Evaluation and treatment of generalized pruritus

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■ Generalized pruritus may be symptomatic of dermatologic disease or it can be a manifestation of a systemic disorder. When the cause of generalized pruritus is not immediately evident, careful clinical and laboratory evaluation and close follow-up are needed to ensure appropriate diagnosis and treatment.

□ INDEX TERM: PRURITUS □ CLEVE CLIN J MED 1990; 57:521-526

PRURITUS is the most common dermatologic symptom that patients present. It accompanies a wide range of skin diseases, most of them characterized by primary lesions such as papules, vesicles, and plaques (*Table 1*).

Generalized pruritus of undetermined origin (GPUO) is continuous itching of at least 3 weeks duration that is unresponsive to 2 weeks of conservative management and unassociated with primary skin lesions. Systemic diseases may be associated with generalized pruritus (*Table 2*); but the prevalence of the association ranges from 14% to 50%, depending on the source of the report.[1-4]

This article discusses the systemic diseases associated with generalized pruritus, and provides recommendations for evaluating the patient with generalized pruritus.

SYSTEMIC DISEASES ASSOCIATED WITH PRURITUS

Uremia

Chronic renal failure is the systemic disease most commonly associated with generalized pruritus.[5] Up to 90% of patients on hemodialysis have either localized or generalized pruritus.[6] These patients complain of severe, paroxysmal itching that tends to be most severe in the summer. In one study, 25% of patients had discomfort soon after hemodialysis and 42% had their most severe pruritus during hemodialysis.[6]

The etiology of uremic pruritus is unknown, but several mechanisms have been proposed. Increased numbers of mast cells have been found in the spleen and bone marrow of uremic patients who have no evidence of systemic mast cell disease.[7] The mast cell proliferation may be related to elevated parathyroid hormone levels. Histamine has been implicated, given the increased sensitivity of uremic patients to intradermal histamine.[8] Calcium hemostasis is defective in uremia, and medical or surgical parathyroidectomy improves the associated pruritus.[9,10] Other possibilities include peripheral neuropathy, xerosis, hypermagnesemia, or accumulation of an unknown pruritogenic substance.

Ultraviolet B phototherapy is the most effective treatment of pruritus associated with uremia. Most patients improve within six treatments; if a second course of therapy is necessary, the response is more rapid.[11] Ultraviolet A has some advantages because of its wider availability and higher safety profile.[12] Emollients are useful for associated xerosis. Other effective treatments include topical capsaicin,[13] lidocaine infusion, intravenous heparin, and oral charcoal. It also helps to

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TABLE 1
SKIN DISEASES ASSOCIATED WITH PRURITUS

Xerosis
Urticaria
Sunburn
Dermatitis herpetiformis
Contact dermatitis
Fungal infections
Fiberglass dermatitis
Pruritic urticarial papules and plaques of pregnancy
Pediculosis
Miliaria
Folliculitis
Polymorphous light eruption
Pityriasis rosea
Lichen simplex chronicus
Psoriasis
Scabies
Insect bites
Atopic dermatitis
Drug reactions
Mycosis fungoides
Bullous pemphigoid
Pemphigus foliaceus
Lichen planus

TABLE 2
SYSTEMIC DISEASES ASSOCIATED WITH GENERALIZED PRURITUS

System involved	Diseases that cause pruritus
Renal	Uremia
Hepatic (obstructive hepatobiliary disease)	Primary biliary cirrhosis
	Drugs (chlorpropamide, oral contraceptives, anabolic steroids)
	Extrahepatic biliary obstruction
	Intrahepatic cholestasis of pregnancy
Hematologic	Polycythemia vera
	Iron deficiency anemia
	Multiple myeloma and paraproteinemia
	Mastocytosis
Endocrine	Thyrotoxicosis
	Hypothyroidism
	Diabetes
Neurologic	Infarcts
	Brain abscess
	Multiple sclerosis
	Tumor
Lymphoreticular neoplasms	Hodgkin's disease
	Lymphoma
Internal malignancy	Systemic carcinoma
	Carcinoid syndrome
Miscellaneous	AIDS
	Sjögren's syndrome
	Dumping syndrome
	Bullous pemphigoid

lower the dialysate magnesium concentration for patients undergoing hemodialysis.

Hepatobiliary diseases

Pruritus may be associated with primary biliary cirrhosis, drug-induced cholestasis (as occurs with chlorpropamide, oral contraceptives, and anabolic steroids), biliary obstruction from intrahepatic or extrahepatic sources, and cholestasis of pregnancy. Cyclic premenstrual pruritus due to recurrent cholestasis has also been reported.[14]

Pruritus may develop weeks or months before other signs and symptoms of hepatic disease. Itching often begins on the hands, feet, and other pressure areas of the skin and is especially severe at night. The presence of the "butterfly sign" suggests chronic obstructive hepatobiliary disease.[15] The butterfly sign is characterized by the relative hypopigmentation of the skin on the mid- to upper back, surrounded by postinflammatory hyperpigmentation.

Although accumulated bile salts have been implicated as the cause of pruritus in hepatobiliary disease, this notion is controversial.[16] Factors that support the role of bile salts include relief of pruritus with bile salt-binding resins such as cholestyramine[17] and the production of pruritus when bile salts are applied to the skin.[18] Nevertheless, other studies on the correlation of itching with serum and skin bile salt concentrations have had conflicting results.[19,20] Furthermore, in some patients phenobarbital relieves pruritus without a decrease in serum bile acids, while in others, androgen therapy is beneficial despite the associated increase in serum bile acid concentration.[21]

The general consensus is that pruritus with hepatobiliary disease is an effect of bile salts on the liver, not the skin. The pruritus is related to the release of an unknown pruritogenic substance that binds to cholestyramine and is photolabile.[22] Supporting this theory is the beneficial effect of rifampin on pruritus associated with primary biliary cirrhosis; this drug inhibits bile acid uptake in the liver and stimulates hepatic enzymatic degradation of bile salts.[23]

Pruritus associated with hepatobiliary disease can be severe and can interfere with quality of life. Cholestyramine is the first treatment of choice; in resistant cases, the drug may be combined with phototherapy.[24] UVA or UVB phototherapy alone is less useful than in the treatment of pruritus associated with uremia. Naloxone, a central opioid antagonist, is beneficial for intractable itching related to primary biliary cirrhosis.[25] Besides rifampin,[23] other treatments include surgical external diversion of bile[26] and plasma perfusion through charcoal coated glass beads.[27]

Hematologic diseases

Patients with polycythemia vera may present with generalized pruritus. The itching is described as "pricking" in quality and lasts from minutes to hours. It starts

after the patient emerges from a shower or bath as the skin begins to cool—hence the term "bath pruritus." The cause of the pruritus is unknown, although elevated plasma and urine histamine levels were detected in one study and correlated with an increase in circulating basophils.[28] Earlier reports claimed that cimetidine was beneficial for these patients,[29,30] but subsequent controlled studies did not confirm efficacy.[31] Aspirin and cyproheptadine (Periactin) have also been used for treatment.

Generalized pruritus has been reported in association with iron deficiency anemia.[32] Although small studies have described relief of pruritus with iron therapy,[33,34] the relationship between generalized pruritus and iron deficiency is questionable. A large series of patients needs to be investigated before any conclusions can be made.

Rarely, benign gammopathy[35] and multiple myeloma[36] are associated with pruritus. Systemic mastocytosis has also been reported in a patient presenting with generalized pruritus and no observable skin lesions.[37]

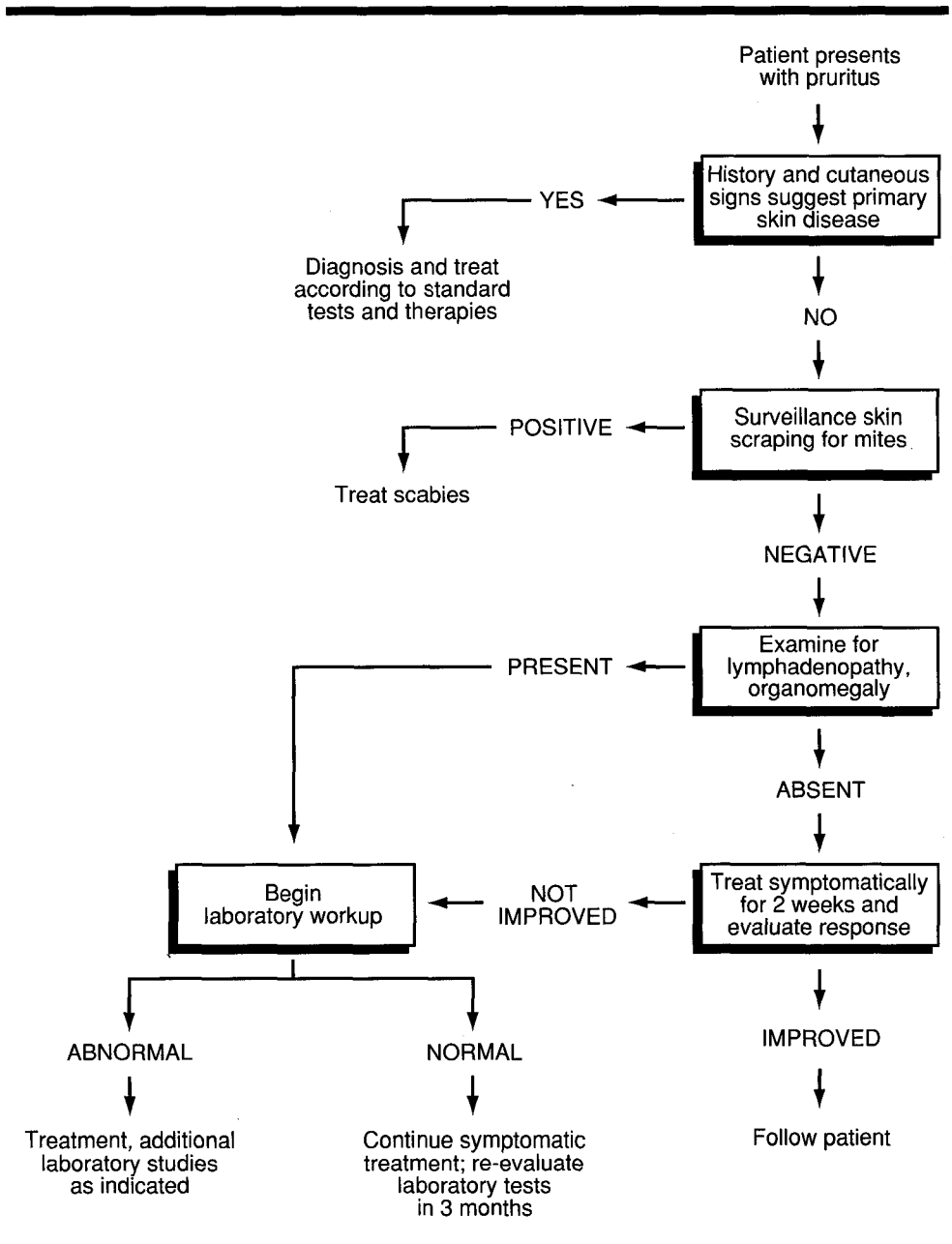

FIGURE 1. Flow chart for evaluating patients with generalized pruritus of unknown origin.

Endocrine disorders

Pruritus may occur in up to 5% of patients with thyrotoxicosis and subside with treatment of the thyroid disorder.[38] Some patients with hyperthyroidism may present with pruritus.[39] Various mechanisms have been suggested for the pruritus associated with hyperthyroidism; these include cutaneous vasodilation, lowered pain threshold, enhanced sensitivity to catecholamines, activation of kalli-kreinkinin system, and prostaglandin mediation.[40]

Hypothyroidism has not been linked to generalized pruritus in controlled studies. Dry skin and associated itching often accompany the hypothyroid state; but GPUO as defined above rarely is solely attributable to

TABLE 3
LABORATORY WORKUP FOR GENERALIZED PRURITUS

Indications	Suggested tests
Screening	CBC with differential
	BUN, creatinine
	Alkaline phosphatase, bilirubin, SGOT
	T_4, TSH
	Glucose
	Chest radiograph
	Stool for occult blood (for patients >40 years)
Follow-up	Serum iron, ferritin
	Serum protein electrophoresis, serum immunoelectrophoresis
	Urine 5-hydroxyindoleacetic acid (5-HIAA)
	Skin biopsy for direct immunofluorescence
	Skin biopsy for special stain (to exclude mastocytosis)
	Stool for ova and parasites
	Radiologic studies as indicated

hypothyroidism.

The association of diabetes mellitus with pruritus has been largely anecdotal.[41] A report that compared 300 diabetic patients with controls showed an increased prevalence of pruritus vulvae, but not generalized pruritus, in the diabetic population.[42] The presence of diabetes does not satisfactorily explain GPUO, although persistent scalp pruritus may be related to diabetes.[43]

Neurologic disorders

Unilateral pruritus has been reported secondary to central nervous system infarct[44] or brain abscess.[45] Paroxysmal itching has also been described in multiple sclerosis.[46,47] Intractable nasal pruritus may be a sign of brain tumor[48] or atypical angina,[49] suggesting that itching may originate in the cerebral cortex. Bombesin, an endogenous opioid peptide, may be a central mediator of pruritus[50]; when administered intrathecally to animals, it produces intense and long-lasting pruritus. This mediator and its antagonist require further investigation.

Lymphoreticular malignancies

Generalized pruritus may be associated with or the presenting symptom of Hodgkin's disease. Opinions conflict regarding the prognostic significance of pruritus in this disease. The Ann Arbor Conference on Hodgkin's disease in 1971 dropped pruritus as a criterion for B categorization, but two later reports disputed this action.[51,52] Further studies are needed to resolve this question.

Non-Hodgkin's lymphoma and mycosis fungoides may also be associated with generalized pruritus.

Internal malignancy

Systemic malignancy is a rare cause for GPUO and does not warrant extensive, cost-consuming, laboratory evaluation.[53] The association of pruritus and internal malignancy was reported in 1942[54]; however, in most instances pruritus was accompanied by some other sign such as rash, and was only rarely the sole presenting symptom. Cormia stated in 1965 that pruritus was an uncommon, although important, symptom of systemic carcinoma—especially if it was severe, prolonged, and localized to the pretibial legs, inner thighs, upper trunk, and extensor surfaces of the upper arms.[55]

Subsequent studies reported that 3% to 26% of patients with generalized pruritus have an underlying malignancy.[1–4] However, when a population of 125 patients with generalized pruritus were followed over a 6-year period, there was no significant increase in malignant neoplasms, except for a slight increase in malignant lymphomas.[56]

Carcinoid tumors[57] have been associated with pruritus—presumably because of a direct effect of mediators on cutaneous vasculature.

Other systemic disorders

Patients with acquired immunodeficiency syndrome may present with generalized pruritus.[58] Pruritus has been reported in 30% of HIV-infected prostitutes.[59] The pruritus associated with HIV infection is generally refractory to treatment, although psoralen and UVA phototherapy (PUVA) may benefit some patients.[60] In many AIDS patients, pruritus may be associated with bacterial folliculitis, with or without atopic eczema or scabies.

Pruritus can be the presenting symptom for Sj?gren's syndrome,[61] dumping syndrome,[62] and bullous pemphigoid.[63]

Psychogenic disorders

Pruritus is aggravated by stress; one study correlated high levels of psychological stress with increased experimentally induced itching.[64] Nevertheless, a diagnosis of psychogenic pruritus should be made with great caution and after careful observation. Itching may reasonably be ascribed to psychogenic factors if there is a relevant history of major psychiatric disease. Fluoxetine (Prozac), 10 mg to 20 mg daily, may be useful for some of these patients.

EVALUATING THE PATIENT

The patient with GPUO requires careful evaluation and long-term follow-up (*Figure 1*). In the absence of primary skin disease, scabies, and lymphadenopathy or organomegaly at the initial visit, a 2-week trial of

symptomatic therapy is appropriate before starting laboratory evaluation.

Conservative symptomatic measures include educating the patient about bathing procedures, especially in fall and winter in cold climates—for example, the use of lukewarm bath water, mild soaps such as Dove or Basis, pat drying instead of rubbing with the bath towel, limited frequency, and immediate application of a moisturizing lotion such as Moisturel or Nivea. A sedating H_1-antagonist such as hydroxyzine, 10 mg to 25 mg bid, as initial therapy is helpful for some patients. Fluorinated topical corticosteroids should be avoided if there is no primary cutaneous disease, but sparing use of nonfluorinated corticosteroid creams and lotions has an antipruritic effect. Menthol-containing lotions such as Sarna appeal to some patients. Also useful is topical pramoxine alone (Prax), with menthol 0.5% (Prame-Gel), or with hydrocortisone (Pramasone). Topical antihistamines should not be used because of their potential for sensitization.

If 2 weeks of symptomatic therapy does not bring relief or significant improvement of symptoms, then initial screening laboratory tests are indicated to rule out underlying systemic disease (*Table 3*), including complete blood count, blood urea nitrogen, creatinine, liver enzymes, thyroid studies, blood glucose, and chest radiograph. Screening for fecal occult blood is appropriate for patients older than 40 years.

If these screening tests are normal, then additional studies may be performed as indicated (*Table 3*). For example, a perilesional skin biopsy may reveal clinically masked primary skin disease such as dermatitis herpetiformis and bullous pemphigoid. Extensive radiographic examinations are unwarranted unless the history or physical examination suggests a need for them.

If this secondary evaluation is unrevealing, then continued symptomatic therapy is warranted. At this point, alternative antihistamines may be indicated, such as cyproheptadine and doxepin (Sinequan). Nonsedating antihistamines have not been helpful in these patients.

Systemic antibiotics may be needed if there are extensive excoriations and secondary infection. A trial of UVB or PUVA phototherapy may be indicated. Localized, disabling pruritus may respond to a soft cast of zinc oxide-impregnated gauze (Domepaste) applied over a soothing topical corticosteroid ointment or tar-based paste.

Reassessment and reevaluation of these patients is crucial; for example, it is not unreasonable to repeat laboratory studies at intervals of 3 to 6 months. Some patients will manifest features of systemic disease after their initial visit,[4] and only careful follow-up will ensure timely diagnosis of occult medical problems.

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