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Case Report

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Genetic and Hormonal Determinations in a Pair of Identical Twins with Early Onset *Psoriasis Vulgaris*: Case Report and a Brief Review of the Literature

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Abstract

Psoriasis vulgaris is a chronic inflammatory dermatosis with major impact on patients' life quality. The etiopathogenesis is multifactorial, depending on complex interactions between genetic and environmental factors.

We present the case of two female patients, identical twins of 33 years old, suffering from psoriasis vulgaris since childhood. Patient A developed specific lesions of psoriasis at the age of 7 and patient B started to develop psoriasis lesions on the scalp two years later. At the age of 31, patient A was diagnosed with psoriatic arthritis. Laboratory test results were within the normal ranges for both patients. Hormonal and immunological determinations revealed the presence of a high level of antithyroidperoxidase antibody in patient A and increased level of prolactin in patient B. Ultrasonographic assessment of the thyroid detected the presence of bilateral micronodules in the first subject. Knowing that early onset psoriasis is associated with the presence of Human Leukocyte Antigen Cw6(HLA-Cw6), we aimed to confirm this hypothesis for our subjects. Although HLA-Cw6 is the most frequent mutation in psoriasis patients and it is present in about two-thirds of the tested subjects,the genetic results for both patients were negative, strengthening the fact that other factors, the environmental one and the hormonal disorders had an important role in their psoriasis pathogenesis. Under these conditions, we emphasize the importance of including a hormonal evaluation approach of psoriasis patients in order to diagnose and treat pathologies that may be related with disease exacerbations.

Keywords*: psoriasis, pathogenesis, genetic, hormones, twins*

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Introduction

Psoriasis vulgaris is a chronic inflammatory dermatosis affecting approximately 2% of the world population with a major impact on patients' quality of life (1). It has a variable clinical aspect, from limited lesions up to extended areas on the entire skin surface, with or without affecting the joints.

Regarding onset age and inheritance, a bimodal distribution has been noticed in a large series of psoriatic patients. Two main types of psoriasis have been suggested: type I with onset before or at the age of 40, positive family history and frequent association with Human Leukocyte Antigen Cw6 (HLACw6); and type II with onset after the age of 40, negative family history and a normal frequency of the Cw6 allele (2).

As a multifactorial disease, with genetic determinism, psoriasis is influenced by the action of different hormones. For example, the thyroid hormones, triiodothyronine (T3) and free thyroxine (T4) cause an increase in the Epidermal Growth Factor (EGF) which leads to epidermal hyperplasia, also determining the proliferation of keratinocytes (3), an aspect commonly found in psoriasis vulgaris. On the other hand, sexual hormones, such as estrogens, modulate the immune responses: either by decreasing the psoriatic inflammation or by stimulating the proliferation at keratinocyte level (4). Prolactin (PRL), a pituitary hormone involved in lactation and reproduction has also been mentioned as an important immune modulator (5). As increased PRL levels seem to be associated with the psoriasis severity, we have also included it in the hormonal investigation of two identical twin psoriasis patients.

Case report

We present the case of two female subjects (patients A and B), identical twins, aged 33 years old, suffering from psoriasis vulgaris since childhood. The criteria for diagnosis were clinically and histologically confirmed (Figure 1). On clinical examination, both patients presented large erythematous, scaly plaques, located on the limbs, trunk, and scalp. Mention should be made that an informed consent had been previously obtained from the two subjects and the protocol was approved by the Institutional Ethical Committee.

Medical history

Family history was positive for psoriasis as a maternal aunt had the onset of the lesions in adolescence. Personal history revealed that patient A had developed specific lesions of psoriasis at the age of 7, during summer time, in a traumatic context at the knee level. Two years later, her sister started developing psoriasis lesions on the scalp.

Regarding treatment, both subjects received topical therapies since childhood, such as corticosteroids, keratolytics, and emollients with moderate response.

At the age of 31, the first sister (patient A) started having joint pains in the lumbar region and the psoriasis lesions extended. She was diagnosed with psoriatic arthritis (PsA), which was kept under control with occasional administration of nonsteroidal anti-inflammatory drugs (NSAIDs) over a period of one year.

At the age of 32 both patients started biological treatment with anti-Tumour Necrosis Factor alpha (antiTNF-alpha) blockers, with favourable response.

Clinical and biological assessment

Clinical diagnosis was confirmed by the histopathological examination of a 6 mm skin punch biopsy, collected from the right thigh of the patients. During physical examination the determination of blood pressure, height (meters), weight (kg), waist circumference, body

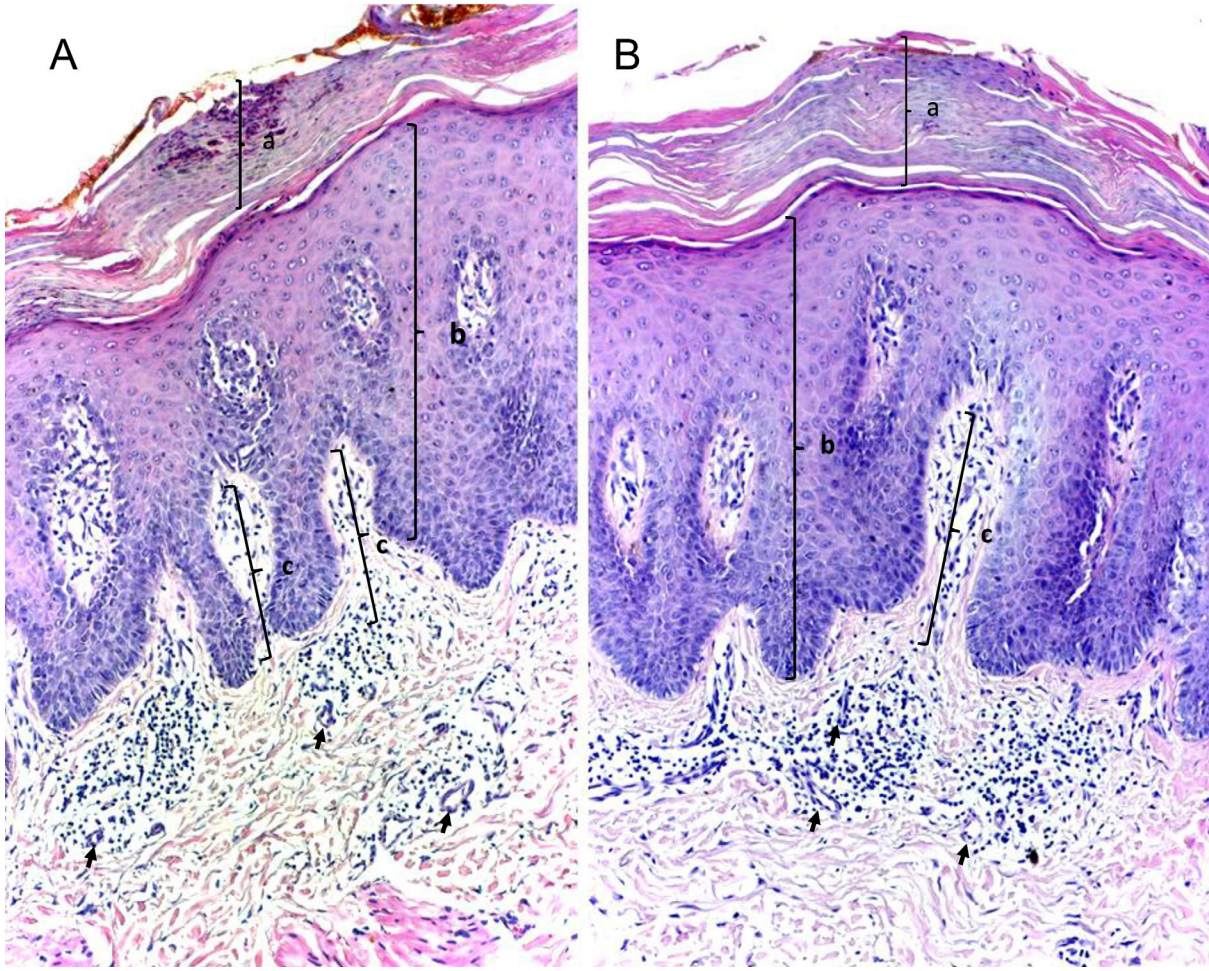

Figure 1. Histopathological examination (HE x40). Patient A (A). Patient B (B).
a: Hyperkeratosis with parakeratosis b: Epidermal achanthosis with regular elongation of rete ridges c: Long edematous dermal papillae Arrows: Large tortuous capillaries and perivascular lymphocytic infiltrate in superficial dermis

mass index (BMI) was performed and the values were within normal range. Psoriasis severity was assessed by using PASI (Psoriasis Area Severity Index), BSA (Body Surface Area), and PGA (Physician Global Assessment) (Table 1).

Our investigation included biological assessment, the blood samples were taken in fasting conditions, in order to perform the following laboratory examinations: full blood count, biochemistry, CRP (reactive C protein), urine analysis, urine pregnancy test, beta-hCG (Human Chorionic Gonadotropin). Both patients recorded results within the normal laboratory range (Table I).

The hormonal status of our patients was also assessed by analysing the level of sexual hormones (estradiol, progesterone, DHEAS (dehydroepiandrosterone), free testosterone), prolactin, on day 21 of the menstrual cycle, using the chemiluminescence assay method. The subjects were neither pregnant or lactating and had regular menstrual periods. The hormonal test results were within the normal range for patient A. Only PRL level was higher than normal for

Table I. Clinical and biological data for the twin female subjects

Assessment	Patient A	Patient B
PASI	40.8	31.6
BSA	52.5	39
PGA	4	4
Weight (kg)	49	54
Height (m)	1.5	1.52
Waist circumference (cm)	75	80
BMI (kg/m^2)	21.77	23.37
Blood pressure (mm/Hg)	120/78	125/75
Glycaemia (mg/dl)(70-105)	78	84
Triglycerides (mg/dl)(<150)	93	55
HDL cholesterol (mg/dl)(>50)	75	72
CRP (mg/dl)(<0.5)	0.42	0.4
beta-hCG	negative	negative

PASI: Psoriasis Area Severity Index; BSA: Body Surface Area; PGA: Physician Global Assessment; BMI: Body Mass Index; HDL cholesterol: high density level cholesterol; CRP:reactive C protein; beta-hCG: Human Chorionic Gonadotropin-beta.

patient B: 65.4 ng/ml (1.9-25 ng/ml). After one year of treatment with antiTNF-alpha blockers, the level of PRL was determined again in patient B but no decrease of the previous value was noticed. The endocrinologist recommended a treatment with Bromcriptine (dopamine antagonist), 2.5 mg every evening for 3 months and the outcome was a return to normal values, indicating that the patient suffered of functional hyperprolactinemia.

The hormonal investigation, performed on both patients, also included the serum levels of thyroid hormones T3, FT4, thyroid-stimulating hormone (TSH), and antithyroidperoxidase antibody (AbTPO), using the carbonylmetalloimmunoassay (CMIA) method. We took into consideration the fact that subjects with hypothyroidism may have an increased level of serum PRL. The results were within normal ranges, except for AbTPO in patient A: 108.79 IU/ml (<5.61 IU/ml). Our investigation led to the conclusion that she suffered from Hashimoto thyroiditis and had not been under any previous specific treatment.

An ultrasonographic assessment of thyroid was performed for both subjects. In patient A, the investigation detected the presence of micronodules of 2-3 mm, disseminated in both thyroid lobes.

As both twins had type I Psoriasis vulgaris with childhood onset and positive family history we also focused on the genetic determination for HLA-Cw6, which was performed using the DNA microarray technique. Surprisingly, the results were negative for both patients.

Discussion

Psoriasis etiology and the inheritance pattern are not entirely elucidated. Previous studies on twin patients revealed greater concordance rates for psoriasis in monozygotic twins (MZ) 65–72%, than in dizygotic twins (DZ), 15–30% (6). In a Danish study from 2013, determination of concordance in older twin pairs, from a National Twin Registry, revealed a heritability of 68% (7). This supports the genetic influence, but

also indicates that genes are not the only factors responsible for the disease.

Previous studies showed that almost two-thirds of psoriasis patients are positive for HLA-Cw6 allele as compared to 10-15% in the large population. This specific allele is the only genetic variant frequently observed to associate with phenotypic features of psoriasis. HLA-Cw6 has been repeatedly indicated as the most significant marker of risk prediction in psoriasis (8). The association between psoriasis and other alleles, such as HLA-A, was investigated before, but only a moderate association was found (2). Knowing that early onset psoriasis is associated with the presence of HLA-Cw6, we aimed to confirm this hypothesis for our subjects, but the results were negative.

Few cases of psoriasis in identical twins are mentioned in literature. In one report, 3-year-old Caucasian twins had been suffering erythroderma since the age of 8 months. The family history was positive for psoriasis, and HLA-Cw6 was detected in both twins (9). In another case, a pair of 12-year-old identical twins have developed psoriasis lesions at the same age and on the same sites (the soles of both feet) (10).

As mentioned before, both subjects presented extensive lesions on more than two symmetrical sites, with a PGA of 4, for each patient. This aspect contrasts with data published by Gudjonsson et al., who concluded that the mean disease severity score was higher in patients with positive HLA-Cw6 (11).

The same study revealed that the presence of psoriatic arthritis was a common finding in the Cw6-negative group (11). Moreover, it seems that HLA-Cw6 has little influence in developing psoriasis arthritis and the presence of HLA-B27 is more characteristic in psoriasis patients with joint disease (12). HLA-Cw6 has been shown to associate with psoriatic arthritis only in patients with younger age of psoriasis onset (13). These characteristics were not observed in patient A, who although HLA-Cw6 negative, presented an early psoriasis onset and psoriatic arthritis.

Further investigations, HLA-B27 among them, are necessary in order to detect other genes related to psoriatic arthritis risk. The next step of our research will focus on exploring the biological differences between the two subjects and other risk factors, which may explain why only one of them has developed arthritis.

Regarding the presence of psoriatic arthritis in twins, literature has described only one case of identical twins with a 15-year history of psoriasis, each developing psoriatic arthritis of the right and respective left second toes, following foot injury (14).

The above mentioned data emphasize the genetic influence in psoriasis patients. However, other etiological factors are involved as well. This multifactorial disease depends on a complex interaction of genetic and environmental factors, which stimulate the secretion of cytokines by lymphocyte T cells. The process leads to keratinocyte proliferation, which is the pathognomonic element of psoriasis.

Sexual hormones and PRL have been mentioned in the pathogenesis of psoriasis, due to their effect on keratinocyte proliferation and to the fact that the disease is thought to be an autoimmune disorder, influenced by psycho-emotional stress (15).

Modified levels of sex hormones, particularly the increase in estrogens, may have an influence on keratinocyte proliferation (4). The number of neutrophils and Th1 cells is reduced and, at the same time, the production of TNF alpha is inhibited (16). On the other hand, abnormal values of estrogen may be a cause of hyperprolactinemia (17).

All the above encouraged us to investigate if the level of sexual hormones was modified in our patients, but the result was within normal ranges.

Prolactine, a polypeptide hormone and a member of type I cytokine family, presents nu-

merous immunomodulatory effects (5). Its role was observed in *in vitro* studies, due to its proliferative effect on keratinocytes and the existence of PRL receptors at this level (18). This aspect provides more support for the hypothesis that PRL plays a role in the pathogenesis of psoriasis. Mention should be made that the patients did not use antipsychotics, antidepressants, opioids, H2 blockers, verapamil or estrogens, substances that could affect hormonal results.

An Egyptian study from 2012 revealed that the serum level of PRL was significantly higher in patients with psoriasis, compared to controls. The PRL level significantly decreased after systemic treatment with MTX (19). However, in our case, the treatment with anti TNF blockers had no influence in decreasing the level of PRL, with a significant improvement of lesions. The normal level was reached only after treatment with Bromcriptine.

Cyclosporine A, a drug used in the treatment of psoriasis, suppresses the binding of PRL to its receptors on T or B cells while another drug, used in psoriasis treatment, alltrans retinoic acid, inhibits the release of PRL from the pituitary gland and the expression of PRL receptors on breast carcinoma cells. A third drug, propylthiouracil, reduces serum PRL levels and improves lesional acanthosis in psoriatic patients (5), (20), (21). Thus, suppressing the production or functions of PRL may be one of the mechanisms for therapeutic efficacy of these antipsoriatic drugs.

Anti-thyroid agents, such as methimazole, thiamazole, and propylthiouracil have been successfully used both locally and systemically in the treatment of psoriasis (22). Although the mechanism is unclear, a possible explanation is that propylthiouracil may have a regulatory effect on T cells in the psoriatic plaque. It may possibly affect the keratin synthesis process by binding to nuclear T3 receptors found in the skin. Also, it can downregulate the level of involucrine, a protein precursor, which has an increased expression in psoriasis (23). This is another aspect suggesting that thyroid hormones may have unknown effects in psoriasis etiopathogenesis.

A complete endocrinological assessment in case of patient A should be taken into consideration, as she presents the association of psoriatic arthritis with Anti-thyroid peroxidase antibodies (AbTPO) and the presence of ultrasonographic modification of the thyroid gland. The aspects described in our patient, have been previously mentioned in literature by Antonelli A et al. In their study, the presence of AbTPO, a hypoechoic thyroid and subclinical hypothyroidism were significantly more frequent in women with psoriatic arthritis than in control women: positive AbTPO titer 28% vs 12%; hypoechoic thyroid 31% vs 16%; subclinical hypothyroidism 25% vs 8% respectively (24).

Psoriasis is also known to be frequently associated with obesity, diabetes mellitus, dyslipidaemia and metabolic syndrome (1), (25). This association was investigated in the two female subjects, but none of the above mentioned diseases was found.

Our report revealed that the twin subjects had a negative HLA Cw6, even though this is a common finding in psoriasis patients.

We are, however, aware of the limitations of the present report, such as short follow-up interval and lack of data validation in larger, long term prospective studies.

Conclusion

The particularity of the case consists of the absence of HLA-Cw6, usually associated with an early onset of the disease and positive family history of psoriasis, which were present in the twin female patients. The hormonal imbalances found in both subjects (the presence of antithyroidperoxidase antibody (AbTPO) and functional hyperprolactinemia in patient B) represent another particularity, suggesting the multifactorial etiopathogenesis of psoriasis.

Our findings may be a first step in improving the protocol of psoriasis patient assessment by starting to perform an endocrinological evaluation, including hormonal, immunological, and imaging tests. The procedure would be useful in order to diagnose and treat diseases that may have an influence in the evolution of psoriasis and improve current therapeutic approaches.

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