

Itching as a systemic disease



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Pruritus is a sensation that emanates from the skin and is transferred through peripheral nerve fibers to the central nervous system. It is easily understood that primary skin disorders, such as atopic eczema, skin dryness, psoriasis, and urticaria, can elicit pruritus. However, certain systemic diseases can cause chronic pruritus, which has a significant effect on the patient's quality of life. In this rostrum we provide an overview of the characteristics, pathophysiology, and mechanisms of pruritus of major systemic underlying diseases, including end-stage renal disease, cholestatic liver disease, endocrine/metabolic diseases, and hematologic/lymphoproliferative diseases. (*J Allergy Clin Immunol* 2019;144:375-80.)

Key words: *Itch, pruritus, systemic disease*

Pruritus, also known as itch, is defined as an unpleasant sensation that results in an urge to scratch. In the last 2 decades, our understanding of the neurobiology of pruritus has been significantly advanced.¹ Numerous pruritogens have been discovered in the skin that activate their cognate receptors. Two major pathways of itch transmission through group C nerve fibers have been discovered, including histaminergic and nonhistaminergic pathways, and the latter were found to have a more pronounced effect in most types of chronic itch. Spinal pathways of itch sensation and brain areas where itch is processed have been elucidated. The molecular mechanisms of itch in patients with primary skin diseases, such as atopic dermatitis and psoriasis, have been reported, and new treatments have been developed.¹

In contrast, the underlying mechanisms and management of pruritus in patients with systemic diseases has been less explored. Of note, this type of pruritus is usually not accompanied by primary skin lesions, but scratching can cause secondary skin lesions, including excoriation, eczematous lesions, prurigo nodules, and lichenification. The objective of this rostrum is to provide an up-to-date overview of the pathophysiology of major

Abbreviations used

ATX: Autotaxin
CTCL: Cutaneous T-cell lymphoma
ESRD: End-stage renal disease
JAK: Janus kinase
KOR: κ -Opioid receptor
LPA: Lysophosphatidic acid
MOR: μ -Opioid receptor
MPN: Myeloproliferative neoplasm
Mrgpr: Mas-related G protein-coupled receptor
OCA: Obeticholic acid
PBC: Primary biliary cirrhosis
PTH: Parathyroid hormone
PV: Polycythemia vera
TGR5: Takeda G protein-coupled receptor type 5
TRP: Transient receptor potential

types of pruritus associated with underlying systemic diseases (Figs 1 and 2).

END-STAGE RENAL DISEASE

Pruritus is a common symptom in patients with end-stage renal disease (ESRD) or advanced chronic kidney disease. It is generally defined as pruritus that appears shortly before the onset of dialysis or at any time after that, without evidence of any other active disease that could explain the pruritus. It is more prevalent in patients undergoing hemodialysis than in those undergoing peritoneal dialysis. The estimated prevalence of ESRD-related pruritus in patients ranged between 22% and 57% in the last decade.² In the Dialysis Outcomes and Practice Patterns Study, which has been the largest epidemiologic study with more than 18,000 patients with ESRD undergoing hemodialysis, moderate-to-extreme pruritus was experienced by 42% of patients undergoing dialysis. Large differences in pruritus were noted between countries and facilities.³ The most commonly affected areas are the back, limbs, chest, and head, even though up to 50% patients reported generalized pruritus.³ Pruritus in patients undergoing hemodialysis is also associated with a greater mortality risk.³ The causes of ESRD-related pruritus are still unclear, but several factors are postulated to be involved.

Endogenous opioid system imbalance hypothesis

The opioid hypothesis proposes that imbalances in expression of μ -opioid receptors (MORs) and κ -opioid receptors (KORs) cause ESRD-related pruritus.⁴ In patients with ESRD-related pruritus undergoing hemodialysis, plasma levels of β -endorphin are greater compared with those in patients without pruritus or healthy control subjects. The ratio of β -endorphin to dynorphin-A is also increased when itch intensity increases.⁵ Animal studies showed that helix-loop-helix family member

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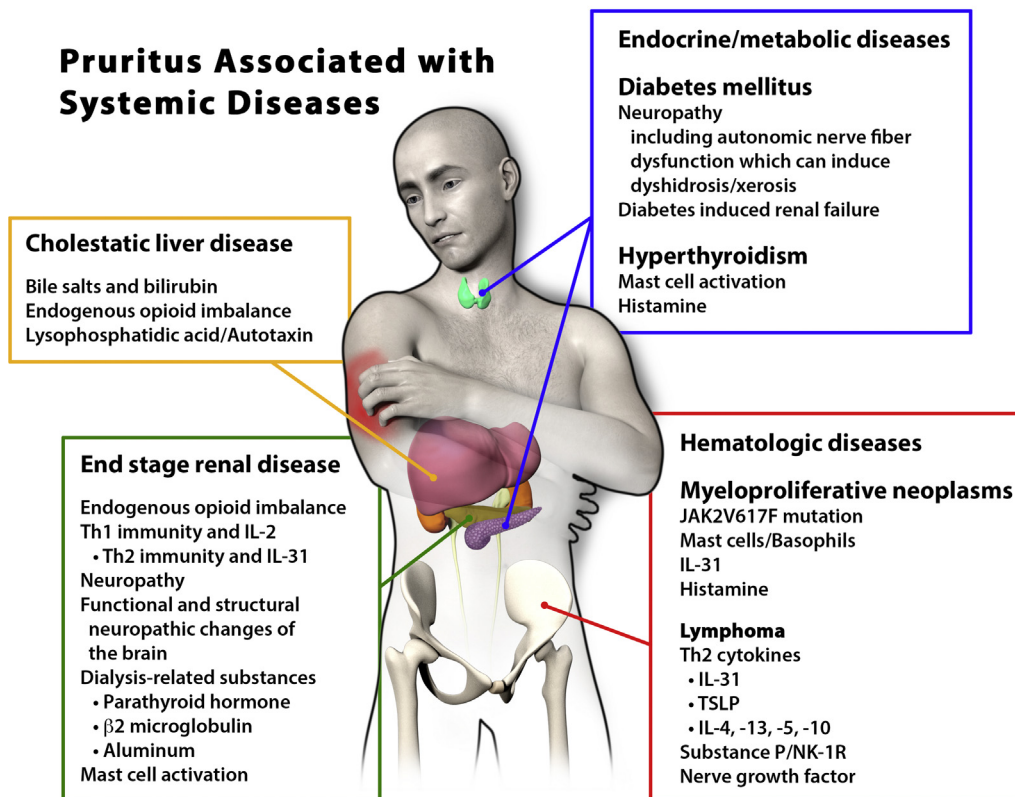


FIG 1. Systemic diseases and pruritus. Many systemic diseases are accompanied by pruritus, and putative factors are involved in pruritus in patients with these systemic diseases. *NK-1R*, Neurokinin 1 receptor.

B5-positive neurons, which are itch-inhibitory neurons, secrete dynorphin-A in the spinal cord. Dynorphin-A exerts its itch-inhibitory function through binding KORs on gastrin-releasing peptide receptor-positive neurons, which transmit the itch sensation. This inhibitory effect is antagonized by MORs, and a representative MOR ligand is β -endorphin.¹ Imbalances in the endogenous opioidergic system and in activation status of MORs and downregulation of KORs are considered to lead to ESRD-related pruritus. In an 8-week, randomized, double-blind, placebo-controlled multicenter trial, nalbuphine (an MOR antagonist and KOR agonist) decreased pruritus, with a meaningful itch reduction of 3.5 on a numeric rating scale.⁶ A KOR agonist, CR845/difelikefalin, is also in a phase 3 clinical trial in the United States.

Alternation of immune status

Another major hypothesis for ESRD-related pruritus is the immunohypothesis. The T_H1 immune response is considered predominant in patients with ESRD-related pruritus. Numbers of T_H1 cells and serum levels of IL-2, a T_H1 -related cytokine, are significantly increased in patients with ESRD-related pruritus undergoing hemodialysis compared with those without pruritus.⁷ UVB phototherapy, one of the effective therapies, are shown to attenuate T_H1 lymphocyte differentiation and hence reduce IL-2 generation.⁸ However, how IL-2 elicits itch is still uncertain.

T_H2 immunity can also be involved in patients with ESRD-related pruritus. IL-31 is an itch-related cytokine

and is produced mainly by activated T_H2 cells.⁹ One article suggested that serum levels of IL-31 were greater in patients with ESRD-related pruritus than in those without pruritus symptoms and were correlated with itch intensity.¹⁰ However, as mentioned above, ESRD-related pruritus is generally considered to be skewed toward T_H1 , and cellular sources of IL-31 in patients with ESRD are to be determined.

Neuropathy

Many patients with ESRD have neuropathy, which is known as uremic neuropathy. There is a significant correlation between paresthesia and ESRD-related pruritus. Itch intensity in patients with ESRD-related pruritus is also correlated with the occurrence of restless leg syndrome, which is thought to be a symptom of uremic neuropathy.¹¹

Functional and structural changes in the brain

Functional and structural changes in the brain are also important factors for patients with ESRD-related pruritus.¹² We have shown that perpetuation of itch in patients with ESRD can lead to modulation of the activation status of itch-related brain areas (eg, anterior cingulate cortex, insula, claustrum, hippocampus, and nucleus accumbens) and alternation of brain connectivity. We also showed that chronic pruritus can decrease gray matter density in the itch-related cortical areas (eg, the frontal, parietal, temporal, and occipital cortices, as well as the primary

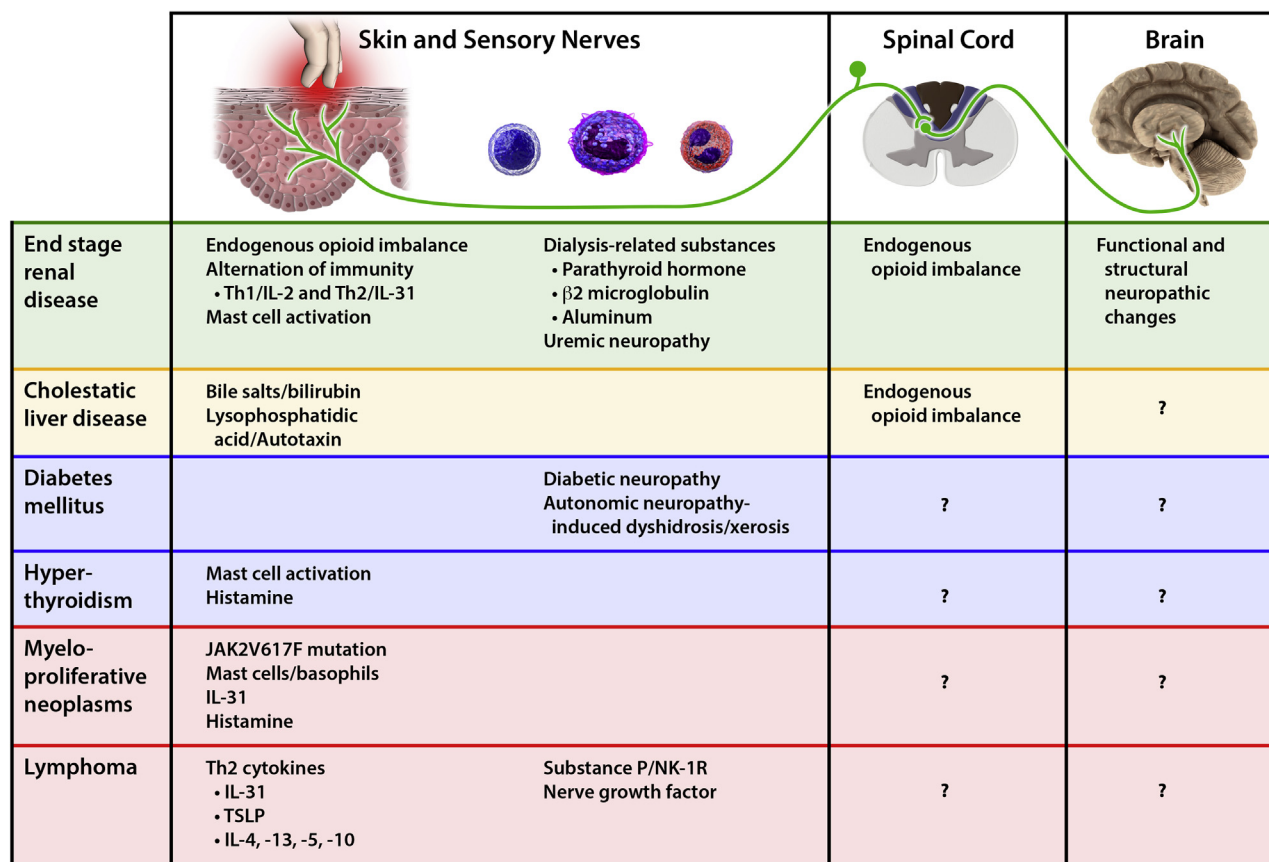


FIG 2. Systemic diseases and itch pathway. Systemic diseases affect itch mediators in the skin and spinal cord. Alternation of nerve fibers (neuropathy) and the brain can also develop because of systemic diseases. ?, Unknown; *NK-1R*, neurokinin 1 receptor.

somatosensory cortex, precuneus, and insula) and increase gray matter density in the brainstem, hippocampus, amygdala, midcingulate cortex, and nucleus accumbens. Furthermore, responses of the brain to nonhistaminergic itch stimuli, which mimic chronic itch, differ significantly from those of healthy control subjects and are correlated with perceived itch intensity.¹²

Others

Parathyroid hormone (PTH) abnormalities caused by secondary hyperparathyroidism are often detected in patients undergoing hemodialysis. Parathyroidectomy for secondary hyperparathyroidism is reported to improve uremic itch intensity.¹³ However, levels of PTH, PTH-related divalent ions (eg, calcium and phosphate ions), and calcium-phosphate products are not necessarily correlated with itch severity.

β 2-Microglobulin is an MHC class I molecule, and patients undergoing hemodialysis have high serum levels of β 2-microglobulin, which sometimes result in dialysis-associated β 2-microglobulin amyloidosis. A recent report showed that β 2-microglobulin elicited scratching behavior in mice, partially through affecting peripheral nerve fibers expressing transient receptor potential (TRP) vanilloid 1, an ion channel involved in itch conduction. This scratching behavior was not attenuated by histamine H1 receptor antagonists.¹⁴

A recent large study demonstrated that patients undergoing hemodialysis with greater serum aluminum levels had a greater

prevalence of ESRD-related pruritus than those with lower aluminum levels. Overall, each 10-fold increase in serum aluminum level was associated with a 5.64-fold increase in the risk of ESRD-related pruritus.¹⁵

Mast cells also partially participate in ESRD-related pruritus. In patients undergoing hemodialysis, numbers of dermal mast cells are increased. In addition, plasma levels of mast cell tryptase are also increased and associated with itch severity.¹⁶ Histamine is a major pruritogen from mast cells, but antihistamines in the majority of cases do not reduce ESRD-related pruritus. Thus mediators other than histamine can be implicated in uremic itch.

CHOLESTATIC LIVER DISEASE

Cholestatic pruritus is caused by a variety of liver diseases with cholestasis (eg, primary biliary cirrhosis [PBC], primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, or hereditary pediatric cholestatic disorders). About 70% of patients with cholestasis report pruritus over the course of these diseases.¹⁷ Cholestatic pruritus typically occurs at the soles and limbs of the feet and palms of the hands, but it also can be generalized.¹⁷ In patients with PBC, cholestatic pruritus can occur before jaundice becomes apparent.

In patients with cholestasis pruritus, high serum/plasma levels of multiple factors are noted, including bile salts, endogenous opioids, lysophosphatidic acid (LPA) and its synthetic enzyme

autotaxin (ATX), histamine, and bilirubin. They seem to be involved in itch, either directly or indirectly.

Bile salts

Bile salts are able to bind to their receptor, Takeda G protein-coupled receptor type 5 (TGR5; also known as G protein-coupled bile acid receptor 1). TGR5 is expressed by neurons in the dorsal root ganglia. TGR5⁺ neurons also express TRP vanilloid 1, TRP ankyrin 1, and gastrin-releasing peptide, all of which are itch mediators involved in itch conduction on sensory nerves. Bile salts can activate these neurons *ex vivo*, and intradermal injection of bile salts can induce scratching behavior in mice.¹⁸ Collectively, bile salts seem to be involved in cholestatic itch, but correlation has not been found yet between serum levels of bile salts and itch intensity in human subjects.¹⁹ TGR5 is also pointed out to be activated by neurosteroids more than bile salts in the central nervous system, which might modulate itch perception.¹⁹

Obeticholic acid (OCA) is a farnesoid X receptor agonist, the ligand of which is bile salts. OCA has shown potential benefit in patients with PBC or nonalcoholic steatohepatitis through reducing liver fat and fibrosis. In clinical trials pruritus was noted as the most common adverse effect with a prevalence of up to 77% in patients with PBC, which sometimes results in discontinuation of OCA.²⁰

Bilirubin

Recently, Meixiong et al²¹ showed that bilirubin can elicit an itch sensation by directly stimulating peripheral nerve fibers through mouse Mas-related G protein-coupled receptor (Mrgpr) A1 or human MrgprX4 receptors. Intradermal injection of bilirubin elicited scratching behavior in mice, and this behavior was abolished in mice treated with an MrgprA1 antagonist or in MrgprA1 knockout mice. Interestingly, the number of scratching bouts was correlated with skin levels of bilirubin but not with serum levels of bilirubin.

Endogenous opioid system imbalance

Livers accumulate and excrete opioids, and liver damage can lead to greater plasma levels of opioids. Some, but not all, patients with cholestatic itch show increased μ -opioid activities compared with healthy control subjects measured based on levels of (D-Ala(2)-mephe(4)-gly-ol(5))enkephalin (DAMGO; a synthetic μ -opioid agonist) equivalents.²² Enhanced activation of MORs and deactivation of KORs can elicit and/or amplify itch sensation (also see the “End-stage renal disease” section).¹ A KOR agonist, nalfurafine, is reported to improve cholestatic itch.²³ Collectively, alternation of the endogenous opioid system can, at least partially, participate in cholestatic pruritus. No reports have clearly shown the correlation between plasma concentrations of endogenous opioids and itch intensity.¹⁹

LPA

LPA and its enzyme ATX have been proposed in the last decade as pruritogens in patients with cholestatic pruritus.²² ATX activity and LPA concentrations in blood are enhanced in patients with cholestasis and correlate with itch intensity. Supporting the role of LPA in cholestatic itch, there is a report suggesting that therapeutic interventions (eg, molecular adsorbent recirculation system or nasobiliary drainage) reduce ATX activity concomitantly

with itch severity.¹⁹ In animal studies intradermal injection of LPA induces scratching behavior in mice in a dose-dependent manner. In addition, LPA is shown to be able to activate sensory neurons through LPA receptor type 5, TRP vanilloid 1, and TRP ankyrin 1.²⁴

ENDOCRINE/METABOLIC DISEASES

Patients with diabetes mellitus often complain of pruritus (diabetes-associated pruritus), and its prevalence is estimated to be from 12.7% to 49%. The pruritus is usually localized, but it can become generalized. Typical affected areas of diabetes-associated pruritus are the scalp, trunk, ankles, feet, and genitals. Pruritus more likely occur in patients with diabetic neuropathy.²⁵ Other causes of diabetes-associated pruritus include diabetes-induced renal failure and autonomic nerve fiber dysfunction (resulting in anhidrosis and dry skin).

Patients with hyperthyroidism, but not hypothyroidism, can have pruritus. There is no apparent correlation between the prevalence of pruritus in patients with hyperthyroidism and the levels of serum free T4 or the autoantibody against the thyroid. The mechanisms are still unclear, but it is postulated that cell-mediated immunity might play a role, which could decrease the mast cell threshold for peptide release, including histamine.²⁶ Of note, antihistamines do not necessarily improve pruritus associated with hyperthyroidism.

HEMATOLOGIC DISEASES

Myeloproliferative neoplasms

Pruritus is one of the most common symptoms associated with myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythosis, and primary myelofibrosis. Patients with MPNs, especially those with PV, often display a characteristic pruritus that occurs on exposure to water within a few minutes (aquagenic pruritus), and the prevalence of aquagenic pruritus in patients with PV is estimated at up to 70%. Aquagenic pruritus is accompanied by intense itching, burning, prickling, warming, stinging, and/or tingling sensations without apparent skin changes. The most common locations of aquagenic pruritus are the upper and lower limbs. Hot water can elicit a more intense itch sensation than cold water. Of note, the onset of aquagenic pruritus often precedes the diagnosis of MPNs.²⁷

The pathogenesis of aquagenic pruritus is unclear, but a gene mutation, mast cells, and basophils are considered to play roles.²⁸⁻³⁰

The Janus kinase (JAK) 2 gain-of-function mutation (*JAK2V617F*) is thought to be involved in the pathogenesis of PV and other MPNs. This mutation is found in 95% of patients with PV and in more than 50% of patients with essential thrombocythosis or primary myelofibrosis. Mutation burden is correlated with the occurrence of aquagenic pruritus.³⁰ In addition, the JAK1/2 inhibitor ruxolitinib improves pruritus in patients with PV.³¹

In human subjects mast cells from patients with MPNs show an increased migratory ability and decreased apoptosis. Mast cells are able to secrete various pruritogens, including histamine, leukotrienes, proteases, and IL-31.²⁸ Plasma IL-31 levels are correlated with pruritus in MPNs.²⁸ Mice expressing the *JAK2V617F* mutation display PV-like phenotypes and experience scratching behavior. In these mice mast cells accumulated in the

skin and skin levels of histamine were increased. Mast cells from these mice exhibited enhanced proliferative signals and resistance to cell death.³²

Basophils, which share some morphologic and functional similarities with mast cells, might also be involved in pruritus in patients with MPNs.²⁹ Patients with aquagenic pruritus have significant peripheral basophilia. In addition, the JAK2 inhibitor attenuates basophil activation. However, it is suggested that peripheral basophil counts do not correlate with pruritus in patients with MPNs.³³

Lymphoma

Pruritus is also a common symptom in patients with lymphoma, both Hodgkin lymphoma and non-Hodgkin lymphoma, and the prevalence of pruritus is around 15% and 25%, respectively.³⁴ Notably, in patients with Hodgkin lymphoma, itch severity is correlated with an advanced stage and might be an indicator of poor prognosis.³⁵ The pathogenesis of pruritus in lymphoma is still uncertain. It is reported that Hodgkin and Reed-Stenberg cells and infiltrating immune cells expressed the T_H2-related pruritogenic cytokine IL-31⁹ and thymic stromal lymphopoietin (TSLP). They also expressed receptors for IL-31, TSLP, or both. These factors did not correlate with the presence of pruritus or with itch severity. However, IL-31 and TSLP can affect eosinophils, mast cells, neutrophils, and basophils. All of these cells are part of the tumor environment in patients with Hodgkin lymphoma and also implicated in those with pruritus.^{29,36-38}

Cutaneous T-cell lymphoma (CTCL) is also accompanied by pruritus, and up to 88% of patients with CTCL complain of pruritus. Patients with advanced-stage CTCL have more severe itch than those with early-stage disease.³⁹

IL-31 is a putative pruritogen in patients with CTCL. Serum levels of IL-31 are greater in patients with CTCL compared with those in healthy control subjects. IL-31 is reported to be produced by the malignant T-cell population, which also express chemokine receptor type 4, and its levels correlate with itch intensity.⁴⁰ Skin expression levels of IL-31 and its receptors (IL-31RA and oncostatin M receptor β) are also greater and correlated with itch intensity.⁴¹ Dexamethasone and histone deacetylase inhibitors (vorinostat and romidepsin) can reduce itch intensity through decreasing numbers of IL-31-expressing T cells.⁴²

Other T_H2-related cytokines than IL-31 can also play a role. Patients with CTCL, especially late-stage CTCL, generally show T_H2 immune responses.⁴³ Patients with CTCL have greater serum levels of IL-4, IL-13, IL-5, and IL-10. These cytokines increase serum IgE levels and induce mast cell degranulation. Patients with mycosis fungoides, one of the most common forms of CTCL, exhibit marked infiltration of mast cells in the affected skin.⁴⁴ IL-4 and IL-13 are also able to directly stimulate peripheral nerve fibers through IL-4 receptor α and JAK1 signaling.⁴⁵

Substance P and its receptor, neurokinin 1 receptor, are also considered to be involved in CTCL-related pruritus. High levels of substance P in keratinocytes were associated with CTCL-related pruritus, and the neurokinin 1 receptor antagonist aprepitant was reported to improve CTCL-related pruritus in case series.⁴⁶ However, a recent controlled study did not demonstrate an antipruritic effect in patients with an advanced stage of CTCL.⁴⁷

Nerve growth factor, which is secreted mainly by epidermal keratinocytes and eosinophils and is involved in pruritus by

increasing sensory nerve sensitivity, has also been reported to be involved in patients with CTCL-related pruritus.⁴⁸

GENERALIZED PRURITUS OF UNSPECIFIED ORIGIN

There is a substantial population for whom no identifiable cause of itch can be found. In a retrospective analysis from a single itch center, 11% (63/597) of patients with a complaint of chronic pruritus had pruritus of unspecified origin.⁴⁹ It is usually a diagnosis of exclusion, and there is currently no standard terminology used to describe this group of patients. Many of these patients are older and have severe chronic itching. These patients often have pruritus for years without receiving adequate relief. The International Forum on the Study of Itch recommends using "chronic pruritus of undetermined or unknown origin" to describe "chronic pruritus with no finding of the underlying origin following completion of diagnostic tests."⁵⁰

CONCLUSION

Several systemic diseases can cause pruritus, and our understanding about mechanisms underlying systemic disease-associated pruritus are continuing to evolve. Itch in patients with systemic diseases is not necessarily inflammatory or allergic, and many factors, such as neural factors and mediators other than inflammatory and/or allergic components, might also be involved. New treatments that target some of the mediators involved (eg, opioids, substance P, itchy cytokines [eg, IL-31], and the JAK/signal transducer and activator of transcription signaling pathway), as well as drugs that target neuropathic damage, will enable us to better treat systemic pruritus.

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