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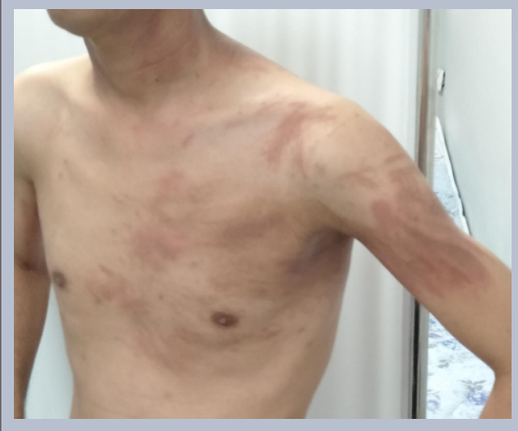

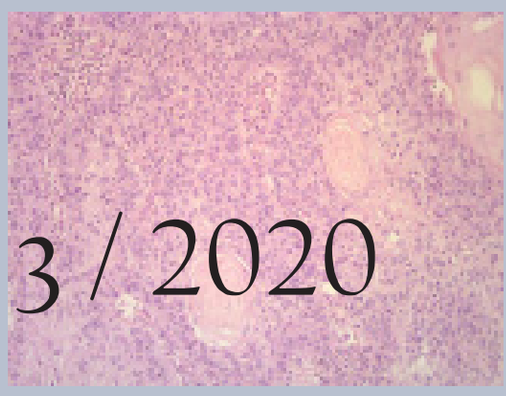

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Editorial Pages

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Editorial Board

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Our Dermatology Online

Original Article

An investigation of the effects of acitretin on erectile function

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ABSTRACT

Background: Acitretin is a second-generation oral retinoid compound used as a treatment option for various dermatological disorders. The effects of the drug on erectile function have not been fully determined yet. We aimed at investigating whether patients taking acitretin develop erectile dysfunction (ED). **Materials and Methods:** The study included 40 male patients who presented to the Dermatology Polyclinic of Okmeydanı Training and Research Hospital between October 2014 and April 2016 and started treatment with acitretin. Exclusion criteria included psychogenic and psychiatric disorders, neurological disorders such as multiple sclerosis, diabetes mellitus and endocrine disorders, arteriogenic and venous disorders, alcohol and tobacco use, penile disorders, obesity, a history of drug use, a score of above 10 points in the Beck Depression Inventory (BDI), hyperlipidemia, and an age above 65 years. Having obtained the informed consent, the patients were asked to complete the International Index of Erectile Function (IIEF) questionnaire before and after three months of therapy. The patients were evaluated by calculating their scores and a statistical analysis was performed. **Results:** A total of 40 patients were included in the study. A comparison of the IIEF scores before and after three months of therapy revealed that the scores were significantly lower after three months of therapy ($P < 0.0001$). ED was diagnosed in 30 patients (75%) at the beginning of therapy and in 35 patients (87.5%) after three months of therapy. A comparison of baseline and 3-month IIEF grades revealed that the number of patients in the second group was significantly greater after three months of therapy with the drug ($P = 0.001$). When the percentage of patients with erectile dysfunction at the baseline and after three months of therapy were compared, no significant change was observed in the percentage of ED at three months ($P = 0.11$). **Conclusions:** Because our study revealed that acitretin may cause ED, we believe that patients should be informed of this potential side effect before initiating treatment.

Key words: Retinoid; Hyperlipidaemia; Acitretin; Erectile dysfunction; Psychiatric

INTRODUCTION

Acitretin is a second-generation oral retinoid used by dermatologists for the treatment of dermatological disorders such as psoriasis, pityriasis rubra pilaris, and lichen planus [1]. Acitretin may cause some common side effects such as dry skin and mucosa, hyperlipidemia, muscle and joint pain, and hepatitis [2].

Erectile dysfunction is defined as the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse. Erectile dysfunction may be due to various reasons, including psychogenic and organic factors, endocrine disorders, and drug use [3].

Data on the effect of acitretin on sexual function is limited. The literature provides no studies that would investigate whether acitretin causes erectile dysfunction in humans. Therefore, in this study, we aimed at investigating whether patients taking acitretin develop erectile dysfunction.

MATERIALS AND METHODS

The study included 40 male patients who presented to the Dermatology Polyclinic of Okmeydanı Training and Research Hospital between October 2014 and April 2016 and started treatment with acitretin for various dermatological disorders. Exclusion criteria included psychogenic and psychiatric disorders, diabetes mellitus,

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neurogenic disorders such as multiple sclerosis, endocrine disorders, arteriogenic and venous disorders, alcohol and tobacco use, penile disorders, obesity, a history of drug use, a score of above 10 points in the Beck Depression Inventory, hyperlipidemia, and an age above 65 years.

The study was approved by the ethics committee of Okmeydanı Training and Research Hospital. All participants provided written consent as approved by the local ethics committee.

The patients were asked to complete the International Index of Erectile Function (IIEF) questionnaire, of which the Turkish version was validated by Turunc et al., before the initiation of the treatment [4,5]. The biochemical parameters of cholesterol and triglyceride levels were measured for all patients at the baseline. The IIEF questionnaire was conducted again after three months of therapy and blood lipid values were measured. Patients with hyperlipidemia, as diagnosed on control examinations, were excluded. The patients were asked to complete the Beck Depression Inventory before and after three months of therapy. Patients with a calculated score of above 10 points were excluded [6,7].

The IIEF-5 questionnaire consisted of 5 questions. The patients were given a score between 1 and 5 based on their responses. Patients who scored 6 to 10 points, based on their responses, were included in the group of severe erectile dysfunction (first group); patients who scored 11 to 16 points were included in the group of moderate ED (second group); and patients who scored 17 to 21 points were included in the group of mild to moderate ED (third group). Patients with scores of 22 to 25 were not considered as having ED and were included in the fourth group. Following the calculation of the scores, a statistical analysis was conducted.

STATISTICAL ANALYSIS

Descriptive statistics of the measurements were calculated as means, Standard Deviations (SD), numbers, and percentages for frequencies and provided in tables. Mean scores before and after the drug were compared with a paired samples t-test. The Wilcoxon signed-rank test was used to compare the baseline and the three-month grades. The significance of the change that occurred in ED outcomes at three months was evaluated with the McNemar's test. In addition, the relationship between the drug dose and the change in score was evaluated with Pearson's correlation analysis and the independent samples t-test was used to determine if any difference occurred between the drug dose in patients with and without ED. Statistical significance was set at $P < 0.05$ and the software SPSS, version 18, was used for calculation.

RESULTS

A total of 40 patients aged 23–61 years (median: 41.2 years) were included in the study. These patients were given acitretin doses ranging from 10 to 35 mg.

A comparison of IIEF scores before and after three months of therapy revealed that the scores were significantly lower after three months of therapy ($P < 0.0001$) (Table 1).

When IIEF grades were compared before and after three months of therapy, it was observed that the number of patients in the second group was significantly higher after therapy, while the number of patients in the third and fourth groups was significantly lower after therapy ($P = 0.001$) (Table 2).

Erectile dysfunction was detected in 30 patients (75%) at the baseline (grade 2 in 12 patients and grade 3 in 18 patients). Erectile dysfunction was diagnosed in 35 patients (87.5%) after three months of therapy (grade 3 in 13 patients and grade 2 in 22 patients).

When the percentage of patients with erectile dysfunction at the baseline and after three months of therapy were compared, no significant change was observed in the percentage of erectile dysfunction at three months ($P = 0.11$) (Table 3).

Table 1: A comparison of the IIEF scores before and after three months of therapy

	N	Mean	SD	p*
Score 1	40	19.05	3.62	**< 0.0001**
Score 2	40	16.975	3.55	

*:Paired-samples t-test

Table 2: A comparison of the IIEF grades before and after three months of therapy

Grade*	Baseline		Month 3		p*
	Number	%	Number	%	
2	12	30.0	22	55.0	**0.001**
3	18	45.0	13	32.5	
4	10	25.0	5	12.5	

*:Wilcoxon signed-rank test

Table 3: A comparison of the percentage of patients with erectile dysfunction at the baseline and after three months of therapy

ED*	Baseline		Month 3		p*
	Number	%	Number	%	
No	10	25.0	5	12.5	0.11
Yes	30	75.0	35	87.5	

*:McNemar's test

The relationship between the change observed when the three-month scores were subtracted from baseline scores (difference between the baseline score and the three-month score) and the dose of the drug was investigated and no significant linear relationship was noted ($r = 0.151$, $p = 0.352$). This suggests that the change in score was not affected by the change in drug dose. In other words, no correlation could be found indicating that the change in score increases or decreases with the increase in drug dose.

Also, no significant difference was observed in doses taken by patients with and without ED at the baseline ($P = 0.362$), and the mean dose taken by the patients with ED was significantly higher at three months ($P = 0.020$). The mean values of drug doses taken by patients with and without ED at the baseline and at three months are provided in Table 4.

DISCUSSION

Retinoids are metabolites and synthetic analogs of vitamin A that play a very important role in dermatological treatments. Acitretin is a retinoid derivative and has been used in the treatment of dermatological disorders since 1988 [2]. Acitretin is a known teratogen that falls into group X, according to the FDA pregnancy classification, and is, thus, contraindicated during pregnancy [1]. Pregnancy is discouraged for three years after discontinuation of the drug in female patients. Such a limitation does not apply to male patients [8]. A study revealed that the amount of acitretin in the seminal fluid of male patients taking acitretin was 1/200,000 of the oral dose. Therefore, acitretin is considered to pose a minimal risk to the fetus while the male patient is taking the drug [9].

There have been some studies in the literature that investigated the effects of acitretin on spermatogenesis. A study of male lizards treated with all-trans retinoic acid revealed that retinoic acid severely depleted the seminiferous epithelium and, therefore, had a significant effect on spermatogenesis [10]. Lauharanta et al. performed the first study evaluating the relationship between acitretin and spermatogenesis. In this study, synthetic retinoids—including etretinate, acitretin, isotretinoin, and retinoic acid—were reported to show dose-dependent inhibition of fructolysis that evaluates sperm motility in ejaculated human spermatozoa in vitro [11]. However, other studies showed no effect of the drug on spermatogenesis. In our country, Sengor et al. conducted a study on rats and determined that the standard and high doses of acitretin did not affect spermatogenesis in rats [12].

There have been some case reports indicating that retinoids may cause sexual dysfunction. Rossi et al. reported erectile dysfunction in a 39-year-old patient with psoriasis after initiation of acitretin therapy. On a follow-up visit, the patient reported an inability to reach and maintain a penile erection sufficient enough to perform a sexual act, beginning from about 45 days after the initiation of therapy [13]. The literature provides two more case reports on the development of impotence associated with the use of etretinate. The development of impotence was observed after the readministration of the drug without the symptoms of depression in one of these cases [14,15].

Although the effects of retinoids on sexual function are not well-known, their effects on the male reproductive system have been investigated in some animal studies [16]. In a study conducted by Csaba et al., rats were divided into three groups: group one was given a single dose of retinol during the neonatal period on day 1 of birth; group two was given retinoic acid subcutaneously on days 1, 3, and 5; and group three was the control group. The sexual activity of the animals was assessed at month 4. The number of inactive males in the group given retinol was observed to be two times higher than in the control group ($P < 0.02$) [17].

The sexual activity of the animals in the group given retinoic acid was observed to be similar to that of the animals in the control group. However, it was noted that the number of single ejaculations was higher in the treatment group than in the control group ($P < 0.02$), while the number of multiple ejaculations was higher in the control group ($P > 0.05$), with a delay in time to the first ejaculation in the treatment group ($P < 0.01$). The authors suggested that neonatal retinoid exposure

Table 4: A comparison of drug doses taken by the patients with and without erectile dysfunction

					Drug dose				
ED at baseline*	N	Mean	SD	p*	ED after 3 months of therapy*	N	Mean	SD	p*
No	10	21.0	10.22	0.362	No	5	15.0	7.75	0.020
Yes	30	24.3	9.80		Yes	35	25.0	9.54	

*:Independent-samples t-test

may have affected sexual parameters because of the binding of nuclear steroid receptors. They reported that there might have been a deficiency in the selectivity of the steroid receptor capacity during early development and these receptors might have caused the abnormal imprinting by binding retinoids [17].

Previous experimental studies have also shown that the perinatal imprinting with retinol in adults causes an increase in the concentration of glucocorticoid receptors in the thymus and the affinity of uterine estrogen receptors [18].

In our study, a comparison of IIEF scores of patients before and after three months of therapy showed a significant reduction in scores after three months of therapy ($P < 0.0001$). Likewise, a comparison of baseline IIEF grades and three-month IIEF grades revealed a significant increase in the number of patients in the second group at three months ($P = 0.001$). However, when the percentage of patients with erectile dysfunction at the baseline and after three months of therapy were compared, a clinically significant increase of 12.5% was observed in the percentage of erectile dysfunction at three months, but without a statistical significance ($P = 0.11$). We believe that this might have been associated with the small number of patients studied.

The mechanism by which acitretin causes erectile dysfunction is unclear. As is known, retinoid receptors are members of a large receptor family that includes glucocorticoids, thyroid hormone, and the vitamin D3 receptor. There are two different nuclear receptor families: RAR (retinoic acid receptors) and RXR (retinoid X receptors). Retinoid X receptors may form a homodimer with another RXR receptor or a heterodimer with other nuclear receptors, such as thyroid hormone or the steroid receptor [19]. Therefore, the possible mechanism seems to be the inhibition of the activity of testosterone by retinoids by binding to the same site at the receptor molecule.

Testosterone plays an important role in the continuation of normal sexual function. Some animal studies found that a deficiency in testosterone may cause ED [20]. Thus, hormone levels may be questioned in patients who have developed retinoid-associated ED.

Some studies investigated the effects of retinoids on hormone levels as well as their androgenic effects but the results were contradictory. A study conducted by Karadag et al. showed that isotretinoin may lead to a slight reduction in pituitary hormone and testosterone levels [21]. Likewise, Rademaker et al. also observed a marked reduction in serum testosterone levels as a result of isotretinoin therapy [22].

However, there have also been studies in the literature that found no isotretinoin-related changes in hormone levels. Torok. et al. observed no significant difference in total testosterone, LH, or FSH with isotretinoin therapy [23]. Similarly, Marynick et al. found no statistically significant changes in serum DHEAS, total testosterone, LH, or FSH with isotretinoin therapy [24].

Gokalp et al. found no statistical difference between total testosterone levels before and after six months of isotretinoin therapy. It was concluded, hence, that isotretinoin does not exert its antiandrogenic effects through total testosterone [25].

Given the controversial results of these studies, we believe that it would be wrong to establish a direct relationship between ED and hormone levels. Rather, we propose that it would be more reasonable to establish such a relationship with the mechanism through binding to steroid receptors.

Nevertheless, our study had its limitations. One was the limited number of patients and the lack of control groups. This was because the patients were unwilling to take part in such a study, and it was difficult to convince them to participate, given the Muslim country that they lived in and the consequent sociocultural differences. In addition, a large number of exclusion criteria had to be selected, as many factors may cause erectile dysfunction. Another limitation was our inability to evaluate hormone levels.

In conclusion, our study showed that acitretin, a retinoid derivative, has the potential to cause ED. We believe, therefore, that patients should be informed of this side effect before initiating treatment.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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Brief Report

Herpes simplex virus serology in genital ulcer disease in a tertiary care hospital

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ABSTRACT

Background: Herpes genitalis is the most common sexually transmitted infection (STI). A herpes simplex virus (HSV) serology test may help in confirming the diagnosis and in identifying asymptomatic cases. Recently, there has been a rise in cases of genital lesions due to HSV-1. **Materials and Methods:** This study was conducted for a period of one and a half years on patients presenting themselves with genital ulcers in the STI clinic. HSV-1 and HSV- 2 serology tests were conducted on all the patients and data was analyzed with descriptive statistics. **Results:** Out of a total number of 68 patients, IgG and IgM were positive in 76.48% and 29.41% of the patients, respectively, for HSV-1. In HSV-2 serology, IgG and IgM were positive in 60.30% and 27.94% of the patients, respectively. Seroprevalence was higher in females. **Conclusion:** HSV-1 serology positivity was found to be higher than HSV-2, which may indicate the rising incidence of HSV-1 causing genital herpes.

Key words: Herpes genitalis; Genital ulcer disease; HSV serology

INTRODUCTION

Herpes genitalis is caused by the herpes simplex viruses (HSVs) consisting of two distinct serovars: HSV-1 and HSV-2. HSV-2 is usually associated with genital infections and is usually diagnosed clinically, but a laboratory confirmation is required particularly because of other conditions with similar presentations. Type-specific HSV antibodies are based on type-specific proteins—gG1 and gG2—and can distinguish between HSV-1 and HSV-2 infections. In practice, the diagnosis is usually reached on clinical grounds and with Tzanck smear, while culture, serology, immunofluorescence, and polymerase chain reaction (PCR) are available only in research centers [1]. Lately, there has been an increasing incidence of HSV-1 causing genital lesions [2,3].

AIMS AND OBJECTS

This study was undertaken to investigate the prevalence of HSV-1 and HSV-2 serology in patients with STI-related genital ulcers attending the STI clinic.

MATERIALS AND METHODS

This cross-sectional study was conducted for a period of one and a half years on patients presenting themselves with genital ulcers in the STI clinic at a tertiary care center in northeast India. HSV-1 and HSV-2 serology (IgG and IgM) tests were undertaken on all patients after taking written consent. HSV serology tests were based on the classic ELISA technique. Descriptive statistics was used to analyze the data. All patients with STI-related genital ulcers willing to undergo the tests were included in the study group, while those with non-venereal genital ulcers, those unwilling to undergo the tests, and those lost to follow-up were excluded from the study.

RESULTS

Out of a total of 68 patients, 53 were males and 15 were females. Sixty-four patients were clinically diagnosed with herpes genitalis, three were cases of syphilis, and one was a case of chancroid. The mean duration

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of disease in males at the time of presentation was 13.52 days while, in females, it was 10.06 days. Table 1 presents the distribution of the duration of disease in the study. Most (30.2%) of the male patients presented themselves after 6–11 days while the majority (53.3%) of females reported earlier, around 0–5 days after the onset of disease. Tables 2a and 2b show HSV-1 serology reports. IgG and IgM were positive in 76.47% and 29.41% of patients, respectively. The seropositivity was higher among females than among males for both IgG and IgM. The results were negative in 22.05% and 32.35% for IgG and IgM, respectively. Tables 3a and 3b show HSV-2 serology findings. IgG and IgM were positive in 60.30% and 27.94%, respectively, with a higher seropositivity rate in females than in males. However, the serology test was negative in 38.23% and 35.30% for IgG and IgM, respectively. IgG of both HSV-1 and HSV-2 was positive in 27 (39.7%) patients; IgM of both HSV-1 and HSV-2 was positive in six (8.8%) patients; while IgG and IgM of both HSV-1 and HSV-2 were positive in 11 (16.2%) patients. There were four (5.8%) patients in whom only IgG for HSV-1 was positive, a single patient in whom IgM for HSV-2 was positive, and no patients in whom only IgG for HSV-2 was positive. In seven (10.3%) patients, the serology was negative for IgG and IgM for both HSV-1 and HSV-2. Among non-herpetic cases, one case of chancroid had positive serology for both HSV-1 and HSV-2 and one case of syphilis had positive serology for HSV-1 (IgG) only. There was a single patient with herpes genitalis presenting themself with herpes labialis and whose IgG for both HSV-1 and HSV-2 were positive while IgM was equivocal for both HSV-1 and HSV-2. None of the other patients had oral lesions suggestive of herpes simplex labialis. The maximum positivity for both HSV-1 and HSV-2 serology was found in the age group of 21–30 years with 19 (27.94%) and 17 (25%) cases, respectively, followed by the age group of 31–40 years with 13 (19.12%) and eight (11.76%) cases, respectively, the most common age group for GUD in the study period. IgG was positive in patients who reported their symptoms as the first episode and IgM was positive in patients with a history of recurrence. Five (7.3%) patients were found to be HIV-infected, out of which three were males.

Table 1: Distribution of the duration of disease at the time of presentation

Duration(days)	Male n (%)	Female n (%)
0-5	16 (30.2)	8 (53.3)
6-11	19(35.8)	5 (33.3)
12-17	6 (11.3)	0 (0.00)
18-23	4(7.5)	0 (0.00)
>23	8 (15.9)	2 (13.3)
Total	53 (100)	15 (100)

Table 2 (a): HSV-1 serology (IgG)

Result	Male, n (%)	Female, n (%)	Total, n (%)
Positive	40 (75.47)	12 (80)	52 (76.48)
Negative	12 (22.64)	3 (20)	15 (22.05)
Equivocal	1 (1.89)	0 (0)	1 (1.47)
Total	53 (100)	15 (100)	68 (100)

Table 2 (b): HSV-1 serology (IgM)

Result	Male, n (%)	Female, n (%)	Total, n (%)
Positive	14 (26.42)	6 (40)	20 (29.41)
Negative	19 (35.85)	3 (20)	22 (32.35)
Equivocal	20 (37.73)	6 (40)	26 (38.24)
Total	53 (100)	15 (100)	68 (100)

Table 3 (a): HSV-2 serology (IgG)

Result	Male, n (%)	Female, n (%)	Total, n (%)
Positive	31 (58.50)	10 (66.67)	41 (60.30)
Negative	21 (39.62)	5 (33.33)	26 (38.23)
Equivocal	1 (1.88)	0 (0)	1 (1.47)
Total	53 (100)	15 (100)	68 (100)

Table 3 (b): HSV-2 serology (IgM)

Result	Male, n (%)	Female, n (%)	Total, n (%)
Positive	14 (26.42)	5 (33.33)	19 (27.94)
Negative	20 (37.74)	4 (26.67)	24 (35.30)
Equivocal	19 (35.84)	6 (40)	25 (36.76)
Total	53 (100)	15 (100)	68 (100)

DISCUSSION

The prevalence of STI during the study period was 2.52% (males: 67.20%; females: 32.79%), out of which GUD constituted 11.01%. The prevalence of STI remained more or less steady compared to an earlier study in the same setting [4].

Serologies for HSV-1 and HSV-2 were done for 68 patients. IgG and IgM were positive in 76.47% and 29.41%, respectively, for HSV-1, while IgG and IgM were positive in 60.29% and 27.94%, respectively, for HSV-2. The age group of 31–40 years was the most common age group for GUD during the study period, as well as for STI in a previous study. [4] In a study on STI among high-risk individuals, the incidence of any STI was the greatest among those aged 25–34 years [5]. However, HSV seropositivity was most common in the younger age group (21–30 years) in this study. HSV-2 positivity rose markedly with age in females while, in males, it remained low in the younger age group [6]. Another study also reported lower seropositivity in the younger age groups [3]. Seropositivity was comparatively higher

in females than in males for both HSV-1 and HSV-2. For HSV-1, IgG seroprevalence was 80% and 75.47% and IgM seroprevalence was 40% and 26.42%, respectively, in females and males. For HSV-2, IgG seroprevalence was 66.67% and 58.5% with an IgM seroprevalence of 33.3% and 26.42%, respectively, in females and males. A study from Karnataka also showed a higher prevalence of HSV-2 serology in females [7].

In the study, IgG was still positive even if patients reported their symptoms as the first episode and IgM was positive even though patients gave a history of recurrence. This may be due to the fact that some patients may already have been infected subclinically or that they may have failed to recognize the clinical signs due to the varied modes of presentation of herpes genitalis. Serological tests were advised regardless of the duration of disease at the time of presentation due to the possibility of patients not turning up for subsequent follow-ups due to the stigma associated with STI. The median time to seroconversion is generally 2–3 weeks after infection, and seroconversion may be delayed up to six months after infection [8]. Moreover, the absence of antibodies to gG-1 and gG-2 does not necessarily rule out the presence of an HSV infection. A negative HSV serology only implies that one has made no antibodies to a particular antigen and a false negative result may occur if the humoral immune response to gG is inadequate or delayed, or if the infecting virus is gG-deficient [9]. In the aforementioned study, IgG of both HSV-1 and HSV-2 was positive in 27 (39.7%) patients; IgM of both HSV-1 and HSV-2 was positive in six (8.8%) patients; while IgG and IgM of both HSV-1 and HSV-2 were positive in eleven (16.2%) patients. Whether these findings denote co-infection with both HSV-1 and HSV-2 needs further evaluation, as only one patient had both oral and genital lesions, and the rest of the patients denied a history of oral lesions. HSV-1 has been identified as the causative agent in the majority of first-episode genital herpes infections [3,8].

In a study from Mumbai, among patients with clinical evidence of genital herpes, 94.2% were positive for both HSV-1 and HSV-2. In the cases of first-episode herpes genitalis, 66% were positive for HSV-1 and HSV-2, whereas, in recurrent genital herpes, 96.4% were positive for HSV-1 and HSV-2. 72.6% of patients without a history suggestive of genital herpes were positive for HSV-2 serology [2]. In the above study, 7.3% of the patients were found to be HIV-infected. In HIV-infected patients, genital herpes may result in severe and atypical clinical presentations [11], which was also seen in some of our patients. There has been evidence of a direct effect of HSV-2 infection on HIV acquisition along with a significantly higher HIV risk associated with the incidence of HSV-2 infection than with prevalent HSV-2 infection [10,11].

CONCLUSION

In the above study, HSV-1 serology was found to be more prevalent than HSV-2 in patients with genital ulcers. Besides, seroprevalence was higher among females than among males for both HSV-1 and HSV-2. More randomized controlled studies with larger sample sizes are recommended in view of the importance of the transmission and acquisition of HIV in association with viral STI-like genital herpes.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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Our Dermatology Online

Case Report

Cutaneous side effects of hydroxyurea in a patient with thrombocytosis

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ABSTRACT

Thrombocytosis is a disorder in which the body produces an abnormally high number of platelets. Hydroxyurea is an anticancer chemotherapy drug used for the treatment of cancer and thrombocytosis. Long-term use of hydroxyurea is associated with cutaneous adverse effects and complications such as leg ulcers and non-melanoma skin cancers. A sixty-year-old male with diagnosed thrombocytosis began treatment with oral hydroxyurea 1000 mg daily four years ago. A year ago, he developed leg ulcers. An examination revealed multiple ulcers the size of a metal pair on both legs, multiple actinic keratoses, and one SCC. We must be aware of the possibility that leg ulcers may be a complication of HU therapy as well as always be careful in taking medical histories. Every nonhealing wound should be completely explored for rapid diagnosis. Prevention and early intervention should, therefore, be the mainstay of treatment.

Key words: Trombocitosis; Hidroxyurea; Leg ulcer

INTRODUCTION

Thrombocytosis is a disorder in which the body produces an abnormally high number of platelets, which play an important role in blood clotting. Platelets are blood particles produced in the bone marrow. They quickly dissolve and their life lasts relatively briefly, on average from 3 to 5 days. Thrombocytosis may be caused by diseases of the blood and bone marrow. When thrombocytosis is caused by bone marrow disorders, it is called autonomic, primary, or essential thrombocytosis or essential thrombocythemia.

The treatment of reactive thrombocytosis is directed to the cause. If the cause is previous surgery or injury that caused significant blood loss, thrombocytosis will not last long.

Essential thrombocytosis, for its treatment, requires the use of cytostatics, antiviral drugs, and aspirin. In most cases, platelet levels return to normal after the treatment of the underlying cause. Exceptionally, removing the spleen may cause lifelong thrombocytosis.

Hydroxyurea is an anticancer chemotherapy drug classified as an antimetabolite. It is used for the treatment of leukemia, thrombocytosis, head and neck cancers, malignant melanoma, and ovarian cancer in the case of no response to standard therapy.

The side effects of hydroxyurea are very rare and almost always reversible after the completion of treatment. The severity of the side effects depends on the dose of the drug: high doses more often cause unwanted effects.

The most common side effect is a low blood count, occurring in more than 30% of patients taking the drug.

The following side effects are less common: hair loss, nausea and vomiting, diarrhea, mouth sores, poor appetite, nail thickening, nail banding, discoloration of the skin or nails, darkening of the skin where a previous radiation treatment has been given.

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In the last years, patients on long-term hydroxyurea and with cutaneous ulcerations have been reported.

Hydroxyurea and Skin Problems

Hydroxyurea is an oral antimetabolite that prevents DNA synthesis and promotes cell death by inhibiting ribonucleoside reductase, an important enzyme in the cell cycle. This drug is used in the treatment of chronic myeloproliferative neoplasms [1]. Long-term use of hydroxyurea is associated with cutaneous adverse effects and complications such as leg ulcers and nonmelanoma skin cancers [2].

Leg ulcers are a relatively frequent issue in patients with thrombocytosis under treatment with hydroxyurea. The pathogenesis may be multifactorial but remains unknown.

Concomitant arterial or venous disease may play a role in the occurrence of ulcerations.

CASE REPORT

We report a patient with diagnosed myeloproliferative disorders who developed hydroxyurea leg ulcers and multiple actinic keratoses. A sixty-year-old male was diagnosed with thrombocythemia five years ago. A year after, he began treatment with oral hydroxyurea 1000 mg daily. A year ago, he developed leg ulcers. An examination revealed multiple ulcers the size of a metal pair on both legs and multiple actinic keratoses. Because AK is difficult to differentiate from other malignancies with the naked eye, we made dermoscopy for the final diagnosis (Fig. 1). All the lesions were treated with cryotherapy except one, which was suspected for a squamous cell carcinoma. The suspicious lesion was removed surgically. Histopathological findings showed a moderately differentiated squamous cell carcinoma with a formation of keratin beads and mild chronic inflammation of the growth front and areas of infiltration (Figs. 2a and 2b).

The bilateral cutaneous ulcerations were painful and well-defined, with a livid border and a yellow fibrinous base. The ulcers had been open continuously without signs of healing for three months and had not responded to local treatment. The treatment involved compression bandages combined with a silver dressing and topical creams, gels, and ointments. None of these treatments gave the desired result.

Biopsy specimens were taken and histopathology revealed dermal fibrosis and occlusion of small capillaries.

Finally, we decided to replace the hydroxyurea with another drug in agreement with the hematologist. Hydroxyurea treatment was discontinued and oral busulfan therapy was started. In just two months, we saw a reduction in the size of the ulcers (Figs. 3a and 3b), with compression bandages and an antiseptic dressing. In three months, the patient recovered completely (Figs. 4a and 4b).

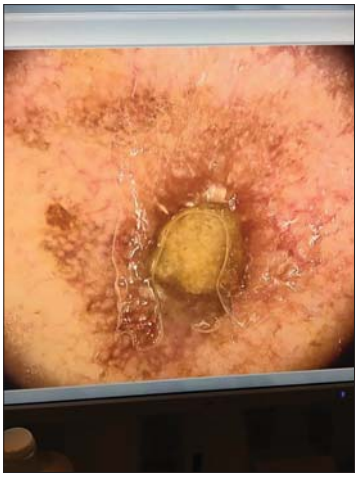

Figure 1: Dermoscopy of actinic keratosis growing into a squamous cell carcinoma: a central mass of keratin, a red pseudonetwork ("strawberry pattern"), and increasing neovascularization.

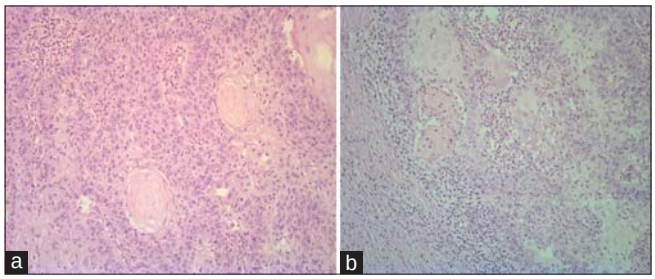

Figure 2: (a-b) Histopathological findings showing a moderately differentiated squamous cell carcinoma with a formation of keratin beads and mild chronic inflammation of the growth front and areas of infiltration.

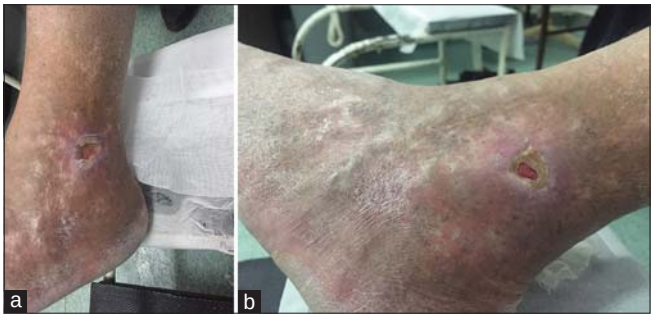

Figure 3: (a-b) Two months after discontinuation of therapy with hydroxyurea: well-defined with a livid border and a shallow base.

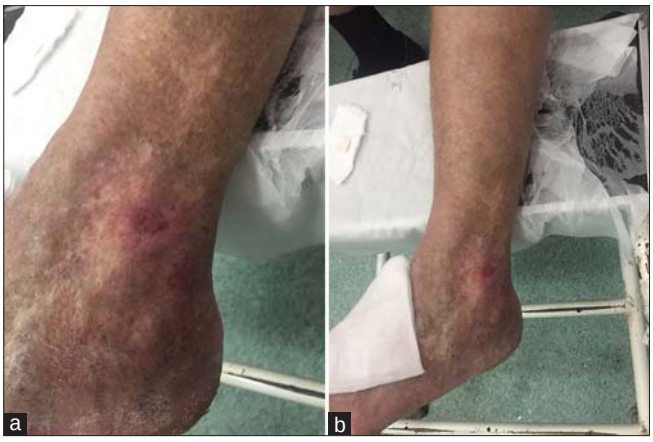

Figure 4: (a-b) Three months after discontinuation of therapy with hydroxyurea: hyperpigmentation at the site of the former ulcer.

DISCUSSION

Hydroxyurea is usually well tolerated with a low toxic effect and is used for myeloproliferative disease therapy. However, cutaneous adverse effects, such as ulceration, have been described. Painful, nonhealing leg ulcers associated with hydroxyurea therapy have rarely been reported [3].

Numerous reported studies confirm the role of hydroxyurea therapy in the occurrence of leg ulcerations.

The pathogenesis of HU-induced ulceration may be multifactorial. Literature data reveals that most patients with HU-induced leg ulcers had been treated with more than 1 g of HU per day for at least one year [4,5]. Poor response to local and systemic therapy is a typical feature of HU-induced leg ulcers, and discontinuation of the drug is often required to achieve complete wound healing. In the case that we described, leg ulcerations developed after four years of treatment with HU. With the discontinuation of HU treatment, the ulcers were reduced. Sometimes, the management of complicated resistant HU-related ulcers requires surgical therapy, such as skin grafting.

CONCLUSION

We must be aware of the possibility that leg ulcers may be a complication of HU therapy and always be extremely careful in taking medical histories. Complications may appear even years after HU treatment.

Every nonhealing wound should be completely explored for rapid diagnosis. Prevention and early intervention should, therefore, be the mainstay of treatment.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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Our Dermatology Online

Case Report

A late onset of nevus of Ota in a 38-year-old female

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ABSTRACT

Nevus of Ota (NOO) is a blue-grey, usually unilateral macule of the face with a distribution following the first two branches of the trigeminal nerve. It is congenital in around 50% of cases. Onset after 25 years of age is rare and may be confused with other diagnoses, especially melanoma. We report the case of a 38-year-old Moroccan female with a late onset of NOO. Although late-onset NOO is rare, it should be kept in mind since there are good results with laser treatment, which can improve the aesthetic damage and, consequently, the quality of life of the patient.

Key words: Naevus of Ota; Congenital; Late onset; Laser

INTRODUCTION

Nevus of Ota (NOO), also known as oculodermal melanocytosis or nevus fuscoceruleus ophthalmomaxillaris, is a mottled, blue-grey macule usually located unilaterally. It is congenital in around 50% of cases, while, in other cases, it appears by the second decade of life [1]. Onset after 25 years of age is rare [2]. We report the case of a Moroccan female patient with a nevus of Ota, which appeared at the age of 38.

CASE REPORT

A 38-year-old Moroccan female presented herself with a solitary, relatively well-defined, blue-grey, mottled patch on the left cheek going to the nasolabial fold with brownish lentigo-like macules on the same cheek of a five-months duration (Fig. 1). Dermoscopy revealed a whitish-gray veil with brownish lentigo-like macules on top and some fine white dander (Fig. 2). The patient stated that the lesion had gradually darkened for the last months. She denied any previous skin lesions or use of topical skin preparations at this site. A skin biopsy revealed dendritic melanocytes with oar extensions filled with melanin pigment. These widely spaced elements within a moderately fibrous dermis are often arranged parallel to the skin surface. An ophthalmological examination revealed a scleral pigmentation on the left eye (Fig. 3) with a normal baseline ophthalmological evaluation. There was no pigmentation of the oral mucosa.

DISCUSSION

Nevus of Ota (NOO) generally presents itself within the first year of life with a second peak around puberty [2]. It is a fairly common pigmentary disorder in Asians. Recent data from a Korean study of 87 cases revealed that the peak age of onset was during the first ten years (50.6%). In these studies, onset after the age of twenty-five years was not seen. In the English literature, only two cases of nevus of Ota had the onset at more than 30 years [1]. Ours is among the rare cases of a late appearance of a nevus of Ota (in a 38-year-old Moroccan female). Clinically, it manifests itself as speckled dark-brown to bluish unilateral macules involving the periorbital region, forehead, temple, cheek, or nose, corresponding to the distribution of the first two branches of the trigeminal nerve [1].

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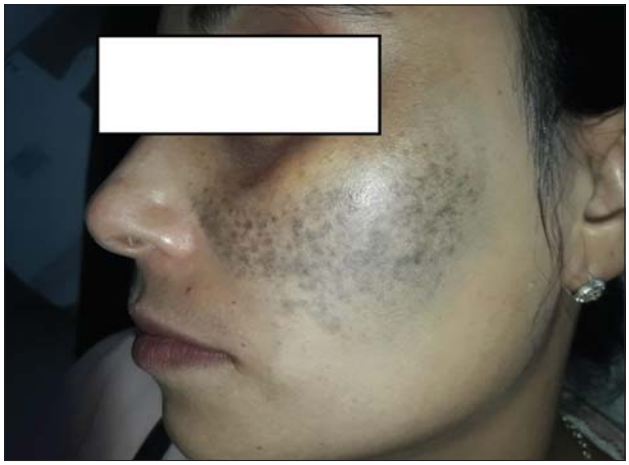

Figure 1: A nevus of Ota on the left cheek.

Figure 2: Dermoscopy of a nevus of Ota.

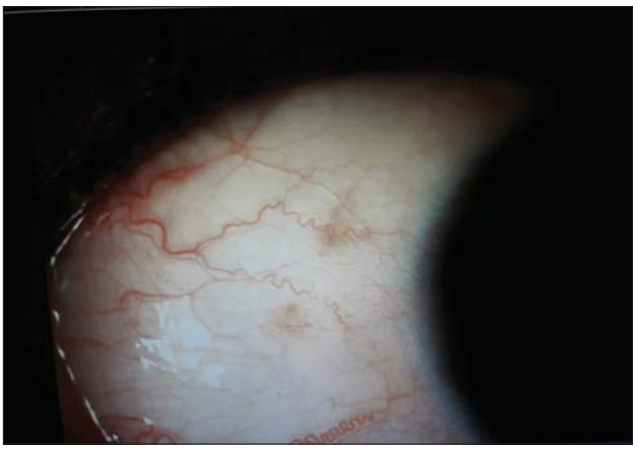

Figure 3: Scleral pigmentation of the left eye.

Q-switched ruby laser (QSRL) has been the type of laser most widely used for NOO. Q-switched alexandrite (QSA) and Nd:YAG lasers are as effective as Q-switched ruby laser. As QSRL has a higher absorption spectrum for melanin, it may lead to pigmentary abnormalities in Asian skin and, hence, Q-switched 1064 nm Nd:YAG laser is the preferred choice for pigmented skin. The same is not true for the Western skin type, for which QSRL is preferred [3]. Recently, however, better results were reported with picosecond lasers, both 755 nm alexandrite and 1064 nm Nd:YAG lasers are efficacious for the treatment of NOO [4].

CONCLUSION

A late and especially acute appearance of a nevus may be confused with a melanoma, hence the importance of increased awareness of the existence of late-onset nevi of Ota, which may help dermatologists in appropriate diagnosis and treatment.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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Our Dermatology Online

Case Report

Dermatomyositis revealing an endometrial papillary serous carcinoma associated with a peritoneal carcinomatosis: A case report

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ABSTRACT

Dermatomyositis is a rare inflammatory disease of connective skeletal muscle tissues. Patients with dermatomyositis have a predisposition for the development of malignant tumors. We report the case of a 69-year-old female who presented herself with two-month face and limb erythemas, muscle weakness, followed by fifteen days of intermittent metrorrhagia. A physical examination revealed typical skin lesions, including erythema, in photo-exposed areas, ragged cuticles, and numerous ulcerations. A blood analysis revealed high muscle enzyme levels. A muscle biopsy revealed myositis and positive anti-TF1 antibodies. An endometrial papillary serous carcinoma was diagnosed by an etiological investigation and classified as stage IV by the FIGO classification. The patient was started on 2 mg/kg/day of prednisolone with concomitant palliative chemotherapy.

Key words: Dermatomyositis; Cancer; Paraneoplastic syndrome

INTRODUCTION

Dermatomyositis is a rare disease characterized by inflammatory myopathy (progressive, symmetric, proximal weakness) and typical skin lesions (Gottron's papules, heliotrope eruptions, periungual telangiectasias, and ragged cuticles). Adults diagnosed with dermatomyositis have an increased risk of malignancy, with the most common tumors being ovarian, cervical, uterine, gastric, and colorectal [1].

We report a case of dermatomyositis revealing an endometrial carcinoma in a Moroccan female.

CASE REPORT

A 69-year-old female consulted for face and limb erythemas associated with muscular weakness present for the last fifteen days and intermittent metrorrhagia present for the last two months.

A physical examination revealed an erythema in photo-exposed areas, hypertrophy, and pain of the cuticles on palpation, as well as numerous ulcerations at the lateral sides of the thighs, lateral sides of the arms, and at the finger pads (Figs. 1 – 3). Blood tests revealed high levels of muscular enzymes, and a muscle biopsy revealed myositis and positive anti-TF1 antibodies. Other examinations revealed endometrial papillary serous carcinoma. Local and general staging revealed multiple diffuse intraperitoneal nodular lesions and masses with an infiltration of mesenteric fat. Hence, the disease was classified as stage IV by the FIGO classification. The patient was started on 2 mg/kg/day of prednisolone with concomitant palliative chemotherapy.

DISCUSSION

The association between dermatomyositis and cancer has been recognized since the report of a case of dermatomyositis and cancer in 1916 by Stertz [2].

How to cite this article: Aburabie H, Zerrouki N, Khouna A, Zizi N, Dikhaye S. Dermatomyositis revealing an endometrial papillary serous carcinoma associated with a peritoneal carcinomatosis: A case report. Our Dermatol Online. 2020;11(Supp. 3):15-17.

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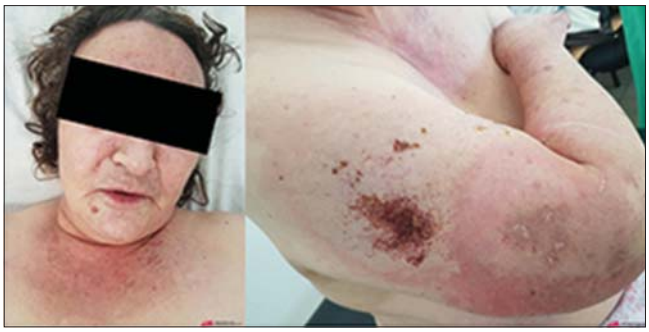

Figure 1: Erythema on the face and upper limbs as well as ulcerations on the arms.

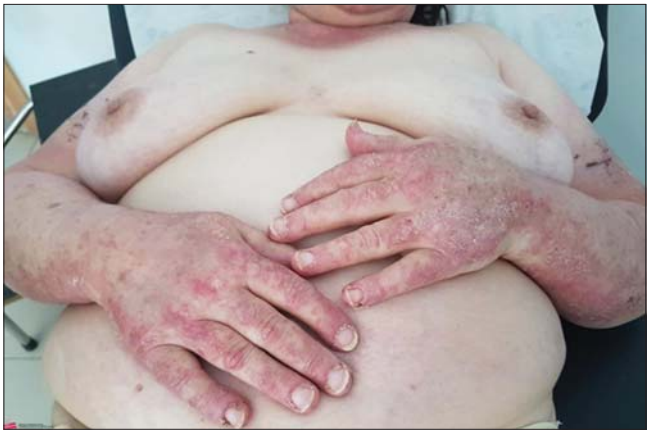

Figure 2: Erythema on the hands with ulceration (Gottron's papules).

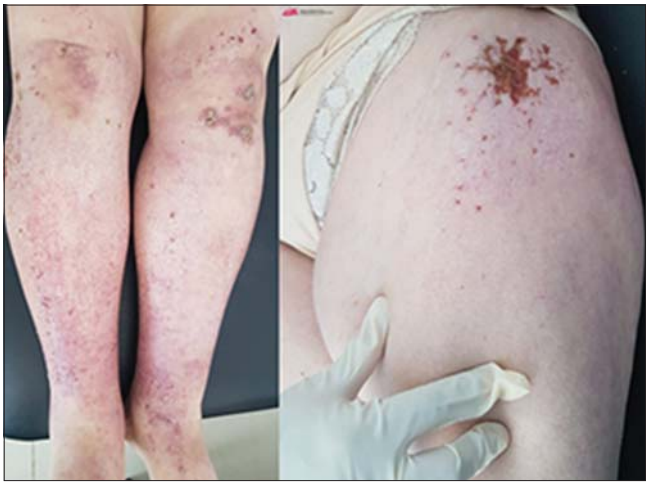

Figure 3: Erythema on the lower limbs with erosive lesions surmounted by hemorrhagic crusts.

While the pathogenesis of dermatomyositis and cancer is incompletely understood, it is thought to be caused by altered humoral and cellular immunity. Myositis-specific autoantigens are expressed at high levels in several cancers known to be associated with the development of inflammatory myopathy. Neoplasia may be detected before, during, or after the diagnosis of dermatomyositis [3].

Currently, the association with lung, pancreatic, stomach, and colon cancers as well as non-Hodgkin lymphomas is well established. Ovarian cancer appears to bear the highest association with dermatomyositis (13.3–26%); breast cancer is less common (13.5%); and the association of dermatomyositis with other gynecologic malignancies, such as endometrial cancer, is relatively rare (1.7%) [2]. One patient out of ten patients with gynecological cancer had endometrial carcinoma associated with dermatomyositis [3,4].

Paraneoplastic dermatomyositis is statistically related with some clinical and biological criteria, such as the sudden onset of symptoms, necrotic lesions or periungual erythema, an age beyond 50 years, and some serum antibodies, such as antibodies to transcription intermediary factor (TIF)-gamma, anti-p155, and antibodies to nuclear matrix protein (NXP)-2, anti-MJ, and anti-p140. Conversely, the presence of myositis-specific (anti-synthetase antibodies, anti-Mi2, and anti-SRP) and myositis-associated antibodies (anti-RNP, anti-PM/Scl) appears to be associated with a decreased risk of malignancy [5].

CONCLUSION

In female patients with DM, a systematic evaluation for a possible gynecologic malignancy should be performed as it may be associated with severe clinical and biological presentations. Thorough history taking and a physical examination, including a rectal examination and breast and pelvic examinations, in females should be performed, as well as a further investigation, including computed tomography, a scan of the chest, abdomen, and pelvis, colonoscopy, mammography, and a Pap smear [1].

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

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Our Dermatology Online

Case Report

Bleomycin-induced flagellate erythema in a patient with a germ cell tumor

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ABSTRACT

Flagellated erythema is a rare skin toxicity specific to bleomycin caused by a low concentration of bleomycin hydrolase at the cutaneous level. Herein, we study a clinical case of flagellate erythema in a 37-year-old male followed for stage-IIIA testicular seminoma of good prognosis. Eight days after administration of the first BEP chemotherapy treatment (bleomycin + etoposide + cisplatin), the patient presented a linear flagellate erythema on the trunk. The patient's condition improved subsequently under symptomatic treatment.

Key words: Flagellated erythema; Skin toxicity; Bleomycin; Testicular Seminoma

INTRODUCTION

Bleomycin is an antitumor antibiotic derived from *Streptomyces verticillus* that, at low concentrations, produces a cytostatic effect by inhibiting mitosis and that, at high concentrations, blocks the incorporation of thymidine in the DNA. This way, the drug stops the S phase of the cell cycle and causes the cleavage of the DNA [1]. Discovered in Japan in 1966, it is generally used in combination with etoposide and cisplatin (the BEP protocol) for the treatment of germ cell tumors and lymphomas [2]. Bleomycin becomes inactivated in most tissues by the enzyme bleomycin hydrolase, which cleaves the ammonia group from the bleomycin. Its side effects are most often seen in the lungs and skin, due to the low concentration of bleomycin hydrolase, which leads to greater accumulation of the drug [3].

Herein, we study a clinical case of cutaneous erythema-type toxicity secondary to the use of bleomycin.

CASE REPORT

The following is a case of a 37-year-old male who consulted for an increased abdominal volume associated with constipation, pollakiuria, and a deterioration of the general state. On examination, the patient had a WHO performance status of 1 and a poorly defined hypogastric sensory mass. An abdominal CT scan revealed a large intraperitoneal hypogastric formation with right iliac and lateral aortic adenopathy. The tumor markers beta human chorionic gonadotropin (beta-hCG) and lactate dehydrogenase (LDH) were raised to 204 IU/mL and 714 U/L, respectively. Alpha-fetoprotein (AFP) was normal, at 1.05 ng/mL. The patient had an orchidectomy. A histological study revealed a malignant tumor proliferation infiltrating the conjunctivo-adipose tissue leading to a germinal tumor. Immunohistochemistry revealed a seminoma with the expression of PLAP+ (placental alkaline phosphatase) and CD117+. A postoperative assessment revealed the level of beta-HCG elevated to 12.7 IU/mL with other markers normal. A thoracoabdominopelvic CT scan revealed three pulmonary nodules and intraperitoneal lymphadenopathy of secondary appearance ranked stage IIIA (according to the updated 2009 AJCC classification) and of good prognosis (according to the International Germ Cell Cancer Collaborative Group classification). A multidisciplinary consultation meeting decided, then, to initiate BEP-type chemotherapy involving bleomycin (DT = 30 UI; J1, J8, J15), etoposide (100 mg/m2; J1 to J5), and

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cisplatin (20 mg/m2; J1 to J5) for testicular seminoma. After the administration of bleomycin, the patient reported persistent cutaneous pruritus of the thorax, limbs, and trunk with linear post-scratching lesions after the eighth day. An examination revealed flagellated erythema associated with linear hyperpigmentation of the thorax (predominant on the anterior surface of the left thorax and the posterior thoracic area), arms (predominantly proximal left), and nape with scratching lesions (Figs. 1a and b). The patient was placed on an oral corticoid and an antihistamine. The patient's condition improved subsequently marked by a clear regression of the pruritus and erythema (Figs. 2a and b).

DISCUSSION

TThe main side effects of bleomycin are seen in the lungs and skin. This is explained by the absence of bleomycin hydrolase in these sites, an enzyme that rapidly inactivates bleomycin in most tissues [3].

Multiple skin toxicities have been reported: infiltrated purplish plaques, scleroderma lesions, erythema multiforme, and hyperkeratotic wart lesions of the knees and elbows. The specific skin toxicity of bleomycin is flagellated erythematous hyperpigmentation. Other rare skin manifestations, such as nail changes, alopecia, and stomatitis, have also been reported [4].

Figure 1: (a and b) Predominant flagellar erythema on the anterior surface of the left hemithorax, the posterior thoracic face, and the proximal left arm one week after the eruption.

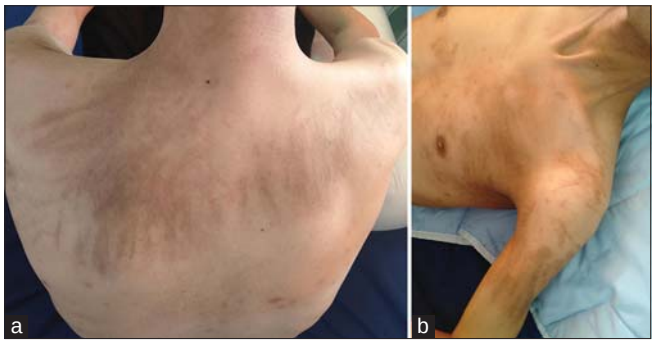

Figure 2: (a and b) Regression of the lesions two weeks later under symptomatic treatment.

Flagellated erythema and linear pigmentation were first described by Moulin in 1970. This specific reaction to bleomycin occurs in approx. 8–20% of patients receiving treatment with bleomycin for lymphomas and germ cell tumors with doses between 15 mg and 285 mg in the cases reported [5].

In our patient, the lesions appeared after the administration of a dose of 60 mg. The average time between treatment and the onset of the rash varies from 12 to 24 hours to 6 months [6].

The diagnosis remains clinical. Lesions predominate in the trunk and proximal limbs [1]. The majority of patients initially develop generalized pruritus several hours to several weeks after the administration of bleomycin. Then, a linear erythematous streak appears, which eventually progresses to a typical flagellated hyperpigmentation [1]. This is the case of our patient, who initially showed persistent pruritus with a secondary appearance of a characteristic flagellated hyperpigmentation after scraping the week following the second injection of bleomycin. The lesions affected the neck, trunk, and arms. This is consistent with data from the literature.

There is no typical histopathological feature characterizing bleomycin-induced flagellated dermatitis. Lesions reported in the literature include melanophages in the skin capillaries, hyperkeratosis, parakeratosis, vesicular pustules, lymphohistiocytic dermal infiltrate, and sometimes lymphocytic vasculitis [1]. Occasionally reported on skin biopsy patches is inflammatory skin infiltration with a predominance of eosinophils. Thus, in the acute phase, one may observe vacuolization in the basal layers of the epidermis, melanin incontinence, and dyskeratotic keratinocytes dispersed. In the later stages, only a handful of postinflammatory changes are found [7].

The etiopathogenesis is uncertain. All the hypotheses are based on the histological or ultrastructural aspects found. Some authors have mentioned a traumatic mechanism by scratching due to intense pruritus or vasodilation responsible for an increase in the concentration of bleomycin in the skin. There follows a reduction in epidermal renewal, which causes prolonged

contact between the melanocytes and the keratinocytes. However, studies have shown the clear appearance of linear streaks in the absence of direct trauma [7].

Regarding the treatment of flagellated erythema, opinions differ. On the one hand, it is reported that the erythema gradually improves six to eight months after stopping treatment. The characteristic residual hyperpigmentation may persist for several months [5]. On the other hand, an improvement in symptoms is observed after the application of topical corticosteroids or the use of systemic corticosteroids and an oral antihistamine. In addition, lesions may reappear with more intensity during a new treatment [8].

CONCLUSION

Flagellated erythema is a rare cutaneous toxicity related to the administration of bleomycin. The management of dermatitis is symptomatic with a good clinical evolution that may sometimes be marked by aesthetic sequelae.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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Our Dermatology Online

Case Report

Generalized bullous fixed drug eruption masquerading as toxic epidermal necrolysis

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ABSTRACT

Fixed drug eruption is an adverse cutaneous drug reaction by which a patient grows a skin lesion each time a drug is taken. Generalized fixed drug eruption is a severe form of fixed drug eruption by which the skin lesions clinically resemble toxic epidermal necrolysis. A female patient presenting herself with generalized bullous fixed drug eruption following the intake of an ofloxacin and ornidazole combination treatment given for diarrhea. We report this case to emphasize the difference between generalized bullous fixed drug eruption and toxic epidermal necrolysis.

Key words: Generalised bullous fixed drug eruption; Toxic epidermal necrolysis; Cyclosporine

INTRODUCTION

Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by dusky red patches or bullae occurring at the same site each time the offending drug is taken. FDE accounts for 10% of adverse cutaneous drug reactions. Generalized bullous FDE is an uncommon variant of FDE characterized by widespread bullae and erosions, which may mimic Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [1]. TEN, like FDE, is associated with a better prognosis than TEN. We report a case of generalized bullous fixed drug eruption (GBFDE) mimicking toxic epidermal necrolysis.

CASE REPORT

A 46-year-old female presented herself to the OPD with generalized itching and multiple erythematous patches and bullae present for the last three days. The patient developed these skin lesions after starting treatment for diarrhea. The patient was prescribed ofloxacin and ornidazole, then developed multiple painful fluid-filled lesions on the thighs, arms, and abdomen in a span of 24 hours (Figs. 1 and 2). The lesions progressed in size and number and ruptured to leave violaceous hyperpigmented patches all over the body. The patient had a similar episode in the past with the same medication.

On cutaneous examination, there were multiple erythematous patches with tense bullae distributed all over the body. Nikolsky's sign was positive. There was no epidermal peeling or target lesions. A routine blood examination was within normal limits. Renal function tests, liver function tests, and a diabetic profile were within normal limits. An electrolyte panel showed no abnormality, and blood and urine cultures were negative. The patient was started on systemic corticosteroids and cyclosporine 3 mg/kg for five days. The intravenous antibiotic linezolid and a topical antibiotic cream were given. The patient showed an improvement of the skin lesions within 48 hours of initiating treatment. There were no new lesions, and the existing lesions were showing signs of healing. The patient was discharged after five days without complications.

DISCUSSION

An adverse drug reaction is a reaction that is noxious and unintended and that occurs at dosages normally used for

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Figure 1: An eroded skin following the rupture of the bullae.

Figure 2: Crusting and pigmentation of the lips.

prophylaxis, diagnosis, or treatment of a disease or for modification of a physiological function. It may range from common transient and benign erythema, occurring 6–9 days after the introduction of a new drug, to the most severe forms, which affect fewer than 1/10,000 patients.

Fixed drug eruption (FDE) characteristically recurs in the same site or sites each time the same drug is administered; with each exposure, however, the number of the sites involved may increase. Acute lesions usually develop 30 minutes to 8 hours after drug administration. Clinically, they appear as sharply marginated, round or oval itchy plaques of erythema and edema becoming dusky violaceous or brown, and sometimes vesicular or bullous. The eruption may initially be morbilliform or scarlatiniform or may resemble erythema multiforme. As healing occurs, crusting and scaling are followed by pigmentation, which may be especially persistent and occasionally extensive, especially in pigmented individuals. The lesions are distributed over the hands, feet, genitalia, and perianal areas.

The drugs most frequently associated with FDE are sulfonamides (in some series, up to 75% of cases), NSAIDs (in particular, phenazone derivatives), barbiturates, tetracyclines, and carbamazepine. Phenolphthalein-induced FDE is seen less commonly as it has been removed from a number of laxative preparations. A non-pigmenting variant of FDE, with large erythematous edematous plaques, has also been described, occurring primarily after the administration of pseudoephedrine [2].

GBFDE presents itself as severe bullous eruptions that may mimic TEN. GBFDE differs from SJS/TEN clinically by a short latent period and a lesser mucosal involvement, and, histopathologically, by a more extensive eosinophilic infiltrate and more dermal melanophages. Immunohistopathology shows more dermal CD4+ cells and FOXP3 cells and fewer intraepidermal CD56+ cells and granulysin+ cells [3,4]. There is decreased serum granulysin in GBFDE. Granulysin is secreted by natural killer cell and cytotoxic T cells, which are responsible for the epidermal necrosis seen in SJS/TEN. Serum granulysin may be detected in SJS/TEN in the early phase of the disease even before skin detachment and mucosa erosions. FDE occurs due to antibody-dependent cellular cytotoxicity. Interleukin 20 is responsible for the site-specificity of the lesions [2].

The treatment of FDE includes antihistamines and topical corticosteroids. GBFDE requires treatment with immunosuppressive drugs. Cyclosporine has shown benefit in the treatment of GBFDE [5]. It inhibits interleukin 2, the Fas receptor, Fas ligand interactions, and CD8+ mediated cytotoxicity. Our patient had severe generalized bullous lesions, less mucosal involvement, without any systemic complications. The patient was started on cyclosporine, and the lesions started showing signs of healing within 48 hours, without any new lesions.

CONCLUSION

We report a case of GBFDE following the intake of an ofloxacin and ornidazole combination, treated successfully with cyclosporine. We emphasize the importance of differentiating GBFDE from TEN/SJD as managing severe TEN/SJS is more challenging than managing GBFDE. A systemic approach and careful

observation are all that is required in the management of a severe drug rash.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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Our Dermatology Online

Case Report

"A tale of a burrowing bug" and Cydnidae pigmentation: A case report

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ABSTRACT

Exposure to insects or to their remains may range in severity from benign or barely noticeable to life-threatening conditions. The morphology of the cutaneous lesions may vary from several-millimeter asymptomatic noninflammatory lesions to large irritant dermatitis lesions, depending on the severity and the insects involved. A 3-year-old child presented with asymptomatic brownish patches on the bilateral soles persistent for a day. The mother gave a history of a visit to a temple and the onset of the lesions after the visit. A detailed examination reached the diagnosis of Cydnidae pigmentation. One of the benign conditions caused by the "burrowing bug" is Cydnidae pigmentation. As the lesions usually involve the acral areas, it has to be differentiated from other pigmented conditions, such as acral melanomas, lentigines, petechiae, and chemical/dye-induced pigmentations.

Key words: Cydnidae pigmentation; Chilocoris assmuthi; Burrowing bug

INTRODUCTION

Human cutaneous disorders may result due to multiple causes, such as nutritional deficiencies, toxins, bacterial or fungal infections, exposure to insects, exposure to chemicals, pollution, and medications. Insects cause varied patterns of dermatologic problems but, usually, these are inflammatory skin lesions [1]. Cydnidae pigmentation is caused by Chilocoris assmuthi, which belongs to the Cydnidae family, to the Hemiptera order, and to the Heteroptera suborder, which is known as the burrowing bug, and which is uncommon in urban areas [2].

CASE REPORT

An anxious, worried mother with a three-year-old son entered our dermatology outpatient department during the monsoon season with complaints of a sudden appearance of brownish patches on the bilateral soles of her son persistent for the last day. The lesions were asymptomatic in nature.

On clinical examination, multiple brown hyperpigmented macules and patches of varying sizes and shapes with streaky pigmentation in several places were present on the plantar aspect of both feet (more on the pressure-bearing sites). They were non-blanchable and non-tender, and the surrounding skin was normal (Fig. 1).

On further investigation, the mother gave a history of visiting a nearby temple and walking barefoot as a custom and of an appearance of these patches after the visit. An examination of the mother revealed similar pigmented lesions on the bilateral soles.

The mother and the child were informed of the benign nature of the condition and were reassured.

DISCUSSION

Insects comprise the most diverse and numerous class of the animal kingdom, hence human contact with them is unavoidable [1]. They may cause skin damage in humans through mouthparts, fangs, stingers, etc.

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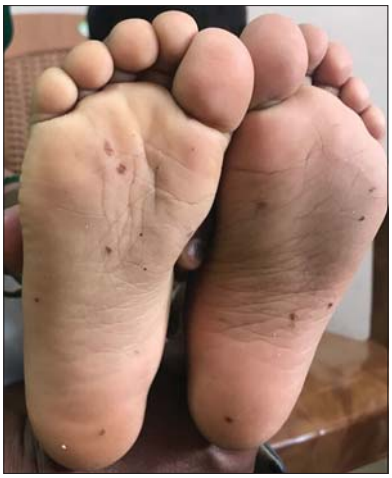

Figure 1: Multiple brownish hyperpigmented macules.

Hypersensitivity may develop against venoms or salivary proteins. Insects may also act as vectors for many infectious diseases [3]. Some of the skin disorders caused by arthropods include cimicosis (bed bug bite), pulicosis (flea infestation), pediculosis and Vagabond's disease (louse infestation), anaphylaxis (bee sting), burns due to the formic acid produced by Formicidae (ants), paederus dermatitis (blister beetle dermatitis), lepidopterism (caterpillar dermatitis), myiasis (maggot infestation), and Cydnidae pigmentation (due to Chilocoris).

The Cydnidae are one of the most speciose families within the Pentatomoidea superfamily and comprise more than 750 species [4]. Its representatives are usually known under the common name of *burrowing bugs* or *burrower bugs* due to their specific way of life, as many of them live in the soil (soil diggers) and feed on roots. Some are above the ground as plant-feeders and may also feed on seeds. They produce an odorous substance from special glands found in the thorax of adult insects, which is part of self-defense and is the cause of the pigmentation [5]. The pigmentation is not accompanied by any signs of inflammation, such as color, dolor, rubor, tumor, or functio laesa. The common site of pigmentation is the acral area, although other sites may sometimes be involved. The pigmentation usually fades away with acetone but not with soap and water [3]. The secretion is a mixture of hydrocarbonates and other derivatives, which functions as a repellent, may cause paralysis in the prey, and serves numerous other purposes, including danger signaling, helping in attracting mates, and, interestingly, exhibiting antimicrobial activity [6]. These insects are usually considered harmless.

In our case, the exogenous pigmentation caused by burrowing bugs was considered the most plausible diagnosis because of the similarities with the previously published cases [2,7,8]. The pigmentation due to these bugs is smaller (several millimeters) with streaky pigmentation and with tapering edges in several places [2]. Dermoscopy shows a cluster of oval to bizarre-shaped brown and shiny globules and clods with a superficial "stuck-on" appearance [3]. This may be differentiated from other causes of pigmentation, which may be due to other arthropods and coloring agents, by the involvement of a larger surface area. In cases of widespread lesions, one of the close differentials is petechiae secondary to dengue, which is also prevalent in the monsoon season. Cydnidae pigmentation may be differentiated from lentigines by the eruptive nature of the lesions and disappearance within several days [8].

CONCLUSION

This case of Cydnidae pigmentation is being published for its rarity. According to the authors' knowledge, this is the fourth case reported. Such pigmentation has to be differentiated from other causes, for instance, exogenous causes of pigmentation, lentigines, acral melanoma, dermatosis neglecta, and postinflammatory hyperpigmentation. The clue to the diagnosis of this pigmentation is a detailed history of brownish, sudden-onset macules of several millimeters with streaky or tapering edges usually occurring in the monsoon season and resolving spontaneously within a week, as well as dermoscopy findings: a "stuck-on" appearance with oval to bizarre-shaped brown shiny globules and clods.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

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