

Langerhans cell collections, but not eosinophils, are clues to a diagnosis of allergic contact dermatitis in appropriate skin biopsies

Background: Langerhans cell collections (LCCs) and eosinophils are traditionally considered histologic clues to allergic contact dermatitis (ACD), but rigorous histologic analyses are limited. We correlated the presence of LCCs and eosinophils in skin biopsies with patch test results in patients evaluated for ACD.

Methods: Charts of all patients patch tested and biopsied at one institution from 2011 to 2013 were reviewed. Biopsies had to have a diagnosis of either spongiotic dermatitis, psoriasiform dermatitis or mixed psoriasiform/spongiotic dermatitis. Various histologic parameters were assessed, including the presence of LCCs and number of eosinophils.

Design: A total of 68 biopsies met study criteria. Of these, 27 (40%) had ≥ 1 LCC. Twenty-one out of 27 (78%) with ≥ 1 LCC were patch test positive; 6 were patch test negative (22%). Of 41 cases with no LCCs, 23 were patch test positive (23/41, 56%) and 18 were patch test negative (18/41, 44%). LCCs were significantly more common in patch test positive patients ($p = 0.046$). Eosinophil count did not significantly differ in patch test positive and negative cases ($p = 0.216$).

Conclusion: LCCs are significantly more common in patch test positive cases. There were no differences with regards to presence of eosinophils between patch test positive and negative groups.

Keywords: allergic contact dermatitis, eosinophils, Langerhans cells, patch testing

Rosa G, Fernandez AP, Vij A, Sood A, Plesec T, Bergfeld WF, Billings SD. Langerhans cell collections, but not eosinophils, are clues to a diagnosis of allergic contact dermatitis in appropriate skin biopsies.

J Cutan Pathol 2016; 43: 498–504. © 2016 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd

Gabriela Rosa^{1*}, Anthony P. Fernandez^{1,2,*}, Alok Vij², Apra Sood², Thomas Plesec¹, Wilma F. Bergfeld^{1,2} and Steven D. Billings^{1,2}

¹Department of Pathology, The Cleveland Clinic, Cleveland, OH, USA and

²Department of Dermatology, The Cleveland Clinic, Cleveland, OH, USA

*The authors contributed equally to this work.

Steven D. Billings,
Department of Pathology, The Cleveland Clinic,
9500 Euclid Ave., L25, Cleveland, OH 44195,
USA
Tel: 216 444 2826
Fax: 216-445-3707
e-mail: billings@ccf.org

Accepted for publication March 5, 2016

Allergic contact dermatitis (ACD) is a type IV hypersensitivity reaction requiring previous sensitization to the offending agent. The gold standard for diagnosing ACD is skin patch

testing, whereby patients exposed to numerous allergens develop a cutaneous inflammatory response to the specific molecule(s) to which they happen to be allergic.¹ The inter-observer

concordance for patch testing is good, with one study showing an 83% concordance among dermatologists.² The sensitivity and specificity of patch testing in ACD is about 70%, depending on the allergen tested.³ However, interpretation of the patient's skin reaction to patch testing by itself is not sufficient to render an ACD diagnosis. Relevance of the skin reaction to patch testing must be determined based on both the patient's allergen exposure and clinical outcome after avoiding pertinent chemicals.⁴

On skin biopsy, the predominant histopathologic finding in ACD is spongiotic dermatitis. However, numerous other dermatitides, such as atopic dermatitis, nummular dermatitis and dyshidrotic eczema, can be microscopically identical to ACD. Therefore, identification of pathologic clues that are indicative of ACD and guide clinicians to consideration of patch testing could be useful.

Langerhans cell collections, within the epidermis, are thought to be a helpful microscopic clue to ACD.^{5–7} The Langerhans cell is an antigen-presenting cell involved in cellular immunity.⁸ In 1976, Silberberg et al. were the first to associate Langerhans cells with ACD.⁹ The authors sensitized guinea pigs to an allergen and electron microscopy showed that there were increased Langerhans cells in the guinea pig skin upon re-exposure to the allergen.⁹ In a later study, using confocal microscopy, Gonzalez et al. found Langerhans cells in two of five patients with patch test-confirmed ACD.¹⁰

On the other hand, some studies suggest that Langerhans cells may play no diagnostic role in ACD biopsies.^{11,12} The presence of eosinophils has also been considered a helpful feature in skin biopsies of ACD.^{6,7,11} In 2003, Wildemore et al. looked at several features in skin biopsies from 18 patch test-confirmed ACD cases and 21 patch test negative cases.¹¹ The only consistent findings in their patch test positive cases were eosinophilic spongiosis and the so-called dermal dendritic fibrohistiocytic cells, whereas Langerhans cells were found in similar frequency in both patch test positive and -negative cases. Vestergaard et al. compared the pathologic findings in ACD vs. irritant contact dermatitis (ICD) and found that follicular spongiosis and lymphocytic exocytosis in the follicular infundibulum were present in six of seven biopsies of ACD.¹² These features were not seen in the cases of ICD. However, presence or absence of Langerhans cells was not specifically mentioned.

Given the paucity of literature on the histopathologic clues of ACD, with only one

small study comparing patch test positive vs. patch test negative cases, we wanted to better evaluate which histopathologic features might be helpful in the diagnosis of ACD. In this study, we assessed several parameters, including presence of Langerhans cell collections and eosinophils, in association with both patch test results and clinical outcome of patients who underwent patch testing.

Methods

We reviewed medical records of all patients who both had a skin biopsy and were patch tested at one institution between October 1, 2011 and October 31, 2013. Patch testing was performed with the North American Contact Dermatitis Group Standard Series (Chemotechnique Diagnostics AB, Vellinge, Sweden) using Finn Chambers (Epitest OY, Tuusula, Finland) on Scanpor tape (SmartPractice, Phoenix, AZ, USA). First and second patch test readings were performed at 48 and 72–168 h, respectively, after initial patch test placement per the North American Contact Dermatitis Group criteria.¹³

Adult patients were tested with the adult standard screening tray, which included 65–70 allergens, and pediatric patients were tested with 39–40 allergens from the standard screening tray. Additional series of allergens and personal products were added as the clinical scenario or occupational history dictated.

Allergic patch test reactions were graded as 1+, 2+ or 3+, as per the North American Contact Dermatitis Group criteria.¹³ Questionable reactions (including macular erythema or a papular eruption involving less than 50% of the area occluded by the patch) were generally coded as non-allergic reactions. If the clinical history suggested relevance, or if other positive reactions to the same allergen but in a different vehicle were found, or if a cross-reacting substance was identified, the investigator had the discretion to make the final determination as to whether the reaction represented a positive patch test. Irritant and allergic reactions were differentiated by the clinician, who considered the morphology and timing of the reaction at each reading. All patch tests and interpretations were made by dermatologists who specialize in ACD and comprehensive patch testing.

Only patients with biopsies revealing a diagnosis of spongiotic dermatitis, psoriasiform dermatitis or mixed psoriasiform/spongiotic dermatitis were included in our study. Biopsies were independently reviewed by two

Table 1. Histopathologic findings in association with patch test results

Histologic feature	Positive patch test (n = 44)	Negative patch test (n = 24)
≥1 Langerhans cell collections	21/44 (47.7%)	6/24 (25%)
No Langerhans cell collections	23/44 (52.3%)	18/24 (75%)
Eosinophils in the dermis (≥10 per 5 HPF)	7/44 (15.9%)	6/24 (25%)
Eosinophils in the dermis (<10 per 5 HPF)	37/44 (84%)	18/24 (75%)
Eosinophils in the epidermis (eosinophilic spongiosis)	0/44 (0%)	0/24 (0%)
Acanthosis (none to minimal)	17/44 (38.6%)	11/24 (45.8%)
Acanthosis (moderate to severe)	27/44 (61.4%)	13/24 (54.2%)
Parakeratosis (none to focal)	21/44 (47.7%)	16/24 (66.7%)
Parakeratosis (continuous or prominent)	23/44 (52.3%)	8/24 (33.3%)
Hyperkeratosis (absent to mild)	24/44 (54.5%)	14/24 (58.3%)
Hyperkeratosis (moderate to severe)	20/44 (45.4%)	10/24 (41.7%)
Spongiosis (none to mild)	24/44 (54.5%)	15/24 (62.5%)
Spongiosis (moderate to severe)	20/44 (45.4%)	9/24 (37.5%)
Neutrophils in the dermis (sparse)	44/44 (100%)	21/24 (87.5%)
Neutrophils in the dermis (moderate to severe)	0/44 (0%)	3/24 (12.5%)
Superficial perivascular chronic inflammation (absent to mild)	16/44 (36.4%)	9/24 (37.5%)
Superficial perivascular chronic inflammation (moderate to severe)	28/44 (63.6%)	15/24 (62.5%)
Deep perivascular chronic inflammation (absent to mild)*	39/44 (88.6%)	19/24 (79.2%)
Deep perivascular chronic inflammation (moderate to severe)*	2/44 (4.5%)	1/24 (4.2%)
Dyskeratosis (<5 in one skin section)	41/44 (93.2%)	23/24 (95.8%)
Dyskeratosis (≥5 in one skin section)	3/44 (6.8%)	1/44 (2.3%)
Exocytosis (none to mild)	34/44 (77.3%)	20/24 (83.3%)
Exocytosis (moderate to severe)	10/44 (22.7%)	4/24 (16.7%)
Follicular spongiosis	1/44 (2.3%)	0/24 (0%)

*Seven biopsies had insufficient dermis to assess for deep perivascular chronic inflammation.

board-certified dermatopathologists (SDB and APF) and one pathology resident physician (GR) who were blinded to patch test results. Various histopathologic findings were assessed (see Table 1), including presence of Langerhans cell collections on routine and CD1a-stained sections (AbD Serotec, clone MCA1567, prediluted, Raleigh, NC) and number of eosinophils per 5 high power fields (HPFs). Patch test results were then correlated with the assessed histopathologic parameters. Statistical analyses by Barnard's exact test were performed.

Results

A total of 68 biopsies from 68 individual patients with a diagnosis of spongiotic dermatitis (65), psoriasiform dermatitis (2) or mixed psoriasiform/spongiotic dermatitis (1) met study criteria. Of the 68 patients, 66 were young adults or adults (ages: 17–94; 35 males and 31 females). Two patients were children, including one male and one female, ages 8 and 12, respectively. Biopsies were performed anywhere from 23 months prior to patch testing to 9 months after patch testing. In the majority of cases, biopsies were performed prior to patch testing (94%, 64/68) and most biopsies were performed within 6 months of patch testing (70%, 48/68).

A total of 44 patients were patch test positive and 24 were patch test negative. In all, 27 (40%) had ≥1 Langerhans cell collections identified in their biopsies (Table 2; Fig. 1A,B). A total of 21 out of 27 (78%) with ≥1 Langerhans cell collections were patch test positive, whereas 6 out of 27 were patch test negative (22%) (Table 2). Of patients with no Langerhans cell collections in their biopsies, 23 were patch test positive (23/41, 56%) and 18 were patch test negative (18/41, 44%). Langerhans cell collections were significantly more common in patch test positive patients (Barnard's exact test, $p=0.046$). Langerhans cell collections were visible on H+E and immunohistochemistry (IHC) in 16 out of 27 cases, H+E only in 8 out of 27 and by IHC only in 3 out of 27 cases. If a positive patch test is considered as the gold standard for diagnosing ACD, Langerhans cell collections have a sensitivity of 48%, a specificity of 75%, a positive predictive value of 78% and a negative predictive value of 44% in ACD.

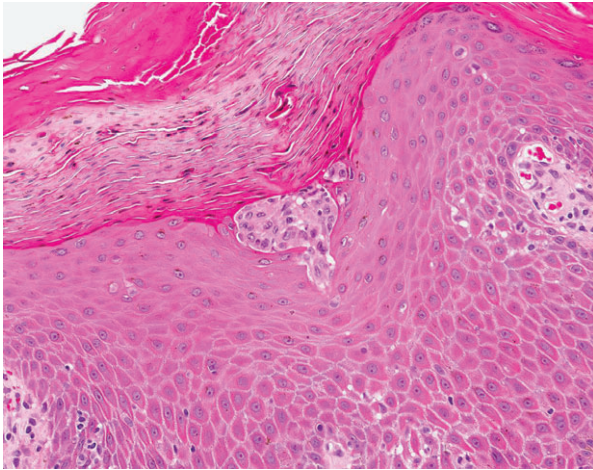
Of patch test positive cases 7 had ≥10 eosinophils/5 HPF, 5 had 2–5 eosinophils/5 HPF and 32 had 0–1 eosinophils/5 HPF (Table 1; Figs. 2 and 3). Of patch test negative cases 6 had ≥10 eosinophils/5 HPF, 1 had 2–5 eosinophils/5 HPF and 17 had

Langerhans cell collections are clues to a diagnosis of allergic contact dermatitis

Table 2. Presence of Langerhans cell collections in association with patch test results

	Positive patch test	Negative patch test
≥1 Langerhans cell collections (n = 27)	21/27 (78%)	6/27 (22%)
No Langerhans cell collections (n = 41)	23/41 (56%)	18/41 (44%)

(A)



(B)

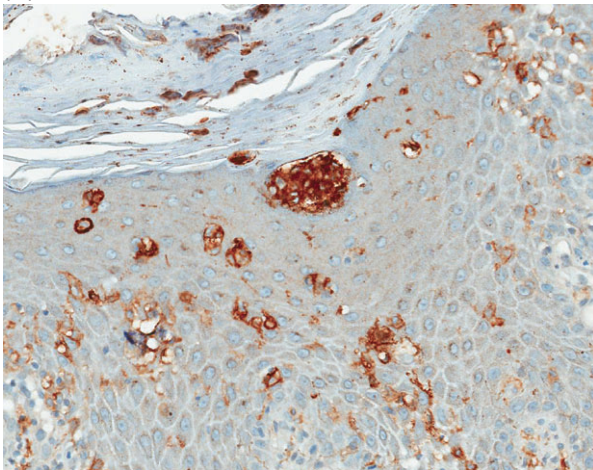


Fig. 1. A) Langerhans cell collection in a biopsy from a 57-year-old woman with a 1+ reaction to thiuram mix, eczema remedy oil and carmine. Her hand dermatitis largely resolved with avoidance of these agents (hematoxylin and eosin, ×200 magnification). B) Langerhans cell collection from the same patient, highlighted by the CD1a stain (×200 magnification).

0–1 eosinophils/5 HPF (Table 1). Eosinophil count did not significantly differ in patch test positive and patch test negative cases, comparing ≥10 eosinophils vs. other ($p=0.216$). In addition, other histopathologic characteristics assessed also did not significantly differ in patch test positive and patch test negative cases

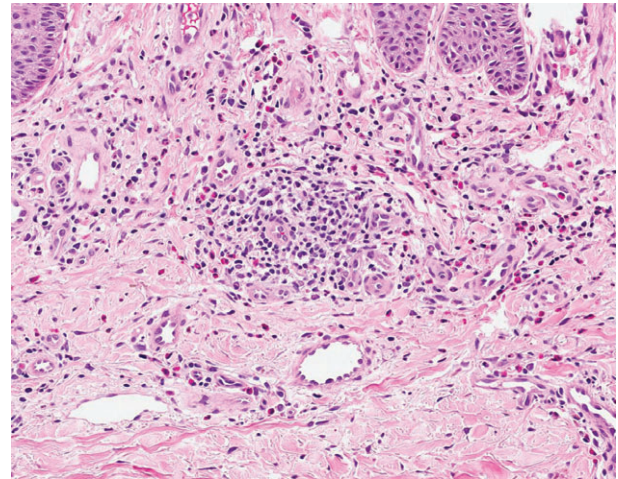


Fig. 2. Numerous eosinophils in a thigh biopsy from a 60-year-old man with diffuse dermatitis. Patch testing was negative (hematoxylin and eosin, ×200 magnification).

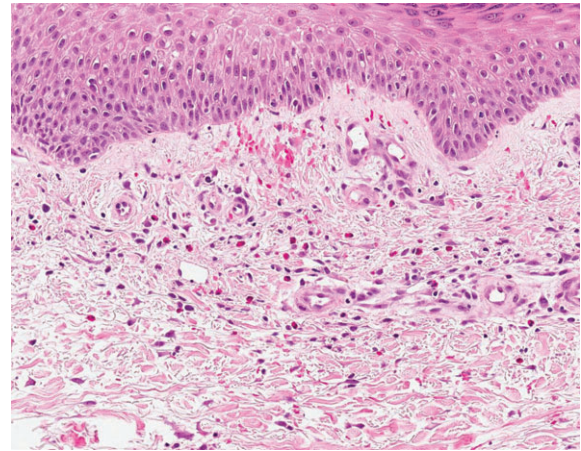


Fig. 3. Numerous eosinophils in a leg biopsy from an 83-year-old man with a 1+ reaction to propylene glycol. With avoidance of the allergen, his rash resolved (hematoxylin and eosin, ×200 magnification).

(Table 1). The majority of patch test positive cases (68%, 30/44) and all patch test negative cases (100%, 24/24) had virtually no eosinophils (0–1 eosinophil in 5 HPF). An analysis of the subset of cases without Langerhans cell collections failed to reveal any histopathologic features that significantly differed in patch test positive compared with patch test negative patients (Table 3). No cases showed eosinophilic spongiosis, and only one case showed follicular spongiosis.

Of patients who were patch test positive ($n=44$), 25 showed resolution of their symptoms with avoidance of the pertinent allergen(s), 8 showed no resolution of symptoms and 11 had no follow-up data. Of the 25 patients who showed

Table 3. Histopathologic findings on cases with no Langerhans cell collections in association with patch test results (total 41)

Histologic feature	Positive patch test (n = 23)	Negative patch test (n = 18)
Eosinophils in the dermis (≥ 10 per 5 HPF)	5/23	4/18
Eosinophils in the dermis (< 10 per 5 HPF)	18/23	14/18
Eosinophils in the epidermis (eosinophilic spongiosis)	0/23	0/18
Acanthosis (none to minimal)	13/23	11/18
Acanthosis (moderate to severe)	10/23	7/18
Parakeratosis (none to focal)	13/23	12/18
Parakeratosis (continuous or prominent)	10/23	6/18
Hyperkeratosis (absent to mild)	16/23	12/18
Hyperkeratosis (moderate to severe)	7/23	6/18
Spongiosis (none to mild)	15/23	12/18
Spongiosis (moderate to severe)	8/23	6/18
Neutrophils in the dermis (sparse)	23/23	15/18
Neutrophils in the dermis (moderate to severe)	0/23	3/18
Superficial perivascular chronic inflammation (absent to mild)	10/23	9/18
Superficial perivascular chronic inflammation (moderate to severe)	13/23	9/18
Deep perivascular chronic inflammation (absent to mild)*	21/23	14/18
Deep perivascular chronic inflammation (moderate to severe)*	1/23	1/18
Dyskeratosis (< 5 in one skin section)	22/23	18/18
Dyskeratosis (≥ 5 in one skin section)	1/23	0/18
Exocytosis (none to mild)	22/23	15/18
Exocytosis (moderate to severe)	1/23	3/18
Follicular spongiosis	1/23	0/18

*Seven biopsies had insufficient dermis to assess for deep perivascular chronic inflammation.

resolution of their symptoms with avoidance of the pertinent allergen(s), supporting a definitive diagnosis of ACD, 11 had ≥ 1 Langerhans cell collections and 14 had no Langerhans cell collections on skin biopsy. Eosinophil counts in these patients were 0–1 eosinophil per 5 HPF in 17 patients, 2–5 eosinophils per 5 HPF in 5 patients and ≥ 10 eosinophils per 5 HPF in 3 patients.

Discussion

Epidemiologic data regarding the true prevalence of ACD is lacking. However, allergic and irritant contact dermatitis, considered together, are estimated to comprise 30% of occupational diseases in industrialized nations.¹⁴ ACD can have major effects on quality of life and can cause patients significant psychological distress.¹⁵ As an occupational exposure, ACD shows similar scores on quality of life indices to Darier disease, Hailey–Hailey disease and chronic idiopathic urticaria.¹⁶ One study in mice suggests that chronic ACD may promote development of cutaneous squamous cell carcinoma.¹⁷ Thus, ACD is a fairly common condition (at least as an occupational exposure) and can cause significant morbidity.

Patients with ACD might not initially be referred for patch testing, as it can be misdiagnosed as other conditions. In particular, ACD

can be a challenging diagnosis in patients with other co-existent skin conditions and in patients who present with ‘atypical’ clinical features. Co-existence of ACD and other skin diseases can be common, with one study of Danish schoolchildren revealing half of adolescents fulfilling criteria for atopic dermatitis also had concomitant ACD.¹⁸ In problematic cases where ACD might not be initially suspected, histopathologic clues to the diagnosis of ACD could be of potential clinical value. In this study, we investigated for potential histopathologic clues for the diagnosis of ACD. As the establishment of the diagnosis of ACD ultimately relies on clinical correlation, we restricted our analysis to patients undergoing patch testing. Only patch test positive patients were considered to have ACD.

In our opinion, evaluating spongiotic dermatitis cases for the presence of Langerhans cell collections is potentially helpful based on our results; however, use of immunohistochemical stains to identify Langerhans cell collections was not particularly helpful. In most of our cases with Langerhans cell collections, they were visible on routine hematoxylin and eosin (H&E) stained sections. Both the CD1a and Langerin immunohistochemical stains are highly sensitive and specific for Langerhans cells, with one study suggesting CD1a is slightly more specific than Langerin.¹⁹ For this reason, we used

CD1a to further assess cases for the presence of Langerhans cell collections. However, only three cases showed Langerhans cell collections by immunohistochemistry alone. This was probably related to sampling, with the immunohistochemical stain representing a deeper aspect of the block than the H&E stained slide.

Our study has limitations. For one, we did not examine additional histopathologic sections in the included cases and cannot completely rule out the possibility that Langerhans cell collections would have been identified with more thorough examination of cases without them. In addition, we cannot rule out the possibility that Langerhans cell collections are more likely to be present if biopsies are performed at certain temporal periods in the course of the cutaneous eruption (e.g. within 1 month after onset of the rash or in a lesion of relatively new onset regardless of the chronicity of the eruption). Furthermore, as eight patients with positive patch tests did not have resolution of their rash with allergen avoidance and eleven were lost to follow-up, we cannot be certain about the significance of Langerhans cell collections in those patients in which they were present. That being said, one of the eight patients whose rash did not resolve was patch test positive to a nearly ubiquitous allergen and another had a positive reaction to an allergen common in the individual's workplace. Therefore avoidance for both of these patients was potentially problematic or not possible.

There is a significant body of literature on the diagnostic role of eosinophils in various dermatologic conditions. For some conditions, such as lupus erythematosus, there is evidence that absence of eosinophils is diagnostically useful.²⁰ In other conditions, such as arthropod bites and psoriasiform skin reactions to TNF- α inhibitors, presence of eosinophils is thought to be a diagnostic clue.^{21,22} Eosinophils are often thought to be associated with allergic conditions, in particular certain drug reactions.^{23,24} The presence of eosinophils, in particular eosinophilic spongiosis has also been suggested to be an important histopathologic feature in ACD.¹¹ In a study of

18 patch test-confirmed ACD cases and 21 patch test negative cases, eosinophilic spongiosis was found in 28% of patch test positive cases and 5% of patch test negative cases.¹¹ Our results are very different, which could be related to our larger study size or possibly timing of the biopsies. There was no difference in the patch test positive and patch test negative cases in terms of dermal eosinophil counts and eosinophilic spongiosis. In fact, in 32 out of 44 (73%) of patch test positive cases, the dermal eosinophil count was 0–1 per 5 high magnification field. Similarly, eosinophilic spongiosis was not found in a single case. This is not entirely surprising. ACD is a type IV hypersensitivity reaction that is a lymphocyte-driven process not dependent on eosinophils. Therefore the absence of a significant eosinophil component in no way argues against the diagnosis of ACD. Again, whether timing of biopsy in correlation with onset of the eruption affects the presence of tissue eosinophilia is admittedly unresolved, but our results reflect routine practice at a large medical center and we believe they are therefore representative of everyday clinical practice.

In summary, the only histopathologic feature associated with patch test-confirmed ACD was the presence of Langerhans cell collections. This study supports the concept that the presence of Langerhans cell collections is a clue to the diagnosis of ACD. In this study, Langerhans cell collections were significantly more common in patients with patch test-confirmed ACD than in patch test negative patients. The sensitivity of this finding is relatively low (48%), but the positive predictive value was relatively strong (78%), as was the specificity (75%). Thus, when Langerhans cell collections are present, it is our opinion the possibility of ACD should be mentioned in the comment section of a pathology report, as this result could prompt the treating physician to refer the patient for patch testing and lead to resolution of the patient's dermatitis with appropriate allergen avoidance.

References

1. Nelson J, Mowad CM. Allergic contact dermatitis: patch testing beyond the TRUE test. *J Clin Aesthet Dermatol* 2010; 3: 36.
2. Bruze M, Bjorkner B, Lepoittevin JP. Occupational allergic contact dermatitis from ethyl cyanoacrylate. *Contact Dermatitis* 1995; 32: 156.
3. Nethercott JR. Practical problems in the use of patch testing in the evaluation of patients with contact dermatitis. *Curr Probl Dermatol* 1990; 2: 4.
4. Mowad CM, Marks JG. Allergic contact dermatitis. In Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*, 3rd ed. Philadelphia: Elsevier, 2012; 233.
5. Billings SD, Cotton J. Spongiotic dermatitis. In *Inflammatory dermatopathology*. New York: Springer, 2011; 5.
6. Patterson JW. The spongiotic pattern. In Weedon's skin pathology, 4th ed. Philadelphia: Elsevier, 2016; 103.
7. Calonjee E, Brenn T, Lazar A. Spongiotic, psoriasiform and pustular dermatoses. In McKee's pathology of the skin with clinical correlations, 4th ed. Philadelphia: Elsevier, 2012; 180.

8. Stingl G, Tamaki K, Katz SI. Origin and function of epidermal Langerhans cells. *Immunol Rev* 1980; 53: 149.
9. Silberberg I, Baer RL, Rosenthal SA. The role of Langerhans cells in allergic contact hypersensitivity. A review of findings in man and guinea pigs. *J Invest Dermatol* 1976; 66: 210.
10. Gonzalez S, Gonzalez E, White WM, Rajadhyaksha M, Anderson RR. Allergic contact dermatitis: correlation of *in vivo* confocal imaging to routine histopathology. *J Am Acad Dermatol* 1999; 40(5 Pt 1): 708.
11. Wildemore JK, Junkins-Hopkins JM, James WD. Evaluation of the histopathologic characteristics of patch test confirmed allergic contact dermatitis. *J Am Acad Dermatol* 2003; 49: 243.
12. Vestergaard L, Clemmensen OJ, Sorensen FB, Andersen KE. Histological distinction between early allergic and irritant patch test reactions: follicular spongiosis may be characteristic of early allergic contact dermatitis. *Contact Dermatitis* 1999; 41: 207.
13. Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; 50: 287.
14. Clark SC, Zirwas MJ. Management of occupational dermatitis. *Dermatol Clin* 2009; 27: 365.
15. Wilk N. Mystery (misery) resolved. *J Am Acad Dermatol* 2004; 51(Suppl. 1): S63.
16. Hutchings CV, Shum KW, Gawkrödger DJ. Occupational contact dermatitis has an appreciable impact on quality of life. *Contact Dermatitis* 2001; 45: 17.
17. Demehri S, Cunningham TJ, Hurst EA, Schaffer A, Sheinbein DM, Yokoyama WM. Chronic allergic contact dermatitis promotes skin cancer. *J Clin Invest* 2014; 124: 5037.
18. Czarnobilska E, Obtulowicz K, Dyga W, Spiewak R. A half of schoolchildren with 'ISAAC eczema' are ill with allergic contact dermatitis. *J Eur Acad Dermatol Venereol* 2011; 25: 1104.
19. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. *Am J Surg Pathol* 2008; 32: 615.
20. Sharon VR, Konia TH, Barr KL, Fung MA. Assessment of the "no eosinophils" rule: are eosinophils truly absent in pityriasis lichenoides, connective tissue disease, and graft versus host disease? *J Cutan Pathol* 2012; 39: 413.
21. Krahel D, Sellheyer K. A scanning microscopic clue to the diagnosis of arthropod assault reaction: alteration of interstitial tissue is more common than a wedge-shaped inflammatory infiltrate. *J Cutan Pathol* 2009; 36: 308.
22. Laga AC, Vleugels RA, Qureshi AA, Velazquez EF. Histopathologic spectrum of psoriasiform skin reactions associated with tumor necrosis factor-alpha inhibitor therapy. A study of 16 biopsies. *Am J Dermatopathol* 2010; 32: 568.
23. Avancini J, Maragno L, Santi CG, Criado PR. Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome: clinical features of 27 patients. *Clin Exp Dermatol* 2015; 40: 851.
24. Hussein MR. Drug-induced skin reactions: a pathologist viewpoint. *Cutan Ocul Toxicol* 2015; 1: 67.