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Pruritus as a sign of systemic disease

Kalina Welz-Kubiak, MD, PhD, Radomir Reszke, MD, Jacek C. Szepietowski, MD, PhD*

Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland

Abstract Pruritus, as one of the most common clinical manifestations in medicine, has been recognized for many centuries. Defined as an unpleasant sensation resulting in the need to scratch, it is divided into acute and chronic stages, based on the duration of the clinical manifestation. Classically, pruritus is associated with cutaneous disorders; however, it may also accompany various systemic disorders, including renal, hepatic, hematologic, or oncologic, and be the first or solitary manifestation of an underlying systemic disease. Additionally, the clinical manifestation may occur as an adverse reaction to drug administration. The pathogenesis of itch is multifactorial, involving various neuromediators and cytokines, with a prominent role of peripheral and central nervous system in its development. Based on an underlying disorder, the affected patients present different clinical patterns of pruritus. Diagnostic approach is based on detailed history taking and physical examination. Frequently, additional diagnostic measures, including laboratory or imaging tests, are performed, especially when the cause of pruritus is unknown. Pruritus remains a challenging clinical manifestation with a significant importance for physicians managing systemic disorders.

Introduction

Pruritus may be considered as the most common and burdensome clinical manifestation in dermatology. Its influence on health-related quality of life (HRQoL) is significant, but its importance as a sign of systemic disorders is underestimated. The European Guideline on Chronic Pruritus[1] describes it as "an unpleasant sensation that provokes the desire to scratch." Acute itching lasts less than 6 weeks, whereas chronic itching (CI) lasts longer than 6 weeks by definition.[2]

Historic perspective

Pruritus is a clinical manifestation mentioned in historic sources, for example, in the Egyptian *Papyrus Ebers,* dating approximately to 1550 BCE, and Greek *Corpus Hippocraticum,* compiled since the 5th century BCE.[3] Itch was also mentioned by Galen (129-216 C.E.) and later by Paul (625-690 C.E.) from Aegina, Avicenna (980-1037), and Avenzoar (1094-1162). The definition of pruritus that remains relevant was proposed by the German physician Samuel Hafenreffer (1587-1660) in 1660.[4] In 1808, Robert Willan (1757-1812) described senile pruritus.[5] Subsequently, the knowledge of pruritus and its pathogenesis has been extensively broadened in the 20th and 21st centuries.[6–13]

Pathogenesis

The complex pathogenesis of pruritus may be regarded in several contexts. In short, exogenous and endogenous factors are released by immune cells, epithelial cells, and endothelial cells, ensuing in activation of signal cascades.[14] Numerous mediators of itch have been described, and the list is

* Corresponding author. Tel.: +48 717842286.
E-mail address: jacek.szepietowski@umed.wroc.pl (J.C. Szepietowski).

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constantly growing. Neurotransmitters are synthesized in the skin by nerve fibers and a variety of cells (Merkel cells, Langerhans cells, activated keratinocytes, melanocytes, granulocytes, lymphocytes, monocytes, macrophages, and mast cells).[15] Among granulocytes, basophils are acknowledged as relevant cells associated with allergic inflammation and pruritus in various cutaneous and systemic disorders.[16] Basophils and mast cells release many inflammatory mediators, including histamine, which is considered a classic mediator of itch. Histamine-responsive unmyelinated C-fibers were proved to serve as an itch-specific neuronal pathway.[10,17] Non-histaminergic itch associated with cowhage was also investigated, revealing that it is associated with protease-activated receptors (PAR) and stimulates different subpopulations of spinothalamic tract neurons than histamine.[12,18] PAR_2 agonists (eg, trypsin or tryptase) induce neurogenic inflammation via release of calcitonin-gene–related protein (CGRP) and substance P (SP)[19] and may induce itch in patients with atopic dermatitis.[20] Acknowledging the role of basophils in allergic inflammation and eliciting pruritus in various cutaneous and systemic disorders, these cells produce not only histamine, proteases, and SP, but also cytokines, chemokines, prostaglandins, and platelet-activating factor.[16] Various interleukins (IL), such as IL-2, IL-4, IL-13, IL-22, and IL-31, and cytokines, such as thymic stromal lymphopoietin (TSLP), also contribute to itching in different clinical entities.[21–26] Itch sensation may be inhibited by painful thermal, mechanical, and chemical stimuli.[27] On the other hand, analgesia reduces pain, frequently resulting in itch intensity increase. Different subtypes of opioid receptors exert opposite effects on pruritus. Stimulation of mu-opioid receptors induces itch, whereas mu-opioid antagonists and kappa opioid agonists diminish this sensation.[28,29]

The statement, "It is the brain that itches,"[27] perfectly summarizes the role of the central nervous system (CNS) in eliciting itch sensation; however, the transmission of pruritogenic impulses to the brain is initiated peripherally. There is an established itch nerve pathway and it begins on the surface of the skin, where external stimuli exert their effect on free nerve endings. Subsequently, the stimuli are transmitted through the unmyelinated C-fibers[10] associated with histamine and the myelinated Aδ-fibers.[30] The impulses reach dorsal roots in spinal cord, and gastrin-releasing peptide (GRP) is released, interacting with its specific receptors (GRPR) in lamina I.[13] The spinothalamic tract ends in several nuclei of thalamus, further projecting to various locations in brain cortex responsible for itch location, intensity, unpleasantness, urge to scratch and execution of scratch movements, and subsequent pleasure along with reward.[18,27,31–33]

Classification of itch

The clinical classification of itch, based on two steps, was proposed in 2007.[2]

- First, a patient suffering from CI is allocated to one of three groups:
  - Pruritus on diseased skin
  - Pruritus on nondiseased skin
  - Chronic scratch lesions
- Second, a patient is allocated to one of six categories based on histologic, laboratory, and radiologic examinations:
  - Dermatologic (I): The cause of pruritus in a "classic" cutaneous disorder (atopic dermatitis, psoriasis, etc).
  - Systemic (II): The underlying causes of pruritus in this group include endocrine and metabolic diseases, infections, hematologic and lymphoproliferative disorders, solid tumors of the internal organs, pregnancy, and drug-induced pruritus.
  - Neurologic (III): Pruritus arises due to abnormalities associated with CNS or peripheral nervous system (PNS).
  - Psychogenic (IV): Also termed "somatoform" or "psychogenic pruritus," this category includes pruritus in the course of psychiatric and psychosomatic disorders.
  - Mixed (V): In this category, at least two underlying causes contribute to the development of itch.
  - Other (VI): The origin of pruritus remains unknown (pruritus of unknown origin; PUO).

Pruritus in systemic conditions

This section reviews epidemiology, pathogenesis, clinical characteristics, and diagnostic measures for pruritus encountered in specialties different from dermatology. The knowledge of the etiologic spectrum of pruritus is useful in the dermatologic setting, as well, especially in case of unclear etiology or suspected multiple causes of pruritus in a single patient. Table 1 presents an overview of possible systemic disorders and conditions associated with pruritus.

It is imperative to acknowledge that in patients initially found to have generalized PUO the instigation of additional diagnostic procedures may eventually unveil the underlying systemic condition.[34–36]

Uremic pruritus

Uremic pruritus, also termed "chronic kidney disease (CKD)–associated pruritus" or "end-stage renal disease chronic itch" (ESRDCI), occurs in patients with significant abnormal renal function with advanced stages of renal damage.[37] Its epidemiology has changed throughout the years. Beginning with 85% of patients on dialysis in the 1970s,[38] it was later revealed that this clinical manifestation affects 42% of hemodialysis (HD) patients in a DOPPS study.[39] In Polish children suffering from CKD stages 3 to 5, pruritus was present in approximately 21%.[40] When appraising larger spectrum of CKD (stages 2 to 5), pruritus affected 19% of subjects.[41] The pathogenesis of uremic pruritus involves numerous

Table 1 Major categories and examples of systemic disorders associated with pruritus

- Chronic kidney disease
- Hepatobiliary disorders
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Hepatitis infection
  - Progressive familial intrahepatic cholestatis
  - Intrahepatic cholestasis of pregnancy
- Endocrine disorders
  - Hypo- and hyperthyroidism
  - Diabetes
  - Hyperparathyroidism
- Hematologic disorders
  - Anemia
  - Polycythemia vera
  - Primary myelofibrosis
  - Hodgkin lymphoma and non-Hodgkin lymphomas
- Malignant solid tumors
- Infectious disorders
  - HIV
  - Syphilis
  - Varicella
  - Zoster
  - Dengue
  - Zika virus infection
  - Toxocarosis
- Pulmonary disorders
  - Sarcoidosis

mechanisms, including metabolic disequilibrium.[42] Increased levels of urea, creatinine, calcium, phosphorus, parathormone (PTH), or vitamin A, or decreased levels of vitamin D were all evaluated as potential culprits.[42–47] Different dialysis methods are also of importance.[48] In clinical practice, patients with CKD frequently present marked dryness of the skin (xerosis). Our group has demonstrated the association of xerosis with uremic pruritus.[48,49] Uremic xerosis occurs as a result of diminished skin-barrier properties, although no direct correlations between pruritus and xerosis, stratum corneum integrity, glycerol content, or surface pH were reported.[50] Seasonal variations of uremic pruritus might be associated with xerosis.[51] The causative roles of microinflammation,[52] neuropathy,[53] HCV infection,[54] or opioid receptors dysregulation[55] were also postulated. Interestingly, the intake of loop diuretics among HD patients was associated with lower prevalence of chronic pruritus.[56]

Clinical characteristics of uremic pruritus differ between reports. In a cohort of 471 patients, 40% described the pruritus intensity as low (mean Visual Analogue Scale (VAS) 1.9 points), 37% as moderate (mean VAS 5.1 points), and 8.1% as severe (mean VAS 8.6 points).[57] In our experience,[58] mean VAS score was 4.1 ± 2.0 points (n = 171); moreover, 38% of subjects reported localized itch (especially on the back, lower extremities, scalp, upper extremities, or abdomen), with 35.4% in at least two locations. Generalized itch concerned 26.6% of respondents. It was also observed that uremic pruritus is more intensive and occurs more often during night.[59,60] The striking symmetry of pruritus and its presence over large areas without dermatomal pattern were reported in a majority of patients.[60] Itch is a dynamic clinical manifestation and several factors or situations may cause its exacerbation (eg, rest, xerosis, heat, sweat, clothing, or stress) or provide certain relief (activity, sleep, hot showers, cold showers, and cold conditions).[59] Uremic pruritus is a clear example of a detrimental impact of pruritus in general on HRQoL. In Polish patients, uremic pruritus was associated with lower HRQoL scores, evaluated by 36-Item Short Form Survey (SF-36) questionnaire (93.0 ± 20.4 versus 99.6 ± 19.9 points; $P = .03$)[61]; moreover, pruritic subjects presented worse general perception of health.

Diagnostic procedures in case of uremic pruritus are aimed at assessing the extent of kidney damage and searching for the underlying disorder. Basic laboratory tests include serum creatinine and urea in case of elderly patients.[62] Further examinations include phosphates, PTH, bicarbonates, urinalysis, urine protein concentration, antinuclear antibodies (ANA), anti-dsDNA antibodies, pANCA and cANCA antibodies, and anti-GBM antibodies. Imaging examinations are based on ultrasonography; rarely computer tomography (CT) or magnetic resonance imaging (MRI) is applied.

Pruritus in chronic hepatobiliary diseases

Pruritus in chronic hepatobiliary diseases is often termed "cholestatic pruritus" due to its possible link to cholestasis. Cholestasis may occur as a result of hepatocellular secretory failure (I), cholangiocellular cholestasis with intrahepatic bile duct damage (II), or cholestasis arising from the obstruction of intrahepatic or extrahepatic bile duct system.[63] It has been known for years that jaundice and pruritus may coexist in a variety of hepatobiliary conditions.[64] The major cholestatic disorders presenting with pruritus include primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), cholangiocarcinoma (CCC), inherited conditions associated with cholestasis, and intrahepatic cholestasis of pregnancy (ICP).[65] Pruritus may also bother patients with chronic hepatitis infections (HBV, HCV).[66,67] Itching is a cardinal syndrome of ICP, whereas in PBC and PSC it appears in up to 70% to 80% of patients.[63] Lesser prevalence rates were determined for subjects with alcoholic liver disease (34.2%) and autoimmune hepatitis (AIH) (24.3%).[68] It was revealed that pruritus in HBV infections affects 11% to 40.6% of patients, whereas in HCV the prevalence ranges from 22% to 58.4%.[66,68,69] A case of generalized pruritus due to acute HAV infection was also published.[70] The incidence of ICP varied between reports especially due to geographic distribution, whereas in Europe the incidence is approximately 1%.[71] Itching in progressive familial intrahepatic cholestasis (PFIC) affected 11% to 100% of reported patients.[72]

The role of bile as a pruritic agent was considered even in ancient Greece by Araeteus of Cappadocia.[73] It was

supposed that elevated serum bile acid levels were the causative factor of itch.[74] Bile salts proved pruritic when tested on blisters due to nonpruritic dermatoses[75]; however, other reports provided no definite association between bile acids and pruritus.[73,76] There are presumptions concerning the role of opioidergic system in generating pruritus in cholestasis, with the central neurotransmission being altered possibly due to higher availability of opioids.[77] Clinically, it was observed that cholestatic pruritus diminished after administration of mu-opioid antagonists (naloxone, nalmefene).[78,79] Similarly, the usefulness of a 5-HT_3 receptor antagonist (ondansetron) infers a relation of cholestatic pruritus with serotonin.[80,81] paragraphA significant advance in the subject was brought by discoveries linking the elevated serum levels of lysophosphatidic acid (LPA) and autotaxin (ATX).[65,82] ATX is an enzyme generating LPA from lysophosphatidylcholine (LPC). LPA is associated with many functions, including the generation of neuropathic pain and gene expression of afferent nerve fibers.[82] Rifampicin, notwithstanding its antibacterial properties, decreases pruritus in PBC.[83] It is possible that antipruritic effects of rifampicin are mediated via pregnane X receptor (PXR) and involve reduced ATX expression.[65] The pathogenesis of pruritus in the course of HCV infection involves cholestasis as well, along with the elevated production of cytokines and chemokines (IL-8, CCL2, CXCL1, CXCL5); the administration of interferon and ribavirin may also contribute to its occurrence.[84]

Hepatic pruritus affects the palms and soles and worsens at night.[85] In a cohort of 1,631 patients suffering from liver diseases, pruritus affected 40.3% of subjects, with the most common body location on the back (63.1% of pruritic patients).[68] Itching appeared less commonly on the abdomen, calf, arm, thigh, neck, head, lower part of the back, face, and foot (29%, 25.8%, 22.6%, 20.7%, 19.1%,18.1%, 16.9%, 16.7%, 16.0%, and 12.6%, respectively); moreover, hands were rarely affected (9.4%). More severe itching ensued during day than night ($P < .001$). Seasonal exacerbation occurred in 45%, among whom 80% reported exacerbation during winter. The investigators revealed that independent factors associated with pruritus included active HBV infection (odds ratio [OR] = 2.51; $P = .043$), PBC (OR = 3.69; $P = .018$), diabetes (OR = 1.57; $P = .010$), and ASPAT levels ≥60 U/L (OR = 2.06; $P = .011$).

Another study assessed 238 subjects with PBC and observed that pruritus was present in 69% of subjects.[86] Of the respondents, 75% reported that itching had been present before establishing the diagnosis of PBC. Thirty-five percent of patients described itch as "bugs crawling," 29.2% as "deep itch," and 17.6% as "relentless." Worse severity of itching was reported during night by 65.2%, with the most common exacerbating factors including heat (61.6%), clothes (20.5%), food (14.2%), and xerosis (3.5%). The most common relieving factor was "something cool" (65%). ICP patients usually experience pruritus in the third trimester and it usually subsides within 48 hours of labor.[71] ICP is associated with significant fetal morbidity and mortality.[87] Among patients with PFIC, it is necessary to emphasize that pruritus usually appears within first 3 months of age and is often severe.[72]

Laboratory examinations that are advised for patients with chronic liver diseases include predominantly serum levels of gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase, bilirubin, ASPAT, ALAT, and screening for the presence of hepatitis.[62] Further investigations may include lactate dehydrogenase, ANA, antimitochondrial antibodies (AMA), antismooth muscle antibodies, and antiactin antibodies. In patients with ICP, monitoring of serum cholic acid and deoxycholic acid is recommended.[71] Imaging studies in assessing cholestatic pruritus include ultrasonography, CT, MRI. In case of suspected PSC, magnetic resonance cholangiogram or endoscopic retrograde cholangiogram may be considered.[62]

Pruritus in endocrine disorders

Endocrine disorders are fairly common in the general population[88] and are often associated with a variety of manifestations, including cutaneous. Occasionally, dermatologic clinical manifestations may initially constitute the primary complaint reported by an affected patient[89]; therefore, the knowledge of cutaneous manifestations of endocrine disorders, including pruritus, is of importance to dermatologists, as they may be the first physicians to be consulted. However, among the abundance of dermatologic clinical manifestations, the prevalence of pruritus differs according to studies, in both thyroid disorders and diabetes, whereas the data on pruritus in hyperparathyroidism are mostly associated with CKD.[46,90,91]

Among cutaneous manifestations of thyroid diseases, pruritus affected 2.7% to 28.1% of subjects.[92–94] In a Turkish study (n = 300) itching affected 20.9% and 26.8% of patients with hypothyroidism and hyperthyroidism, respectively.[94] In a cohort of 236 patients with thyrotoxicosis, pruritus constituted the most common complaint in 6.8% of patients.[95] According to textbooks and review papers, hypothyroidism and hyperthyroidism are commonly associated with generalized pruritus[96]; however, the majority of studies revealed few patients with generalized pruritus as a result of thyroid disorders.[34–35,97–99] In an American study (n = 44), hypothyroidism was responsible for 11.4% cases of generalized pruritus,[100] whereas in a recent prospective study, hypothyroidism and hyperthyroidism were responsible for 10.4% and 6.3% cases of severe generalized pruritus, respectively.[36] As for diabetes, a classic study (n = 500) reported that pruritus bothered 6.6% of patients with diabetes.[101] In a Scottish cohort of outpatients with diabetes (n = 330), compared with healthy controls (n = 100), generalized pruritus occurred in a likewise proportions (2.7% versus 1%; nonsignificant P value).[102] Vulvar pruritus was diagnosed more often in diabetes (18.4% versus 5.6%; $P < .05$). Later studies have determined the prevalence of pruritus in patients with diabetes in a range of 15.6% to 60.2%.[103–106] In a prospective

evaluation of 49 patients with generalized pruritus, diabetes was determined as a cause in 12.5%.[36] Interestingly, in a cohort of 238 young patients with insulin-dependent diabetes, only one case (0.4%) of generalized pruritus was reported.[107]

Scarce data account for the pathogenesis of itch in endocrinopathies; nevertheless, a possible factor explaining the presence of pruritus in hypothyroidism is xerosis.[108] Autoimmune mechanisms were postulated in a case of prurigo nodularis in the course of Hashimoto disease.[109] The presence of warm and moist skin may contribute to itching in hyperthyroidism,[108] as cutaneous vasodilatation could lower the itch threshold.[110] Additionally, the presence of antithyroid antibodies, such as antithyroid peroxidase (anti-TPO) or antithyreotropin receptor antibodies (ATRAs), might induce urticaria,[111] the latter obviously presenting with pruritus. The significance of elevated serum levels of chenodeoxycholic acid was also investigated.[112] The treatment of hyperthyroidism with 131-iodine was reported to induce cholestatic jaundice accompanied by pruritus.[113] In diabetes, elevated postprandial blood glucose levels were observed in patients with generalized pruritus.[105] It was reported that, among CKD patients on HD with coexisting diabetes, itch intensity assessed by VAS was correlated with calcium-phosphorus product, PTH, and HbA_{1c}.[114] Other factors possibly include fungal infections, diabetic neuropathy, and impairment of cutaneous microcirculation, thermoregulation, and sudomotor functions.[105] The impairment of these functions contributes to xerosis; it was demonstrated that the improvement of diabetic xerosis with emollients was associated with itch alleviation.[115] Pruritus in secondary hyperparathyroidism was correlated with serum calcium[116] and PTH levels,[91] whereas parathyroidectomy diminished the clinical manifestation.[46,90]

In diabetes, besides infrequent cases of generalized pruritus,[34–36,97–100] characteristic presentations involved the scalp[117] or vulva.[102] The relationship between anogenital pruritus and diabetes could be explained by fungal infections with *Candida albicans* or dermatophytes.[118] Additionally, a Japanese study revealed that truncal pruritus of unknown origin may denote diabetic polyneuropathy.[119] In a study among 385 patients with type 2 diabetes, 28.5% experienced pruritus with associated complaints, including difficulties in falling asleep (24.5%), disturbances of sleep (15.1%), resulting in soporifics intake in 9.5%.[105] In a long-lasting diabetes accompanied by polyneuropathy, pruritus of the arms and legs may ensue; this stimulates scratching, possibly complicated with severe infection and subsequent amputation.[120] Pruritus in patients with CKD and secondary parathyroidism was described as severe and intolerable.[46] Among 37 patients with CKD and secondary parathyroidism, parathyroidectomy lessened itch intensity, as measured by VAS, from 5.4 ± 3.2 to 1.8 ± 1.5 points ($P < .001$).[90] Another report described a case of primary hyperthyroidism manifesting as a localized inguinal pruritus.[121]

Diagnostic workup of a patient suspected of or found to have pruritus associated with endocrine disorders is based on laboratory and imaging examinations: the former include TSH, T3, T4, anti-TPO, ATRAs, glucose (including postprandial), HbA1c, PTH, calcium, phosphates, and vitamin D.[2,105,114]; the latter include ultrasonography of thyroid gland and parathyroid glands, scintigraphy, and MRI. Additionally, in case of polyneuropathy, nerve function tests may be considered.[119]

Pruritus in hematologic disorders

Anemia

Anemia is a common health issue worldwide, with an estimated global prevalence of 32.9% in 2010.[122] Iron deficiency is considered as a leading global cause of anemia. Dermatologic manifestations of anemia are profuse and concern both skin and its appendages.[123] Over the years, pruritus has also been reported as a result of anemia.[124–126] In a large cohort of Finnish patients (23,189 men and 19,902 women), 162 men and 736 women presented serum transferrin saturation under 15%, as well as hemoglobin levels below 13 g/dL and below 12 g/dL, respectively.[127] Anemia predisposed to the occurrence of pruritus in men (13.6% versus 5.3% in men without anemia; $P < .001$) and women (7.4% versus 5.1% in women without anemia; $P < .01$). No data concerning itch distribution (localized or generalized) were provided.

Itching in anemia is explained by a possible alteration in the functions of various enzymes, resulting in metabolic disturbances.[118] Decreased synthesis of DNA might contribute to diminished cutaneous turnover and skin thinning, and negatively affect the synthesis of elastic fibers in the skin.[126] Additionally, low cyanocobalamin serum level was associated with pruritus.[99] Interestingly, iron deficiency after venesections did not result in generalized pruritus in a group of 21 patients.[128] The pruritus associated with anemia was reported as generalized in several studies.[99,124–126] Other mucocutaneous manifestations of iron deficiency were also noted.[124] Pruritus disappeared entirely within 7 to 10 days of initiating therapy with iron.[124–126] Laboratory examinations in pruritus due to anemia include complete blood count, MCV, MCHC, lactate dehydrogenase, ferritin, and transferrin saturation.[62] Optionally, bone marrow aspiration with iron staining might be performed.

Myeloproliferative disorders

Myeloproliferative disorders (MPDs) are malignant hematologic neoplasms, including chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocytosis (ET), chronic eosinophilic leukemia (not otherwise specified; NOS), and unclassifiable myeloproliferative neoplasms.[129] A large study involving 1,179 patients with MPDs revealed that pruritus was the second most common

constitutional clinical manifestation affecting 52.6%, with fatigue being present in 81.1% of subjects.[130] Pruritus affected 65% of patients with PV, 50% with PMF, and 40% with ET. In the following section, we have reviewed pruritus in the context of PV and PMF, with an emphasis on aquagenic pruritus (AP).

Polycythemia vera

Pruritus in PV usually appears in a form of AP, which is characterized by marked sensations of itching, stinging, tingling, or burning after contact with water, without the presence of lesions on the skin.[131] AP is a common clinical manifestation in PV, affecting 5% to 69% of patients,[131–134] and may be associated with other conditions such as myelofibrosis, lactose intolerance, hypereosinophilic syndrome, acute lymphoblastic leukemia, myelodysplastic syndrome, juvenile xanthogranuloma, or metastatic carcinoma of the cervix.[135–140] Association with senility, psychogenic causes, or idiopathic cases were also reported.[135,141,142] The latter may occur in up to 69.2% of patients presenting with AP.[135]

A complex pathogenesis of AP in PV involves increased numbers of mononuclear cells and eosinophils in the papillary dermis and epidermis (especially after water exposure), edema and vasodilatation of upper portion of the dermis, the abundance of mast cells in the skin, increased cutaneous fibrinolytic activity, and activation of acetylcholinesterase.[134,143–146] JAK2V617F mutation, a crucial finding in PV, promotes activation and hypersensitivity in basophils, are also more prevalent in this disease.[147] Small-fiber neuropathy involving itch or pain transmitting C-fibers was also postulated in idiopathic AP.[148] Iatrogenic causes induced by pharmacotherapy (eg, antimalarials, testosterone, or clomipramine) may also contribute to AP without underlying PV.[149–151]

AP may be the first clinical manifestation of PV,[152] preceding the diagnosis by up to 38 years.[131] Our group has investigated 102 patients with an established diagnosis of PV, among whom 41.2% complained of AP.[133] There was a wide range of AP duration (0 to 44 years), with a mean duration of 6.6 ± 8.6 years. More than half of the patients suffered from AP every day. The values for itch intensity assessed by VAS were 5.2 ± 2.4 points (the maximal intensity) and 4.8 ± 1.9 points (mean intensity). Interestingly, itch intensity (measured by VAS and 4-Item Itch Questionnaire) was negatively correlated with hemoglobin concentration and hematocrit level.[153] Contact with water provoked AP after more than 5 minutes in 40.5% of patients, whereas 33.3% stated that AP appeared within 1 to 5 minutes of contact, or immediately (up to 1 minute) (26.2%).[133] Itch exacerbation was reported after contact with hot water by 57.1% subjects, yet rarely with cold water (1.9%). Concerning itch distribution, 45.2% of patients complained of AP limited to a few regions of the body (usually to upper and lower limbs and less frequently to the torso). Pruritus specific to one part of the body occurred in 33.4%, whereas generalized pruritus affected 21.4% of patients. AP in PV was also associated with significant burden, manifesting with higher rates of depression, anxiety, and QoL impairment.[154] Another group investigated 441 patients, among whom AP affected 68.3% of patients.[131] Patients with AP suffered from gout, erythromelalgia, splenomegaly, and CNS vascular problems more commonly and experienced negative impact on various QoL-associated domains (role, emotional, cognitive and social functioning; dyspnea; insomnia; fatigue; pain; financial difficulties). Pruritus in PV was also associated with lower risk of arterial thrombosis at diagnosis (8% versus 17%; $P = .01$) and during follow-up (16% versus 30%; $P = .003$).[132] Additionally, pruritus occurred more frequently in smokers (12% versus 24%; $P = .004$), patients with diabetes (5% versus 11%; $P = .04$), and patients with high *JAK2*V617F allele burden ($P = .002$).

When suspecting PV as a cause of AP, possible laboratory examinations include complete blood count, erythrocyte sedimentation rate, and *JAK2*V617F mutation.[62,96] Other investigations (oxygen saturation, serum erythropoietin level) may aid in differentiating with secondary erythrocytosis. Further diagnostic procedures include bone marrow biopsy (with subsequent assessment of its morphology). Imaging studies include ultrasonography, CT, and MRI of the spleen.

Primary myelofibrosis

PMF is a myeloproliferative disorder characterized by clonal myeloproliferation, reactive bone marrow fibrosis, osteosclerosis, angiogenesis, extramedullary hematopoiesis, abnormal cytokine expression, and a variety of clinical manifestations.[155] In a cohort of 566 patients with PMF, pruritus was documented as present in 16% and absent in 26%.[156] The presence of pruritus was associated with marked leukocytosis (23% versus 11%; $P = .01$), whereas leukopenia (8% versus 24%; $P = .002$) and *MPL*W515 mutation (0% versus 10%; $P = .02$) were less common in patients with pruritus. No correlations with PMF stage or prognosis were determined. Another report by this group focused on 51 patients from the previous study who suffered from PMF-associated pruritus.[157] AP was reported in 56.9% patients. Severe pruritus, described as intractable, disabling, and incapacitating, affected 64% of patients. These patients required treatment, with the complete response being achieved mostly with JAK inhibitors (53%) and immunomodulatory drugs (50%).

Lymphoproliferative disorders

According to the WHO 2016 classification, lymphoid neoplasms involve mature B-cell neoplasms, mature T and NK neoplasms, Hodgkin lymphoma (HL), posttransplant lymphoproliferative disorders (PTLD), as well as histiocytic and dendritic cell neoplasms.[158] From the clinical point of view, lymphomas are frequently divided into HL and non-HL (NHL). Both groups of lymphomas have been associated with pruritus.

Hodgkin lymphoma

The presence of pruritus or prurigo nodularis is the second most common cutaneous presentations in HL after dermatitis and occurred in 36.1% of patients.[159] Itching was correlated with the presence of *Staphylococcus aureus;* however, therapy with antibiotics resulted in alleviation of the clinical manifestation. Similar prevalence (35.8%) was reported by Italian researchers.[160] The latter study included 360 patients with HL, among whom mild pruritus affected 25% patients, whereas in 5.8% its intensity was severe and generalized. Patients with severe pruritus had shorter survival than patients with mild or no itching. The authors proposed to include pruritus in the B category, which comprises fever above 38°C, night sweats, and weight loss of more than 10% of the body. Pathogenesis of itching in HL may include the Th2 lymphocyte response and production of IL-10, IL-4, IL-5, IgE, and hyperosinophilia.[159]

Pruritus may precede the diagnosis of HL by up to 4 years[161]; it frequently starts on the legs, with the highest frequency during night and subsequent generalization of the sensation.[62] The disappearance of generalized pruritus associated with HL may denote spinal cord progression.[162] Itching paroxysm may also be preceded by transient generalized hyperhidrosis and subsequent appearance of pruritus between the fingers and on the palms, with further generalization.[163]

Non-Hodgkin lymphoma

Among 62 patients with NHL, pruritus was a rare finding (3.2% of patients).[164] NHL group comprises a wide group of conditions, among which cutaneous T-cell lymphomas (CTCL) may also be distinguished. CTCL forms commonly encountered in dermatologic practice include mycosis fungoides (MF) and Sezary syndrome (SS). In a study on 551 CTCL patients, pruritus affected 66% overall (with 61% in MF and 94% in SS).[165] Sixty-two percent of patients with early-stage disease reported itching, whereas 83% in late-stage disease. Mean pruritus values were as follows (with 10 as the maximal value): 4.2 (standard error of the mean [SEM] = 0.18) in entire cohort; 3.4 (SEM = 0.19) in early-stage disease; 6.6 (SEM = 0.36) in late-stage disease. There was a statistically significant difference between itch intensity in MF(3.6; SEM = 0.18) and SS (7.7; SEM = 0.37) ($P < .001$). SS is more often pruritic as a result of eosinophilia, Th2 cytokine profile, and staphylococcal colonization. Another investigation conducted among patients with mycosis fungoides revealed higher prevalence of pruritus (88%).[166] In another study on 100 patients with CTCL, 88% complained of pruritus in the preceding 4 weeks.[167] The mean itch intensity (VAS) was 3.2 ± 3.2 points. The Skindex-29 questionnaire was used to assess the QoL impairment, revealing a strong correlation with VAS (r = .719; $P < .001$).

Diagnostic approach in cases of pruritus possibly associated with lymphomas includes complete blood count, including thrombocytes, blood smear, erythrocyte sedimentation rate, and lactate dehydrogenase.[62,96] Frequently, bone marrow biopsy is performed, with subsequent evaluation of chromosomal aberrations. Imaging studies, such as sonography, CT, MRI, positron emission tomography, provide data concerning involvement of lymph nodes and internal organs.

Pruritus associated with malignancies

The presence of pruritus in a patient with malignancy is often referred to as paraneoplastic pruritus; however, not all cases of pruritus associated with malignancy are "true" examples of paraneoplastic pruritus. This term has been defined as a sensation of itch that is regarded as a systemic (not local) reaction to the presence of a tumor or a hematologic malignancy, induced neither by the local presence of cancer cells nor by therapy.[168] Paraneoplastic pruritus disappears with remission of the tumor and recurs with its relapse. Paraneoplastic pruritus is usually associated with hematologic malignancies reviewed previously (eg, PV or lymphomas), whereas solid tumors are considered as less frequent causes. In a wider sense, pruritus associated with malignancies arises due to toxic products of necrotic tumor cells, host immune response to cutaneous implants of tumor, and increased susceptibility of the skin to external irritant factors, but also cholestasis, compression of sensory nerve fibers, and neuropathy ensuing due to antitumor pharmacotherapy.[118,169]

Several epidemiologic studies have provided data concerning pruritus in malignancy. A 6-year follow-up study on 125 patients with generalized pruritus revealed that cancer screening seems unnecessary.[170] Among 700 patients found to have malignancy, Turkish investigators found that the commonest cutaneous findings were tinea pedis (and/or onychomycosis) (11.3%), xerosis (8.4%), and pruritus (5.9%). These 41 pruritic patients suffered from carcinomas of gastrointestinal system (10 patients), breast (7), hematological malignancies (6), head and neck (5 patients), lung (5), genitourinary neoplasms (4), bone (2), and brain tumors (2).[171]

Another population-based study included 8,744 patients with chronic pruritus and 31,580 subjects in the control group.[172] Interestingly, the hazard ratio (HR) for any malignancy was only 1.14 (95% confidence interval [CI] 0.98-1.33). Certain malignancies occurred more often, including bile duct malignancy (HR 3.71; 95% CI 1.55-8.97) and hematologic malignancy (HR 2.02; 95% CI 1.48-2.75). A recent study focused on 16,925 patients with chronic pruritus (with control group consisting of 4,679,528 healthy subjects).[173] In a 5-year period, 17.2% subjects with chronic pruritus developed malignancy and were 5.76 times more likely to present underlying malignancy compared with patients without pruritus (OR 5.76; 95% CI 5.53-6.00). The common malignancies included hematologic (28%; mainly NHL), cutaneous (20%; most commonly basal cell carcinoma), breast (10%), respiratory tract (7%), and hepatic (6%). In an prospective study,[36] 44 patients with generalized pruritus without

primary skin lesions were evaluated. Malignancy proved to be the underlying cause in 8.3%. The authors speculated that itching could occur due to a possible central mechanism resulting from the activation of gray matter in the brain. Chest X ray, sonography of the abdomen, and lymph node assessment are recommended for patients suffering from chronic pruritus for at least 6 months.

Several cutaneous conditions may denote internal or hematologic malignancy and present with itching. The examples include generalized granuloma annulare, dermatomyositis, transient acantholytic dermatosis (Grover disease), erythroderma, paraneoplastic pemphigus, eruptive seborrheic keratoses (Leser-Trelat sign), malignant acanthosis nigricans, or Bazex syndrome.[174]

Pruritus in infectious diseases

Similar to pruritus, infectious diseases elicited by various causative factors have concerned patients for many centuries, occasionally coexisting together. Human immunodeficiency virus (HIV) infection affected 36.9 million people in 2017, with 1.8 million new infections and 900,000 AIDS-related deaths.[175] Pruritus is a frequent clinical manifestation in HIV, arising from skin infections, infestations, papulosquamous disorders, photodermatosis, xerosis, adverse drug reactions, or systemic disorders (eg, CKD, hepatitis, or lymphoproliferative disorders).[176] Its pathogenesis is complex, although hypereosinophilia; elevated IgE, IgA, IL-4, IL-5, and sCD23; reduced interferon gamma production by mitogen-stimulated peripheral blood mononuclear cells (PBMCs); and high viral load were all investigated as causative factors.[177] In a cohort of 303 HIV-positive subjects, Spanish researchers reported that pruritus affected 31% of subjects with HIV, most commonly due to xerosis (51.2% of pruritic patients), seborrheic dermatitis (13.8%), and interdigital tinea pedis (9.6%).[178] Pruritic patients presented higher viral loads ($P = .006$), whereas no correlations with antiretroviral therapy were found.

In another study among 201 American patients with HIV, the prevalence of itch was very high (45%), with marked intensity (5.1 ± 2.8 points on average as assessed by VAS).[179] Women experienced itching more often than men (60% versus 39%; $P = .003$). Chronic pruritus affected 45% of subjects, whereas 54% reported pleasure after scratching. Thirty percent complained of 2 to 4 itching episodes daily, whereas 38% reported more itching during night. Decreased QoL was observed more commonly in pruritic subjects; the authors emphasized the impact of emotions on the different domains of ItchyQol questionnaire, higher scores for women, the role of HIV-associated dermatoses, as well as the role of sweating and heat as factors negatively influencing QoL. Other viral disorders, such as varicella,[180] zoster,[181] dengue,[182] chikungunya fever,[183] and Zika infection,[184] may also be accompanied by pruritus. Concerning disorders caused by bacteria, secondary syphilis is considered as a disease that usually does not itch; however, reports of pruritic cutaneous manifestations of this "great imitator" have been published.[185–188]

Severe intractable pruritus may also occur due to gastritis associated with *Helicobacter pylori*.[189] Among *H pylori*–positive patients (n = 134) suffering from pruritic cutaneous diseases (pruritus, prurigo nodularis, nummular dermatitis, chronic urticaria) early-stage gastric cancer was detected in 5 subjects.[190] Parasitic diseases such as toxocariasis or filariasis may also account for generalized pruritus and pruritic dermatoses in a significant number of subjects.[191,192]

Pruritus in cardiology

Pruritus is a clinical manifestation that is very rarely associated with cardiologic conditions. In a Swedish research project, patients with chronic heart failure (CHF) and coronary artery disease (CAD) were investigated (n = 130 each; 85 and 82 subjects answered the questionnaire, respectively).[193] Pruritus affected 40% and 23.2% in the last 3 months, respectively ($P = .019$). Compared with normal population (n = 678), CHF suffered from pruritus more often (13.6% versus 3.8%; $P < .001$). Among subjects reporting pruritus, daily itching affected patients with CHF more often than those with CAD (84.2% versus 57.6%, $P = .049$). Pruritus was mostly experienced on the torso (75% of pruritic patients with CHF), lower extremities (65.5%), and upper extremities (50%). Pharmacotherapy influenced itch prevalence, with angiotensin-receptor blockers ($P = .014$), loop diuretics ($P = .001$), levaxin ($P = .008$), and allopurinol ($P = .002$) increasing its prevalence, whereas angiotensin-converting enzyme inhibitors were associated with a lower prevalence ($P = .014$). Recently, our group has investigated 87 patients with acute heart failure and observed that pruritus affected 16%.[194] Of these, 71.4% reported pruritus in the last 3 days, with a mean intensity of 5.4 points (VAS) and 5.5 points (NRS). Seventy-one percent of pruritic subjects reported localized pruritus (mostly to the arms and legs).

Pruritus may also occur in the cardiologic setting due to pacemaker dermatitis,[195,196] or present as a unique clinical manifestation of pacemaker pocket infection.[197] Interestingly, marked itching in the course of atopic dermatitis predisposes to infective endocarditis caused by *S aureus*.[198,199]

Pruritus in pulmonology

Disorders of respiratory tract could also be related to itching in specific situations. Asthmatic attacks are preceded by itching in up to 26.7% to 70% of subjects.[200,201] Case reports have documented intractable generalized pruritus in the course of pulmonary sarcoidosis.[202,203] The latter was also associated with generalized itching after a hot bath, as well as alcohol-induced pain in the lymph nodes.[204] Among 102 patients with

pulmonary tuberculosis (TB), the most common cutaneous manifestations included xerosis (13.3%) and pruritus (11.6%).[205] Both the direct role of an underlying infection and adverse drug reactions were possible culprits. In another report, the treatment of underlying infection provided itch resolution within 3 weeks.[206] Prurigo nodularis was also associated with pulmonary TB.[207]

Conclusions

Pruritus is a frequent and bothersome clinical manifestation encountered in all medical specialties. The underlying disorders are not only of purely cutaneous origin but may also be associated with systemic conditions and/or drug intake. Pruritus may be the first and only clinical manifestation denoting the presence of severe systemic disorders. Detailed history taking and a physical examination, as well as additional diagnostic investigations, may provide a clue as to its origin, thus facilitating successful therapy aimed at an underlying disorder.

References

1. Weisshaar E, Szepietowski JC, Darsow U, et al. European guideline on chronic pruritus. *Acta Derm Venereol* 2012;92:563-581.
2. Ständer S, Weisshaar E, Mettang T, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 2007;87:291-294.
3. Terranova M, Guarneri C, Guarneri F, et al. Some historical and epistemological remarks on itch and pruritus. *Dermatol Ther* 2005;18:283-287.
4. Weisshaar E, Grüll V, König A, et al. The symptom of itch in medical history: highlights through the centuries. *Int J Dermatol* 2009;48:1385-1394.
5. Ward JR, Bernhard JD. Willan's itch and other causes of pruritus in the elderly. *Int J Dermatol* 2005;44:267-273.
6. Graham DT, Goodell H, Wolff HG. Neural mechanisms involved in itch, itchy skin, and tickle sensations. *J Clin Invest* 1951;30:37-49.
7. Shelley WB, Arthur RP. Studies on cowhage (Mucuna pruriens) and its pruritogenic proteinase, mucunain. *AMA Arch Derm* 1955;72:399-406.
8. Arthur RP, Shelley WB. The role of proteolytic enzymes in the production of pruritus in man. *J Invest Dermatol* 1955;25:341-346.
9. Handwerker HO, Forster C, Kirchhoff C. Discharge patterns of human C-fibers induced by itching and burning stimuli. *J Neurophysiol* 1991;66:307-315.
10. Schmelz M, Schmidt R, Bickel A, et al. Specific C-receptors for itch in human skin. *J Neurosci* 1997;17:8003-8008.
11. Steinhoff M, Neisius U, Ikoma A, et al. Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003;23:6176-6180.
12. Reddy VB, Iuga AO, Shimada SG, et al. Cowhage-evoked itch is mediated by a novel cysteine protease: a ligand of protease-activated receptors. *J Neurosci* 2008;28:4331-4335.
13. Sun YG, Zhao ZQ, Meng XL, et al. Cellular basis of itch sensation. *Science* 2009;325:1531-1534.
14. Steinhoff M, Bienenstock J, Schmelz M, et al. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. *J Invest Dermatol* 2006;126:1705-1718.
15. Misery L. Atopic dermatitis and the nervous system. *Clin Rev Allergy Immunol* 2011;41:259-266.
16. Hashimoto T, Rosen JD. *Sanders KM, et al.* Exp Dermatol: Possible roles of basophils in chronic itch. 2018. [Epub ahead of print].
17. Schmelz M, Hilliges M, Schmidt R, et al. Active "itch fibers" in chronic pruritus. *Neurology* 2003;61:564-566.
18. Davidson S, Zhang X, Khasabov SG, et al. Pruriceptive spinothalamic tract neurons: physiological properties and projection targets in the primate. *J Neurophysiol* 2012;108:1711-1723.
19. Steinhoff M, Vergnolle N, Young SH, et al. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000;6:151-158.
20. Steinhoff M, Ständer S, Seeliger S, et al. Modern aspects of cutaneous neurogenic inflammation. *Arch Dermatol* 2003;139:1479-1488.
21. Fallahzadeh MK, Roozbeh J, Geramizadeh B, et al. Interleukin-2 serum levels are elevated in patients with uremic pruritus: a novel finding with practical implications. *Nephrol Dial Transplant* 2011;26:3338-3344.
22. Oetjen LK, Mack MR, Feng J, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell.* 2017;171:217-228.e13.
23. Oh MH, Oh SY, Lu J, et al. TRPA1-dependent pruritus in IL-13-induced chronic atopic dermatitis. *J Immunol* 2013;191:5371-5382.
24. Lou H, Lu J, Choi EB, et al. Expression of IL-22 in the skin causes Th2-biased immunity, epidermal barrier dysfunction, and pruritus via stimulating epithelial Th2 cytokines and the GRP pathway. *J Immunol* 2017;198:2543-2555.
25. Takamori A, Nambu A, Sato K, et al. IL-31 is crucial for induction of pruritus, but not inflammation, in contact hypersensitivity. *Sci Rep* 2018;8:6639.
26. Wilson SR, Thé L, Batia LM, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell* 2013;155:285-295.
27. Paus R, Schmelz M, Bíró T, et al. Frontiers in pruritus research: scratching the brain for more effective itch therapy. *J Clin Invest* 2006;116:1174-1186.
28. Ko MC, Song MS, Edwards T, et al. The role of central mu opioid receptors in opioid-induced itch in primates. *J Pharmacol Exp Ther* 2004;310:169-176.
29. Ko MC, Husbands SM. Effects of atypical kappa-opioid receptor agonists on intrathecal morphine-induced itch and analgesia in primates. *J Pharmacol Exp Ther* 2009;328:193-200.
30. Tekatas A, Arican O, Guler S, et al. Pruritus: do ad fibers play a role? *J Dermatol* 2014;41:98-101.
31. Mochizuki H, Papoiu ADP, Nattkemper LA, et al. Scratching induces overactivity in motor-related regions and reward system in chronic itch patients. *J Invest Dermatol* 2015;135:2814-2823.
32. Mochizuki H, Schut C, Nattkemper LA. et a. Brain mechanism of itch in atopic dermatitis and its possible alteration through non-invasive treatments. *Allergol Int* 2017;66:14-21.
33. Papoiu AD, Nattkemper LA. Sanders KM, et al. *Brain's reward circuits mediate itch relief a functional MRI study of active scratching PLoS One* 2013;8, e82389.
34. Zirwas MJ, Seraly MP. Pruritus of unknown origin: a retrospective study. *J Am Acad Dermatol* 2001;45:892-896.
35. Afifi Y, Aubin F, Puzenat E, et al. Pruritus sine materia: a prospective study of 95 patients. *Rev Med Interne* 2004;25:490-493.
36. Alizadeh N, Mirpour SH, Golmohamadi R, et al. Chronic generalized pruritus without primary skin lesions: a longitudinal prospective observational study. *Int J Dermatol* 2019;58:273-278.
37. Szepietowski JC, Schwartz RA. Uremic pruritus. *Int J Dermatol* 1998;37:247-253.
38. Mettang T. Pruritus in renal disease. In: Carstens E, Akiyama T, eds. Itch: Mechanisms and Treatment. Boca Raton, FL: CRC Press/Taylor & Francis; 2014. p. 47-59.
39. Pisoni RL, Wikström B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2006;21:3495-3505.

40. Wojtowicz-Prus E, KilIis-Pstrusinska K, Reich A, et al. Chronic kidney disease-associated pruritus in children. *Acta Derm Venereol* 2016;96:938-942.
41. Solak B, Acikgoz SB, Sipahi S, et al. Epidemiology and determinants of pruritus in pre-dialysis chronic kidney disease patients. *Int Urol Nephrol* 2016;48:585-591.
42. Kurban MS, Boueiz A, Kibbi AG. Cutaneous manifestations of chronic kidney disease. *Clin Dermatol* 2008;26:255-264.
43. Duque MI, Thevarajah S, Chan YH, et al. Uremic pruritus is associated with higher kt/V and serum calcium concentration. *Clin Nephrol* 2006;66:184-191.
44. Momose A, Funyu T, Wada R, et al. AQP-3 in the epidermis of haemodialysis patients with CKD-associated pruritus is overexpressed. *J Clin Exp Nephrol* 2016;1:7.
45. Ragab BF, Youssef SS, Abou Seif KH, et al. Evaluation of serum levels of calcium and phosphorus in uremic pruritus patients before and after narrow band ultraviolet B phototherapy. *J Egypt Women Dermatol Soc* 2013;10:160-165.
46. Massry SG, Popovtzer MM, Coburn JW, et al. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 1968;279:697-700.
47. Gokustun D, Bal AZ, Sezer S, et al. 25-hydroxy vitamin D deficiency may be the secret actor in the pathogenesis of uremic pruritus in hemodialysis patients. *J Clin Nephrol Res* 2016;3:1053.
48. Szepietowski JC, Sikora M, Kusztal M, et al. Uremic pruritus: a clinical study of maintenance hemodialysis patients. *J Dermatol* 2002;29:621-627.
49. Chorążyczewska W, Reich A, Szepietowski JC. Lipid content and barrier function analysis in uraemic pruritus. *Acta Derm Venereol* 2016;96:402-403.
50. Yosipovitch G, Duque MI, Patel TS, et al. Skin barrier structure and function and their relationship to pruritus in end-stage renal disease. *Nephrol Dial Transpl* 2007;22:3268-3272.
51. Gilchrest BA, Stern RS, Steinman TI, et al. Clinical features of pruritus among patients undergoing maintenance hemodialysis. *Arch Dermatol* 1982;118:154-156.
52. Kimmel M, Alscher DM, Dunst R. The role of microinflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transpl* 2006;21:749-755.
53. Zakrzewska-Pniewska B, Jedras M. Is pruritus in chronic uremic patients related to peripheral somatic and autonomic neuropathy? Study by R-R interval variation test (RRIV) and by sympathetic skin response (SSR). *Neurophysiol Clin* 2001;31:181-193.
54. Chiu YL, Chen HY, Chuang YF, et al. Association of uraemic pruritus with inflammation and hepatitis infection in haemodialysis patients. *Nephrol Dial Transpl* 2008;23:3685-3689.
55. Wikström B, Gellert R, Ladefoged SD, et al. Kappa opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005;16:3742-3747.
56. Hayani K, Kunzmann K, Mettang T, et al. Lower prevalence of chronic itch in haemodialysis patients on loop diuretics: results from GEHIS (German Epidemiological Hemodialysis Itch Study). *J Eur Acad Dermatol Venereol* 2017;31:1333-1337.
57. Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012;92:502-507.
58. Heisig M, Reich A, Szepietowski JC. Is uremic pruritus still an important clinical problem in maintenance hemodialysis patients? *J Eur Acad Dermatol Venereol* 2016;30:e198-e199.
59. Zucker I, Yosipovitch G, David M, et al. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol* 2003;49:842-846.
60. Mathur VS, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol* 2010;5:1410-1419.
61. Susel J, Batycka-Baran A, Reich A, et al. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. *Acta Derm Venereol* 2014;94:276-281.
62. Weisshaar E, Szepietowski JC, Darsow U, et al. European guideline on chronic pruritus. *Acta Derm Venereol* 2012;92:563-581.
63. Kremer AE, Bolier R, van Dijk R, et al. Advances in pathogenesis and management of pruritus in cholestasis. *Dig Dis* 2014;32:637-645.
64. Brick IB. Pruritus and jaundice. *JAMA* 1950;142:198.
65. Kremer AE, van Dijk R, Leckie P, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions. *Hepatology* 2012;56:1391-1400.
66. Suzuki K, Tamano M, Katayama Y, et al. Study of pruritus in chronic hepatitis C patients. *World J Gastroenterol* 2014;20:17877-17882.
67. Biernacka A, Nizynski D, Inglot M, et al. Assessment of pruritus in patients with viral hepatitis B and C. *Dermatol Rev/Przegl Dermatol* 2018;105:264-272.
68. Oeda S, Takahashi H, Yoshida H, et al. Prevalence of pruritus in patients with chronic liver disease: a multicenter study. *Hepatol Res* 2018;48:E252-E262.
69. Bonacini M. Pruritus in patients with chronic human immunodeficiency virus, hepatitis B and C virus infections. *Dig Liver Dis* 2000;32:621-625.
70. Sula B, Tekin R. Generalized pruritus secondary to acute hepatitis A: a case report. *JMID* 2015;5:184-186.
71. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2009;15:2049-2066.
72. Baker A, Kerkar N, Todorova L, et al. Systematic review of progressive familial intrahepatic cholestasis. *Clin Res Hepatol Gastroenterol* 2019;43:20-36.
73. Ghent CN, Bloomer JR. Itch in liver disease: facts and speculations. *Yale J Biol Med* 1979;52:77-82.
74. Herndon Jr JH. Pathophysiology of pruritus associated with elevated bile acid levels in serum. *Arch Intern Med* 1972;130:632-637.
75. Kirby J, Heaton KW, Burton JL. Pruritic effect of bile salts. *Br Med J* 1974;4:693-695.
76. Ghent CN, Bloomer JR, Klatskin G. Elevations in skin tissue levels of bile acids in human cholestasis: relation to serum levels and to pruritus. *Gastroenterology* 1977;73:1125-1130.
77. Bergasa NV. The pruritus of cholestasis. *J Hepatol* 2005;43:1078-1088.
78. Bergasa NV, Alling DW, Talbot TL, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. *Ann Intern Med* 1995;123:161-167.
79. Bergasa NV, Alling DW, Talbot TL, et al. Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: a controlled study. *J Am Acad Dermatol* 1999;41:431-434.
80. Raderer M, Müller C, Scheithauer W. Ondansetron for pruritus due to cholestasis. *N Engl J Med* 1994;330:1540.
81. Schwörer H, Hartmann H, Ramadori G. Relief of cholestatic pruritus by a novel class of drugs: 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists: effectiveness of ondansetron. *Pain* 1995;61:33-37.
82. Kremer AE, Martens JJ, Kulik W, et al. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. *Gastroenterology* 2010;139:1008-1018.
83. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double blind, crossover, randomized trial. *Gastroenterology* 1988;94:488-493.
84. Alhmada Y, Selimovic D, Murad F, et al. Hepatitis C virus-associated pruritus: etiopathogenesis and therapeutic strategies. *World J Gastroenterol* 2017;23:743-750.
85. Hegade VS, Kendrick SF, Rehman J, et al. Itch and liver: management in primary care. *Br J Gen Pract* 2015;65:e418-e420.
86. Rishe E, Azarm A, Bergasa NV. Itch in primary biliary cirrhosis: a patients' perspective. *Acta Derm Venereol* 2008;88:34-37.

87. Davies MH, da Silva RC, Jones SR, et al. Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid. *Gut* 1995;37:580-584.
88. Golden SH, Robinson KA, Saldanha I, et al. Clinical review: prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. *J Clin Endocrinol Metab* 2009;94:1853-1878.
89. Feingold KR, Elias PM. Endocrine-skin interactions. Cutaneous manifestations of pituitary disease, thyroid disease, calcium disorders, and diabetes. *J Am Acad Dermatol* 1987;17:921-940.
90. Chou FF, Ho JC, Huang SC, et al. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg* 2000;190:65-70.
91. Makhlough A, Emadi N, Sedighi O, et al. Relationship between serum intact parathyroid hormone and pruritus in hemodialysis patients. *Iran J Kidney Dis* 2013;7:42-46.
92. Artantaş S, Gül U, Kiliç A, et al. Skin findings in thyroid diseases. *Eur J Intern Med* 2009;20:158-161.
93. Krishna AV, Prasad KN, Reddy DS, et al. A clinical study of cutaneous manifestations in patients with thyroid disorders. *J Evolution Med Dent Sci* 2016;5:5489-5500.
94. Takir M, Özlü E, Köstek O, et al. Skin findings in autoimmune and nonautoimmune thyroid disease with respect to thyroid functional status and healthy controls. *Turk J Med Sci* 2017;47:764-770.
95. Ramanathan M, Abidin MN, Muthukumarappan M. The prevalence of skin manifestations in thyrotoxicosis—a retrospective study. *Med J Malaysia* 1989;44:324-328.
96. Millington GWM, Collins A, Lovell CR, et al. British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. *Br J Dermatol* 2018;178:34-60.
97. Beare JM. Generalized pruritus. A study of 43 cases. *Clin Exp Dermatol* 1976;1:343-352.
98. Sommer F, Hensen P, Böckenholt B, et al. Underlying diseases and co-factors in patients with severe chronic pruritus: a 3-year retrospective study. *Acta Derm Venereol* 2007;87:510-516.
99. Polat M, Oztas P, Ilhan MN, et al. Generalized pruritus: a prospective study concerning etiology. *Am J Clin Dermatol* 2008;9:39-44.
100. Kantor GR, Lookingbill DP. Generalized pruritus and systemic disease. *J Am Acad Dermatol* 1983;9:375-382.
101. Greenwood AM. A study on the skin in five hundred cases of diabetes. *JAMA* 1927;89:774-776.
102. Neilly JB, Martin A, Simpson N, et al. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. *Diabetes Care* 1986;9:273-275.
103. Rao GS, Pai GS. Cutaneous manifestations of diabetes mellitus. *Indian J Dermatol Venereol Leprol* 1997;63:232-234.
104. Mahajan S, Koranne RV, Sharma SK. Cutaneous manifestation of diabetes mellitus. *Indian J Dermatol Venereol Leprol* 2003;69:105-108.
105. Ko MJ, Chiu HC, Jee SH, et al. Postprandial blood glucose is associated with generalized pruritus in patients with type 2 diabetes. *Eur J Dermatol* 2013;23:688-693.
106. Al-Mutairi N, Zaki A, Sharma AK, et el. Cutaneous manifestations of diabetes mellitus. Study from Farwaniya hospital, Kuwait. *Med Princ Pract.* 2006;15:427-430.
107. Yosipovitch G, Hodak E, Vardi P, et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. *Diabetes Care* 1998;21:506-509.
108. Cohen KR, Frank J, Salbu RL, et al. Pruritus in the elderly: clinical approaches to the improvement of quality of life. *P T* 2012;37:227-239.
109. Rishi R, Ringwala S, Tracy J, et al. Prurigo nodularis and Hashimoto thyroiditis. *Ann Allergy Asthma Immunol* 2014;113:673-674.
110. Isaacs NJ, Ertel NH. Urticaria and pruritus: uncommon manifestations of hyperthyroidism. *J Allergy Clin Immunol* 1971;48:73-81.
111. Bansal AS, Hayman GR. Graves disease associated with chronic idiopathic urticaria: 2 case reports. *J Investig Allergol Clin Immunol* 2009;19:54-56.
112. Kinsey MD, Donowitz M, Wartofsky L, et al. The correlation between pruritus and elevated serum chenodeoxycholic acid (CDC) levels in hyperthyroidism. *Gastroenterology* 1976;70:859-977.
113. Hasan MK, Tierney WM, Baker MZ. Severe cholestatic jaundice in hyperthyroidism after treatment with 131-iodine. *Am J Med Sci* 2004;328:348-350.
114. Afsar B, Elsurer Afsar R. HbA1c is related with uremic pruritus in diabetic and nondiabetic hemodialysis patients. *Ren Fail* 2012;34:1264-1269.
115. Seité S, Khemis A, Rougier A, et al. Importance of treatment of skin xerosis in diabetes. *J Eur Acad Dermatol Venereol* 2011;25:607-609.
116. Tajbakhsh R, Joshaghani HR, Bayzayi F, et al. Association between pruritus and serum concentrations of parathormone, calcium and phosphorus in hemodialysis patients. *Saudi J Kidney Dis Transpl* 2013;24:702-706.
117. Scribner M. Diabetes and pruritus of the scalp. *JAMA* 1977;237:1559.
118. Krajnik M, Zylicz Z. Understanding pruritus in systemic disease. *J Pain Symptom Manag* 2001;21:151-168.
119. Yamaoka H, Sasaki H, Yamasaki H, et al. Truncal pruritus of unknown origin may be a symptom of diabetic polyneuropathy. *Diabetes Care* 2010;33:150-155.
120. Dorfman D, George MC, Tamler R, et al. Pruritus induced self injury behavior: an overlooked risk factor for amputation in diabetic neuropathy? *Diabetes Res Clin Pract* 2014;103:e47-e48.
121. Haber R, Helou J, Kechichian E, et al. Intractable localized inguinal pruritus as a sign of primary hyperparathyroidism. *J Med Liban* 2017;65:123-124.
122. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014;123:615-624.
123. Marks J, Shuster S. Anemia and skin disease. *Postgrad Med J* 1970;46:659-663.
124. Lewiecki EM, Rahman F. Pruritus. A manifestation of iron deficiency. *JAMA* 1976;236:2319-2320.
125. Valsecchi R, Cainelli T. Generalized pruritus: a manifestation of iron deficiency. *Arch Dermatol* 1983;119:630.
126. Tammaro A, Chello C, di Fraia M, et al. Iron-deficiency and pruritus: a possible explanation of their relationship. *Int J Res Dermatol* 2018;4:605-606.
127. Takkunen H. Iron-deficiency pruritus. *JAMA* 1978;239:1394.
128. Tucker WF, Briggs C, Challoner T. Absence of pruritus in iron deficiency following venesection. *Clin Exp Dermatol* 1984;9:186-189.
129. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391-2405.
130. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. *Cancer* 2007;109:68-76.
131. Siegel FP, Tauscher J, Petrides PE. Aquagenic pruritus in polycythemia vera: characteristics and influence on quality of life in 441 patients. *Am J Hematol* 2013;88:665-669.
132. Gangat N, Strand JJ, Lasho TL, et al. Pruritus in polycythemia vera is associated with a lower risk of arterial thrombosis. *Am J Hematol* 2008;83:451-453.
133. Lelonek E, Matusiak Ł, Wróbel T, et al. Aquagenic pruritus in polycythemia vera: clinical characteristics. *Acta Derm Venereol* 2018;98:496-500.
134. Jackson N, Burt D, Crocker J, et al. Skin mast cells in polycythaemia vera: relationship to the pathogenesis and treatment of pruritus. *Br J Dermatol* 1987;116:21-29.
135. Heitkemper T, Hofmann T, Phan NQ, et al. Aquagenic pruritus: associated diseases and clinical pruritus characteristics. *J Dtsch Dermatol Ges* 2010;8:797-804.
136. Newton JA, Singh AK, Greaves MW, et al. Aquagenic pruritus associated with the idiopathic hypereosinophilic syndrome. *Br J Dermatol* 1990;122:103-106.
137. Ratnaval RC, Burrows NP, Marcus RE, et al. Aquagenic pruritus and acute lymphoblastic leukaemia. *Br J Dermatol* 1993;129:348-349.
138. McGrath JA, Greaves MW. Aquagenic pruritus and the myelodysplastic syndrome. *Br J Dermatol* 1990;123:414-415.

139. Handfield-Jones SE, Hills RJ, Ive FA, et al. Aquagenic pruritus associated with juvenile xanthogranuloma. *Clin Exp Dermatol* 1993;18:253-255.
140. Ferguson JE, August PJ, Guy AJ. Aquagenic pruritus associated with metastatic squamous cell carcinoma of the cervix. *Clin Exp Dermatol* 1994;19:257-258.
141. Sekar CS, Srinivas CR, Jacob S. Aquagenic pruritus: beneath water "lies." Indian J Dermatol 2011;56:446-447.
142. Kligman AM, Greaves ME, Steinman H. Water-induced itching without cutaneous signs. *Arch Dermatol* 1986;122:183-186.
143. Abdel-Naser MB, Gollnick H, Orfanos CE. Aquagenic pruritus as a presenting symptom of polycythemia vera. *Dermatology* 1993;187:130-133.
144. Abdel-Naser MB, Zaki MS, Musa MH, et al. Cutaneous mononuclear cells and eosinophils are significantly increased after warm water challenge in pruritic areas of polycythemia vera. *J Cutan Pathol* 2007;34:924-929.
145. Lotti T, Steinman HK, Greaves MW, et al. Increased cutaneous fibrinolytic activity in aquagenic pruritus. *Int J Dermatol* 1986;25:508-510.
146. Bircher AJ, Meier-Ruge W. Water-induced activation of acetylcholinesterase. *Arch Dermatol* 1988;124:84-89.
147. Pieri L, Bogani C, Guglielmelli P, et al. The JAK2V617 mutation induces constitutive activation and agonist hypersensitivity in basophils from patients with polycythemia vera. *Haematologica* 2009;94:1537-1545.
148. Cao T, Yong AA, Tan KB, et al. Idiopathic aquagenic pruritus: pathogenesis and effective treatment with atenolol. *Dermatol Ther* 2015;28:118-121.
149. Jimenez-Alonso J, Tercedor J, Jaimez L, et al. Antimalarial drug-induced aquagenic-type pruritus in patients with lupus. *Arthritis Rheumatol* 1998;41:744-745.
150. Liu M, Shinkai K. Reversible aquagenic pruritus associated with testosterone-induced erythrocytosis. *J Am Acad Dermatol* 2014;70:e139-e140.
151. Mendlowicz MV, Lima JL, Fontenelle LF. Aquagenic pruritus induced by clomipramine. *Gen Hosp Psychiatry.* 2013;35:577.e3-e4.
152. Lelonek E, Szepietowski JC. Aquagenic pruritus: first manifestation of polycythemia vera. *Dermatol Open J* 2016;1:3-5.
153. Lelonek E, Matusiak Ł, Wróbel T, et al. Aquagenic pruritus in polycythemia vera: a cross-sectional study. *J Am Acad Dermatol* 2017, https://doi.org/10.1016/j.jaad.2017.10.021. [Epub ahead of print].
154. Lelonek E, Matusiak Ł, Wróbel T, et al. Burden of aquagenic pruritus in polycythaemia vera. *Acta Derm Venereol* 2018;98:185-190.
155. Tefferi A. Primary myelofibrosis: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2014;89:916-925.
156. Vaa BE, Wolanskyj AP, Roeker L, et al. Pruritus in primary myelofibrosis: clinical and laboratory correlates. *Am J Hematol* 2012;87:136-138.
157. Vaa BE, Tefferi A, Gangat N, et al. Pruritus in primary myelofibrosis: management options in the era of JAK inhibitors. *Ann Hematol* 2016;95:1185-1189.
158. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375-2390.
159. Rubenstein M, Duvic M. Cutaneous manifestations of Hodgkin's disease. *Int J Dermatol* 2006;45:251-256.
160. Gobbi PG, Attardo-Parrinello G, Lattanzio G, et al. Severe pruritus should be a B-symptom in Hodgkin's disease. *Cancer* 1983;51:1934-1936.
161. Omidvari S, Kholasteh HN, Mohhamadianpanah M, et al. Long-term pruritus as the initial and sole clinical manifestation of occult Hodgkin's disease. *Indian J Med Sci* 2004;58:250-252.
162. Olsson H, Brandt L. Relief of pruritus as an early sign of spinal cord compression in Hodgkin's disease. *Acta Med Scand* 1979;206:319-320.
163. Stadie V, Marsch WCH. Itching attacks with generalized hyperhydrosis as initial symptoms of Hodgkin's disease. *J Eur Acad Dermatol Venereol* 2003;17:559-561.
164. Carlesimo M, Narcisi A, Rossi A, et al. Cutaneous manifestations of systemic non-Hodgkin lymphomas (NHL): study and review of literature. *J Eur Acad Dermatol Venereol* 2014;28:133-141.
165. Vij A, Duvic M. Prevalence and severity of pruritus in cutaneous T cell Lymphoma. *Int J Dermatol* 2012;51:930-934.
166. Demierre MF, Gan S, Jones J, et al. Significant impact of cutaneous T-cell lymphoma on patients' quality of life. Results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer* 2006;107:2505-2511.
167. Wright A, Wijeratne A, Hung T, et al. Prevalence and severity of pruritus and quality of life in patients with cutaneous T-cell lymphoma. *J Pain Symptom Manag* 2013;45:114-119.
168. Weisshaar E, Weiss M, Mettang T, et al. Paraneoplastic itch: an expert position statement from the Special Interest Group (SIG) of the International Forum on the Study of Itch (IFSI). *Acta Derm Venereol* 2015;95:261-265.
169. Kremer AE, Feramisco J, Reeh PW, et al. Receptors, cells and circuits involved in pruritus of systemic disorders. *Biochim Biophys Acta* 1842;2014:869-892.
170. Paul R, Paul R, Jansen CT. Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. *J Am Acad Dermatol* 1987;16:1179-1182.
171. Kılıç A, Gül Ü, Soylu S. Skin findings in internal malignant diseases. *Int J Dermatol* 2007;46:1055-1060.
172. Fett N, Haynes K, Propert KJ, et al. 5-Year malignancy incidence in chronic pruritus patients: a population-based cohort study aimed at limiting unnecessary screening practices. *J Am Acad Dermatol* 2014;70:651-658.
173. Larson VA, Tang O, Ständer S, et al. Association between itch and cancer in 16,925 pruritus patients: experience at a tertiary care center. *J Am Acad Dermatol* 2019;80:931-937.
174. Yosipovitch G. Chronic pruritus: a paraneoplastic sign. *Dermatol Ther* 2010;23:590-596.
175. UNAIDS. UNAIDS data 2018. Available at:http://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf. Accessed January 10, 2019.
176. Singh F, Rudikoff D. HIV-associated pruritus etiology and management. *Am J Clin Dermatol* 2003;4:177-188.
177. Milazzo F, Piconi S, Trabattoni D, et al. Intractable pruritus in HIV infection: immunologic characterization. *Allergy* 1999;54:266-272.
178. Blanes M, Belinchon I, Portilla J, et al. Pruritus in HIV-infected patients in the era of combination antiretroviral therapy: a study of its prevalence and causes. *Int J STD AIDS* 2012;23:255-257.
179. Kaushik SB, Cerci FB, Miracle J, et al. Chronic pruritus in HIV-positive patients in the southeastern United States: its prevalence and effect on quality of life. *J Am Acad Dermatol* 2014;70:659-664.
180. Tebruegge M, Kuruvilla M, Marfarson I. Does the use of calamine or antihistamine provide symptomatic relief from pruritus in children with varicella zoster infection? *Arch Dis Child* 2007;91:35-36.
181. Özdemir M, Tüzün Y. Herpes zoster and pruritus. *Int J Dermatol* 2004;43:779-780.
182. Thomas EA, John M, Bhatia A. Cutaneous manifestations of dengue viral infection in Punjab (north India). *Int J Dermatol* 2007;46:715-719.
183. Cunha BA, Leonichev VB, Raza M. Chikungunya fever presenting with protracted severe pruritus. *IDCases* 2016;6:29-30.
184. Veletzky L, Knafl D, Schuster C. Zika virus-induced itching eruption in a returning traveller from Brazil. *Int J Inf Dis* 2017;54:13-14.
185. Janier M, Hegyi V, Dupin N, et al. European guideline on the management of syphilis. *J Eur Acad Dermatol Venereol* 2014;28:1581-1593.
186. Highman WJ. Itching in syphilis. *Arch Dermatol Syphilol* 1922;5:63-68.
187. Cole GW, Amon RB, Russell PS. Secondary syphilis presenting as a pruritic dermatosis. *Arch Dermatol* 1977;113:489-490.
188. Cervoni GE, By CC, Wesson SK. An atypical syphilis presentation. *Cutis* 2017;100:E25-E28.
189. Kandyil R, Satya NS, Swerlick RA. Chronic pruritus associated with *Helicobacter pylori*. *J Cutan Med Surg* 2002;6:103-108.
190. Shiotani A, Sakurane M, Furukawa F. Helicobacter pylori-positive patients with pruritic skin diseases are at increased risk for gastric cancer. *Aliment Pharmacol Ther* 2004;20:80-84.

191. Gavignet B, Piarroux R, Aubin F, et al. Cutaneous manifestations of human toxocariasis. *J Am Acad Dermatol* 2008;59:1031-1042.
192. Olumide YM, Oresanya F. Generalized pruritus as a presenting symptom in Nigeria. *Int J Dermatol* 1987;26:171-173.
193. Niklasson O, Boman K, Stenberg B. The prevalence and characteristics of pruritus in patients with heart failure. *Br J Dermatol* 2015;172:1541-1546.
194. Ponikowska M, Biegus J, Zymliński R, et al. Pruritus in patients with acute heart failure, 9th World Congress on Itch, October 15-17, 2017, Wroclaw. *Poland Acta Derm Venereol* 2017;97:PP68.
195. Matsubara T, Sato T, Ohnishi S, et al. Pacemaker dermatitis induced by backpack strap friction. *Am J Med* 2015;128:e1-e2.
196. Raja Y, Desai PV, Glennon PE. Pacemaker-mediated dermatitis. *EP Europace* 2008;10:1354.
197. Kilit C, Amasyali B, Astarcioglu MA, et al. Is pruritus over the pacemaker pocket may be a sign of a serious complication? *Int J Cardiovasc Acad* 2015;1:24-25.
198. Mohiyiddeen G, Brett I, Jude E. Infective endocarditis caused by Staphylococcus aureus in a patient with atopic dermatitis: a case report. *J Med Case Rep* 2008;2:143.
199. Micallef MJ, Ramphul A. Infective endocarditis in a patient with atopic dermatitis. *JC Cases* 2016;13:153-154.
200. Orr AW. Prodromal itching in asthma. *J R Coll Gen Pract* 1979;29:287-288.
201. Shneerson J. Non-respiratory symptoms of acute asthma. *Thorax* 1986;41:701-702.
202. Goldberg A, Lang A, Mekori YA. Prolonged generalized pruritus associated with selective elevation of IgA as the presenting symptoms of sarcoidosis. *Ann Allergy Asthma Immunol* 1995;74:387-389.
203. Yogarajah M, Sivasambu B, Aina O. Intractable pruritus: do we think of pulmonary sarcoidosis? *Chest* 2015;148:629A.
204. Sharma OP, Balchum OJ. Alcohol-induced pain and itching on hot-shower in sarcoidosis. *Am Rev Respir Dis* 1972;106:763-766.
205. Kansal HM, Goel S. Cutaneous manifestations in cases of pulmonary tuberculosis: a clinical profile. *JIACM* 2013;14:284-286.
206. Taeb A, Cheriyath P. Generalized pruritus as the primary symptom of pulmonary tuberculosis. *Am J Respir Crit Care Med* 2015;191: A3263.
207. Saporito L, Florena AM, Colomba C, et al. Prurigo nodularis due to Mycobacterium tuberculosis. *J Med Microbiol* 2009;58: 1649-1651.