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Eruption of palmoplantar pustular psoriasis in patient treated with anti-androgen therapy for prostate cancer and aggravation of lesions after statin treatment

Case Report

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Abstract: The article focuses on the eruption of palmoplantar pustular psoriasis, which was documented in a 53-year-old man diagnosed with prostate cancer with bone metastases. This clinical finding was made during routine hormone therapy and palliative radiotherapy. The local improvement in skin lesions was achieved following administration of topical ointments and the use of UVA 311 nm radiation therapy. The management of prostate cancer in this subject resulted in malaise, onset of diabetes mellitus and increased concentration of serum lipids. Interestingly, a few days after the statin treatment was initiated, the intensive pustule eruption was observed as well as severe pain and burning sensation in the palms and soles. The dermatological treatment led to significant improvement. The patient is still receiving oncological therapy and is monitored by dermatologists on a regular basis.

Keywords: Psoriasis • Prostate cancer • *Hormone therapy* • *Statin*

1. Introduction

Psoriasis represents an immune-mediated chronic inflammatory skin disease. Cutaneous manifestation is always a predominant clinical feature. However, several reports suggested that there might be a link between psoriasis and disorders of other organs, including malignancy [1,2]. The complex etiopathogenesis of psoriasis includes interaction of various genetic, environmental and immunological factors.

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It is well known that certain factors are likely to trigger skin lesions or cause significant worsening of the clinical condition. The following factors were identified: injuries, Streptococcal infection, sunburn, some medications, emotional stress, anxiety, smoking habit, alcohol abuse or hormonal imbalance. In this case report the potential triggering factors include primary disease, drugs, anti-androgen treatment or stress. The manuscript focuses on the first case, in which the palmoplantar pustular psoriasis was induced in a patient with prostate cancer due to the cancer treatment and then aggravated by statins.

2. Case Report

In December 2011, a 53-year-old man was admitted to the Dermatology Outpatient Clinic with well-demarcated erythematous plaques, 6-7 cm in diameter, with small yellowish pustules on his soles and right palm. The lesions had been observed for four months and the patient had been treated with topical steroids and salicylic acid without clinical improvement. The eruption was probably associated with anti-androgen therapy and palliative radiotherapy because of prostate cancer (T2N0M1) diagnosed in November 2010. The patient had neither personal nor family history of psoriasis. There were no other triggering factors such as smoking, contact sensitizers, signs of infections.

The diagnosis of prostate cancer was stated on the basis of a biopsy which indicated gland cancer tissue Gleason 4 + 4 = 8. The scintigraphic examination confirmed the presence of metastases in the skeletal system. The pathological tissue was detected in the following areas: clavicles, the right elbow joint, the left 7th rib, L1-L3 vertebrae and pubic and ischial bones. The level of PSA was 24 ng/ml. Since November 2010 the patient had been treated with a hormone therapy: triptorelin 11.25 mg every 6 weeks with flutamide 250 mg three times a day. A decrease in PSA concentration was observed. In November 2011 the previous treatment was discontinued due to a gradual increase of pain in the skeletal system and an increase in PSA level up to 95.13 ng/ml. The next scheme of hormone therapy was introduced and it contained goserelin 10.8 mg with 3 month breaks with bicalutamide 50 mg 3x1 tablet and biphosphonate-pamidronate disodium intravenously in the dosage of 90 mg every month. Palliative radiotherapy was performed using 6MV X-rays on the pelvis and spinal area Th12-L5, with an overall dose of 20 Gy given in 5 fractions.

The histology of skin lesions revealed typical features of pustular psoriasis–multiple subcorneal pustules, acanthosis, parakeratosis and hyperkeratosis of the epidermis and elongated rete ridges with capillaries in dermal papillae surrounded by mononuclear inflammatory infiltration (Figure 1).

In March 2012 the patient was admitted to the Department of Internal Medicine due to elevated fasting glucose blood level of up to 160 mg/dl. The oral glucose tolerance test confirmed the diagnosis of diabetes. Long acting insulin titrated to the daily dose of 10 units as well as 30 mg of gliclazid MR per day were introduced and this treatment resulted in satisfactory management of glycaemia. Because the patient was previously diagnosed with arterial hypertension and chronic atrial fibrillation the daily treatment regimen including 25 mg of carvedilol, 5 mg of ramipril and 1.5 mg of indapamide SR was continued. The anticoagulant treatment (acenocoumarol) was continued with an adequate control of INR in the range of 2.17 to 3.3. The ECG revealed ST segment abnormalities in multiple leads manifested by horizontal ST segment depressions in leads I, aVL and V3-V6 of up to 1mm. The echocardiography showed no left ventricle contractility disorders with the EF of 70%. Hemodynamically insignificant mitral and tricuspid regurgitation waves were documented on a Doppler ultrasound.

The laboratory tests revealed hypercholesterolemia and the treatment with simvastatin at the daily dose of 20 mg was initiated accordingly. Within a few days from the introduction of simvastatin therapy, aggravation of skin lesions was observed (Figure 2). Due to the potential link between the mentioned lipid lowering agent and the deterioration of the subject's skin lesions, the simvastatin treatment was discontinued and dermatological consultation was ordered. The patient then received clemastine intravenously at the dose of 4 mg daily, 75 mg of rutoside and 300 mg of ascorbic acid per day

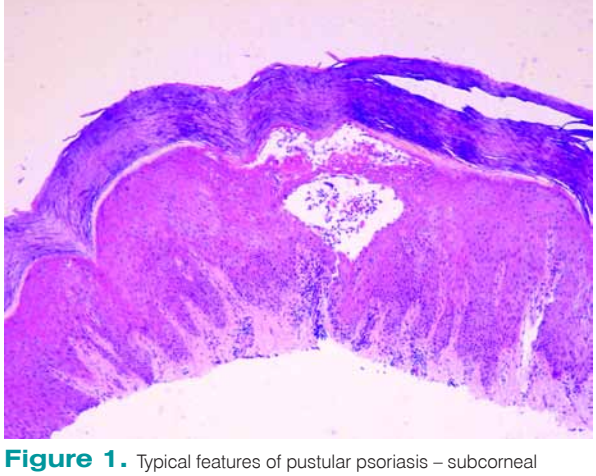

Figure 1. Typical features of pustular psoriasis – subcorneal pustule, acanthosis, parakeratosis and hyperkeratosis of the epidermis and elongated rete ridges with capillaries in dermal papillae surrounded by mononuclear inflammatory infiltration (H&E; objective magnification 5x)

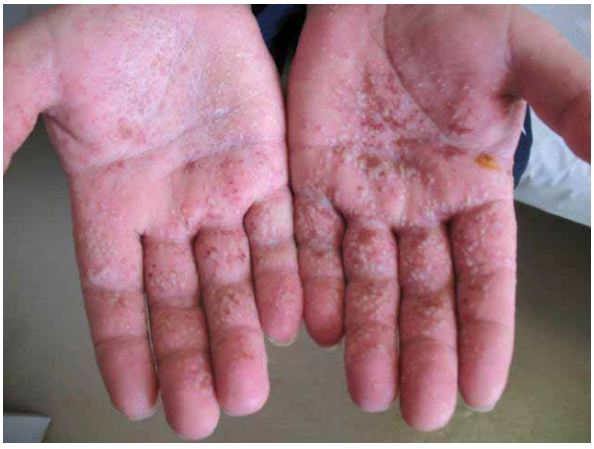

Figure 2. Multiple small yellowish pustules on the palms.

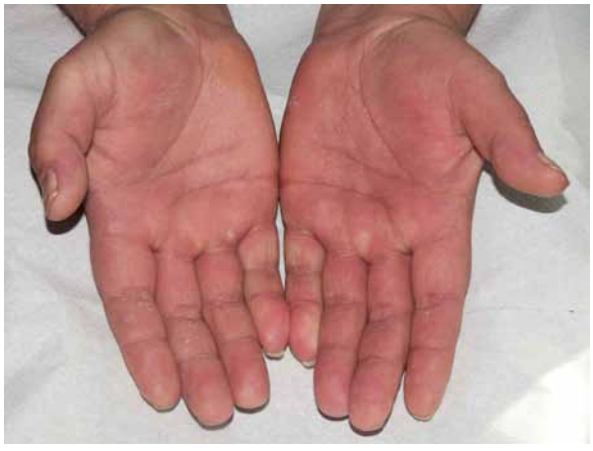

Figure 3. The palms after the treatment.

along with local application of tar ointment. A significant local improvement on the palms and soles was noted after several days of this treatment (Figure 3).

The dermatological treatment was continued with the local UVA radiation dosed from 0.03 J/cm^2 to 0.18 J/ cm^2 and tar ointment in concentration from 2 to 15%. The patient received different antihistaminic drugs (fexofenadine, desloratadine) as well as vitamin PP. The treatment resulted in improvement of palmoplantar pustular psoriasis.

The patient still underwent the anti-androgen treatment. Since April 2012, there has been a significant decrease of pain noted and the PSA level lowered to 10.38 ng/ml. In the conducted imaging examinations (CT) no regression of the disease was observed.

3. Discussion

As far as we are concerned, this case represents the first report describing the patient with prostate cancer and palmoplantar pustular psoriasis, in whom the skin condition was induced by the cancer treatment and then aggravated by statins.

In the available literature there is some evidence to suggest a relationship between psoriasis and cancerogenesis [1,2]. In our report the anti-androgen treatment caused the manifestation of psoriasis. It is well known that anti-androgen treatment in yet not well-defined mechanisms alters hormonal homeostasis and autoimmunological response.

Hormone deprivation therapy is one of the basic methods of diffused prostate cancer treatment. Its aim is to eliminate the influence of endogenous androgens on cancer cells. LH-RH (luteinizing hormone-releasing hormone) or GnRH (gonadotropine releasing hormone) analogues are used most often. LH-RH analogues stimulate the hypothalamus leading to excess and non-pulsatile LH-RH secretion that results in the loss of anterior pituitary gland sensitivity to react to this hormone. The decrease in luteinizing hormone (LH) production, which normally stimulates Leydig cells to produce testosterone, results in the reduction of the testosterone level to the range normally seen after surgical castration. Non-steroid anti-androgens, flutamide or bicalutamide, are used to complete this effect by blocking competitively the cellular receptors for androgens [3].

Androgens, including testosterone, play a significant role in immune mechanisms of the organism [3-6]. The research proved that castration and lowering the level of testosterone may lead to the development of immunological illnesses such as diabetes, multiple sclerosis, thyroid or joint inflammation in experimental animal models [7-9]. The testosterone administration in castrated animals can prevent or decrease the severity of these diseases [10-12]. Despite experimental data regarding the role of androgens in the process of modification of the immunological response, the exact mechanism of testosterone effect is still unknown. It is accepted that testosterone lowers IFN-γ expression and increases the expression of anti-inflammatory cytokine IL-10 by autoantigen-specific T lymphocytes [11]. The significant role of testosterone in modification of the immunological response and in the process of inflammation development is confirmed by the fact that the prostate cancer has become the model of studies on immunotherapy used in the treatment of cancer [13,14].

Moreover, it has been shown that androgens may influence the production and release of two crucial psoriasis pathogenesis cytokines, namely TNF and IL-6. In a series of studies both TNF levels and mitogen induced inflammatory response mediated by TNF were decreased by androgens [15-18]. The production of IL-6 was also blocked on the mRNA level by dihydrotestosterone [15]. What is particularly interesting in the study

of 72 men with localized prostate cancer, who received GnRH agonists, is the serum IL-6 levels were inversely correlated with serum total testosterone [18].

Although data is sparse, one may speculate that in our case anti-androgen effect of GnRH agonists might have induced cutaneous eruption through androgen-TNF feedback.

In our patient the psoriatic symptoms occurred one month after changing the scheme of hormone therapy. It is probably caused by drugs and androgen deprivation. Goserelin as a LH-RH synthetic analogue leads to an initial increase in the testosterone production in men. Eventually, after a period of about 21 days, the LH production is significantly reduced due to receptor down regulation, and sex hormones concentrations reach castration levels. Bicalutamide is a non-steroid anti-androgen which blocks androgen receptors and prevents testosterone and other androgens from binding to the receptors. It was shown that bicalutamide has even four times stronger influence on the prostate androgen than flutamide [19]. The course of psoriasis is modulated by pregnancy, menstruation and menopause. It has been proven that androgens protect against autoimmunization and show an immunomodulative activity [20]. However, hormone influence on psoriasis in male population was not studied so far. It cannot be excluded that anti-androgen therapy may influence manifestation of psoriasis.

What is more, cancer diagnosis and implementation of any oncological treatment are associated with an intense stress, which is why we cannot exclude the possible impact of stress hormones in our patient.

A similar case was described in 2010, in which psoriasis occurred due to hormonal treatment. That patient was also treated with the same scheme of hormone therapy because of prostate cancer. In contrast to our patient, who had diffuse disease and bone metastases, the other patient had localized and low risk prostate cancer [20]. Our case is then not the only one describing the possible link between anti-androgen therapy and psoriasis manifestation. Despite the lack of any other reports of this kind the hypothesis of this link cannot be rejected.

In the mentioned case presented by Ziółkowska et al. [20] psoriasis was documented to worsen one month after starting the therapy and quickly improved 3 days after hormonal treatment termination. In our case psoriatic lesions appeared during the first anti-cancer treatment and progressed after changing the androgen deprivation scheme. Authors of the aforementioned report attribute to some extent the possible connection between the antiandrogen therapy and psoriasis flare to the immunomodulatory effects of the androgens [20].

In another report [21] buserelin acetate, a GnRH agonist, induced or exacerbated palmoplantar pustulosis in two Japanese patients during ovulation inducement therapy. In one of the described subjects eruption appeared two days and in the second case approximately one month after introduction of hormonal treatment. In one of the described patients hormonal therapy was continued because of good control of cutaneous symptoms with topical medications. In the second patient there was slight improvement of condition after stopping the buserelin. It is worth mentioning in the context of possible additional aggravating factors that both of the above described women were smokers. Authors concluded that GnRH agonist may induce palmoplantar pustular psoriasis via hormonal shift or interaction between GnRH and TNF.

Statins are primarily considered as cholesterol-lowering agents. Recently, it was discovered that statins possess an immunomodulatory activity by supporting a Th1/Th2 skew to Th1, altering lymphocyte migration, inhibition of MHC-II induction and cytokine release on antigen-presenting cells, inhibition of mast cell degranulation and inhibition of Th17 cells and IL-17 production [22,23]. There was one pilot study performed by Shirinsky et al. in which statins was used specifically for the treatment of psoriasis [24]. At the end of 8 weeks of the treatment with simvastatin 40 mg/d, the researchers found a statistically significant decrease in the mean PASI score. The aggravation of psoriasis was observed after gemfibrozil [25], atorvastatin [26] and pravastatin therapy [27]. Eruption or aggravation of pustular psoriasis after the treatment with statins was not observed so far.

Disclosures

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