WHAT IS YOUR DIAGNOSIS?

1. What is your diagnosis on the basis of the clinical and histologic findings?
   a. Mycosis fungoides
   b. Tinea manuum
   c. Urticaria
   d. Allergic contact dermatitis (ACD)
   e. Fixed drug eruption

Figure 1. Images courtesy of Mariya Miteva, Dr Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami

Editorial note: Welcome to the Journal of Investigative Dermatology (JID) SnapshotDx Quiz. In this monthly online-only quiz, the first question (“What is your diagnosis?”) relates to the clinical image shown, while additional questions concern the findings reported in the JID article by Gadsbøll et al. (2020) (https://doi.org/10.1016/j.jid.2019.07.722).

Detailed answers and a list of relevant references are available following the Quiz Questions below.

QUIZ QUESTIONS

1. What is your diagnosis on the basis of the clinical and histologic findings?
   a. Mycosis fungoides
   b. Tinea manuum
   c. Urticaria
   d. Allergic contact dermatitis (ACD)
   e. Fixed drug eruption

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2. Which of the following answers is TRUE?
   a. Among γδ and αβ T cells, only the latter are found in human epidermis.
   b. Histopathology reliably distinguishes ACD from irritant contact dermatitis and atopic dermatitis.
   c. Exposure of the skin to contact allergen induces the accumulation of allergen-specific CD8+CD69+CD103+ T cells in the skin.
   d. In humans, Vδ1 T cells (the major subset of γδ T cells) possess dendritic shape as in rodents.
   e. CD4+CCR10+ memory T cells disappear from the dermis after the clinical resolution of ACD.

3. Which of the following answers is FALSE according to the article by Gadsbøll et al. (2020)
   a. Exposure to allergens leads to the generation of CD8+ epidermal resident memory T (T_RM) cells (skin T_RM cells).
   b. Dendritic epidermal T cells (DETCs) are not required for the generation of CD8+ epidermal T_RM cells after exposing the skin to an allergen.
   c. Expansion of the CD8+ epidermal T_RM cell population after allergen re-exposure is mediated solely by local proliferation in the epidermis and not by recruitment from the circulation.
   d. CD8+ epidermal T_RM cells have a higher respiratory capacity than DETCs.
   e. The magnitude of the cutaneous hypersensitivity reaction and the frequency of CD8+ epidermal T_RM cells directly correlate with the dose of the allergen.

See the following pages for detailed answers
DETAILED ANSWERS

1. What is your diagnosis on the basis of the clinical and histologic findings?

CORRECT ANSWER: d. Allergic contact dermatitis (ACD).

The image shows a patient with ACD. ACD is a disease typified by a localized eruption secondary to a delayed-type hypersensitivity reaction (Rashid and Shim, 2016). Occupational exposures are frequent, with nearly 40% of patients having positive patch testing that identifies a relevant occupational contactant (DeKoven et al., 2018). Acutely, ACD is characterized by pruritus localized to a well-demarcated area of erythema, often with vesiculation. Over time, this may give way to a lichenified or fissured dermatitis (Murphey et al., 2020). Histology of ACD typically demonstrates a spongotic dermatitis (including eosinophilic spongiosis as noted on the image) with an associated superficial lymphocytic perivascular infiltrate. These features are shared with irritant contact dermatitis (ICD) as well as atopic dermatitis (AD), and histology does not reliably differentiate these entities. Specific findings suggestive of ACD, including increased deep dermal infiltrate, absence of papillary dermal edema, reduced CD34 expression, and increased CD3+ T cells relative to ICD and AD, did not reach statistical significance. Between these three histologically similar conditions, only increased eosinophils in AD relative to ICD and ACD was found to be significant (Frings et al., 2018).

Discussion of incorrect answers:

a. **Mycosis fungoides:** Cutaneous T-cell lymphoma (CTCL) is a non-Hodgkin lymphoma with infiltration of the skin by malignant T lymphocytes. Mycosis fungoides (MF) is the most common form of CTCL, accounting for 55% of the cases (Trautinger et al., 2017). The incidence of CTCL is approximately 6.4 per million persons, with improvements in diagnosis likely accounting for reports of increased incidence (Phyo et al., 2020). Many clinical and histopathologic features of MF are nonspecific, resulting in a median time from onset of symptoms to diagnosis of between 3 and 4 years. In addition to consistent clinical and histopathologic features, the diagnosis of MF can be supported by demonstrating clonality of T cells between lesions at different sites as well as the loss of pan T-cell antigens such as CD2, CD5, and CD7 in the malignant lymphocytes (Wilcox, 2016). Skin-directed therapies for MF include topical corticosteroids, topical mechlorethamine, topical hexarotene, UV phototherapy, and radiation therapies. Systemic therapies, which are often combined with skin-directed therapies, include retinoids, IFN-α, methotrexate, chemotherapies, immunotherapies, and extracorporeal photopheresis (Trautinger et al., 2017).

b. **Tinea manuum:** Tinea manuum is a common superficial fungal infection of the hands, most commonly caused by dermatophytes from the genera *Epidermophyton*, *Trichophyton*, and *Microsporum*. Tinea infections are among the most common infections worldwide. When affecting the palmar hands, the infection takes on a dry, scaling appearance. This typically presents solely on the dominant hand in combination with bilateral tinea pedis on the one hand, two-foot syndrome; however, bilateral palmar infection is possible (Moriarty et al., 2012). The most commonly implicated dermatophytes in the United States are *Trichophyton rubrum*, *T. mentagrophytes*, and *T. tonsurans*, and tinea infections occur in up to 70% of adults (Drake et al., 1996). With appropriate history and clinical examination findings, diagnosis can be verified with potassium hydroxide preparation or fungal culture. Treatment may be a topical application of imidazoles, allylamines, or ciclopirox olamine; however, systemic therapy with antifungals can be used in inflammatory or widespread cases (Drake et al., 1996).

c. **Urticaria:** Urticaria presents with pruritic wheals with or without angioedema and can be divided into acute and chronic forms with a delineation of a 6-week duration. Chronic urticaria can further be divided into spontaneous and inducible types. Inducible types may be secondary to triggers, including exposure to temperature changes, pressure, vibration, UV radiation, and contact with water (Kudryavtseva et al., 2019). Acute urticaria is idiopathic in the majority of cases. When triggers are identified, the most common are infections, drug reactions, and food allergies. In noninducible cases of chronic urticaria, up to 30% of cases have associated autoantibodies to the high-affinity IgE receptor FcεRIα or IgA. Histopathologic findings of urticaria include upper dermal edema with mild perivascular and interstitial mixed inflammation (Antia et al., 2018b). Second-generation antihistamines are first line for the treatment of chronic urticaria, and data do not support the superiority of an individual agent relative to another. The dosing required to treat chronic urticaria is commonly greater than the approved doses, with most cases requiring two to four times the recommended doses (Antia et al., 2018a).

d. **Fixed drug eruption:** Fixed drug eruption (FDE) is a cutaneous drug eruption that presents with dusky red to brown patches on the skin and mucosa. The patches recur at the same sites during recurrences owing to resident populations of intraepidermal memory CD8+ T lymphocytes. The most common offending medications are antibiotics and nonsteroidal anti-inflammatory drugs. Similar to Stevens–Johnson syndrome and toxic epidermal necrolysis, cytotoxic Fas, Fas-ligand, perforin, and granzyme B play an important role in FDE. In contrast to the image in this question stem, the histopathology of FDE typically demonstrates apoptotic keratinocytes, vacuolar interface change, pigment incontinence,
and a superficial perivascular inflammatory infiltrate with the presence of eosinophils (Cho et al., 2014).

2. Which of the following answers is TRUE?

CORRECT ANSWER: c. Exposure of the skin to contact allergen induces the accumulation of allergen-specific CD8+CD69+CD103+ T cells in the skin.

CD8+CD69+CD103+ resident memory T (T_{RM}) cells in the skin are directly involved in the production of the rapid hypersensitivity reaction that occurs on exposure to a previously encountered contactant (Gadsbøll et al., 2020). Gamradt et al. (2019) demonstrated that circulating effector T cells involved in the early acute hypersensitivity reaction give way to these T_{RM} cells, which can persist in the skin for several weeks. Subsequent re-exposure produces the expansion of this cell population and also by the influx of circulating CD8+ T cells. Gadsbøll et al. (2020) demonstrated further that the T_{RM} cells displace dendritic epidermal T cells (DETCs) and that the magnitude of the hypersensitivity reaction correlated with both the frequency of CD8+ T_{RM} cells and the dose of the allergen.

Discussion of incorrect answers:

a. Among γδ and αβ T cells, only the latter are found in human epidermis: This statement is false because both γδ and αβ T cells are found within the human epidermis (Gadsbøll et al., 2020). These resident T-cell populations may function in immune surveillance in the skin and participate in skin homeostasis through the production of insulin-like GF-1, and their dysfunction may play a role in the chronicity of nonhealing wounds (Toulon et al., 2009).

b. Histopathology reliably distinguishes ACD from irritant contact dermatitis and atopic dermatitis: This statement is false because there is considerable overlap between histopathologic features of ACD, ICD, and AD. All three of these conditions commonly demonstrate a spongiotic dermatitis with superficial perivascular lymphocytic infiltrates. Frings et al. (2018) performed a retrospective analysis of the histologic and immunohistochemistry findings from 35 biopsy specimens from 28 patients. With the exception of an increased presence of eosinophils in biopsies from AD, there were no significant differences in routine histology or immunophenotyping among these disorders (Frings et al., 2018).

d. In humans, Vδ1 T cells (the major subset of γδ T cells) possess dendritic shape as in rodents: This statement is false. Although Vδ1 T cells do account for the major subset of γδ T cells in human skin, they do not have the specific dendritic shape as seen in rodent DETCs (Sutoh et al., 2018). In rodents, the development of these cells is dependent on Skint1 gene expression. Humans express a SKINT1L gene, in which inactivating mutations are thought to be responsible for this lack of a discrete dendritic shape. Interestingly, chimpanzees demonstrate similar nonfunctional Skint1 expression and DETC morphology to humans, but Old World monkeys possess functional Skint1 sequences and a population of dendritic-shaped γδ T cells. These findings suggest that the functionality of this gene, which plays a major role in the phenotype of these resident T cells, was lost in a hominoid ancestor (Mohamed et al., 2015).

e. CD4+CCR10+ memory T cells disappear from the dermis after clinical resolution of ACD: This is false. By treating skin with oxazolone to produce ACD, Wang et al. (2010) demonstrated that CCR4 and CCR10 are upregulated on CD4+ T lymphocytes in lymph nodes, which leads to the recruitment of these cells to the skin affected by ACD. After the clinical resolution of the ACD, however, these cells persist in the skin and may mediate the accelerated inflammatory responses seen after repeated exposures to contactants. This is in contrast to ICD, in which these cells were not detected after clinical resolution. Taken together, the findings suggest that the presence of CD4+CCR10+ T cells is likely allergen mediated (Moed et al., 2004).

3. Which of the following answers is FALSE according to the article by Gadsbøll et al. (2020)?

CORRECT ANSWER: c. Expansion of the CD8+ epidermal T_{RM} cell population after allergen re-exposure is mediated solely by local proliferation in the epidermis and not by recruitment from the circulation.

This choice is FALSE. According to the article by Gadsbøll et al. (2020), the expansion of CD8+ T_{RM} cells occurred both by local proliferation and by an influx of CD8+ T cells from circulation. In this article, mice were exposed to dinitrofluorobenzene (DNFB) allergen. The change in the number of CD8+ T_{RM} cells was monitored. In a portion of mice, however, FTY720 was administered. FTY720, also known as fingolimod, is an immunomodulator, with the applications as a treatment for multiple sclerosis and as an anticancer therapy. FTY720 seeks to T cells to lymphoid tissues through the antagonism of sphingosine-1-phosphate 1 receptor (White et al., 2016). This sequestration prevented their recruitment to the skin. In this subset of mice, a significant reduction of CD8+ T_{RM} cells was noted after exposure to DNFB compared with the subset of those without lymphocyte sequestration. They demonstrated that approximately 40% of the T_{RM} expansion is due to the recruitment of CD8+ T cells from circulation (Gadsbøll et al., 2020).

Discussion of incorrect answers:

a. Exposure to allergens leads to the generation of CD8+ epidermal resident memory T (T_{RM}) cells (skin T_{RM} cells): This is true. On exposure to an allergen, allergen-specific CD8+CD69+CD103+ T_{RM}
cells accumulate in the skin and then mediate the hypersensitivity reactions that occur on exposure to the allergen. This article compared the composition of epidermal T-cell populations in control mice with that of mice sensitized to the experimental allergen, DNFB. In the control group, the majority of T cells in the epidermis were Vγ3+CD69+CD103+ DETCs. In these control mice, CD4+ and CD8+ cells were rare. In the experimental group, however, allergen exposure resulted in an increased presence of CD8+CD69+CD103+ T_{RM} cells to account for 60% of the total epidermal T-cell population. CD4+CD69+ T cells also increased to a lesser degree (Gadsbøll et al., 2020).

b. **Dendritic epidermal T cells (DETCs)** are not required for the generation of CD8+ epidermal T_{RM} cells after exposing the skin to an allergen: This is true. In this article, an experimental mouse model without the expression of TCRβ and therefore without DETCs was evaluated. After the exposure of these mice to DNFB allergen, a major population of T_{RM} cells was still produced. Therefore, these T_{RM} cells are generated independently of DETCs (Gadsbøll et al., 2020).

d. **CD8+ epidermal T_{RM} cells have a higher respiratory capacity than DETCs**: After exposure to allergen, the DETC population decreases in the epidermis as the T_{RM} population increases. Gadsbøll et al. (2020) determined the bioenergetics profiles of the epidermal T-cell populations by looking at the basal oxygen consumption rate and extracellular acidification rate. These were significantly increased in T_{RM} cells compared with those of DETCs, possibly accounting for a survival advantage and resultant persistence within the epidermis of CD8+ T_{RM} cells compared with that of DETCs (Gadsbøll et al., 2020).

e. **The magnitude of the cutaneous hypersensitivity reaction and the frequency of CD8+ epidermal T_{RM} cells directly correlates with the dose of the allergen**: Gadsbøll et al. (2020) exposed mice to DNFB and measured ear thickness at several time points. Ear thickness was used to determine the magnitude of the contact hypersensitivity (CHS) reaction. Ear thickness and therefore the magnitude of CHS reaction was proportional to the number of CD8+ T_{RM} cells, the number of exposures to an experimental allergen, and the dose of that allergen (Gadsbøll et al., 2020).

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**REFERENCES**


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