WHAT IS YOUR DIAGNOSIS?

Figure 1. Images credit to Mariya Miteva, University of Miami.

Editorial note: Welcome to the Journal of Investigative Dermatology (JID) Snapshot Dx Quiz—In this monthly online-only quiz, the first question (“What is your diagnosis?”) relates to the clinical image above, while additional questions concern the findings reported in the JID article by Imanishi et al (https://doi.org/10.1016/j.jid.2017.09.047)

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

QUIZ QUESTIONS

1. What is your diagnosis based on the clinical, trichoscopic and pathologic images?
   a. seborrheic dermatitis
   b. scalp psoriasis
   c. lichen planopilaris
   d. discoid lupus erythematosus
   e. dissecting cellulitis of the scalp

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2. Which of the following answers is TRUE?
   a. The bulge of the hair follicle contains immunologically privileged epithelial stem cells.
   b. Lichen planopilaris (LPP) results from a CD8+ T-cell mediated attack and loss of the immune privilege of the bulbar epithelial stem cells.
   c. In Epithelial mesenchymal transition (EMT) the mesenchymal proteins fibronectin and vimentin are downregulated.
   d. Significantly reduced PPAR-γ levels have been detected in affected but not in unaffected tissue in LPP.
   e. The bulge of the healthy hair follicles is characterized by the downregulation of α-melanocyte-stimulating hormone (MSH) and transforming growth factor (TGF)β2 and CD200.

3. Which of the following answers is FALSE according to the article by Imanishi et al.?
   a. Hair follicles from lesional LPP show morphological and ultrastructural signs for EMT within the epithelial stem cell niche.
   b. All EMT related genes were expressed in both lesional and non-lesional biopsies from the same patient with LPP.
   c. EMT signature was not observed in every single patient with LPP.
   d. Bulge EMT can be experimentally induced in healthy human hair follicles ex vivo.
   e. PPAR-γ stimulation by a topically applied PPAR-γ modulator (currently undergoing clinical trials in acne vulgaris) partially reverses the EMT signature in normal and LPP affected hair follicles.

See following pages for detailed answers.
DETAILED ANSWERS

1. What is your diagnosis based on the clinical, trichoscopic and pathologic images?

Correct answer: C. Lichen planopilaris

Lichen planopilaris (LPP) is a follicular type of lichen planus (LP) that presents as a primary lymphocytic cicatricial alopecia resulting in an irreversible hair loss. It usually starts as a single or more patches of alopecia with perifollicular erythema and hyperkeratosis on the vertex and may progress to involve large areas of the scalp leaving areas of erythema and hyperkeratosis on the vertex and may progress (Assouly and Reygagne 2009). Patients usually complain of pruritus, pain, and/or burning sensation. LPP is more common among women with a ratio of 1.8 - 9:1 and the peak age of onset is between 30 and 60 years (Lyakhovitsky et al. 2015). Approximately 30% of patients also present with the cutaneous and oral lesions of lichen planus (Kang et al. 2008) and 16.5% have concomitant frontal fibrosing alopecia (FFA) which is currently considered a separate type of lymphocytic cicatricial alopecia with similar histologic features (Galvãez-Canseco and Sperling 2018; Saceda-Corralo et al. 2018). Examination of active LPP lesions with dermoscopy reveals perifollicular casts around the proximal portion of the hair shafts, perifollicular erythema whereas dermoscopic examination of late lesions reveals loss of follicular openings, fibrotic white dots, acquired pili torti, hair tufts, milky red areas, and scattered hyperpigmentation (Miteva and Tosti 2013). On histological examination, LPP is characterized by altered follicular architecture with areas of follicular dropout, absent sebaceous glands and lichenoid infiltrate and perifollicular concentric fibrosis most pronounced at the level of the isthmus and infundibulum. Some follicles form compound follicular structures which fuse by the outer root sheaths (goggle like structures) or the connective tissue sheaths (eye like structures) (Miteva 2013; Sperling 2001).

Discussion of incorrect answers:

a. Seborrheic dermatitis (SD) is a common inflammatory dermatological condition with incidence of 1 to 3% of the general population peaking in the first three months of life, puberty, and at age 40 to 60 (Borda and Wikramanayake 2015; Gupta et al. 2004). SD classically presents with greasy, yellow scales on an erythematous base involving areas rich in sebaceous glands including scalp, retroauricular area, nasolabial folds, eyelids, and eyebrows (Borda and Wikramanayake 2015; Gupta et al. 2004). Although the exact pathomechanism of SD is unknown, proliferation of Malassezia species is a known contributing factor (Borda and Wikramanayake 2015; Gupta et al. 2004). Common dermoscopic findings of SD include dotted vessels, comma vessels, arborizing vessels, linear vessels, and hairpin vessels (Rudnicka et al. 2012). Red dots and globules, loss of follicular openings, and glomeruloid vessels are classically absent in SD (Kibar et al. 2015; Kim et al. 2011). On histological examination, acute and subacute SD demonstrate superficial lymphohistiocytic perivascular as well as perifollicular infiltrate with spongiosis, psoriasiform hyperplasia and neutrophils in the scale crust at margins of follicular ostia (shoulder parakeratosis), whereas chronic lesions show marked psoriasiform hyperplasia and parakeratosis with dilation of venules in the surface plexus (Park et al. 2016).

b. Scalp psoriasis is characterized by visible scaly plaques and is a common initial presentation of psoriasis and may be found in up to 80% of psoriasis patients (George et al. 2015). Alopecia can be associated with scalp psoriasis, possibly due to a higher proportion of hairs in the catagen and telogen stages (Shah et al. 2018). However, the architecture of the lower portion of the hair follicles is largely preserved without a significant immune infiltrate, likely explaining why alopecia is rare as growth of the hair is unaffected (Ruano et al. 2016). Dermoscopy of scalp psoriasis demonstrates red dots and globules, twisted red loops, and glomerular vessels (Kibar et al. 2015). Histologically, scalp psoriasis is characterized by epidermal hyperplasia which can be irregular, there can be mounds of parakeratosis with neutrophils, epidermal spongiosis, perifollicular inflammation, increased catagen/telogen counts, and loss or atrophy of sebaceous glands (Werner et al. 2008).

c. Discoid lupus erythematosus (DLE) of the scalp is another primary lymphocytic cicatricial alopecia that typically presents with multiple hairless patches. Common morphological features of DLE alopecia are atrophy of the skin with discoloration and erythema, usually without follicular hyperkeratosis (Fabbri et al. 2004). Dermoscopic findings of DLE alopecia include loss of follicular ostia, follicular keratotic plugs, arborizing vessels, honeycomb pigmented network, dyschromia, and variable scaling (Miteva and Tosti 2013). Follicular red dots are considered a specific early dermoscopic feature for DLE (Tosti et al. 2009). Histologically, DLE alopecia shows epidermal atrophy with follicular hyperkeratosis, perifollicular and pericrincine lymphocytic infiltrate, thickened basement membrane, and basal vacuolar degeneration (Fabbri et al. 2004; Nambudiri et al. 2014). There are two histological patterns
described recently on horizontal sections, including alopecia areata like pattern and lichen planopilaris like pattern (Chung and Goldberg 2017).

e. Dissecting cellulitis of the scalp, also known as perifolliculitis capitis abscedens et suppurativa or Hoffman disease, is a primary neutrophilic cicatricial alopecia that initially presents with boggy areas of the scalp, inflammatory nodules, pustules, and sinuses that evolve into scarring alopecia (Syed et al. 2018). Dissecting cellulitis of the scalp is part of the follicular triad along with hidradenitis suppurativa and acne conglobata (Syed et al. 2018). On dermoscopy, dissecting cellulitis of the scalp displays black dots and yellow dots, vellus hairs, and broken hairs (Segurado-Miravalles et al. 2016; Tosti et al. 2013). Histological examination of dissecting cellulitis of the scalp shows diffuse dense mixed cell infiltrate predominantly in the lower portion of the dermis with granulation tissue and granulomatous foci. The early lesions may show preserved follicular architecture with increased catagen/telogen count and there is a chance for successful regrowth at this stage. Later disease shows sinus tracts and follicular drop out with fibrosis (Gaopande et al. 2015).

2. Which of the following answers is TRUE?

Correct answer: A. The bulge of the hair follicle contains immunologically privileged epithelial stem cells.

The hair follicle is composed of 3 separate regions: bulb, isthmus, and infundibulum. The infundibulum is the region spanning from the opening of the sebaceous gland to the follicular orifice. The isthmus is the short region from the arrector pili muscle insertion to the opening of the sebaceous gland. The hair follicle bulb is the proximal part of the hair follicle. The bulge is located at the insertion of the arrector pili muscle. This is where epithelial stem cells (eSC) reside. The bulge is characterized by high keratin (CK) 15 and CD200 expression on eSC (Purba et al. 2014). Notably, eSC in this area are negative for connexin 43, a known marker of quiescence (Purba et al. 2017). Expression of MHC class Ia and II is downregulated in these cells resulting in decreased presentation of self-antigens. This environment, coupled with a reduced number of resident immune cells make the bulge an immunologically privileged site for eSC (Harries et al. 2018; Harries et al. 2013; Meyer et al. 2008). Overall, the immune privileged bulge represents a reservoir of eSC that are protected from autoimmune attack. However, loss of the immune privilege, as seen in LPP, make eSC vulnerable to autoimmune destruction.

Discussion of incorrect answers:

b. Interferon (IFN)-γ secreted by plasmacytoid dendritic cells is a potent inducer of the collapse of the physiological immune privileged bulge observed in LPP (Harries et al. 2018; Harries et al. 2013; Meyer et al. 2008). This collapse of the immune privileged bulge was also observed ex vivo in non-lesional skin from LPP patients exposed to IFN-γ (Harries et al. 2018; Harries et al. 2013; Meyer et al. 2008). Following the IFN-γ induced destruction of the immune privileged bulge, CD8+ T cells can induce apoptosis of bulge eSC (Harries et al. 2013).

c. Epidermal to mesenchymal transition (EMT) is the process by which epithelial cells lose their epithelial characteristics including cell polarity and cell to cell contact to acquire mesenchymal characteristics (Harries et al. 2018; Lamouille et al. 2014). This process is integral in development, stem cell biology, wound healing, and cancer progression (Harries et al. 2018; Lamouille et al. 2014). EMT is characterized by loss of expression of E-cadherin, an epithelial marker, and increased expression of vimentin, a mesenchymal marker. EMT promoting cytokines such as IFN-γ and transforming growth factor (TGF)-β promote EMT via modulation of the transcription factors SNAIL, zinc-finger E-box-binding (ZEB) and other basic helix-loop-helix transcription factors (Kalluri and Weinberg 2009; Lamouille et al. 2014).

d. Peroxisome proliferator-activated receptor (PPAR)-γ is a nuclear hormone receptor that is involved in keratinocytes differentiation and epidermal lipid synthesis (Schmuth et al. 2008). Karnik et al. reported that microarray analysis showed that both affected and unaffected tissue from LPP patients showed downregulated levels of PPAR-γ as compared to normal controls (Karnik et al. 2009). Additionally, targeted deletion of PPAR-γ in stem cells of follicular bulge in mice results in scarring alopecia that resembles the human disease (Karnik et al. 2009). Thus, PPAR-γ plays a critical role in maintenance of the pilosebaceous unit and in the pathogenesis of LPP.

e. The bulge is an immune privilege site characterized by immuno-inhibitory molecules contributing to an immuno-inhibitory milieu. These include alpha-melanocyte-stimulating hormone (α-MSH), TGF-β2, and CD200 (Christoph et al. 2000; Harries et al. 2018; Meyer et al. 2008). This, paired with lower numbers of T-cells, Langerhans cells, in addition to the virtual absence of MHC class I expression, cause the bulge to be an immune privileged site (Christoph et al. 2000; Harries et al. 2018).
3. Which of the following answers is FALSE according to the article by Imanishi et al.?

Correct answer: B. All EMT related genes were expressed in both lesional and non-lesional biopsies from the same patient with LPP.

This answer is FALSE. Imanishi et al. reported that several EMT-related transcripts, including twist family bHLH transcription factor 1 (TWIST1), zinc finger E-box binding homeobox 2 (ZEB2), fibronectin 1 (FN1), α-smooth muscle actin 2 (ACTA2), and epithelial membrane protein 1 (EMP1), were non detectable in non-lesional biopsy of LPP patients. However, some EMT-related transcripts, such as the epithelial bulge marker CD44, were present in both lesional and non-lesional biopsies from LPP patients.

Discussion of incorrect answers:

a. This answer is true. Imanishi et al. observed that the bulge compartment in LPP lesions presented with breakdown of the tight segregation typically observed between epithelial stem cells and the surrounding hair follicle mesenchyme. This morphological observation was further confirmed by transmission electron microscopy, where fibroblastoid cells were observed within lesional bulge epithelium (Imanishi et al. 2018).

c. This answer is true. mRNA analysis of lesional bulge as compared to non lesional bulge from the same LPP patient demonstrated increased levels of EMT-related genes including TWIST1, ZEB2, FN1, ACTA2, and FN1, in some, but not all, lesional bulge samples. These findings may suggest a possible correlation with disease severity or underscore the transient nature of EMT (Imanishi et al. 2018).

d. This answer is true. Full length human anagen VI hair follicles were exposed *ex vivo* to a cocktail of EMT-promoting agents including epidermal growth factor, transforming growth factor (TGF-β1), IFN-γ, and the selective E-cadherin inhibiting peptide A. Within 3 days, this resulted in significantly decreased levels of E-cadherins and significantly increased levels of vimentin and SLUG, thus recapitulating the expression profile seen in EMT (Imanishi et al. 2018).

e. This answer is true. Imanishi et al. showed that PPAR-γ stimulation with a PPAR-γ modulator significantly reduced the number of SLUG⁺ or vimentin⁺ cells both before and after EMT induction. This suggests that PPAR-γ stimulation may be capable of partially reversing early EMT. To support this, skin-cultured LPP cultured in serum-free conditions supplemented with a PPAR-γ modulator showed increased levels of E-cadherins and SLUG (Imanishi et al. 2018).