WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of Alexander Herbst, 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 shown, while additional questions concern the findings reported in the JID article by Pogatzki-Zahn et al. (2020) (https://doi.org/10.1016/j.jid.2019.05.029).

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 findings?
   a. Chronic pruritus
   b. Polymorphous light eruption
   c. Pityriasis rosea
   d. Guttate psoriasis
   e. Scleredema
2. **Which of the following answers is TRUE?**
   a. Sensitization of itch can occur only centrally.
   b. Neuropathic pruritus is rarely associated with neuropathic pain.
   c. Cutaneous unmyelinated C nerve fibers are the only nerve subtype responsible for pruritus transmission in the skin.
   d. Patients with prurigo nodularis and atopic dermatitis (AD) have an increased density of substance P–positive cutaneous nerve fibers.
   e. IL-31 is downregulated in the skin of patients with prurigo nodularis and AD.

3. **Which of the following answers is FALSE according to the article by Pogatzki-Zahn et al. (2020)?**
   a. In patients with chronic pruritus (CP), stimulation with cowhage leads to higher pruritus intensity than matched healthy controls.
   b. Skin biopsies from patients with CP show significantly reduced intraepidermal nerve fiber density compared with healthy controls.
   c. Patients with brachioradial pruritus show decreased thermal thresholds (warm detection threshold) compared with healthy controls.
   d. Conditioned pain modulation studies show a robust inhibition in both healthy controls and in patients with CP.
   e. It can be concluded that an impaired central inhibitory system is contributing to the maintenance of pruritus, and thus, to the chronicity of CP.

See following pages for detailed answers
DETAILED ANSWERS

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


The image shows a patient with chronic pruritus (CP). The sensation of itch (or pruritus) is a symptom of different etiologies, and its pathophysiology is multifactorial. Recent studies suggest that the sensation of pruritus is the result of a complex neural modulation involving peripheral and central nervous systems and the immune system (Oetjen et al., 2017). In the skin, C and Aδ fibers transmit the sensation of itch (Potenzieri and Undem, 2012). Cutaneous pruriceptors include (i) histamine-sensitive C-fibers that are mechano-insensitive (Binder et al., 2008) and (ii) mechano-sensitive, heat-sensitive, and histamine-insensitive C-fibers, which also belong to the family of C-fiber nociceptors that can also transmit pain (Pogatzki-Zahn et al., 2020). The latter pruriceptor can be activated by cowhage, specifically a proteinase called mucunain (Mucuna pruriens) (Johanek et al., 2007).

The sensory input to the brain from the pruriceptors results in the human behavior of scratching, causing direct injury to the skin, usually shaped as linear papules and plaques that are often crusted with blood- and serum-derived material as seen in the image. Thus, the presence of pruritus can be visually detected on the skin, corroborating the patient’s stated history of chronic itch. Some areas of the skin will become lichenified with repeated scratching. Prurigo nodularis can result if a patient has been chronically scratching the same areas for an extended period. Furthermore, prurigo nodularis occurs in the setting of CP and typically appears as multiple, symmetrically distributed, hyperkeratotic, and intensely itching papules and nodules (Zeidler et al., 2018), which are much thicker and more hyperkeratotic than what is seen in the image provided in this quiz. There are multiple causes of prurigo nodularis, ranging from primary dermatologic, systemic, neurologic, and psychiatric conditions (Zeidler et al., 2018). Prurigo nodularis is associated with increased dermal levels of nerve growth factor and neuropeptides such as calcitonin gene-related peptide and substance P (Zeidler et al., 2018). Newer therapeutic options include inhibitors of IL-31, neurokinin, and opioid receptors, in addition to traditional treatments of phototherapy, topical steroids, topical calcineurin inhibitors, and immunosuppressants such as cyclosporine (Zeidler et al., 2018). It should be noted that notalgia paresthetica can be associated with CP and is a sensory neuropathy of the back that manifests as a well-defined, hyperpigmented patch with a stippled appearance, located medially or inferiorly to the scapula (Ansari et al., 2019). Patients often experience localized pruritus and pain associated with remissions and relapses (Ansari et al., 2019). Affected areas on the back can be associated with macular amyloidosis, which likely represents cutaneous deposition of degenerated keratin after repeated skin trauma (Bernhard, 1991). Treatment options include topical agents (such as capsaicin, tacrolimus, topical anesthetics, and topical amitriptyline), system agents (such as gabapentin, botulinum toxin A, and narrow band UVB (Ansari et al., 2019).

Thus, patients with CP often have an underlying diagnosis that explains why they are itching, including atopic dermatitis (AD). In CP, obtaining the history, other physical examination findings, and laboratories are critical to determine the cause of pruritus.

Discussion of incorrect answers:

b. Polymorphous light eruption: Polymorphous light eruption is a dermatosis induced by UV exposure in people genetically susceptible to this eruption and is the most common immune-mediated photodermatosis (Guarrera, 2017). It is commonly expressed as papules and plaques of varying morphologies (erythema-multiforme—like papules, insect bite—like wheals, purpuric papules, vesicles, and blisters) (Guarrera, 2017). The lesions often itch and burn and are in the V-area of the chest, arms, forearms, legs, and upper part of the back and rarely the face (Guarrera, 2017). The lesions often develop within a few hours to days after UV-light exposure and can last several days. The condition can be itchy and can be treated with topical steroids and reduction in UV-light exposure.

c. Pityriasis rosea: Pityriasis rosea (PR) is a very common dermatosis that classically first appears as a solitary, scaly, pink- or skin-colored plaque known as the herald patch. Over the course of days to weeks, the patient will develop multiple, discrete, scaly papules and plaques with a cigarette paper texture overlying many of the papules. PR is not significantly associated with intractable pruritus, and in most of the patients, the rash resolves in the course of two months (Urbina et al., 2017). The papules shown in the image do not represent those typical of PR. Although the exact cause of PR is unclear, human herpesvirus (HHV)-6 and HHV-7 are associated (Drago et al., 2016).

d. Guttate psoriasis: Guttate psoriasis (GP) is a variant of psoriasis that appears as an acute, generalized eruption of raindrop papules with fine scale similar to that seen in classic psoriasis vulgaris (Mahé, 2016). Guttate psoriasis can be pruritic; however, the papules in the image shown do not depict the classic overlying scale seen in that of GP. GP frequently occurs following an upper respiratory tract
2. Which of the following answers is TRUE?

CORRECT ANSWER: d. Patients with prurigo nodularis and AD have an increased density of substance P-positive cutaneous nerve fibers.

Substance P (SP) is a neuropeptide found in cutaneous nociceptive nerve terminals that, when released, modulates immune and vascular responses. SP leads to neurogenic inflammation (Peters et al., 2006; Potenzieri and Undem, 2012). SP is also expressed by human mast cells, implicating its role in allergic inflammation (Potenzieri and Undem, 2012; Toyoda et al., 2000). SP-invoked itch involves histamine release from mast cells (Fjellner and Hägemark, 1981; Potenzieri and Undem, 2012). SP further activates mast cells themselves to promote degranulation and release of histamine (Ebertz et al., 1987; Suzuki et al., 1995). Histamine can also, in turn, evoke the release of SP; thus, there is a bidirectional link between histamine and neuropeptides in the process of inflammation in the skin (Rosa and Fantozzi, 2013). Furthermore, SP and other neuropeptides can be directly released from the cutaneous peripheral nerve terminals (Suvas, 2017). These nerves also contain the receptor for SP, known as neurokinin 1 receptor (NK1R) (Suvas, 2017); this localized SP release and binding can contribute to local inflammation in response to infection or injury in many tissues (Donkin et al., 2007; Suvas, 2017). Patients with prurigo nodularis and AD have an increased density of SP-positive cutaneous nerve fibers, meaning the nerve fibers are producing SP (Abadía Molina et al., 1992; Haas et al., 2010; Potenzieri and Undem, 2012; Sugiura et al., 1997). Because SP preferentially activates neurokinin receptors (Potenzieri and Undem, 2012), there are novel treatments to target pruritus. Aprepitant, for example, is a selective NK1R antagonist, and it attenuated itch severity in patients with chronic pruritus (Potenzieri and Undem, 2012; Ständer et al., 2010).

Discussion of incorrect answers:

a. Sensitization of itch can occur only centrally: This statement is false because sensitization of itch can occur in both the central and peripheral nervous systems (Potenzieri and Undem, 2012; Yosipovitch et al., 2003). In the associated article, the authors found that patients with CP had a disturbance of peripheral nerve fiber density and increased sensitivity to pruritic stimuli by cowhage, suggesting a peripheral sensitization to these stimuli (Pogatzki-Zahn et al., 2020). Furthermore, the effectiveness of central descending inhibition was impaired in all patient groups (AD, brachioradial pruritus [BRP], and chronic prurigo of nodular type), suggesting that both the central and peripheral nervous systems are involved in the modulation of itch and pain sensations in patients with CP (Pogatzki-Zahn et al., 2020).

b. Neuropathic pruritus is rarely associated with neuropathic pain: This statement is false because neuropathic pruritus is frequently associated with neuropathic pain (Misery et al., 2014). Hypersensitization to stimuli is a hallmark in both neuropathic pruritus and neuropathic pain (Misery et al., 2014). Many disorders of the central and peripheral nervous systems (e.g., stroke and herpes zoster, respectively) can cause both neuropathic itch and neuropathic pain (Steinhoff et al., 2018). Although not completely understood, neuropathic itch and pain both overlap in pathophysiology, sensitization mechanisms, and therapeutic options (Steinhoff et al., 2018). In the brain, any type of lesions that damage itch circuits can cause neuropathic itch; these locations are also associated with neuropathic pain (the lateral spinothalamic tracts, thalamus, and somatosensory cortex), supporting the concept of the overlap between itch and pain in the central nervous system (Steinhoff et al., 2018). For example, input from mechanoreceptors can inhibit spinal itch processing through interneurons expressing neuropeptide Y; itch and pain are inhibited by light stroking and firm pressure, potentially explaining why tight wraps or clothing can improve both neuropathic itch and neuropathic pain (Steinhoff et al., 2018). Various treatments can target neuropathic pain; for example, sensitization to topical TRPV1 receptor agonists (such as capsaicin) have been used to treat neuropathic pain and have
shown some benefit in treating neuropathic itch as well (Misery et al., 2014; Szolcsányi, 2004). Given the overlap in neural circuitry, treatments with evidence of efficacy for CP may also be used to potentially treat neuropathic pain.

c. **Cutaneous unmyelinated C nerve fibers are the only nerve subtype responsible for pruritus transmission in the skin:** This statement is false because both unmyelinated C-fibers and thinly myelinated Aδ-fibers transmit the sensation of itch (Potenzieri and Undem, 2012). There are numerous mediators (biogenic amines, peptides, proteases, and cytokines) that are able to stimulate these nerve fibers (Potenzieri and Undem, 2012). As with histamine, cowhage was found to effectively stimulate C-fibers; but unlike histamine, the subtype of C-fiber excited by cowhage is a mechanically sensitive C-fiber (Namer et al., 2008; Potenzieri and Undem, 2012). Studies have found that mechanically insensitive Aδ-fibers were excited by histamine but not cowhage, whereas mechanically sensitive Aδ-fibers were excited by cowhage (Potenzieri and Undem, 2012), indicating that subtypes of these fibers dictate the classes of molecules that stimulate them.

e. **IL-31 is downregulated in the skin of patients with prurigo nodularis and AD:** This statement is false because IL-31 is highly upregulated in the skin of patients with CP, such as AD and prurigo nodularis (Neis et al., 2006; Potenzieri and Undem, 2012; Sonkoly et al., 2006). IL-31 is a member of the IL-6 family of cytokines, and it binds to IL-31 receptor α and oncostatin M receptor β (Potenzieri and Undem, 2012; Zhang et al., 2008). Nemolizumab, an anti–IL-31 receptor α mAb, improved pruritus, dermatitis, and sleep in adults with moderate-to-severe AD that was uncontrolled by topical treatments in a phase II, 12-week, randomized, double-blind, placebo-controlled trial and was efficacious and well tolerated for up to 64 weeks at least (Kabashima et al., 2018), indicating the relevance of IL-31 as a mediator of CP in patients.

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

**CORRECT ANSWER:** d. Conditioned pain modulation studies show a robust inhibition in healthy controls and in patients with CP.

Pogatzki-Zahn et al. (2020) used a set of neurologic and morphologic measurements in patients with CP and matched controls to examine the impact of pruritus pathways and endogenous inhibition by condition pain modulation; a total of 40 patients with CP of inflammatory origin (AD), 40 patients with neuropathic origin (BRP), and 40 patients with chronic prurigo of nodular type (PN) (a model of chronic scratching), along with 40 matched healthy control (HC) subjects participated in the study (Pogatzki-Zahn et al., 2020). For the conditioned pain modulation (CPM) study, the CPM effect was defined as the percentage of the endogenous inhibitory effect. In the cohort, 13 patients with AD, 16 patients with BRP, 14 patients with PN, and 22 HC participated in the CPM portion of the study. HCs’ CPM had robust inhibitory activity, whereas the patients with CP lacked this CPM inhibitory activity (Pogatzki-Zahn et al., 2020). In the experiments, a test stimulus was applied to induce pain; all patient groups had a similar response rating compared with the HC group. In HCs, the pain intensity ratings decreased significantly both during and after stimulation (when restimulated 5 minutes after the initial stimulus), indicating a robust endogenous inhibition; however, in the AD, BRP, and PN groups, there was no decrease in pain during the test or when restimulated 5 minutes after the first stimulation, suggesting a lack of endogenous inhibition (Pogatzki-Zahn et al., 2020).

**Discussion of incorrect answers:**

a. **In patients with CP, stimulation with cowhage leads to higher pruritus intensity than matched healthy controls:** In the study, a total of 40 patients with CP of inflammatory origin (AD), 40 patients with neuropathic origin (BRP), and 40 patients with chronic PN (a model of chronic scratching), along with 40 matched HC subjects, were stimulated with pruritic substances (cowhage, histamine, and capsaicin) and a negative control (NaCl) in a double-blind, randomized order at four predefined locations on the body. After stimulation, pruritus intensity was assessed on a visual analog scale as long as a sensation of pruritus persisted or for a maximum of 30 minutes. In patients with all types of CP, cowhage stimulation resulted in a significantly increased sensory perception of pruritus compared with other active substances (Pogatzki-Zahn et al., 2020). This result suggested that there is a significant role of cowhage-activated C-fibers in modulation of pruritus and a likely sensitization of these fibers in patients with CP.

b. **Skin biopsies from patients with CP show significantly reduced intraepidermal nerve fiber density compared with healthy controls:** This statement is true on the basis of the evidence supported by the results of the study (Pogatzki-Zahn et al., 2020). The frequency of abnormal warm detection threshold (WDT) is approximately 10–20% across CP groups, and all patients showed a loss of function in this
Patients with BRP showed decreased WDT compared with healthy controls. Individual WDT in patients correlated with intraepidermal WDT compared with healthy controls. Individual parameter. Patients with BRP showed decreased WDT compared with healthy controls (Pogatzki-Zahn et al., 2020). For quantitative sensory testing, the highest specificity occurs for WDT to detect small-fiber degeneration (Ridehalgh et al., 2018). Qualitative sensory testing did not detect significant functional abnormalities in any parameter assessed, with the exception of an increase in WDT (the temperature at which a patient detected the sensation of warmth) in patients with BRP (Pogatzki-Zahn et al., 2020). The frequency of abnormal warm WDT is approximately 10–20% across CP groups, and all patients showed a loss of function in this parameter (Pogatzki-Zahn et al., 2020). Individual WDT in patients correlated with IENFD, indicating a C-fiber loss of function similar to what has been found in small-fiber neuropathies (Pogatzki-Zahn et al., 2020; Scherens et al., 2009).

It can be concluded that an impaired central inhibitory system is contributing to the maintenance of pruritus and, thus, to the chronicity of CP: On the basis of the findings in the article, CP of different origins (whether it be AD, BRP, or PN) showed a similar pattern of peripheral sensitization of fibers sensitive to mechanical, thermal, and chemical stimuli; rarefaction of intraepidermal nerve fibers; and impaired endogenous inhibition, the latter of which indicates that a central nervous system dysregulation is responsible for a lack of decreased sensory perception (Pogatzki-Zahn et al., 2020). The role of impaired central inhibition in the perpetuation of chronic pain states is supported by several studies (Martel et al., 2013; Normand et al., 2011; Wilder-Smith et al., 2010). In this study, in the HC group, the pain intensity ratings decreased significantly both during and after stimulation (when restimulated 5 minutes after the initial stimulus), indicating a robust endogenous inhibition; however, in the AD, BRP, and PN groups, there was no decrease in pain during the test or when restimulated 5 minutes after the first stimulation, suggesting a lack of endogenous inhibition (Pogatzki-Zahn et al., 2020). Although in this study the stimulus was pain, recent studies suggest that endogenous inhibition on pain and itch involves similar pathways (van Laarhoven et al., 2010). However, the authors of this study admit that it remains unclear whether the impairment of central pain inhibition is a cause of CP or a consequence of it. Furthermore, it may be possible that healthy individuals with impaired endogenous inhibition of pain and itch may be at a higher risk to develop CP, or a decreased inhibitory system may develop during the natural course of CP (Pogatzki-Zahn et al., 2020).

REFERENCES


