

## Pruritus: A Sign of Underlying Disease

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**P**ruritus is defined as a cutaneous sensation that provokes the desire to scratch. It is intended to serve a protective function to remove pruritogenic stimuli (eg, insect, poison ivy, metals). Pruritus is a common manifestation of dermatologic conditions including xerotic eczema (ie, dry skin), atopic dermatitis, and contact dermatitis but may also result from systemic diseases. Up to 50% of patients who have pruritus without an obvious dermatologic cause also have an underlying systemic disease process, such as renal insufficiency, cholestasis, a hematologic disorder, or malignancy.<sup>1</sup> Persistent pruritus not otherwise explained by an obvious dermatologic condition should prompt an investigation for an underlying systemic cause.

### PATHOPHYSIOLOGY

All cases of pruritus cannot be explained by one single mechanism. Pruritus originates in the terminal nerve endings within the skin<sup>2</sup> and can be elicited by inflammation, dryness, contact exposure, and other allergic responses. In allergic responses, histamine is the classic mediator; however, this is not always the case. In other conditions in which pruritus is a manifestation, such as chronic kidney disease, cholestasis, and lymphoma, serotonin may play a role.<sup>3,4</sup> Serotonin excites nociceptive C-fibers, which in turn produces an itch. Marked elevations in serotonin levels have been found in dialysis patients with pruritus.<sup>5</sup>

### CAUSES OF PRURITUS

A thorough history and physical examination is essential in the evaluation of pruritus. Many dermatologic conditions are evident by characteristic rashes and distribution of itching. A systemic process rarely causes localized itching. In a retrospective study of 50 patients that attempted to determine how frequently pruritus of unknown origin was systemic, 11 patients had a systemic cause of pruritus.<sup>1</sup> Of these 11 patients, 7 had pruritus as their initial symptom of systemic disease, and liver disease was the most common underlying cause.<sup>1</sup>

### GENERAL PRINCIPLES OF PRURITUS

- Defined as a cutaneous sensation that provokes the desire to scratch.
- All cases cannot be explained by one single mechanism.
- Localized itching is rarely caused by a systemic process.
- The itch of dry skin, or xerosis, occurs most often during winter.
- Can be a sign of underlying disease in up to 50% of cases.
- May precede the development of a disease by several years.

### Dermatologic Causes

Common dermatologic causes of pruritus include xerosis, atopic dermatitis, contact dermatitis, eczema, folliculitis, psoriasis, and drug eruption. Xerosis is a common cause of pruritus, especially during the winter months, and is usually a result of increased bathing frequency and use of strong soaps. In fact, a study by Thaïpisuttikul<sup>6</sup> noted xerosis to be the most common cause of pruritus. Areas most commonly affected include the lower legs, back, and abdomen. Xerosis can exist alone or occur in combination with another process. Atopic dermatitis is a common, chronic skin condition characterized by xerosis, pruritus, and inflammation and is most common among persons affected by asthma and allergic rhinitis. Contact dermatitis requires exposure to exogenous substances (eg, poison ivy, nickel, latex) that results in a pruritic reaction. Eczema and dermatitis are sometimes used synonymously to denote a pattern of skin inflammation characterized by erythema and pruritus. Folliculitis is characterized by papules and pustules scattered commonly on the chest, back,

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**Table 1.** Systemic Causes of Pruritus

<b>Hepatic</b>	<b>Endocrine</b>
Cholestasis (eg, primary biliary cirrhosis, pregnancy, oral contraceptives)	Thyroid diseases
Hepatitis	Carcinoid syndrome
<b>Renal</b>	<b>Malignant</b>
Chronic renal failure	Solid tumors
<b>Hematologic</b>	Lymphomas
Polycythemia vera	Leukemias
Iron deficiency anemia	<b>Other</b>
	AIDS
	Drugs (eg, opioids)

and thigh regions. Psoriasis has characteristic plaques on extensor surfaces. Various rashes are known to produce an itch, probably through excitation of C-fibers in the skin. Drug eruptions may present as an urticarial or maculopapular rash, and itch is common. Drug reactions are idiosyncratic because they are unpredictable based on the pharmacology of the drug. A detailed drug history is essential, and prior drug exposure is key. The time to onset with a new drug exposure can be as short as 7 days.<sup>7</sup>

### Systemic Causes

Pruritus can be an important sign of a significant underlying disease in up to 50% of cases.<sup>1</sup> Pruritus may precede the development of a disease by several years.<sup>8</sup> Renal, hepatic, and malignant causes are common systemic processes that may manifest as pruritus (**Table 1**). Physical examination of the skin, lymph nodes, liver, and spleen is imperative in assessing for an underlying cause.

**Cholestasis.** Pruritus is a well-established sign of cholestasis. The pathogenesis of pruritus in cholestasis is poorly understood, and discussion of existing hypotheses is beyond the scope of this article. Primary biliary cirrhosis is a classic example of a pruritogenic cholestatic condition. Other causes of cholestasis include pregnancy, oral contraceptives, and biliary obstruction. Other hepatic processes, such as hepatitis, may have cholestasis as a component even though it is not the major manifestation, and these processes are associated with specific hepatic enzyme abnormalities on biochemical testing. The hepatic pattern (elevated serum levels of alanine aminotransferase and aspartate aminotransferase) is seen in viral hepatitis, drug toxicity, ischemia, Wilson's disease, hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, and autoimmune hepatitis. The cholestatic pattern (abnormalities of serum alkaline

phosphatase and  $\gamma$ -glutamyltransferase) is seen in biliary obstruction (eg, stone, stricture, tumor, chronic pancreatitis), drug toxicity, primary biliary cirrhosis, and primary sclerosing cholangitis. However, hepatic or cholestatic patterns are rarely isolated; rather, hepatic enzyme abnormalities are usually mixed.

Cholestasis is caused by any condition in which bile excretion from the liver is blocked, which can occur either in the liver (intrahepatic) or in the bile ducts (extrahepatic). Extrahepatic cholestasis can be caused by stones in the common bile duct, bile duct tumors, pancreatitis, pancreatic tumors and pseudocysts, primary sclerosing cholangitis, bile duct strictures, and bile duct compression due to a mass on a nearby organ (eg, gastric tumor). Intrahepatic cholestasis can be caused by primary biliary cirrhosis, viral hepatitis, alcoholic liver disease, pregnancy, and drug toxicity.

**Malignancy.** In cancer patients, pruritus may be directly or indirectly related to the malignancy. Indirect associations occur when cholestasis is a manifestation of the cancer (eg, pancreatic cancer, hepatic metastasis) or when pruritus occurs as a result of cancer treatments. Alternatively, pruritus may be an early sign of pancreatic cancer.<sup>9</sup> Pancreatic cancer usually does not cause definitive symptoms until survival is severely compromised.<sup>9</sup>

The frequency, intensity, and prognostic significance of pruritus was evaluated in 360 patients with Hodgkin's disease. Ninety patients had mild itching on admission and showed the same survival rate as the 249 nonpruritic cases; the remaining 21 patients who presented with severe pruritus had a shorter survival rate than patients with mild pruritus or patients without pruritus.<sup>10</sup> Long-term pruritus can be the initial clinical manifestation of occult Hodgkin's disease.<sup>8</sup> Pruritus as a result of Hodgkin's disease is thought to be caused by release of histamine; although the mechanism is poorly defined, it has been reported to respond to H<sub>2</sub> blockers (eg, cimetidine).<sup>11,12</sup> Pruritus also may be a presenting manifestation in patients with cutaneous T-cell lymphoma.

**Hematologic disorders.** Polycythemia vera is a myeloproliferative disorder characterized by erythrocytosis that leads to an elevated hemoglobin and erythrocyte mass. Patients may present with pruritus that is most prominent after bathing,<sup>13</sup> erythromelalgia (burning pains of the distal extremities), and headaches as well as dizziness secondary to hyperviscosity. The major cause of mortality in polycythemia vera is thrombotic events. Phlebotomy is the mainstay of therapy for polycythemia vera, but myelosuppressive agents are also used. Symptomatic treatment of pruritus is accomplished with H<sub>1</sub>- and H<sub>2</sub>-blocking antihistamines. Erythromelalgia can be treated with aspirin.

Although rare, iron deficiency with or without anemia has also been reported as a cause of generalized pruritus.<sup>14</sup> The pathogenesis of pruritus due to iron deficiency is largely unknown. Iron deficiency–induced pruritus responds to and resolves with iron supplementation, which should be continued until iron stores return to normal. Signs of iron deficiency in addition to pruritus include glossitis and angular cheilitis.

**Endocrine disorders.** Pruritus can occur in patients with hyperthyroidism and may be due to the warm, moist skin that frequently accompanies hyperthyroidism; the exact reason why this occurs is unknown. Hyperthyroidism-associated pruritus may also occur as a result of cholestatic jaundice in some cases.<sup>15,16</sup> Rarely, pruritus accompanies hypothyroidism, which may be attributable to xerosis. Pruritus has also been associated with multiple endocrine neoplasia II (ie, Sipple's syndrome), in which parathyroid hyperplasia and elevated histamine levels are found.<sup>17</sup> Other reports of endocrinopathies associated with pruritus exist;<sup>18</sup> pruritus is known to be a paraneoplastic syndrome in other solid tumors. Treatment of the underlying disease typically resolves the pruritus.

### Overlapping Conditions

Some dermatologic causes of pruritus may overlap with systemic causes. Xerosis is common in chronic kidney disease and may be the major cause of pruritus in these patients.<sup>19</sup> Szepietowski et al<sup>19</sup> evaluated the frequency of uremic pruritus in hemodialysis patients, and a marked relationship was demonstrated between xerosis intensity and pruritus prevalence. Significantly more patients with very rough skin had pruritus compared with those with slightly dry skin. Other links between underlying diseases and pruritus have not been made, such as in cases of malignancy-associated pruritus, where the pathophysiology of pruritus is unknown.

In patients with AIDS, other pruritic dermatoses exist. Pruritus is one of the most common symptoms encountered in patients with HIV, and a skin rash can sometimes be the initial presentation of HIV infection. Causes of pruritus in HIV patients include primary dermatologic disorders, skin infections, infestations, photo-dermatitis, xerosis, and lymphoproliferative disorders. Drug eruptions (ie, allergic reactions) are also common in patients who are HIV positive. Itching can also result from systemic diseases that HIV-positive patients acquire, such as chronic kidney disease, liver disease, or systemic lymphoma.<sup>20</sup> In a study of 223 HIV-positive patients, the most frequently detected dermatoses were dermatoses of fungal etiology, desquamating disorders (eg, psoriasis), seborrheic dermatitis, xerosis, and viral derma-

**Table 2.** Treatment of Pruritus

#### Topical

Emollients (moisturizers)  
Cooling agents (eg, calamine lotion)  
Corticosteroids  
Doxepin  
Capsaicin  
Anesthetics (eg, lidocaine, benzocaine)

#### Systemic

Antihistamines (eg, hydroxyzine, diphenhydramine)  
Antidepressants (eg, doxepin, amitriptyline)  
Opioid antagonists (eg, naltrexone, nalmeferine)  
Serotonin antagonists (eg, ondansetron, paroxetine)

#### Disease-specific

##### Xerosis

Humidify dry indoor environment  
Avoid excessive soap use

##### Cholestasis

Cholestyramine  
Rifampicin  
Naltrexone

##### Polycythemia vera

Aspirin

##### Chronic kidney disease

Ultraviolet B phototherapy  
Dialysis  
Transcutaneous electrical nerve stimulation

tos.<sup>21</sup> The number of dermatoses tended to increase during the more advanced stages of HIV infection.<sup>21</sup>

### THERAPY

Treatment of chronic pruritus is imperative to prevent complications such as lichen simplex chronicus (a localized skin thickening in response to intense scratching), and prurigo nodularis (a variant of lichen simplex chronicus in which 1- to 2-cm nodules develop on the skin). Topical treatment of prurigo nodularis with capsaicin is an effective and safe regimen that clears skin lesions.<sup>22</sup> Localized infections and cellulitis may also result from excoriations. Treatment of pruritus depends on its underlying cause (**Table 2**).

#### General Treatment Measures

Xerosis can be managed with topical agents, such as moisturizers, and by humidifying a dry indoor environment, especially in winter. Treatment for atopic dermatitis consists of avoidance of triggers and administration of

topical emollients, steroids, and immune-response modifiers (eg, tacrolimus, pimecrolimus) that block the release of inflammatory mediators.<sup>23</sup>

### Disease-Specific Treatment Measures

**Malignancy.** Treatment of pruritus associated with malignant disease is directed towards effective management of the underlying cause. Endoscopic stent placement is the standard treatment for patients with extrahepatic malignant biliary strictures who are not candidates for surgical resection. Stenting has been shown to relieve jaundice and pruritus in these patients.<sup>24</sup> Disease-specific treatment also includes corticosteroids for Hodgkin's lymphoma and paroxetine for paraneoplastic itch from other malignancies.<sup>25</sup> In the case of Hodgkin's lymphoma, the pruritus may resolve after the first cycle of chemotherapy.<sup>8</sup>

**Cholestasis.** A study designed to test the efficacy of ursodeoxycholic acid (UDCA) in pruritus associated with cholestasis of pregnancy found that UDCA is effective and safe in these patients. After 3 weeks of treatment with UDCA, patients had a significant improvement in pruritus, serum bilirubin, and transaminase levels.<sup>26</sup> Primary biliary cirrhosis is a chronic, progressive disease for which there is no definitive treatment other than liver transplantation. Pruritus is best treated with cholestyramine, rifampicin, and opioid antagonists. Liver transplant is indicated for cases of liver failure and intractable pruritus.<sup>27</sup> In patients with cholestasis from other causes that do not receive symptomatic relief from cholestyramine, the use of opiate antagonists (eg, naloxone, naltrexone) is beneficial.<sup>28</sup>

**Chronic kidney disease.** In patients with renal disease, serotonin receptor antagonists have been evaluated as a treatment of uremic pruritus with questionable results.<sup>29</sup> Even treatment with classic antihistamines was not of proven therapeutic benefit for these patients.<sup>30</sup> However, ultraviolet B phototherapy and ondansetron have been shown to be effective in uremic patients.<sup>31</sup> Because xerosis is common in patients with chronic kidney disease and may be the major cause of pruritus in these cases, its treatment is imperative.

### CONCLUSION

Pruritus is a common manifestation of dermatologic conditions, but pruritus can also result from an underlying systemic disease. Many dermatologic conditions are evident by characteristic rashes and distribution of itching; however, a systemic process rarely causes localized itching. Pruritus associated with systemic disease can precede the diagnosis by several years. Renal, hepatic, and malignant causes are common sys-

temic processes that can manifest with pruritus. Therefore, a thorough history and physical examination is essential in the evaluation of pruritus. In assessing patients with pruritus, a complete blood count and tests of liver function, thyroid function, and renal function should be performed.

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