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CASE REPORT

Reversible bilateral postauricular adult seborrheic dermatitis due to sodium valproate-valproic acid combination

Mehmet Hamdi ORUM[1], Dilek ORUM[2], Osman CEVIK[3]

[1] *Elazığ Mental Health and Diseases Hospital,Department of Psychiatry, Elazığ, Turkey*
[2] *Elazığ Fethi Sekin City Hospital, Department of Psychiatry, Elazığ, Turkey*
[3] *Elazığ Fethi Sekin City Hospital, Department of Dermatology, Elazığ, Turkey*

ABSTRACT
The combination of sodium valproate-valproic acid, commonly used to treat epilepsy and bipolar disorder, may result in cutaneous reactions. In this case report, we presented a bilateral postauricular seborrheic dermatitis associated with sodium valproate-valproic acid use. A sodium valproate-valproic acid combination was introduced to the therapy of a 68-year-old male patient who had been diagnosed with schizophrenia and was on clozapine in order to potentially avoid seizures associated to the medication. On the fifteenth day of drug addition, crusting appeared on the back skin of both ears of the patient. While the patient had a history of clozapine use, there was no history of sodium valproate use or similar cutaneous symptoms. The current condition was associated with the sodium valproate-valproic acid combination and the drug was discontinued. Following discontinuation of the medication, the crusting decreased and disappeared completely after two weeks. The patient's schizophrenia-related treatment was completed and he was discharged. No cutaneous reaction was observed again during follow-up. It should be noted that cutaneous reactions may be associated with the use of sodium valproate-valproic acid combination.

Keywords: Sodium valproate, valproic acid, side effects, seborrheic dermatitis

ÖZET
Sodyum valproat-valproik asit kombinasyonuna bağlı iki taraflı postauriküler erişkin seboreik dermatiti
Bipolar bozukluk ve epilepsi tedavisinde sıklıkla kullanılan sodyum valproat-valproik asit kombinasyonu kutanöz reaksiyonlara neden olabilir. Bu olgu sunumunda sodyum valproat-valproik asit kullanımına bağlı gelişen iki taraflı postauriküler seboreik dermatiti sunduk. Şizofreni tanısıyla klozapin kullanmaya başlayan 68 yaşındaki erkek hastada, klozapine bağlı olası nöbetlerin önlenmesi amacıyla tedaviye sodyum valproat-valproik asit kombinasyonu eklendi. İlaç ilavesinin onbeşinci gününde hastanın her iki kulağının arka derisinde kabuklanma oluştu. Hastanın özgeçmişinde klozapin kullanım öyküsü mevcutken, sodyum valproat kullanımı ya da benzeri kutanöz semptomu öyküsü yoktu. Mevcut durum sodyum valproat-valproik asit kombinasyonuna bağlandı ve ilaç kesildi. İlacın kesilmesini takiben kabuklanmalar azaldı ve iki hafta sonra tamamen ortadan kalktı. Hastanın şizofreni tedavisi tamamlanarak taburcu edildi. Takip sırasında yeniden herhangi bir kutanöz reaksiyon gözlenmedi. Sodyum valproat-valproik asit kombinasyonunun kullanımıyla kutanöz reaksiyonların ortaya çıkabileceği unutulmamalıdır.
Anahtar kelimeler: Sodyum valproat, valproik asit, yan etkiler, seboreik dermatit

INTRODUCTION

Sodium valproate-valproic acid combination (SV-VPA), which is frequently used as a mood stabilizer in psychiatry, is an important antiepileptic. In psychiatric disorders such as schizophrenia, where mood stabilizing drugs are not routinely used, SV-VPA can be added to the treatment when psychotropic drugs that lower the seizure threshold, such as clozapine, are started [1]. SV-VPA increases the level of gamma amino butyric acid (GABA), an inhibitory neurotransmitter, through voltage-dependent sodium channel blockade, increases brain GABA levels by stimulating GABA-synthesizing enzymes such as glutamic acid dehydrogenase, prevents the reuptake of GABA from neurons and glial cells, and used as a broad-spectrum antiepileptic by inhibiting calcium current in

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Corresponding author: Mehmet Hamdi ORUM
Address: Elazığ Mental Health and Diseases Hospital, Psychiatry Outpatient Clinic
Elazığ — Turkey, 23200
E-mail: mhorum@hotmail.com
Phone: +90 538 220 75 58
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T-type calcium channels in high doses [2]. SV-VPA is completely absorbed from the gastrointestinal tract, but the rate of absorption varies depending on the pharmaceutical form. Maximum plasma concentration occurs 1-6 hours after ingestion of enteric-coated tablets, which are frequently preferred in adult psychiatry. While the serum therapeutic level is 50-100 µg/mL, its half-life is 9-18 hours [3].

According to the drug package insert, bleeding diathesis, anemia, hyponatremia, extrapyramidal disorders, sedation and headache are common side effects associated with the use of SV-VPA. Pancytopenia, leukopenia, syndrome of inappropriate ADH secretion, hyperandrogenism and pleural effusion are uncommon side effects associated with the use of SV-VPA. Bone marrow failure, agranulocytosis, macrocytic anemia, hypothyroidism, and reversible dementia are rare side effects associated with the use of SV-VPA. Skin side effects associated with SV-VPA use are very rare [4]. This study aimed to examine reversible bilateral postauricular seborrheic dermatitis (SD) caused by SV-VPA, which is used to prevent possible seizures due to clozapine, in a male patient followed with a diagnosis of schizophrenia.

CASE REPORT

A 68-year-old widowed male patient living in a city centre was admitted to the emergency department of a mental health and diseases hospital with complaints such as non-compliance with medical treatment, aggression, delusions, hallucinations, decreased self-care, and insomnia, and was hospitalized with a diagnosis of schizophrenia. In the history taken, it was learned that he had symptoms of schizophrenia for more than 45 years, had multiple hospitalizations, and had been incompatible with medical treatment in recent months. He had used drugs such as haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, amisulpride, quetiapine, biperiden, alprazolam, lorazepam, diazepam, escitalopram, sertraline, and aripiprazole in the past. The patient, who had insufficient caregiver support, had dozens of hospitalizations. The patient was rehospitalized with a diagnosis of schizophrenia according to DSM-5 [5]. The patient was planned to be placed in a nursing home following his current hospitalization. Since it was thought that his medical treatment could be monitored regularly in the nursing home, the patient was started on clozapine 12.5 mg/day and the dose was gradually increased to 600 mg/day. SV-VPA 500 mg/day (Depakin Chrono BT 500 mg long-acting split-film tablet contains sodium valproate 333 mg and valproic acid 145 mg, equivalent to 500 mg sodium valproate activity) was added to the treatment for the possible seizure side effect of clozapine, and one week later the SV-VPA dose was increased to 1000 mg/day. Quetiapine 200 mg/day was added to the treatment for the patient's complaint of insomnia. On the fifteenth day of SV-VPA addition, erythematous patches, plaques, and mild itching were observed on the back skin of both ears of the patient (Figure 1). Blood examination revealed white blood cell (WBC) value as 7.12 (10^3/uL), neutrophil 81%, lymphocyte 12%, eosinophil 0.3%, monocyte 5.1%, creatinine 0.87 mg/dL, blood urea nitrogen 30.2 mg/dL, aspartate aminotransferase 21 u/L, alanine aminotransferase 15 u/L. The patient's eating habits had not changed in recent days. It was not possible for hospitalized patients to access any food, medicine or substance from outside. The patient had no history of alcohol, substances or additional medical diseases. Vital signs such as fever, pulse rate, and blood pressure were within normal limits. There were no signs or symptoms suggestive of infection. No history of animal bites or similar was reported. While the patient had a history of clozapine use, there was no history of SV-VPA use or similar cutaneous symptoms. The patient was consulted to dermatology and after a dermoscopic examination, the current condition was evaluated as drug-induced SD. No recommendations were made other than drug discontinuation and close monitoring. Due to discontinuation of SV-VPA, the dose of clozapine, which generally poses a risk of seizures above 500 mg/day, was reduced to 400 mg/day [6]. The patient was evaluated every other day in the inpatient treatment unit. Following discontinuation of SV-VPA, SD gradually decreased and completely disappeared at the end of two weeks. The change of cutaneous reaction is shown in Figure 1. After receiving clozapine 400 mg/day and quetiapine 200 mg/day for two months, the patient's treatment for schizophrenia was finished, and they were released. A repeat cutaneous reaction did not occur throughout the outpatient follow-up. Informed consent was obtained from the patient for the publication of his data, and the patient and his relatives were warned about the cutaneous reaction linked with the usage of SV-VPA. This rare side effect, thought to be due to SV-VPA, was reported to the Turkish Medicines and Medical Devices Agency within the scope of the pharmacovigilance studies of the Turkish Ministry of Health (Case Number=01-651-937625). The patient's Naranjo Adverse Drug Reaction Probability Scale (NADRPS) score was 6 [7].

DISCUSSION

Because there was a temporal relationship between both, this case report was assessed as reversible SD associated with SV-VPA. Other possible causes of the dermatitis, such as drugs, food, substance, animal bite, and infection, were excluded. Drug-related side effect severity was determined via NADPRS. NADPRS consists of ten questions; There were 3 response options: yes, no and unknown; There are scores such as -1, 0, +1, +2; It is a scale interpreted as definite if the overall score is 9 or higher, probable for 5-8 points, possible for 1-4, and finally unlikely if the score is 0 [7]. In this case report, the NADRPS score indicated a possible relationship between medication use and cutaneous side effect.

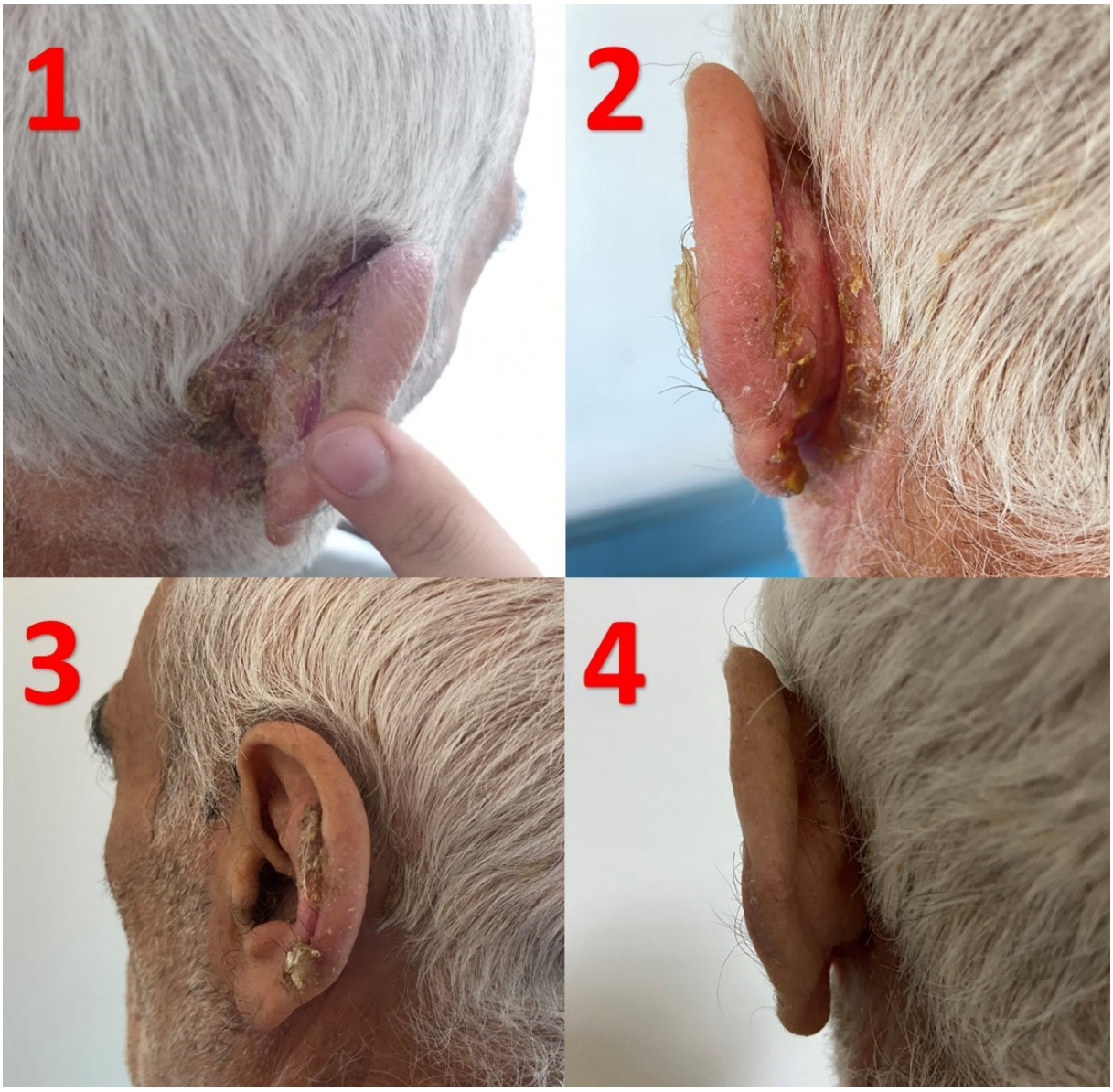

Figure 1. Alteration of side effect over time (1=The day the side effect was noticed; 2=Four days after stopping the drug; 3=Seven days after stopping the drug; 4=Two weeks after stopping the drug)

Clozapine, which is an FDA-approved atypical antipsychotic medication, lowers the seizure threshold and doses above 600 mg/day cause seizures in 4.4% of patients as compared to only 2.7% and 1.0% of patients receiving 300-600 mg/day and <300 mg/day, respectively. An antiepileptic is added to the treatment of patients for these possible seizures due to clozapine. It is preferred that this added antiepileptic is also a mood stabilizer. SV-VPA is one of the most frequently preferred drugs for this purpose [6]. There are limited reports in the literature that SV-VPA causes cutaneous side effects.

Few studies have reported the influence effect of VPA on skin healing, with controversial results. On the other hand, SV-VPA causes cutaneous drug eruptions [8]. Cutaneous drug eruptions associated with SV-VPA can range from hyperpigmentation [9] to severe Stevens-Johnson syndrome [10]. Localized morphea [11], Rowell's syndrome [12], acute generalized exanthematous pustulosis [13], cutaneous pseudolymphoma [14], and Henoch-Schönlein purpura [15] are some rare cutaneous side effects due to VPA. Psoriasiform eruption due to VPA has been reported relatively more frequently [16]. When the literature is examined, it is seen that the relationship between SD and mood stabilizers has not been adequately investigated. In their review of adverse cutaneous drug reactions, Bliss and Warnock [17] stated that mood stabilizers such as carbamazepine, lithium carbonate, oxcarbazepine, gabapentin and VPA were blamed in cases of drug-

induced SD. When the content of the review [17] is examined, it is seen that the reference given to SD belongs to the article titled "psoriasiform eruption induced by anticonvulsants" by Brenner et al. [18] When this article [18] was examined, no data could be obtained regarding the relationship between VPA and SD. One might think that Bliss and Warnock [17] wrote SD while trying to write psoriasiform eruption. Diaz-Perez et al. [19] reported a case of pityriasis amiantacea with a SD-like clinic that occurred after VPA therapy. Pityriasis amiantacea, which is usually seen in children and is characterized by flaking and large plaques tightly adhered to the scalp and hair, usually begins in the teens and progresses to more typical psoriasis in 2-15% of pediatric patients. Pityriasis amiantacea can also be observed as a complication or continuation of lichen simplex, SD, atopic dermatitis, and streptococcal infection [20]. However, our patient is in the adult age group and has bald skin involvement. As a result, no data on VPA-related adult SD could be found in the literature.

According to our best knowledge, this is the only case of reversible and localized SD due to SV-VPA. SD is a chronic inflammatory skin disease presenting with a yellowish papulosquamous morphology in areas rich in sebaceous glands, particularly the scalp, face, and body folds. SD, limited to the bilateral postauricular region, must be differentiated from hypersensitivity reactions, psoriasis, tinea versicolor, rosacea, allergic or irritant contact dermatitis. Hypersensitivity reactions are often characterized by lymphadenopathy, hepatitis, eosinophilia, mucocutaneous rash and fever. These drug-related reactions can be life-threatening when the kidneys, liver, gastrointestinal tract or nervous system are affected. In angioedema, mucous membranes may be involved and therefore swallowing and ventilation may be impaired. In our case, the patient had no additional findings other than dermatitis. Discontinuation of the drug was sufficient for the clinic to improve. SD and psoriasis are difficult to differentiate because they are chronic inflammatory skin diseases that have similar clinical and pathological features. The hallmarks of SD are spongiosis, dermal inflammation, and horizontal orientation of dilated blood vessels. In addition, in psoriasis, scaling is more common and the lesions are silver-gray-white in color. These easily identifiable patterns are specific for SD and can distinguish it from plaque psoriasis. Contact dermatitis may develop due to some substances that come into contact with our skin. Chemical substances are the most common causes of contact dermatitis and occur almost exclusively on skin areas including the hands. The case mentioned in this study is hospitalized and therefore has limited access to chemicals. In the case, the area of involvement is limited to the postauricular region. These features, as well as the temporal relationship between drug use and skin rash in the case, enabled the diagnosis of contact dermatitis to be excluded. SD due to SV-VPA has been distinguished from rosacea due to its features such as lack of crusting, telangiectasia and edema. In tinea versicolor, the fact that skin rashes usually appear on the back and chest and that the rash is not red and itchy has been used in the differential diagnosis [21].

Proposed mechanisms for the pathogenesis of SD include abnormal shedding of keratinocytes, disruption of the skin's microbiota, increased presence of unsaturated fatty acids on the skin surface, disruption of cutaneous neurotransmitters [22]. The pathogenesis of drug-related SD remains unclear. Impaired lymphocyte transformation, delayed hypersensitivity, and decreases in epidermal cyclic adenosine-monophosphate may be the possible cause of drug-related skin reactions [23]. Stress-induced SD should not be overlooked in patients diagnosed with psychiatric disorders. The side effect present in this patient was associated with the medication [24].

CONCLUSION

Clinical features of dermatoses may cause diagnostic uncertainty, but a detailed history, physical course of the disease and clinical findings are often sufficient to reach the correct diagnosis. We were able to determine that SV-VPA was the cause of the SD in this instance because the SD lesions completely cleared after the medicine was stopped and there was no sign of a relapse. Clinicians' questioning of skin-related side effects, especially in the first days of SV-VPA treatment, will make it easier to recognize possible side effects early. Drug side effects have an important place in patients who discontinue their medication without the knowledge of their physician. Discussing the possible side effects of medications with the patient and explaining the process to the patient in case of a possible side effect will ensure that the therapeutic relationship between the patient and the physician is maintained. Reporting drug-related side effects to the Ministry of Health will increase awareness on this issue, as a matter of fact, side effect notification was made in this study as well. To clarify the mechanisms underlying the incidence of SV-VPA-induced SD, more research is required.

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REFERENCES

1. Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. CNS Drugs 2015;29(2):101–11.
2. Zhu MM, Li HL, Shi LH, Chen XP, Luo J, Zhang ZL. The pharmacogenomics of valproic acid. J Hum Genet 2017;62(12):1009–14.

3. Swaiman KF, Ashwal S. Pediatric Neurology Principles and Practice. St. Louis, Missouri: Mosby, 3th Edition, 1999; 629–718.
4. https://titck.gov.tr/storage/Archive/2020/kubKtAttachments/UYGUNKT_a3ee1b7b-cfc3-41af-b96c-4494a0928734.pdf. Date of Access: 14/10/2023.
5. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA.
6. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. Neurology 1991;41(3):369–71.
7. Kose S, Akin E, Cetin M. Adverse drug reactions and causality: The Turkish version of naranjo adverse drug reactions probability scale. Psychiatry Clin Psychopharmacol 2017;27(2):205–6.
8. Biondo-Simões R, Biondo-Simões MLP, Ioshii SO, Robes RR, Dall'Antonia MO. The effects of valproic acid on skin healing: experimental study in rats. Acta Cir Bras 2022;37(4):e370403.
9. Giménez-García R, Carrasco-Molina S, Zambrano-Centeno B. Valproic acid-induced hyperpigmentation. ARC Journal of Dermatology 2017;2(1):16–8.
10. Rashid M, Kashyap A, Undela K. Valproic acid and Stevens-Johnson syndrome: a systematic review of descriptive studies. Int J Dermatol 2019;58(9):1014–22.
11. Ferzli GT, El-Tal Ael-K, Kibbi AG, Mikati MA. Localized morphea: a rare adverse effect of valproic acid. Pediatr Neurol 2003;29(3):253–5.
12. Kacalak-Rzepka A, Kiedrowicz M, Bielecka-Grzela S, Ratajczak-Stefanska V, Maleszka R, Mikulska D. Rowell's syndrome in the course of treatment with sodium valproate: a case report and review of the literature data. Clin Exp Dermatol 2009;34(6):702–4.
13. Sahu P, Sahoo SK, Dayal S, Khanna J. Acute generalized exanthematous pustulosis secondary to Valproate: An uncommon cutaneous reaction of a common drug. J Young Pharm 2016;8(1):56–8.
14. Cogrel O, Beylot-Barry M, Vergier B, et al. Sodium valproate-induced cutaneous pseudolymphoma followed by recurrence with carbamazepine. Br J Dermatol 2001;144(6):1235–8.
15. Koumaki D, Papadavid E, Panayiotides I, Shtukkert E, Dinopoulos A, Rigopoulos D. Henoch-Schönlein purpura in a child induced by valproic acid. Clin Transl Allergy 2015;5(1):15.
16. Gul Mert G, Incecik F, Gunasti S, Herguner O, Altunbasak S. Psoriasiform drug eruption associated with sodium valproate. Case Rep Pediatr 2013;2013:823469.
17. Bliss SA, Warnock JK. Psychiatric medications: adverse cutaneous drug reactions. Clin Dermatol 2013;31(1):101–9.
18. Brenner S, Wolf R, Landau M, Politi Y. Psoriasiform eruption induced by anticonvulsants. Isr J Med Sci 1994;30(4):283–6.
19. Diaz-Perez JA, Joyce JC, Cibull TL, Victor TA. Development of Pityriasis Amiantacea after Valproic Acid Therapy. Int J Trichology 2018;10(5):237–9.
20. Gupta LK, Khare AK, Masatkar V, Mittal A. Pityriasis amiantacea. Indian Dermatol Online J 2014;5(1):63–4.
21. Clark GW, Pope SM, Jaboori KA. Diagnosis and treatment of seborrheic dermatitis. Am Fam Physician 2015;91(3):185–90.
22. Tucker D, Masood S. Seborrheic Dermatitis. [Updated 2023 Feb 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551707/.
23. Tsankov N, Angelova I, Kazandjieva J. Drug-induced psoriasis: recognition and management. Am J Clin Dermatol 2000;1(3):159–65.
24. Misery L, Touboul S, Vinçot C, Dutray S, Rolland-Jacob G, Consoli SG, Farcet Y, Feton-Danou N, Cardinaud F, Callot V, De La Chapelle C, Pomey-Rey D, Consoli SM; Pour le Groupe Psychodermatologie. Stress and seborrheic dermatitis. Ann Dermatol Venereol 2007;134(11):833–7.