

Allergic Contact Dermatitis to Testosterone and Estrogen in Transdermal Therapeutic Systems

To the Editor:

A 74-year-old male patient with the diagnosis of hypogonadism presented with a rash at the site of Androderm 5 mg/24 hour patch application. He was instructed to apply triamcinolone acetonide 0.1% ointment underneath the testosterone patch, but the rash did not improve. He ultimately underwent patch testing. Patch tests to testosterone in an ethanol vehicle at concentrations (1%, 2.5%, 5%, and 10%) were negative. However, at the same concentrations in a petrolatum vehicle, the patient developed positive reactions at all concentrations during follow-up at 72 hours, which increased in reactivity at 96 hours. The Androderm transdermal therapeutic systems (TTS) patch contained testosterone, ethanol, purified water, glycerol, glyceryl monooleate, methyl laurate, carbomer copolymer (type B), and sodium hydroxide.¹ He was patch tested to components provided by the manufacturer, with a positive to testosterone in petrolatum but no reaction to all others. Consequently, the Androderm TTS patch was discontinued, and he was switched to testosterone intramuscular injections without any systemic or local dermatitis.

A 43-year-old female patient who was on oral estrogen replacement therapy was switched to an estrogen TTS patch due to a concern for developing recurrent cancer, thromboembolic disease, and cardiac dysrhythmias. She developed intense pruritus within hours of Vivelles estrogen TTS patch application and had similar symptoms with Evamist transdermal spray. She ultimately developed erythematous pruritic dermatitis with induration surrounding the areas where the patch and transdermal spray were applied. The patch test result was positive for the suspected products previously mentioned, but also positive to other commercial topical estrogen products as well as estrogen in an ethanol vehicle. Test results with the other components of the TTS system were negative, confirming that estrogen itself was the culprit antigen.

Interestingly, the patient presented in case 2 developed a delayed type IV hypersensitivity to topical estrogen but was tolerant to the oral form, and the patient in case 1 tolerated subsequent intramuscular testosterone. It is not clear why some patients can tolerate sex hormones systemically

but will consistently develop dermatitis with topical application. One theory lies in the mechanism of how dendritic cells in the skin present the hormone to T-cells.² Similar to the patient in case 2, Boehncke et al³ also reported a woman who developed allergic contact dermatitis (ACD) after she was switched from oral estrogen to an estradiol TTS.

The appropriate concentration and vehicles for patch testing are not known, and the correct selection of vehicles for patch testing is crucial for evaluating suspected contact dermatitis.^{4,5} We performed our patch testing with testosterone 1%, 2.5%, 5%, and 10% in petrolatum and another set in ethanol. The fact that the patient had negative patch test results to testosterone in an ethanol vehicle but positive patch tests with the petrolatum vehicle suggests that petrolatum enhances the antigenicity of the active ingredient.

It is also unclear what is the preferred method for testing estradiol topically. Some recommend estradiol patch testing be done at 5% in petrolatum, but in case 2, ethanol was used.³ In fact, several studies have demonstrated that estradiol elicited reactions with lower concentrations in ethanol than petrolatum.

The most common adverse effects associated with TTS are skin findings including irritant contact dermatitis and ACD. There are no guidelines on how to test for ACD to hormones in a TTS, but if one suspects ACD despite the negative skin patch test result, both ethanol and petrolatum vehicles should be considered.

Von Ta, MD

Andrew A. White, MD

Scripps Clinic Medical Group
San Diego, CA

William K. Chin, MD

Navy Medical Center
San Diego, CA

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Address reprint requests to: Von Ta, MD, Scripps Clinic, 3811 Valley Centre Drive, San Diego, CA 92130. E-mail: vonanhta@gmail.com.

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Chemicals Found in Poplar-Type Propolis

To the Editor:

Recently, my review article on propolis was published in *Dermatitis* (De Groot AC. Propolis: a review of properties, applications, chemical composition, contact allergy, and other adverse effects. *Dermatitis* 2013;24:263–282). Propolis (bee glue) is an extremely complex substance, which may contain well more than a hundred components; only some examples were mentioned in the article. Meanwhile, after contacting one of the world's leading experts on propolis, Prof Vassya S. Bankova from Sofia, Bulgaria, she; one of her co-workers, Dr Milena Popova; and I reviewed the relevant literature and composed a list of all chemicals found by analytical investigation in the most widely used propolis, the “poplar-type” propolis. This list contains 344 compounds, subdivided into chemical categories and tabulated alphabetically with synonyms, Chemical Abstract Service numbers and references. The PFD file (ISBN/EAN: 978-90-813233-0-7, 11 pages) can be downloaded free of charge from https://www.researchgate.net/profile/Anton_De_Groot2 or through the Web site of the American Contact Dermatitis Society, <http://www.contactderm.org/i4a/pages/index.cfm?pageid=3518>.

Please feel free to forward the article to anyone you think may be interested. Suggestions for improvement are most welcome!

Anton de Groot, MD, PhD
Acdegroot publishing
Department of Dermatology
University of Groningen
Wapserveen, Netherlands

Resolution of Occupational Dermatitis Related to Manganese Exposures

To the Editor:

Manganese (Mn) is a transitional metal element, commonly used in industrial metal alloys. There are few reports about patients with Mn allergy.^{1–3} As far as we know, there are only 2 case reports of Mn allergic contact dermatitis in which both patients demonstrated positive reaction to Mn patch testing.^{1,3} Herein, we describe a patient with a positive patch test

to Mn whose dermatitis resolved after his retirement from his work at a Mn processing plant.

A 55-year-old white man who worked as an instrument technician in a Mn-producing factory for 38 years presented with erythematous scaly patches on both arms and the dorsum of the hands for 5 years. He worked in an office adjacent to the Mn processing plant. A routine safety monitoring of his work environment revealed high levels of Mn-containing dust on his desk. The patient and his family denied any history of atopy. In addition, none of other workers in that facility had any dermatitis similar to this patient.

Patch testing with the North American Tray and extended metal tray, including 2.5% of Mn (II) chloride (MnCl₂), was performed. The readings were done at 48, 72, and 168 hours after test placement. The results were all negative, except for Mn, which revealed reactivity at 2+, with negative delayed readings (72 and 168 hours). Because of persistent dermatitis that required the use of super-potent topical corticosteroids and his occupational exposure to Mn, we repeated patch testing to Mn during a period of 4 years on the upper back, and skin test reactivity varied from +/–2 to 2+ at 48 hours, with consistently negative delayed readings. These patch tests were interpreted as irritant reactions, and we discussed the possible relevance to the patient's work-related exposures. He was not able to change the nature of his work.

MnCl₂ is a potential allergen included in the extended metal series. However, irritant reactions to Mn patch testing are common. Eighteen patients with metal implants were studied with the extended metal series. Eight patients (44%) showed irritant reactions to 5% MnCl₂.⁴ Another study using 2.5% MnCl₂ (MnII) showed a higher rate of irritant reactions than Mn(III) or Mn(VII) at the same concentration. In addition, this study also confirmed that only Mn(II) was toxic to human keratinocytes.⁵ We interpreted the skin reactivity to Mn patch test in our patient as an irritant reaction, indicating that the commercially available concentration for Mn testing may be too high.

Three years after his retirement from his work at the Mn processing plant, his dermatitis had completely resolved, no longer requiring the use of topical corticosteroid therapy. Considering the high rate of irritant patch test reactions to Mn, our initial interpretation of the patch test reaction to

Address reprint requests to Papapit Tuchinda, MD, Department of Dermatology, University of Maryland, Baltimore; and Department of Dermatology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. E-mail: papapitt@gmail.com.

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Mn was that of an irritant reaction. Considering the clinical correlation with the patient's marked improvement of his chronic dermatitis after permanent removal from his workplace exposures to Mn, we are now interpreting the significance of the positive patch test as being allergic in nature.

Papapit Tuchinda, MD†

Department of Dermatology

University of Maryland

Baltimore, MD

and Department of Dermatology

Faculty of Medicine

Siriraj Hospital, Mahidol University

Bangkok, Thailand

*Yaqian Liu, MD**

Department of Dermatology

University of Maryland

Baltimore, MD

Antonella Tammaro, MD‡

Department of Dermatology

University of Maryland

Baltimore, MD

and Department of Dermatology

University la Sapienza

Rome, Italy

*Erin Harberts, BS**

*Ronald Goldner, MD**

*Anthony A. Gaspari, MD**

Department of Dermatology

University of Maryland

Baltimore, MD

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Screening for Hand Dermatitis in Health Care Workers

To the Editor:

Health care workers are at high risk for occupational dermatitis with health and economic implications.^{1,2} Although screening has been suggested as a useful prevention tool for occupational skin disease, there is little information regarding the feasibility or usefulness of screening for dermatitis in the workplace.³ The objective of this study was to determine the feasibility of using a questionnaire and physical examination as screening tools to identify workers with hand dermatitis in the health care sector.

The study was a prospective observational survey approved by the St Michael's Hospital research ethics board. The target population was health care personnel at St Michael's Hospital, Toronto, Canada, who attended the employee health unit (EHU) for routine visits over a 6-week period. Of a total eligible population of 1020 visitors to the EHU, 141 were invited to participate in the study and 139 participated.

A self-administered questionnaire collected basic demographic information, occupation, cutaneous symptoms in the past 12 months, chemical and physical workplace exposures, and prevention activities. After completion of the questionnaire, the dorsal and palmar aspects of the hands of each respondent were examined for cutaneous findings by a nurse in the EHU, with a differentiation between mild dryness and eczema. Simple descriptive statistics and univariate analysis by χ^2 and the Student *t* test were used.

The participant group was representative of the hospital staff with respect to distribution of occupations, particularly with respect to wet work (62% in each group). The mean age of the participants was 37, and 70% were female. Hand dermatitis was present in 30.5% of respondents based on history and/or physical examination. Nineteen percent reported hand dermatitis over the past year, 18% had findings of dermatitis on examination, and 6% had both.

Exposure characteristics are presented in Table 1. The majority of participants used gloves and hospital-dispensed cleanser and washed their hands more than 10 times per workday. Those involved in wet work reported increased use of gloves (RR = 3.3, *P* < 0.0001) and hospital-dispensed cleanser (RR = 1.5, *P* < 0.0001) and were 4.8 times more likely to report hand eczema in the past year than those involved in dry work

Address reprint requests to D. Linn Holness MD, MHSc, Department of Occupational and Environmental Health, St Michael's Hospital, 30 Bond St, Toronto, Canada. E-mail: holnessl@smh.ca

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TABLE 1. Workplace Exposure Characteristics (Reported as % of Total Respondents or of Subset)**Cutaneous Hazards**

Glove use
% using gloves at work 65%

Cleanser use
Hospital-dispensed antimicrobial soap 76%

Hand soap 49%

Water only 4%

Hand washing frequency
<5 times/workday 11%
5–10 times/workday 31%
11–20 times/workday 28%
>20 times/workday 30%

Preventative Strategies

Emollient use
% Using emollient at least once/workday 75%

Skin protection training
% Receiving training on skin hazards and prevention methods such as hand washing methods and use of gloves 35%
If received training, how long ago?
<2 y ago 40% (of those trained)
2–5 y ago 34% (of those trained)
>5 y ago 20% (of those trained)

($P = 0.0016$). Only 34.6% of respondents reported receiving skin protection training.

Findings of hand dermatitis and characteristics of workplace skin exposure were similar to other reports. The relatively high prevalence of hand dermatitis and the significant possible consequences support the use of screening and intervention in health care workers. Secondary prevention interventions have been used in health care workers with improved outcomes, particularly for those workers with mild disease.^{4,5} What these studies have not addressed are the components and feasibility of a screening program. This study has demonstrated that implementation of a screening questionnaire and clinical examination was feasible in the setting of the EHU. The major obstacle to widespread use would be availability of time for the workers in the EHU to carry out the screening and follow-up. This will be explored in future studies in addition to survey modifications, such as adding the use of topical treatments, which could impact physical findings.

Sharon Shin MD
Toronto, Canada

D. Linn Holness MD, MHSc
Department of Occupational and Environmental Health

St Michael's Hospital
Toronto, Canada
Li Ka Shing Knowledge Institute
St Michael's Hospital
Toronto, Canada

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Carbamazepine-Induced DRESS With Severe Eosinophilia Confirmed by Positive Patch Test

To the Editor:

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe and potentially life-threatening disease. Carbamazepine is among the most frequently reported anti-convulsant drug causes of this syndrome.

Here, we present an unusual case of carbamazepine-induced DRESS with profound eosinophilia confirmed by positive patch test.

A 54-year-old woman presented with a generalized erythematous rash and fever. Her medical history was significant for hypertension treated with captopril. She had been taking carbamazepine (200 mg/d) for 3 months for idiopathic seizures. She denied taking any other drugs before or during the eruption.

At admission, her temperature was 38.9°C. On physical examination, diffuse erythematous rash was noted over the trunk, the face, and extremities with evident facial edema. She had palpable bilateral cervical lymphadenopathy. Initial laboratory tests showed leukocytosis of $12.6 \times 10^9/L$ with eosinophilia of $6.6 \times 10^9/L$. A myelogram showed an increased number of eosinophil precursors with no other abnormalities.

Address reprint requests to Neila Fathallah, MD, Department of Clinical Pharmacology, Faculty of Medicine of Sousse, Avenue Mohamed Karoui, Sousse 4002, Tunisia. E-mail: neilafathallah@gmail.com.

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Viral serology and antinuclear antibodies were all negative. Microscopic stool examination for ova and parasites was negative, as was *Strongyloides stercoralis* serology. Other common causes of eosinophilia were ruled out and were negative.

By fulfilling the proposed criteria of the scoring system for classifying DRESS, our patient was a definite case of carbamazepine-induced DRESS with a final score of 6 (Table 1).

Her symptoms resolved after withdrawal of carbamazepine. Her pathological laboratory findings returned to normal ranges within 4 weeks, although captopril therapy was maintained.

Patch tests for carbamazepine performed 6 weeks after complete recovery induced a strongly positive skin reaction in 48 and 72 hours.

Eosinophilia, although part of the acronym of DRESS, is present only in approximately 40% of cases and is generally moderate, rarely exceeding $1.5 \times 10^9/L$.¹ In our patient, eosinophilia exceeded $6.6 \times 10^9/L$, nearly 4.5-fold the usual upper limits of eosinophilia in DRESS. Eosinophil counts might be a prognostic marker of drug eruption. In fact, eosinophils contribute to tissue damage through the release of various toxic granule proteins such as eosinophilic cationic

protein, eosinophil-derived neurotoxin, and eosinophil peroxidase, which could directly destroy involved tissue or amplify the inflammatory cascade by recruiting other effector lymphocytes into the inflammatory loci.² The importance of eosinophil levels in DRESS as a predictive factor of its severity is now well recognized. The scoring system for classifying DRESS/Hypersensitivity Syndrome cases underlies the importance of eosinophilia. In fact, eosinophilia exceeding $1.5 \times 10^9/L$ is quoted 2 points. In our patient, although eosinophilia was extremely high, the evolution was surprisingly favorable.

The main causes of hypereosinophilia are allergic disorders and parasitosis. In our case, unusual high levels of eosinophilia lead us to rule out other less frequent causes of hypereosinophilia, including hematological malignancies, connective tissue disease such as rheumatoid arthritis, and infectious disease such as scabies, human immunodeficiency virus, and allergic bronchopulmonary aspergillosis.³

Patch testing can be helpful in confirming the imputability of drug-induced DRESS, where delayed hypersensitivity mechanisms are involved. Recent studies have reported more favorable patch testing results with antiepileptic drug-induced

TABLE 1. Scoring System for Classifying DRESS Cases as Definite, Probable, Possible, or No Case

Score	−1	0	1	2	Patient's Score
Fever $\geq 38.5^\circ\text{C}$	No/U	Yes			0
Enlarged lymph nodes		No/U	Yes		1
Eosinophilia		No/U			2
Eosinophils			$0.7\text{--}1.499 \times 10^9$	$\geq 1.5 \times 10^9 L^{-1}$	
Eosinophil, if leucocytes $< 4.0 \times 10^9$			10%–19.9%	$\geq 20\%$	
Skin involvement					
Skin rash extent (% body surface area)		No/U	$>50\%$		1
Skin rash suggesting DRESS	No	U	Yes		
Biopsy suggesting DRESS	No	Yes/U			
Organ involvement					
Liver		No/U	Yes		
Kidney		No/U	Yes		1
Lung		No/U	Yes		
Pancreas		No/U	Yes		
Other organs		No/U	Yes		
Resolution ≥ 15 d	No/U	Yes			0
Evaluation of other potential causes					
Antinuclear antibody					
Blood culture					
Serology for HAV/HBV/HCV					
Chlamydia/mycoplasma					
If none positive and ≥ 3 of above negative			Yes		1
					Total score, 6

Final score < 2 , no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5 definite case.

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; U indicates unknown/unclassifiable.

DRESS, where the proportion of relevant and specific positive patch tests was relatively high. In carbamazepine-induced DRESS, the positive rate of patch tests has been reported to be elevated, generally exceeding 70%. Thus, patch test is considered as a useful complementary investigation to confirm the imputability of carbamazepine in DRESS.⁴

Clinicians should be aware of the possibility of a rare entity of DRESS with profound eosinophilia. The rule out of other possible diagnoses should not delay the interruption of the suspected drug and the beginning of supportive therapies.

Neila Fathallah, MD

Raoudha Slim, MD

Slaheddine Rached, MD

Chaker Ben Salem, MD

Department of Clinical Pharmacology

Faculty of Medicine of Sousse

Sousse, Tunisia

Najet Ghariani, MD

Rafaa Nouira, MD

Department of Dermatology

Farhat Hached Hospital

Sousse, Tunisia

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Hepatitis Due to Mycophenolate Mofetil Used to Treat Atopic Dermatitis and Allergic Contact Dermatitis

To the Editor:

Mycophenolate mofetil (MMF) was started as a corticosteroid-sparing agent for a 48-year-old woman with severe atopic

dermatitis and allergic contact dermatitis, at a dose of 500 mg 3 times daily. After a month, her dermatitis improved significantly, but she was noted to develop a biochemical hepatitis, with blood alanine aminotransferase (ALT) rising from 22 IU/L before starting MMF to 418 IU/L and aspartate aminotransferase (AST) from 20 IU/L at baseline to 139 IU/L. We reduced the MMF dose to 500 mg twice daily, but after 2 weeks, both ALT and AST rose to 821 and 203 IU/L, respectively. Throughout this time, she denied abdominal pain, malaise, yellowing of skin, dark urine, or light stools. Medical history was unremarkable and she denied use of alcohol or herbal products; her only other medication was hydroxyzine, which she only took intermittently. Complete blood count and serologic test results for hepatitis A, B, and C were negative, but antinuclear antibodies were positive for a speckled pattern at 1:160. We discontinued MMF and requested a consult from our hepatology clinic, which agreed with our impression of MMF-induced hepatitis. Repeat blood tests 1 month after stopping MMF revealed normal ALT and AST levels.

Although gastrointestinal symptoms such as nausea, vomiting, and diarrhea are commonly associated with MMF treatment, elevated blood hepatic aminotransferases are extremely rare.^{1–4} In our case, there was a strong temporal relationship between starting MMF and development of the biochemical hepatitis. Buttressing the causal relationship were negative serologies for the most common hepatic viral infections, exclusion of other drugs or hepatotoxic agents, and rapid resolution of the hepatitis after stopping MMF.

The very rare reports of MMF-induced elevations in hepatic transaminases include a study by Balal et al of 79 organ transplant patients treated with MMF, 11 of whom had modest elevations in liver enzymes. The median time of increase in transaminases was 28 days (range, 4–70 days). In their study, liver enzymes returned to normal values 16 days (range, 4–210 days) after either complete withdrawal of the drug or, in some patients, a reduction in MMF dose to 50%.² Hantash and Fiorentino reported 2 patients with severe atopic dermatitis on MMF who developed elevated liver enzymes in a range similar to our case.³ Toxic hepatitis with AST and ALT up to 750 IU/L occurred in a patient with anti-neutrophil cytoplasmic antibody–positive vasculitis treated with MMF.⁴ Lastly, another case presented by Loupy et al⁵ highlighted mycophenolate sodium–induced hepatotoxicity in a renal transplant patient. Similarly, elevated liver enzymes returned to normal after withdrawal of mycophenolate.

We conclude that MMF is a relatively safe immunosuppressive drug and a good steroid-sparing agent. However, we must not be lulled into a completely benign perspective. Especially because of its increasing use, including for refractory atopic and allergic contact dermatitis, we must

Address reprint requests to Roselynn H. Nguyen, MD, the University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX. E-mail: Roselynn.Nguyen@gmail.com.

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continue to monitor adverse effects and consider the rare possibility of hepatitis due to drug hypersensitivity.

Roselynn H. Nguyen, MD

Department of Dermatology

The University of Texas Southwestern Medical Center
Dallas, TX

Roselynn.Nguyen@gmail.com

Ponciano D. Cruz, Jr, MD

Department of Dermatology

The University of Texas Southwestern Medical Center
Dallas, TX

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