skin of right mammary region **(A)** and left submanfdibular region **(B)**.

lesions of dartos muscle of the scrotum, labia majoris and erectile muscle of the nipple are classified under genital leiomyoma (4).

In 1880 Besnie classified leiomyomas as solitary and multiple (3). Multiple piloleiomyoma develops generally between the ages of 10 and 30; however, solitary piloleiomyoma develops further in life.

Although it can be seen in patients of varying age groups, it is more frequently seen between the second and fourth decade of life (1, 4). *Arishima et al* reported a 6-year-old boy with a vascular leiomyoma and *Lotfi et al* presented a 5-month-old boy with cutaneous leiomyoma; furthermore, there are isolated case reports of children, including a case where light brown lesions were discovered on the soles of a newborn (5, 6). Leiomyomas do not depend on gender or race and can be developed sporadically or transmitted genetically (7).

Cutaneous leiomyomas can be located asymmetrically on the extensor muscles of the limbs, chest, face and even on the scalp (8). Genital leiomyomas are solitary papulonodules or pedunculated papules located on the scrotum, vulva, or nipple. Angioleiomyomas, which include solid, cavernous, or venous subtypes, are derived from the tunica media of small arteries and veins and typically present on the extremities (9).

Solitary and multiple piloleiomyoma are different entities. In women, multiple cutaneous leiomyoma can be associated with uterine leiomyomas as a part of Reed's syndrome (10). Multiple piloleiomyomas have different kinds of dispersion. The most common is grouped dispersion, as well as disseminate, segmental and zosteriform type dispersions can be seen. The common localization for multiple piloleiomyomas is the trunk, while for solitary lesions it is limbs (4, 11).

The main discomfort of the lesions is the pain and there are two points of view about the cause of pain. According to one of them, the tumor in itself puts pressure on the nerves; therefore, the patient feels pain. Other scientists claim that the pain is caused by the contractions of the muscle which is triggered by cold weather, friction and emotions (3).

Solitary lesions may be confused with dermatofibroma, pseudolymphoma, trichoepithelioma, lipoma, cylindroma, poroma even *Leishmania* (12). Multiple lesions should usually be differentiated from molluscum contagiosum, sarcoidosis, neurofibroma, angiolipoma, nevus, lipoma, eccrine spiradenoma, metastases and angioleiomyoma (4).

Histopathologically, cutaneous leiomyomas are not different from other leiomyomas and they consist of spindle cell proliferation, a mixture of collagen and smooth muscle cells,

presented by well-circumscribed nodules. The tumor is usually located in the reticular dermis; in some cases, the lesion may grow to papillary dermis and can be a cause of flattening and thinning of the surface epidermis. The borders of tumor are prominent, but there is no capsule (13). Smooth muscle cells that form the tumor have fibrillary eosinophilic cytoplasm and blunt-ended nuclei. Although no significant atypia was observed in these cells, moderate anisonucleosis in the nuclei, hyperchromasia and pleomorphism in the 10% of general cell population can be seen in some cases. Prominent nucleoli have not been reported. Necrosis and mitotic activity were not observed in these lesions. The relationship between lesion and peripheral nerves appears more clearly in angioleiomyomas (13). On immunohistochemical examination, diffuse cytoplasmic staining with smooth muscle actin in spindle cells is characteristic. Smooth muscle actin and S100 have an important role in differentiation of these lesions from neurofibromatosis. The low staining rate with Ki 67 and staining profile of p53 can distinguish these lesions from malignant counterparts (13–15). Molecular studies showed fumaratehydratase germ mutation in all cases presenting with multiple lesions. In cases with mutations, these lesions can be cutaneous manifestation of Multiple Cutaneous and Uterine Leiomyomatosis (MCUL, OMIM 150800) and Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC, OMIM 605839) syndromes (16).

Spontaneous regression is not characteristic for the majority of piloleiomyomas (10). Treatment depends on our expectations and therefore it is divided into two types: cosmetic and symptomatic. In general, to achieve the cosmetic aim solitary piloleiomyoma is extracted by surgery. But recurrences have been reported to occur from six weeks to more than 15 years following excision (10). But the same treatment method cannot be realized on multiple piloleiomyoma, and in that case we should prevent the symptoms. When multiple lesions are present and painful, calcium channel blockers or alpha-adrenergic blockers can help. In some cases gabapentin has been reported as a method for treating the pain (17). Cryotherapy and electrocoagulation is an alternative treatment method but according to studies they are not so effective. Ablation therapy by CO_2 laser has satisfactory results (18). Moreover, injection of Botulinum toxin might be offered as an adjuvant therapy for pain relief by inhibiting the release of neu-

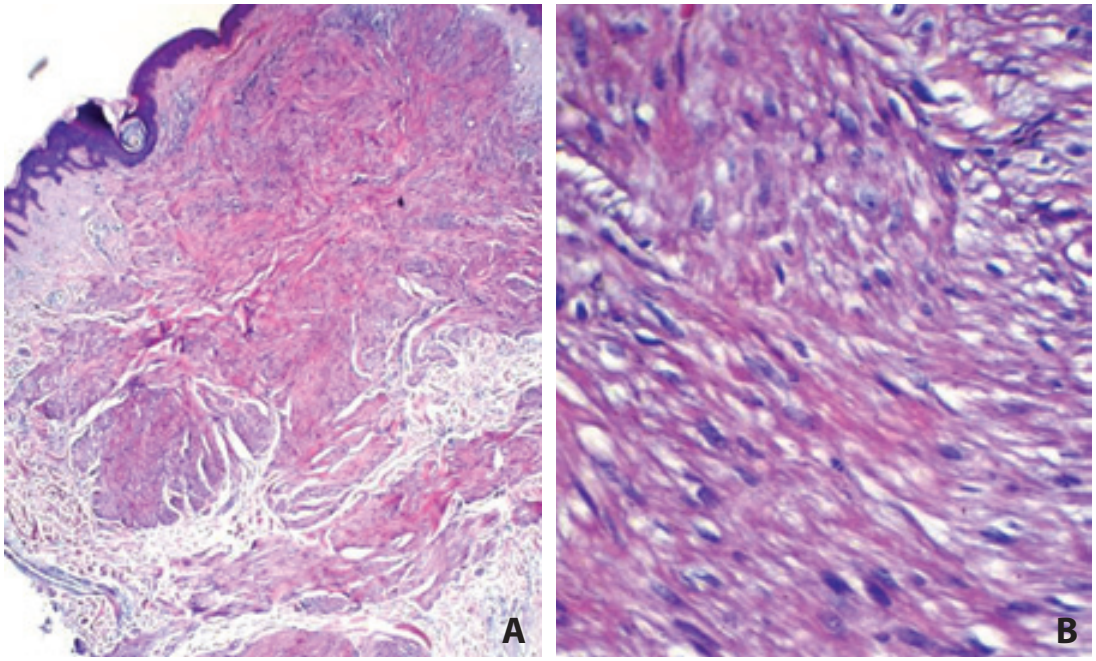

Figure 2. Well-circumscribed nodule composed of spindle cells in the dermis(**A**; HE×40): without any atypia, mitotic activity and necrosis in the spindle cells (**B**; HE×400).

ropeptides, including substance P and glutamate, thus reducing central pain signals (19).

Conclusion

In conclusion, although piloleiomyoma is a tumor, it is rare and a benign neoplasm. Other than pain and discomfort seen on the trunk and limbs of the body there are no serious symptoms. The ideal treatment method option is surgery, but the problem with that treatment is that the lesions have tendency to recur. Medicamentous therapy plays a limited role, but calcium-channel blockers and α-adrenergic blockers may help in palliating or eliminating associated pain through inhibition of smooth muscle contraction. Due to the rarity of this illness and lack of conclusive treatment it is open for discussion.

Abbreviations

MCUL – Multiple Cutaneous and Uterine Leiomyomatosis
HLRCC – Hereditary Leiomyomatosis and Renal Cell Carcinoma

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Piloleiomiom manifestovan u vidu multiplih kutanih nodula – prikaz slučaja

Sažetak

Uvod. Piloleiomioma je redak benigni tumor čiji je uzrok mišić erektor dlake a predstavlja 5% svih leiomioma. Može biti solitaran i multipli, Multiple lezije su još uvek izazov za kliničare pošto su opcije za njihovo lečenje veoma ograničene. **Prikaz slučaja.** Prikazujemo slučaj dvadesetpetogodišnjeg muškarca, koji je imao bolne papule i nodule na vratu i grudima u trajanju od tri godine. Prilikom fizikalnog pregleda viđene su multiple

crvenobraon papule i noduli na koži u desnoj mamarnoj regiji i levoj submandibulanroj regiji. Histopatološkim pregledom uzorka panč (*punch*) biopsije otkriveni su jasno izraženi noduli sastavljeni od vretenastih ćelija. Slučaj je prijavljen kao kutani leiomiom (piloleiomiom). Pacijent je dobio 5 mg amlodipina dnevno i bio je pod kontrolom. **Zaključak.** Idealna opcija lečenja pilolei-omioma je hirurška ekscizija, ali problem kod tog tretmana je što lezije imaju tendenciju recidiva. Medikamentna terapija ima ograničenu ulogu, ali blokatori kalcijumovih kanala i α-adrenergični blokatori mogu pomoći u olakšavanju ili eliminisanju pratećeg bola tako što inhibiraju kontrakciju glatkih mišića.

Ključne reči: Leiomiomi; Kožne neoplazme; Tumori glatkih mišića; Biopsija; Blokatori kalcijumskih kanala; Alfa-adrenergični antagonisti; Retke bolesti

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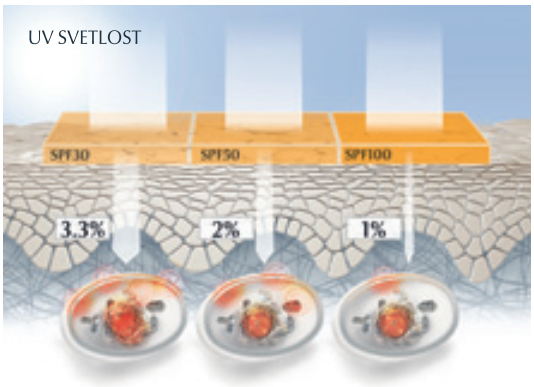

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