The Generalized Rash: Part II. Diagnostic Approach

JOHN W. ELY, MD, MSPH, and MARY SEABURY STONE, MD
University of Iowa Carver College of Medicine, Iowa City, Iowa

Although it is important to begin the evaluation of generalized rash with an inclusive differential diagnosis, the possibilities must be narrowed down by taking a focused history and looking for key clinical features of the rash. Part I of this two-part article lists the common, uncommon, and rare causes of generalized rashes. In part II, the clinical features that help distinguish these rashes are described. These features include key elements of the history (e.g., travel, environmental exposures, personal or family history of atopy); characteristics of individual lesions, such as color, size, shape, and scale; areas of involvement and sparing, with particular attention to palms, soles, face, nails, sun-exposed areas, and extensor and flexor surfaces of extremities; pruritic or painful lesions; systemic symptoms, especially fever; and dermatologic signs, such as blanching, and the Koebner phenomenon. (*Am Fam Physician.* 2010;81(6):735-739. Copyright © 2010 American Academy of Family Physicians.)

This is part II of a two-part article on generalized rashes. Part I, "Differential Diagnosis," appears in this issue of *AFP* on page 726.

Accurate diagnosis of the generalized rash can be difficult because of the nonspecific appearance of many rashes. If the diagnosis is not obvious, the physician must resist the common tendency to prematurely close the diagnostic process and instead generate an inclusive differential diagnosis. Part I of this two-part article discusses the common, uncommon, and rare causes of generalized rashes.[1] Part II describes the clinical features that help distinguish these rashes.

Keys to Diagnosis

HISTORY

When the diagnosis of a generalized rash is not obvious, patients should be asked about recent travel, insect and plant exposure, drug exposure (including over-the-counter drugs, alternative medications, and illicit drugs), contact with persons who are ill, pets, hobbies, occupational exposures, chemical exposure, chronic illness, sexual history, and recent systemic symptoms, especially fever *(Table 1)*. Patients should be asked about pruritus, painful lesions, the initial site of involvement, and any personal or family history of atopy (e.g., asthma, allergic rhinitis, childhood eczema).

The patient's age may help narrow the possible diagnoses. For example, acute maculopapular rashes in children are usually caused by viral infections, whereas in adults they are usually caused by drug reactions.[2] Some rashes are rare in children (e.g., nummular eczema, lichen planus, dermatitis herpetiformis), whereas others are rare in adults (e.g., roseola, Kawasaki disease, scarlet fever).

Patients should be asked about pruritus, because some conditions routinely cause intense pruritus (e.g., scabies, urticaria, atopic dermatitis), whereas others are usually nonpruritic (e.g., seborrheic dermatitis, secondary syphilis, many viral exanthems; *Table 2*). Most generalized rashes are not painful, but Sweet syndrome, Kawasaki disease, and Stevens-Johnson syndrome are exceptions.

Systemic symptoms, especially fever, can help narrow the differential diagnosis.[3,4] Rashes accompanied by fever are most commonly associated with infections, but drug eruptions and rheumatologic diseases can also cause fever. Although most maculopapular rashes that are associated with fever are caused by self-limited viral infections, empiric antibiotics and laboratory testing are indicated when the history, geography, demographics, and systemic manifestations

Table 1. Generalized Rash: Conditions Suggested by Patient History

Historical finding	*Conditions*
Chemicals	Contact dermatitis
Chronic illness	Dermatitis herpetiformis
	Seborrheic dermatitis
Contact with ill persons	Fifth disease (i.e., erythema infectiosum)
	Meningococcemia
	Roseola (i.e., exanthem subitum, sixth disease)
	Rubella
	Rubeola
	Scarlet fever
	Varicella
	Viral exanthem, nonspecific
Drug exposure	Lupus (subacute cutaneous lupus erythematosus)
	Drug eruption
	Urticaria (i.e., hives)
Hobbies	Contact dermatitis
Insect and arthropod exposure	Insect bites
	Lyme disease
	Rickettsialpox
	Rocky Mountain spotted fever
	Scabies
Occupational exposures	Contact dermatitis
Plant exposure	Contact dermatitis
Recent systemic symptoms, fever	Fifth disease (i.e., erythema infectiosum)
	HIV acute exanthem
	Kawasaki disease
	Meningococcemia
	Roseola (i.e., exanthem subitum, sixth disease)
	Rubella
	Rubeola
	Scarlet fever
	Varicella
	Viral exanthem, nonspecific
Sexual history	HIV acute exanthem
	Secondary syphilis
Travel	Insect bites
	Lyme disease
	Rickettsialpox
	Rocky Mountain spotted fever

HIV = human immunodeficiency virus.

Table 2. Generalized Rash: Conditions Associated with Pruritus

Common	**Variable**	**Absent or rare**
Atopic dermatitis	Drug eruption*	Fifth disease (i.e., erythema infectiosum)*
Contact dermatitis	Erythema multiforme	HIV acute exanthem*
Insect bites	Folliculitis	Keratosis pilaris
Lichen planus	Guttate psoriasis	Lyme disease*
Nummular eczema	Kawasaki disease*	Meningococcemia*
Scabies	Pityriasis rosea	Miliaria rubra (i.e., prickly heat, heat rash)
Urticaria (i.e., hives)	Psoriasis (plaque psoriasis)	Rocky Mountain spotted fever*
Varicella*	Tinea corporis	Roseola (i.e., exanthem subitum, sixth disease)
	Toxic epidermal necrolysis*	Rubella*
	Toxic shock syndrome (late)*	Scarlet fever*
	Viral exanthem, nonspecific	Seborrheic dermatitis
		Secondary syphilis*
		Staphylococcal scalded skin syndrome*
		Stevens-Johnson syndrome*

NOTE: *Table includes all common rashes and all rashes that can have serious consequences for the patient or pregnant contacts of the patient (designated by *).*

HIV = human immunodeficiency virus.

suggest a more serious infection (e.g., meningococcemia, Lyme disease, Rocky Mountain spotted fever). Petechial rashes require immediate decisions about empiric antibiotics, but life-threatening infections characterized by petechiae (e.g., meningococcemia, Rocky Mountain spotted fever) can start as nonspecific maculopapular rashes.[5]

PHYSICAL EXAMINATION

Characteristics of the rash itself can help narrow the differential diagnosis. In dermatologic diagnosis, it is often helpful to focus on the clinical appearance of the rash after determining the patient's primary symptom, but before taking a more focused history.[6] This approach may not be intuitive to primary care physicians, who would normally take a complete history first and then perform a physical examination. The size of individual lesions can vary from pinpoint to total-body redness (i.e., erythroderma; *Table 3)*. The shape of individual lesions and their tendency to cluster can also provide important clues. For example, linear patterns of erythema or vesicles are typical of poison ivy; oval lesions are typical of pityriasis rosea; round lesions are typical of nummular eczema; annular lesions are typical of tinea corporis; and geometric patterns may imply a contact component. The color of the lesions should also be noted. Although most generalized rashes are pink or red, lichen planus is characterized by violaceous lesions, and secondary syphilis by red-brown lesions.

In addition to the rash itself, the physician should evaluate the patient's lymph nodes, neurologic status, body temperature, and general appearance. Patients with fever and toxic appearance require prompt evaluation and possibly empiric treatment before reaching a definitive diagnosis.

Dermatologic Signs. Several dermatologic signs may help narrow the differential diagnosis. For example, the Koebner phenomenon (i.e., development of typical lesions at the site of trauma) is characteristic of psoriasis and lichen planus.[7] The Nikolsky sign (i.e., easy separation of the epidermis from the dermis with lateral pressure) is associated with staphylococcal scalded skin syndrome and toxic epidermal necrolysis.[8] The value of the Auspitz sign (i.e., the appearance of bleeding points when scale is removed from psoriatic lesions) in the diagnosis of patients with psoriasis has been questioned because of its low sensitivity and specificity.[9] Blanching of erythematous lesions with brief downward pressure implies that the erythema is the result of vasodilation rather than dermal hemorrhage. Blanching is characteristic of drug eruptions, viral exanthems, Kawasaki

Table 3. Generalized Rash: Conditions Suggested by Size of Lesions

Size of lesions	*Conditions*
Pinpoint	Folliculitis
	Keratosis pilaris
	Scarlet fever*
1 mm to 1 cm	Guttate psoriasis
	Insect bites†
	Lichen planus
	Miliaria rubra (i.e., prickly heat, heat rash)
	Rocky Mountain spotted fever*
	Roseola (i.e., exanthem subitum, sixth disease)
	Rubella*
	Scabies
	Varicella*
1 to 25 cm	Lyme disease*
	Nummular eczema
	Tinea corporis
	Urticaria (i.e., hives)
Variable	Atopic dermatitis
	Contact dermatitis
	Drug eruption*
	Erythema multiforme
	Fifth disease (i.e., erythema infectiosum)*
	HIV acute exanthem*
	Kawasaki disease*
	Meningococcemia*
	Pityriasis rosea
	Psoriasis (plaque psoriasis)
	Seborrheic dermatitis
	Secondary syphilis*
	Staphylococcal scalded skin syndrome*
	Stevens-Johnson syndrome*
	Toxic epidermal necrolysis*
	Viral exanthem, nonspecific
Erythroderma possible	Atopic dermatitis
	Drug eruption*
	Psoriasis (plaque psoriasis)
	Sézary syndrome (i.e., chronic cutaneous T-cell lymphoma)
	Toxic shock syndrome*

NOTE: *Table includes all common rashes and all rashes that can have serious consequences for the patient or pregnant contacts of the patient (designated by *).*

HIV = human immunodeficiency virus.

†—Some insect bites may be larger than 1 cm.

Table 4. Generalized Rash: Involvement of Palms and Soles

Common	Variable	Absent or rare
Contact dermatitis	Atopic dermatitis	Fifth disease (i.e., erythema infectiosum)*
Erythema multiforme	Drug eruption*	Folliculitis
Kawasaki disease*	HIV acute exanthem*	Guttate psoriasis
Rocky Mountain spotted fever*	Lichen planus	Insect bites
Rubella*	Meningococcemia*	Keratosis pilaris
Scabies (in infants)	Psoriasis (plaque psoriasis)	Lyme disease*
Secondary syphilis*	Urticaria (i.e., hives)	Miliaria rubra (i.e., prickly heat, heat rash)
Staphylococcal scalded skin syndrome*		Nummular eczema
Stevens-Johnson syndrome*		Pityriasis rosea
Tinea corporis		Roseola (i.e., exanthem subitum, sixth disease)
Toxic epidermal necrolysis*		Scarlet fever*†
Toxic shock syndrome*		Seborrheic dermatitis
		Varicella*
		Viral exanthem, nonspecific

NOTE: *Table includes all common rashes and all rashes that, if left untreated, can have serious consequences for the patient or pregnant contacts of the patient (designated by *).*

HIV = human immunodeficiency virus.

†—Palms and soles can desquamate.

disease, roseola, and scarlet fever, whereas the lesions of meningococcemia and the late petechial stage of Rocky Mountain spotted fever do not blanch. The physician should note the presence and quality of scale (e.g., psoriasis, tinea corporis, pityriasis rosea); whether the lesions are evanescent (e.g., urticaria) or stable (e.g., erythema multiforme); and whether lesions tend to become confluent (e.g., urticaria) or remain discrete (e.g., insect bites). When atopic dermatitis is considered, the physician should search for other signs of atopy, such as palmar hyperlinearity, infraorbital folds (Dennie-Morgan lines), dry skin, and lichenification.[10,11]

Rash Location. Many rashes tend to avoid or favor certain regions of the body. Physicians should note whether the rash involves the palms, soles, mucous membranes, face, scalp, or extensor or flexor surfaces of extremities. For example, psoriasis usually does not involve the central face, and many generalized rashes avoid the palms and soles, whereas secondary syphilis, erythema multiforme, and rickettsial infections typically include the palms and soles *(Table 4)*. Keratosis pilaris commonly involves the posterolateral upper arms. Scabies involves the fingers, finger webs, wrists, elbows, knees, groin, buttocks, penis, axillae, belt line, ankles, and feet. Seborrheic dermatitis most often involves the scalp margins, the area behind the ears, external ear canals, base of eyelashes, eyebrows, nasolabial folds, and central chest. Patients should be asked where the rash first appeared, because some rashes have a characteristic progression. For example, pityriasis rosea often starts with a relatively large herald patch on the trunk or proximal extremity several days before the smaller oval lesions appear. Rocky Mountain spotted fever often starts on the wrists and ankles before spreading centrally.[5]

TESTS

Blood tests that may be helpful include a complete blood count to determine the presence of leukocytosis or thrombocytopenia, and serologic studies to identify various infectious causes. Mineral oil mounts and potassium hydroxide scrapings can be helpful when scabies or dermatophytes are considered. Skin biopsy, with or without direct or indirect immunofluorescence, is often helpful, especially to confirm lichen planus, dermatitis herpetiformis, mycosis fungoides, and staphylococcal scalded skin syndrome.[12]

"Don't-Miss" Rashes

"Don't-miss" rashes are those that can have serious consequences for the patient or pregnant contacts of the patient. These rashes include various infectious diseases, such as meningococcemia, Lyme disease, and Rocky

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Systemic symptoms, and involvement of palms, soles, and nails can help distinguish various rashes.	C	3, 4
When evaluating generalized rash, physicians should determine the patient's primary symptom, then focus on the clinical appearance of the rash before taking a more focused history to help narrow down the differential diagnosis.	C	6

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Mountain spotted fever. Many of these rashes are associated with fever and manifest as petechiae or purpura.[4] However, there are notable exceptions, such as Lyme disease, which is not petechial, and drug eruptions, which may not be associated with systemic symptoms. Don't-miss rashes can usually be ruled out on the basis of clinical features and demographics, but sometimes further testing is indicated. Some patients should be treated immediately, before a diagnosis can be established. For example, toxic-appearing children and adults with petechiae should be treated immediately for presumed meningococcemia, before undergoing any further evaluation.[13] Patients from Oklahoma, Tennessee, Arkansas, or the southern Atlantic states who present in the spring or summer with fever, myalgia, and headache—with or without a rash—should be strongly considered for antibiotic treatment of Rocky Mountain spotted fever while awaiting the results of serology or skin biopsy.[14,15] If the physician cannot distinguish between meningococcemia and Rocky Mountain spotted fever on clinical grounds (a common occurrence), patients should be treated for both before undergoing diagnostic tests.[4,16]

The Authors

JOHN W. ELY, MD, MSPH, is a professor of family medicine at the University of Iowa Carver College of Medicine, Iowa City.

MARY SEABURY STONE, MD, is a professor of dermatology and pathology at the University of Iowa Carver School of Medicine.

Address correspondence to John W. Ely, MD, MSPH, University of Iowa Carver College of Medicine, 200 Hawkins Dr., 01291-D PFP, Iowa City, IA 52242 (e-mail: john-ely@uiowa.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Ely JW, Stone MS. The generalized rash: Part I. Differential diagnosis. *Am Fam Physician*. 2010;81(6):726-734.
2. Drago F, Rampini E, Rebora A. Atypical exanthems: morphology and laboratory investigations may lead to an aetiological diagnosis in about 70% of cases. *Br J Dermatol*. 2002;147(2):255-260.
3. Aber C, Alvarez Connelly E, Schachner LA. Fever and rash in a child: when to worry? *Pediatr Ann*. 2007; 36(1):30-38.
4. Schlossberg D. Fever and rash. *Infect Dis Clin North Am*. 1996;10(1):101-110.
5. Drage LA. Life-threatening rashes: dermatologic signs of four infectious diseases. *Mayo Clin Proc*. 1999; 74(1):68-72.
6. Brodell RT, Helms SE. Approach to the diagnosis of skin disease. In : Dale DC, Federman DD, eds. *ACP Medicine*. http://www.acpmedicine.com (subscription required). Accessed July 2, 2009.
7. Boyd AS, Neldner KH. The isomorphic response of Koebner. *Int J Dermatol*. 1990;29(6):401-410.
8. O'Connell NH, Mannix M, Philip RK, et al. Infant staphylococcal scalded skin syndrome, Ireland, 2007—preliminary outbreak report. *Euro Surveill*. 2007;12(24): pii=3220. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3220. Accessed January 19, 2010.
9. Bernhard JD. Auspitz sign is not sensitive or specific for psoriasis. *J Am Acad Dermatol*. 1990;22(6 pt 1): 1079-1081.
10. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol*. 2003;49(6):1088-1095.
11. Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. *Immunol Allergy Clin North Am*. 2002;22(1):1-24.
12. Boyd AS, Neldner KH. Lichen planus. *J Am Acad Dermatol*. 1991;25(4):593-619.
13. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39(9):1267-1284.
14. Centers for Disease Control and Prevention. Consequences of delayed diagnosis of Rocky Mountain spotted fever in children—West Virginia, Michigan, Tennessee, and Oklahoma, May-July 2000. *MMWR Morb Mortal Wkly Rep*. 2000;49(39):885-888.
15. Chapman AS, Bakken JS, Folk SM, et al., for the Tickborne Rickettsial Diseases Working Group, CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. *MMWR Recomm Rep*. 2006;55(RR-4):1-27.
16. Sexton DJ. Treatment of Rocky Mountain spotted fever. http://www.uptodate.com (subscription required). Accessed November 22, 2008.