SnapshotDx Quiz: November 2019
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WHAT IS YOUR DIAGNOSIS?

Figure 1. Image credit: Emily Y. Chu, MD, PhD, Department of Dermatology, University of Pennsylvania.

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 Witte-Händel et al. (2019) (https://doi.org/10.1016/j.jid.2018.11.018).

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

QUIZ QUESTIONS

1. A 40-year-old female presents with tender, recurrent abscesses that contain terminal hairs and extensive scarring. What is your diagnosis?
   a. Furunculosis
   b. Hidradenitis suppurativa (HS)
   c. Cutaneous blastomycosis
   d. Pilonidal sinus disease
   e. Folliculitis

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2. Which of the following is INCORRECT according to the paper by Witte-Händel et al.?
   a. IL-1\(\beta\) was highly active in HS and identified as a driver of a pathogenetic cascade that leads to immune cell infiltration and local tissue destruction in HS.
   b. IL-1 receptor antagonist was not elevated in patients with HS.
   c. There was a significant inverse relationship between blood serum amyloid A (SAA) and high-density lipoprotein cholesterol levels. Therefore, the IL-1\(\beta\) pathway may contribute to the cardiovascular comorbidities in patients with HS.
   d. IL-1\(\beta\) expression in HS lesions was 130-fold higher than IL-1\(\beta\) expression in both psoriasis and healthy skin.
   e. Among the analyzed cell types, dermal fibroblasts were the broadest and most potent producers of IL-1\(\beta\) target molecules.

3. Which biomarker is recommended by Witte-Händel et al. to reflect the grade of inflammation in patients with HS and the activity of the pathway of interest?
   a. Matrix metalloproteinase-3
   b. Tumor necrosis factor-\(\alpha\)
   c. IL-6
   d. IL-1\(\beta\)
   e. SAA

See following pages for detailed answers.
DETAILED ANSWERS

1. A 40-year-old female presents with tender, recurrent abscesses that contain terminal hairs and extensive scarring. What is your diagnosis?

CORRECT ANSWER: b. Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease characterized by painful, recurrent abscess formation. The abscesses are typically in the axillae, inguinal area, submammary area, and anogenital regions (Kimball et al., 2016). HS, also known as acne inversa, can occur wherever there are pilosebaceous units. These pus-filled abscesses or nodules often rupture and release a thick, odiferous supplicative material. Even as an individual lesion heals, recurrent lesions and chronic draining sinus tracts form. This leads to extensive scarring, which may be debilitating (Margesson and Danby, 2014). HS tends to develop after puberty and affects both sexes. HS has a global prevalence between 1% and 4%. This variation in the prevalence may be due to the differences in the subpopulations studied, as HS could be underrepresented or overrepresented in certain studies (Micheletti, 2014).

The exact pathophysiology of HS is not fully understood. However, follicular occlusion is believed to be the primary event in HS. Apocrine gland involvement does not always exist with HS. The histopathology of HS shows follicular hyperkeratosis with plugging and dilatation of the hair follicle in early lesions. Perifolliculitis with neutrophils, lymphocytes, and histiocytes may also be seen. Biopsies of more advanced disease show stratified epithelium lining sinus tracts with marked supplicative inflammation. Frequently, desquamated keratin and hair shafts are present within the dense fibrosis adjacent to sinus tracts in HS. In the late stage of the disease, there is extensive fibrosis (Jemec et al., 1997).

Discussion of incorrect answers:

a. Furunculosis: Furunculosis is incorrect as furuncles typically present as solitary lesions. A central follicular structure may also be present, which is not typically present in HS lesions. The cutaneous infections caused by *Staphylococcus aureus* tend to be localized within the dermis (Bologna, 2012).

b. Cutaneous blastomycosis: Cutaneous blastomycosis typically results from a primary pulmonary infection, although direct skin inoculation of the organism may also occur in some instances (Azar et al., 2014). Unlike HS, cutaneous blastomycosis forms verrucous and/or crusted plaques with sharply demarcated wavy margins (Wolff et al., 2016a).

d. Pilonidal sinus disease: This is incorrect as the axilla is the wrong site for pilonidal sinus disease. Pilonidal sinus disease is thought to be due to the obstruction of the hair follicles in the natal cleft. The obstruction of the hair follicle induces an infection that may result in abscess formation and eventually a sinus cavity (Muzi et al., 2018).

e. Folliculitis: This answer choice is incorrect because the degree of scarring seen in the image provided usually does not happen with folliculitis. Usually, folliculitis heals without scarring. Folliculitis may be nontender or slightly tender. With folliculitis, papules are confined to the ostium of the hair follicle and may be surrounded by an erythematous halo (Wolff et al., 2016a).

2. Which of the following is INCORRECT according to the paper by Witte-Händel et al.?

CORRECT ANSWER: d. IL-1β expression in HS lesions was 130-fold higher than IL-1β expression in both psoriasis and healthy skin.

This is incorrect according to the results by Witte-Händel et al. (2019).

In the study, approximately 30 mediators in lesional skin of patients with HS were compared with expression patterns in healthy donor skin and psoriatic lesions. Psoriatic lesions were used as a model disease for a chronic inflammatory skin condition (Witte-Händel et al., 2019). IL-1 acts on several cells as an inflammatory mediator via its two forms, IL-1α and IL-1β. In psoriatic lesions, IL-1β levels are increased (Schön et al., 2001). IL-1α was only minimally increased in HS lesions when compared with psoriatic and healthy skin. In the study, IL-1β expression was elevated in lesional psoriatic and HS skin when compared with the healthy skin. IL-1β levels in HS lesions were 130 times higher than that of the IL-1β levels in healthy skin. IL-1β levels in HS lesions were eight times higher (not 130 times higher) than the IL-1β levels in lesional psoriatic skin (Witte-Händel et al., 2019).

Discussion of incorrect answers:

a. IL-1β was highly active in HS and identified as a driver of a pathogenetic cascade that leads to immune cell infiltration and local tissue destruction in HS: This is correct based on the findings of Witte-Händel et al. (2019). This is supported by the data of the study by Witte-Händel et al. The data shows elevated levels of IL-1β mRNA and protein in lesional HS skin when compared with healthy skin.
control skin and psoriatic lesions. When immune cells, microvascular dermal endothelial cells, dermal fibroblasts, and keratinocytes were exposed to IL-1β, there was a prominent upregulation of molecules such as chemokines that attracted neutrophilic granulocytes, enzymes involved in extracellular matrix remodeling and degradation, and immune-modulatory cytokines. Evidence of an active IL-1β pathway in the blood was also supported by the levels of IL-6 in the blood of patients with HS exceeding the levels of IL-6 in healthy patients. The study showed that elevated levels of IL-6 were induced in dermal endothelial cells and dermal fibroblasts by IL-1β. When combined with IL-6, IL-1β had a synergistic effect on serum amyloid A levels in the blood of patients HS. In addition, about 39% to 63% of the transcripts that were upregulated by IL-1β in immune cells, microvascular dermal endothelial cells, dermal fibroblasts, and keratinocytes in vitro were also upregulated in HS lesions (Witte-Händel et al., 2019). This further supports the hypothesis that the IL-1β pathway is highly active in HS.

b. IL-1 receptor antagonist was not elevated in patients with HS: This is correct based on the findings of Witte-Händel et al. (2019). The study showed that HS lesions had increased levels of IL-1β expression. This increase in IL-1β expression was not accompanied by an increase in the IL-1 receptor antagonist (IL-1RA). This resulted in a high IL-1β/IL-1RA ratio of 0.849 in HS lesions. The IL-1β/IL-1RA ratios in psoriatic lesions and healthy skin were 0.070 and 0.008, respectively (Witte-Händel et al., 2019). If IL-1RA had been elevated in HS lesions, this probably would have led to decreased expression of the target molecules (matrix metalloproteinase [MMP]-1, MMP3, CXCL1, and IL-6) observed.

c. There was a significant inverse relationship between blood serum amyloid A (SAA) and high-density lipoprotein cholesterol levels. Therefore, the IL-1β pathway may contribute to the cardiovascular comorbidities in patients with HS: This is correct based on the findings of Witte-Händel et al. (2019). IL-1β and IL-6 were shown to increase both isoforms of serum amyloid A (SAA), SAA1 and SAA2. In the study by Witte-Händel et al., a significant inverse relationship between high-density lipoprotein (HDL) cholesterol and SAA was found. As IL-1β and IL-6 increase SAA levels, a decrease in HDL levels may be observed. When SAA is secreted as the predominant apolipoprotein during the acute phase reaction, it replaces apolipoprotein A-I on plasma HDL cholesterol particles. This results in altered HDL-mediated cholesterol delivery to cells. Additionally, the integration of SAA into HDL cholesterol during inflammation converts the a priori protective lipoproteins into proatherogenic and inflammatory particles (Khovdunkhit et al., 2000; Salazar et al., 2000; Vaisar et al., 2015; Van Lenten et al., 1995). It has also been shown that subjects with low HDL cholesterol levels carry a 2- to 3-fold increased mortality risk of coronary artery disease and stroke (Weverling-Rijnsburger et al., 2003). These processes may be an explanation for the increase in cardiovascular comorbidities seen in patients with HS.

e. Among the analyzed cell types, dermal fibroblasts were the broadest and most potent producers of IL-1β target molecules: This is correct based on the findings of Witte-Händel et al. (2019). Because the IL-1β receptor was widely expressed in dermal fibroblasts, the response to IL-1β stimulation was analyzed in this cell type using a comprehensive RNA deep-sequencing approach, quantitative real-time reverse transcriptase—PCR (RT-qPCR), and ELISA. The Protein Analysis Through Evolutionary Relationships classification scheme also helped to identify the major functional groups within the transcript upregulated by IL-1β. These groups were molecules involved in extracellular matrix remodeling, chemokines, adhesion molecules, cytokines, and signal transduction elements (Witte-Händel et al., 2019).

3. Which biomarker is recommended by Witte-Händel et al. to reflect the grade of inflammation in patients with HS and the activity of the pathway of interest?

CORRECT ANSWER: e. SAA

Witte-Händel et al. recommended the use of blood SAA as a biomarker to reflect the activity of the IL-1β pathway and the grade of inflammation in patients with HS. SAA is an acute phase protein that is induced by IL-1β and IL-6 in hepatocytes (Witte-Händel et al., 2019). In the study, HS lesions had strong IL-1β activity. Exposure of hepatic HepG2 cells to IL-1β and IL-6 in vitro resulted in an increase in SAA levels. When blood samples of patients with HS were examined for SAA by ELISA and compared with healthy controls, marked increases were detected. In vivo, it is possible that the elevated SAA levels in the blood of patients with HS were a result of IL-1β and IL-6 activity on hepatocytes. Supporting its use as a biomarker, SAA had a positive correlation with disease severity and no correlation with disease duration. If used as a biomarker, SAA levels in the blood could be used to monitor the progress of treatment.
The study also found that there was no correlation between age and SAA levels. Interestingly, there was an inverse relationship between HDL and SAA. The integration of SAA with HDL cholesterol during inflammation converts these a priori protective lipoproteins into proatherogenic and inflammatory particles (Khovidhunkit et al., 2000; Salazar et al., 2000; Vaisar et al., 2015; Van Lenten et al., 1995). This may explain why many patients with HS have hypertriglyceridemia, low levels of HDL, hyperglycemia, and central obesity.

According to Witte-Händel et al., current scoring systems such as the Hurley score and Sartorius score cannot capture modest changes in the disease and/or are too complicated for clinical use. Using blood SAA as a biomarker for HS may provide clinicians with an objective tool to monitor the activity of the IL-1β pathway and the grade of the inflammation in patients with HS.

Discussion of incorrect answers:

a. Matrix metalloproteinase-3: This is false based on the data presented in the paper by Witte-Händel et al. According to the findings described in the manuscript by Witte-Händel et al., IL-1β upregulates the expression of several molecules involved in the remodeling of the extracellular matrix. MMPs are the main enzymes involved in extracellular matrix degradation. MMP activity is increased in inflamed or diseased tissues (Bonnans et al., 2014). MMP3 was one of the enzymes upregulated by IL-1β in the data presented. RT-qPCR showed markedly elevated expression of MMP3 under IL-1β influence. ELISA-quantified proteins from cultured skin biopsy samples also showed significantly higher levels of MMP3 in HS lesional skin when compared with healthy control skin and perilesional HS skin. When MMP3 levels in blood samples from patients with HS were compared with the healthy control participants, the levels did not differ. This explains why MMP3 was not considered to be a routine blood biomarker for HS.

b. Tumor necrosis factor-α: Serum levels of tumor necrosis factor-α (TNF-α) were not tested by Witte-Händel et al. TNF-α is a pleiotropic cytokine produced by macrophages and other cell types in the body. TNF-α is a pro-inflammatory agent that is rapidly released after infection and is considered a master regulator of pro-inflammatory cytokine production. It is believed that TNF-α plays a critical role in the development of many chronic inflammatory diseases (Parameswaran and Patial, 2010). Anti-TNF-α agents are frequently used in the treatment of HS. Although HS serum levels were not tested for TNF-α in the study conducted by Witte-Händel et al., HepG2 hepatocytes treated with TNF-α did not show a significant increase in SAA gene expression when analyzed using RT-qPCR. Also, TNF-α only had a minimal effect on the production of total SAA protein. TNF-α was therefore not proposed to be useful as a biomarker for HS in this study by Witte-Händel et al.

c. IL-6: This is false based on the data presented in the paper by Witte-Händel et al. IL-6 is a cytokine that is strongly upregulated during infection or inflammation and has been implicated for the induction of the hepatic acute phase response. According to data provided by Witte-Händel et al., blood levels of IL-6 were significantly increased in patients with HS but were too low to be utilized as a routine biomarker.

d. IL-1β: This is false according to the data and paper by Witte-Händel et al. The IL-1β pathway was the pathway of interest in this study. IL-1β is a pro-inflammatory cytokine that is elevated during inflammatory events like psoriatic or HS lesions. In the study, levels of IL-1β in the blood samples were elevated in patients with HS. However, levels of IL-1β did not reach a level of significance to be measured as a biomarker. Subsequently, the influence of IL-1β on SAA expression in hepatic HepG2 cells in vitro was observed. The data showed increased mRNA expression of SAA isoforms (SAA1 and SAA2) in response to IL-1β stimulation. This further supported the idea of having SAA as a biomarker to give insight into the activity of the IL-1β pathway (Witte-Händel et al., 2019).

REFERENCES


