WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of Kathleen M. Nemer, St. Louis, MO

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 a JID article by Harden et al. (2020) (http://doi.org/10.1016/j.jid.2020.08.013).

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

QUIZ QUESTIONS

1. What is your diagnosis?
   a. Pseudofolliculitis barbae
   b. Acute cutaneous lupus
   c. Acne vulgaris
   d. Papulopustular rosacea
   e. Dermatomyositis
2. What did Harden et al. (2020) demonstrate regarding the role of IL-1β in this disease?
   a. IL-1β protein levels are elevated in the serum of individuals with this disease.
   b. Exposure of keratinocytes to UVR results in the release of IL-1β.
   c. IL-1β plays no role in the pathogenesis of this disease.
   d. IL-1β expression is associated with known comorbidities of this disease, including dementia.
   e. IL-1β treatment induces a transcriptional and proteomic signature of this disease in nonlesional skin.

3. Which of the following do Harden et al. (2020) report in their study?
   a. Increased expression of TRPV3 in skin explants derived from individuals with this disease.
   b. Upregulation of CXCL5 protein in lesional skin–conditioned media compared with that in nonconditioned media.
   c. Upregulation of the MAPK and TNF signaling pathways in skin explants with this disease compared with those in nonlesional skin.
   d. All the above.
   e. None of the above.

See the following pages for detailed answers.
1. What is your diagnosis?

**CORRECT ANSWER:** d. Papulopustular rosacea.

Papulopustular rosacea (PPR) is a chronic inflammatory syndrome characterized by a combination of erythema, telangiectasias, papules, and pustules; increased skin sensitivity; and thickening or phymatous changes of the skin (Gallo et al., 2018; Harden et al., 2020; Marson and Baldwin, 2020). These symptoms primarily present in a centrofacial distribution, which includes the cheeks, chin, nose, and middle forehead (Gallo et al., 2018). Rosacea impacts females and males equally and typically presents in middle age (Gether et al., 2018). Whereas rosacea has been most frequently reported in individuals with lighter skin types, it does not appear to be more common in any particular genetic ancestry group (Gallo et al., 2018; Marson and Baldwin, 2020). In addition to a genetic risk component (Chang et al., 2015), environmental triggers include UV light, intense emotions and stress, and heat or spice exposure (Harden et al., 2020; Marson and Baldwin, 2020). The immune and nervous systems and vascular and microbiome dysregulation are all thought to contribute to the pathophysiology (Harden et al., 2020; Marson and Baldwin, 2020). In their *Journal of Investigative Dermatology* article, Harden et al. (2020) propose a mechanism of PPR pathogenesis where IL-1β stimulates MAPK and TNF pathway signaling to drive inflammation. Treatment of PPR includes avoidance of environmental triggers such as UV light or spicy foods; gentle skin hygiene and photoprotection; brimonidine and oxymetazoline for persistent erythema; topical ivermectin or azelaic acid; and metronidazole or oral tetracycline antibiotics for papules and pustules (Ebbelaar et al., 2018; Elewski et al., 2003; Marson and Baldwin, 2020; Stein et al., 2014). In the provided clinical photo, the diagnosis of PPR is supported by the centrofacial distribution of papules without comedones, underlying erythema, and telangiectasias.

**Discussion of incorrect answers:**

a. **Pseudofolliculitis barbae:** Pseudofolliculitis barbae (PFB), known colloquially as razor bumps, is a common and chronic inflammatory condition characterized by the formation of papules and pustules in skin regions from which hair is removed (Nussbaum and Friedman, 2019; Taylor et al., 2017). It classically presents on the face in the beard distribution, but similar processes can impact other hair-bearing skin subjected to frequent shaving, including the scalp, axillae, and pubic areas. PFB is thought to occur when hair shafts disrupt the perifollicular epidermis either owing to natural curling or secondary to growing angularly to the skin surface, resulting in a foreign body response and associated sterile inflammation (Nguyen et al., 2015; Nussbaum and Friedman, 2019; Taylor et al., 2017). PFB is most often observed in men who shave regularly, especially those with coarse, curly hair characteristic of some individuals with African, Hispanic, and Middle Eastern genetic ancestries (Nussbaum and Friedman, 2019; Taylor et al., 2017), but can also be observed in women with hirsutism (Nguyen et al., 2015) who shave or depilate. A genetic variant in the KRT75 gene has also been identified as being associated with PFB (Winter et al., 2004). The mainstay of treatment for PFB is discontinuation of shaving, although alternative methods of hair removal may also be beneficial (Taylor et al., 2017). The use of preshave and postshave hydration and moisturizing strategies, including the use of topicals containing benzoyl peroxide, may minimize symptoms (Nussbaum and Friedman, 2019; Ray et al., 2016; Taylor et al., 2017). Topical antibiotics can be considered for PFB presenting with pustules, and severe cases may require oral treatment (Nussbaum and Friedman, 2019; Taylor et al., 2017). PFB is primarily distinguished from PPR by the distribution of lesions along the entirety of the shaved region and the lack of underlying confluent erythema, supported by a history consistent with hair removal.

b. **Acute cutaneous lupus erythematosus:** Acute cutaneous lupus erythematosus (CLE) is one of many dermatologic manifestations of lupus erythematosus (LE) (Werth, 2005). The classic presentation is the malar or butterfly rash: erythematosus patches or plaques on the cheeks and nasal bridge that spare the nasolabial folds (Okon and Werth, 2013; Tsokos, 2020; Werth, 2005). However, the rash of CLE can be more widespread, involving any sun-exposed skin, and appears as symmetric macules and papules that may be pruritic (Okon and Werth, 2013; Tsokos, 2020). Similar to dermatomyositis (DM), the rash can involve the backs of the hands, but unlike DM, it does not show a predilection for overlying the joints of the hands (Tsokos, 2020; Werth, 2005). Acute CLE is frequently associated with active systemic LE (SLE), and it most commonly affects patients in the third decade of life (Okon and Werth, 2013). As with other autoimmune conditions, CLE is more common in females than in males. Diagnosis often involves antibody testing for antinuclear antibody and double-stranded DNA, both of which are often positive in patients with SLE (Tsokos, 2020). The mainstay of treatment is photoprotection with high sun-protection factor sunscreen and sun-protective clothing as well as the avoidance of any inducing
Acne Vulgaris: Acne vulgaris (AV) is a common and multifactorial disorder of the pilosebaceous unit (Zaenglein et al., 2016). AV’s clinical features include seborrhea, noninflammatory comedones, inflammatory pustules and nodules, and scarring (Knutsen-Larson et al., 2012; Williams et al., 2012). The distribution of lesions tracks with the density of pilosebaceous glands in the skin, with the face, neck, chest, and back commonly being impacted (Knutsen-Larson et al., 2012; Williams et al., 2012). Disease severity is determined by the combination and number of AV features (Hayashi et al., 2008; Zaenglein et al., 2016). AV most commonly impacts adolescents, secondary to androgen-induced changes in sebum production and composition (Harper, 2020; Zouboulis et al., 2014), but lesions can also persist into adulthood (Collier et al., 2008). Males are more commonly impacted at younger ages, whereas postadolescent acne is more common in women (Collier et al., 2008; Dreno and Poli, 2003; Williams et al., 2012). The risk for developing AV is genetic, with family history being a risk factor (Dreno and Poli, 2003; Knutsen-Larson et al., 2012) and a recent GWAS suggesting a contribution of genetic variants impacting pilosebaceous unit development (Petridis et al., 2018). There are four major pathogenic factors contributing to AV: follicular hyperkeratinization leading to the formation of comedones, increased or different sebum production within sebaceous follicles, overgrowth of Cutibacterium acnes, and inflammation (Harper, 2020; Knutsen-Larson et al., 2012; Williams et al., 2012). However, the order and relative contribution of each of these factors to AV pathogenesis remain an area of active investigation (Harper, 2020). AV treatments include a spectrum from skin hygiene, topical benzoyl peroxide, topical retinoids, topical antibiotics, and oral antibiotics to oral isotretinoin, depending on the severity of the symptoms (Harper, 2020; Knutsen-Larson et al., 2012; Williams et al., 2012; Zaenglein et al., 2016). Estrogen-containing oral contraceptives and spironolactone can also be considered for the treatment of acne in women (Zaenglein et al., 2016). AV is distinguished from PPR by the presence of comedones, the lack of confluent erythema, and an anatomical distribution beyond the central face.

e. Dermatomyositis: DM is a rare inflammatory myopathy that presents with erythematous skin lesions, some of which are considered pathognomonic (Koler and Montemarano, 2001; Mainetti et al., 2017; Muro et al., 2016). Pathognomonic cutaneous lesions of DM include Gottron’s papules—violaceous papules classically on the dorsal surface of the interphalangeal or metacarpophalangeal joints—and Gottron’s sign—erythematous macules along the extensor tendons of the extremities (Koler and Montemarano, 2001; Mainetti et al., 2017). Other cutaneous lesions of DM include the heliotrope rash, which presents as violaceous edema of the eyelids, as well as other erythematous to violaceous photo-distributed rashes, including the shawl sign and facial erythema (Koler and Montemarano, 2001; Mainetti et al., 2017; Muro et al., 2016; Thompson et al., 2018). Photosensitivity is a common feature (Mainetti et al., 2017). Interestingly, the cutaneous manifestations of DM have been observed to precede muscle symptoms by months to years (Lam and Vleugels, 2012; Mainetti et al., 2017; Rockerbie et al., 1989). DM diagnosis follows a bimodal age distribution, from a mean age of 7 years for juvenile DM onset (Mainetti et al., 2017; Patwardhan et al., 2012) to a mean age of 40 years for onset of the adult form (Koler and Montemarano, 2001; Mainetti et al., 2017). As with other autoimmune disorders, females have a higher risk of DM than males, and genetic studies have identified associations between some HLA haplotypes and DM (Thompson et al., 2018). UV light is also postulated to contribute to DM pathogenesis on the basis of the observations of geographic correlations between UV intensity and the risk for DM (Okada et al., 2003). Considerations for the management of the cutaneous manifestations of DM include physical photoprotection, pharmacological photoprotection with antimarial, topical corticosteroids, and intravenous immunoglobulin (Lam and Vleugels, 2012; Mainetti et al., 2017). The cutaneous manifestations of DM are differentiated from PPR on the basis of the pathognomonic Gottron’s lesions, systemic
2. What did Harden et al. (2020) demonstrate regarding the role of IL-1β in this disease?

CORRECT ANSWER: e. IL-1β treatment induces a transcriptional and proteomic signature of this disease in nonlesional skin.

Harden et al. (2020) replicated the previously reported (Buhl et al., 2015; Casas et al., 2012; Dajnoki et al., 2017; Shih et al., 2020) upregulation of IL-1β expression in PPR tissues (Figure 2), applied pathway analysis to highlight MAPK and TNF signaling pathway involvement in PPR (Figure 3), and leveraged network analysis to suggest a central role of IL-1β in these signaling pathways in the context of PPR (Figure 3). Together, these findings suggest an important role for IL-1β in the pathogenesis of PPR. To test this hypothesis, Harden et al. (2020) performed an ex vivo experiment in which they exposed nonlesional skin from individuals with PPR to exogenous IL-1β exposed nonlesional skin from individuals with PPR to exogenous IL-1β and then quantified gene and protein expression. Compared with baseline, Harden et al. (2020) found that exposure to IL-1β induced similar transcriptional and proteomic changes to what they observed in PPR tissues. Whereas this experiment has the limitations inherent to any ex vivo experiment, for example, only testing the response of tissue-resident cells, it does suggest that IL-1β may be central to PPR pathogenesis.

Discussion of incorrect answers:

a. IL-1β protein levels are elevated in the serum of individuals with this disease: Whereas studies have identified differences in the expression of cytokines and ILs in the biofluids of individuals with and without rosacea (Falay Gur et al., 2018; Yilmaz et al., 2009), this study focused on gene expression in tissue and protein expression in condition media. Harden et al. (2020) found IL-1β mRNA levels to be increased in PPR tissues but did not measure IL-1β protein levels in the conditioned media or serum.

b. Exposure of keratinocytes to UVR results in the release of IL-1β: Exposure of skin to UVR has been demonstrated to result in increased IL-1β expression (Brink et al., 2000; Gerber et al., 2011; Salzer et al., 2014). Whereas UVR exposure is a trigger for PPR, this study did not investigate UVR. Harden et al. (2020) do postulate that UVR may contribute to PPR through IL-1β–mediated inflammation (Figure 6).

c. IL-1β plays no role in the pathogenesis of this disease: Harden et al. (2020) provide gene expression and ex vivo experimental evidence to support a central role for IL-1β in their proposed model of PPR pathogenesis (Figure 6).

d. IL-1β expression is associated with known comorbidities of this disease, including dementia: IL-1β is a proinflammatory cytokine that is produced by cells throughout the body and is involved in responding to infection and injury (Dinarello, 1996; Lopez-Castejon and Brough, 2011). In this study, Harden et al. (2020) provide evidence for an important role of IL-1β in PPR pathogenesis. Interestingly, IL-1β has also been associated with known rosacea comorbidities (Haber and El Gemayel, 2018; Harden et al., 2020), including dementia (Shaftel et al., 2008).

3. Which of the following do Harden et al. (2020) report in their study?

CORRECT ANSWER: d. All of the above.

Answers a, b, and c are all reported by Harden et al. (2020) in their study. Please see the discussion of incorrect answers for more details.

Discussion of incorrect answers:

a. Increased expression of TRPV3 in skin explants derived from individuals with this disease: Heat and spice are known to be triggers of rosacea symptoms, including flushing (Harden et al., 2020; Marson and Baldwin, 2020). TRPV3 is a nonselective cation channel that is primarily expressed in keratinocytes and has important roles in skin development and function, including cutaneous sensation (Deng et al., 2020). TRPV3 is heat sensitive and becomes more sensitive secondary to repeated stimulation with heat (Xiao et al., 2008; Xu et al., 2002). Thus, the increased expression of TRPV3 in PPR skin explants by Harden et al. (2020) (Figure 2) and others (Sulk et al., 2012) may explain the heat and spice sensitivity of patients with this disease.

b. Upregulation of CXCL5 protein in lesional skin–conditioned media compared with that in nonconditioned media: Harden et al. (2020) observed both an increase in CXCL5 gene expression in PPR tissues as well as an increase in CXCL5 protein expression in lesional skin–conditioned media. CXCL5 is a cytokine that is produced in response to inflammatory signaling by IL-1 or TNF-α (Chang et al., 1994). It is involved in neuroinflammation (Wang et al., 2016) and angiogenesis (Rowland et al., 2014; Strieter et al., 2005) and mediates UVR-induced pain (Dawes et al., 2011). Thus,
CXCL5 may contribute to PPR’s features of UVR sensitivity and vascular dysregulation (Harden et al., 2020).

c. Upregulation of the MAPK and TNF signaling pathways in skin explants with this disease compared with those in nonlesional skin: Harden et al. (2020) demonstrate an upregulation of both the MAPK and TNF signaling pathways on the basis of a gene pathway analysis of the genes they identified to be differentially expressed between PPR and nonlesional skin explants (Figure 3). This upregulation was additionally observed in their proteomic data of explant-conditioned media. Both MAPK and TNF are major signaling pathways involved in several physiologic and pathological processes, including cell proliferation (Plotnikov et al., 2011) and inflammation (Aggarwal, 2003), respectively.

ORCID
UMber Dube: https://orcid.org/0000-0001-9324-1927

REFERENCES


Buhl T, Sulk M, Nowak P, Buddenkotte J, McDonald I, Aubert J, et al. Gating of the MAPK and TNF signaling pathways on the basis of a gene pathway analysis of the genes they identified to be differentially expressed between PPR and nonlesional skin explants (Figure 3). This upregulation was additionally observed in their proteomic data of explant-conditioned media. Both MAPK and TNF are major signaling pathways involved in several physiologic and pathological processes, including cell proliferation (Plotnikov et al., 2011) and inflammation (Aggarwal, 2003), respectively.


