



Skin Rashes that Involve Palms and Soles: An Internist's View

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Abstract

Skin rash involving palms and soles can be a manifestation of serious underlying medical condition. Some of these conditions are acute conditions, requiring immediate recognition and treatment. Others, while not life-threatening, need recognition to avoid transmission to others. Finally, some are associated with serious inflammatory, hematologic, and oncologic conditions that need to be suspected and diagnosed in a timely manner, but are not immediately life-threatening. In this paper we have provided a review of medical conditions that are associated with rash involving palms and soles.

Introduction

Primary care providers often are in the position to evaluate and manage patients who present with rash. In fact, rash is one of the common conditions encountered in clinical practice [1-3]. Differential diagnosis of diseases presenting with rash can be broad, and at times challenging [4]. However, description of the lesions, as well as distribution of rash allow for narrowing the differential diagnosis. One such case is when rash involves palms and soles, which significantly narrows the diagnostic possibilities. In this review, we aim to discuss differential diagnosis of rashes involving palms and soles, with the aim of providing a practical guide for primary care clinician to diagnose the etiology in a timely manner. We will divide the medical conditions presenting with palms and soles rash based on acuity and presence or absence of fever. We will attempt to provide a simple diagnostic approach to clinicians to evaluate and treat patients in a timely manner, and recognize urgent conditions easily.

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Conditions Associated with Palms and Soles Rash

Acute febrile illnesses caused by a bacterial agent, with generalized rash involving palms and soles

In this category several life-threatening conditions are discussed, for which a delay in diagnosis could result in increased mortality and timely diagnosis is of utmost importance. *Neisseria meningitidis* infection, Toxic shock syndrome, and Rocky Mountain spotted fever have the highest mortality if not treated in a timely manner. Other potentially life-threatening conditions include rat-bite fever, caused by *Streptobacillus moniliformis*, human monocytic ehrlichiosis, and subacute infective endocarditis. Murine typhus has lower mortality among these conditions. Secondary syphilis, while mostly afebrile and subacute, can at times present more acutely and with low-grade fever. While mortality from secondary syphilis is low, timely recognition has public health implications and delay in diagnosis is not warranted.

Meningococcal infection, although more common in early life, can occur at any age. Presentation is usually acute with fever, with or without meningeal signs, and can rapidly progress to sepsis and shock. Rash is present in up to 2/3 of the cases and can involve palms and soles. Rash is typically petechial/purpuric, although a maculopapular blanching eruption has also been reported. The appearance of rash usually heralds poor prognosis. Both meningococemia and meningococcal meningitis can rapidly progress to shock and death. Currently mortality is about 9% to 16% in meningitis and meningococemia [5]. High degree of suspicion, early institution of antibiotic therapy, and early referral to intensive care is warranted.

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*. It is endemic in south-Atlantic, the Pacific, and west south-central United States. The states with the highest incidences of Rocky Mountain spotted fever are North Carolina and Oklahoma. The incubation period of RMSF ranges

from 2 to 14 days, with a median of 7 days. Early in the disease fever, myalgia, and headaches are prominent, as well as gastrointestinal symptoms. Rash appears on the 3rd to 5th day and will ultimately be present in about 90% of patients overall. It typically will appear first around the wrists and ankles and will involve palms and soles in 1/3 to 2/3 of the cases [6]. Mortality is low when treatment with tetracyclines is started within 5 days of the onset of symptoms. However, when treatment is delayed, there is significant increase in mortality up to 23% [7].

Rat-bite fever, caused by *Streptobacillus moniliformis*, is another cause of febrile rash involving palms and soles. After the bite of a rat, which may be healed and forgotten by the time patient develops symptoms, there is an incubation period which is usually less than 10 days. Sudden onset of fever, chills, headache heralds the onset of the disease. Patients often have GI symptoms, arthralgias, and septic arthritis. Significant leukocytosis and false positive nontreponemal syphilis serologies are frequent laboratory abnormalities. Rash usually appears 2 to 4 days after onset of fever and commonly involves palms and soles and extremities. Rash may be maculopapular, morbilliform, petechial, vesicular or pustular. Approximately 50% of patients develop asymmetrical polyarthritis or true septic arthritis. In many cases fever resolves on its own. However, in some cases fever may relapse in an irregular pattern for weeks or months. Untreated mortality can be up to 13%. Complications include endocarditis, meningitis, as well as involvement of lung, liver, and other organs with infection and/or abscess formation [8].

Two types of skin lesions, involving palms and soles, can be seen in infective endocarditis. Janeway lesions are non-tender maculae on the extremities, especially on toes and the soles of the feet, but also on fingers and palms of the hands. They are purpuric lesions caused by septic emboli, usually in acute infective endocarditis. Osler nodes, on the other hand, are tender and believed to be immune-complex related in subacute infective endocarditis. They are small subcutaneous nodules, ranging from red to purple, and are primarily found on pulp spaces of the terminal phalanges of the fingers and toes, soles of the feet, and the thenar and hypothenar eminences of the hands [9].

Tick-borne human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis*. It is most commonly reported from south-central and southeastern United States. After an incubation period of 1 to 2 weeks following tick exposure, patients present with fever, headache, myalgia, nausea, arthralgias, and malaise. Other organ systems including lungs, gastrointestinal, and central nervous system can also be involved. Rash happens in 30% to 40% of patients, can be petechial, macular, maculopapular, or a diffuse erythematous rash. It usually occurs 5 days into the illness, may involve extremities, trunk, face, and rarely palms and soles [10].

Toxic shock syndrome is a rare condition caused by *Staphylococcus aureus* or group A streptococcus infections. It is an acute febrile illness accompanied by a diffuse, blanching, erythroderma. Pharyngitis, strawberry tongue, conjunctivitis, or vaginitis, may be seen. Palmar edema and erythema is common [11].

Secondary syphilis involves the skin and mucus membranes in the majority of cases. The rash usually begins on the trunk and proximal extremities as small macular lesions that evolved into macule brownish red papules. They can be scaly and at times hyperkeratotic. Pustular lesions have been reported. Involvement of palms and soles is common. Mucus patches and alopecia are other

characteristics of this rash. Other symptoms that can be present include fever, malaise, pharyngitis, anorexia, weight loss, arthralgias, and myalgias. Involvement of other organs, including liver with elevated serum alkaline phosphatase, uveitis, and CNS involvement should be considered [12].

Murine typhus is caused by *Rickettsia typhi* and transmitted to human by rat and cat fleas. It is especially prevalent in tropical and subtropical seaboard regions. In the United States the majority of cases are seen in South Texas and Southern California. Following an incubation period of 1 to 2 weeks, patients present with fever, headache, myalgia, and gastrointestinal symptoms. Rash is common but may be missed in dark-skinned individuals. It is macular, maculopapular, or petechial and mostly distributed on the trunk. Involvement of palms and soles by the rash of murine typhus is seen in about 3% of cases. The disease is usually mild; however, involvement of central nervous system, lungs and kidneys may occur and require hospitalization. Among hospitalized adults with murine typhus mortality up to 4% has been reported [13].

Viral disease presenting with palm and sole rash

Chikungunya virus is an important cause of febrile illness in Africa and Asia. It is transmitted to humans by the bite of *Aedes* mosquitoes. Disease is characterized by fever, and prominent joint pain that may persist for months. In late 2013, chikungunya virus was found for the first time in the Americas on islands in the Caribbean. Beginning in 2014, chikungunya virus disease cases were reported among U.S. travelers returning from affected areas in the Americas. Several cases of local transmission have also been reported in Florida and Texas since then [14]. Skin rash is a common manifestation of the disease, and can present early in the febrile period, or after a few days of delay. An erythematous maculopapular rash affecting the trunk and extremities were the most common. However, a few patients will have involvement of palms, and soles. The rash is mostly non-pruritic [15].

Herpes simplex virus-associated erythema multiforme is another condition that can present with rash involving palms and soles. It is a complication of HSV reactivation. Patients present with fixed target or "bull's eye" lesions distributed diffusely in the body, with predilection for palms and soles. This condition usually occurs within 10 days of oral or genital HSV reactivation and resolves without complication, but may happen during subsequent reactivations.

Measles is still common in some countries in Europe, Asia, and Africa. Travelers to these countries who get infected can bring the disease to the United States, where most cases occur in people who have not been vaccinated. Disease presents with fever and a non-pruritic rash. The rash is erythematous, maculopapular, usually begins on the face and proceeds down the body to involve the extremities, including the palms and soles [16].

Hand Foot Mouth Disease (HFMD) is mostly caused coxsackievirus A16 and enterovirus 71. It usually occurs in children younger than 10 years. The most common systemic findings are fever, myalgia, and malaise. This is followed 1 to 2 days later by the appearance of mucocutaneous lesions, which last approximately 7 to 10 days with spontaneous resolution. Lesions could be papular and vesicular. They involve palms, soles, distal extremities, and buttocks. Oropharyngeal ulcerations are common, typically painful, and may precede the exanthem [17]. Parechoviruses are RNA viruses that mostly cause gastrointestinal and respiratory illness in very young. They can cause

a syndrome indistinguishable from HFMD in neonates and young infants [18].

Papular Purpuric "Gloves-and-Socks" Syndrome (PPGSS) is a rare disease, usually associated with *parvovirus* B19 infection. The syndrome is characterized by edema and erythema of the dorsal and palmar surfaces of the distal extremities with sharp margins at the wrists and ankles, followed by pruritic and sometimes painful multiple erythematous papular and purpuric lesions. Occasionally, similar lesions appear on cheeks, elbows, knees, trunk, buttocks, and the inner aspects of the thighs. Patients usually have fever, asthenia, anorexia, arthralgia, myalgia, and lymphadenopathy. The condition is self-limiting [17].

Varicella virus infection typically will spare palms and soles. However, rarely atypical presentations of varicella infection involving palms and soles have been described [19].

Smallpox and Monkeypox are the other two viral infections that can be associated with rash involving palms and soles. The former has been eliminated. Monkeypox occurs in Africa, mainly in Democratic Republic of Congo. If monkeypox is suspected in the United States, a history of exposure to African mammals imported as exotic pets should be sought [20].

Infectious agents with palm and sole lesions without fever

Scabies is caused by scabies mite *Sarcoptes scabiei* var. *hominis*. Severe forms of scabies, crusted or Norwegian scabies, are seen among the homeless, institutionalized older adults, the mentally retarded, and the immunocompromised [21]. The lesions, caused by mites burrowing into the skin, are often quite pruritic and have a predilection for finger webs, the ulnar border of the hand, around the wrists and elbows, the anterior axillary fold, nipples and penis and, in infants, the palms and soles. On the palms and soles lesion can appear as papules or blisters in infants [22]. Involvement of palms and soles also occurs in adults especially in the more severe forms of scabies such as crusted scabies and Norwegian scabies, often seen in HIV-infected and immunosuppressed patients [21].

Pseudomonas aeruginosa is a cause of outbreaks of folliculitis associated with the use of under chlorinated whirlpools and hot tubs. Patients often present with follicular, macular, papular, vesicular, or pustular lesions on any part of the body that has been immersed in the contaminated water. Nodular lesions on the palms and soles are less common, hand-foot syndrome, is clinically distinct rash in which the pathogenesis of palm and sole involvement remains unknown. Children often present with painful, self-limited, tender, erythematous nodules on palms and soles. The condition is reminiscent of idiopathic palmoplantar hidradenitis, which is an uncommonly reported condition also with an unknown pathogenesis [23].

Dermatophytosis is the infection of skin and keratinized tissue by dermatophyte molds. Involvement of the feet is common, often with involvement of interdigital areas by pruritic, erythematous erosions or scales. Hyperkeratotic (moccasin-type) tinea pedis is a distinct variety characterized by a diffuse hyperkeratotic eruption involving the soles and medial and lateral surfaces of the feet with variable degree of underlying erythema. Infection of the hand usually involves the palmar surface. A characteristic syndrome involving only one hand and two feet (Two Feet-One Hand Syndrome) has been described, however, in some patients both hands may be affected [24,25]. Id reaction is probably a cell-mediated immune response that occurs

after therapy of dermatophytosis has been started. The eruption is typically pruritic, papular, or vesicular, and sometimes follicular. It usually begins on the face and spreads to the trunk. The palms and soles may be involved [26].

Systemic disease presenting with palm and sole rash, with or without fever

A number of drug reactions can present with rash involving palms and soles. Notable among these is the drug rash with eosinophilia and systemic symptoms (DRESS syndrome). DRESS syndrome is characterized by fever, cutaneous eruption, and involvement of several internal organs-most commonly the liver. The cutaneous reaction usually begins 2 to 6 weeks after the drug is started and presents as a widespread erythematous eruption on the face, upper trunk, and upper extremities and is accompanied by fever, facial and periorbital edema, and/or exfoliative dermatitis. Eruption may rarely involve the palms and soles. Scaling and/or desquamation may occur with healing. The most common drug class implicated is anticonvulsants, including phenytoin, lamotrigine, and carbamazepine; other drugs known to cause this syndrome include allopurinol, minocycline, dapsone, and sulfonamides. Early cessation of the drug implicated is essential to hasten patient recovery [27].

Kawasaki Disease (KD) is a systemic vasculitis, presenting as an acute febrile illness of childhood with a predilection to involve coronary arteries, potentially causing coronary artery aneurysms. Patients present with fever from 1 to 4 weeks, bilateral conjunctival injection, erythema of the oral and pharyngeal mucosa with strawberry tongue, erythema of the hands and feet, rash, and cervical lymphadenopathy. There is diffuse erythema and edema of hands and feet with involvement of palms, soles. Periungual desquamation of the fingers and toes begins 2 to 3 weeks after the onset of illness and may progress to involve the entire hand and foot. Timely recognition of this condition is critical, as prompt treatment significantly decreases the risk of coronary artery aneurysm formation [28].

Adult-onset Still's disease is an inflammatory systemic disorder characterized by cyclic fever, arthralgia, sore throat/pharyngitis, and rash. The rashes typically consist of small, discrete, non-pruritic, salmon-pink maculopapules, which is transient and often coincides with the fever spikes. It can occur on the proximal limbs or trunk, and rarely involves the face, palms or soles of the feet [29].

Acute Cutaneous Lupus Erythematosus (ACLE): The typical presentation of localized ACLE involves the face in the form of malar rash. On the other hand, generalized ACLE is seen in only 5% to 10% of SLE patients, and presents as a widespread morbilliform or exanthematous eruption, consisting of multiple erythematous confluent macules and papules that spread out symmetrically over the entire body, often also involving the palmar and plantar surfaces, as well as the backs of the hands and extensor surfaces of the fingers. ACLE typically involves the interphalangeal areas and spares the knuckles. Lesions are more prominent in sun-exposed areas [30].

SAPHO syndrome (synovitis, acne, plantar pustulosis, hyperostosis and osteitis) is a systemic inflammatory condition that presents with pustular lesions on palms and soles, severe acne and hidradenitis suppurativa, sterile osteitis and hyperostosis. The condition runs a relapsing and remitting course and often presents in young adults 30 to 50 years old. The most common skin manifestations are those of palmoplantar pustulosis (small, sterile, yellowish pustules on the palms and soles) and severe acne, as well as hidradenitis suppurativa. Osteitis typically is multifocal and affects

Table 1: Some of the important associations of palms and soles rash.

Acute and Potentially Life-Threatening Conditions
Meningococcal infection
Rocky Mountain Spotted Fever
Rat-bite fever
Infective endocarditis
Human monocytic ehrlichiosis
Toxic shock syndrome
Murine typhus
Dress syndrome
Kawasaki disease
Contagious Conditions that Require Timely Diagnosis
Syphilis
Measles
Hand-foot-mouth disease
Scabies
Conditions that May have Public Health Implications
Chikungunya virus (mosquito-borne)
Monkeypox
Hematologic/Oncologic Associations
Cutaneous T-cell lymphomas
Mastocytosis
Palmoplantar keratoderma
Erythromelalgia
Cowden disease
Association with other Underlying Systemic Inflammatory Diseases
Adult-onset Still's disease
Acute Cutaneous Lupus Erythematosus
SAPHO syndrome
Reactive arthritis

chest wall bones, followed by pelvis and spine. Systemic symptoms of fever, weight loss, and generalized malaise are rare. Bone biopsy maybe needed to rule out infectious osteomyelitis [31,32].

Reactive arthritis (formerly Reiter's syndrome) is composed of a variable combination of non-gonococcal urethritis, arthritis, ocular findings, oral ulcers, and skin lesions. Reiter's syndrome can follow sexually acquired, non-gonococcal infections of the genital tract, or gastrointestinal tract infections, such as *shigella*, *Yersinia enterocolitica*, or *campylobacter*. Skin rash, may present with hyperkeratotic lesions in genital areas and be mistaken for psoriasis. Crusted erythematous papules and plaques with a predilection for the soles of the feet, and uncommonly palms, are referred to as keratoderma blennorrhagica and can be confused with palmoplantar psoriasis or secondary syphilis lesions [33].

Hematologic/oncologic conditions associated with rash involving palms and soles

Mastocytosis is a disorder of mast cells characterized by tissue mast cell hyperplasia involving the skin, bone marrow, and other organs. Adult-onset mastocytosis can be asymptomatic or present with variable symptoms such as rash, pruritus, flushing, abdominal pain, diarrhea, palpitations, dizziness, and syncope. In adult-onset

mastocytosis the lesions are usually small, monomorphic, reddish-brown or pink-red macules and papules. Rash involves the trunk and proximal extremity commonly, but distal extremities and palms and soles can be involved as well [34].

Cutaneous T-cell lymphomas, including mycosis fungoides and Sézary syndrome, can involve palms and soles, often as a part of diffuse erythroderma. Erythroderma is an erythematous skin condition in which confluent patches and/or plaques involve greater than 80% body surface involvement. It is intensely pruritic, and often associated with skin atrophy, lichenification, and fissuring. Hyperkeratosis of the palms and soles is common in this condition [35]. Diagnosis may require multiple skin biopsies and referral to expert dermatologist is strongly advised.

Palmoplantar Keratodermas (PPKs) represent a heterogeneous group of hereditary and acquired disorders of cornification characterized by prominent hyperkeratosis of the skin on the palms and soles. Hyperkeratosis can be diffuse, focal, or punctate. Inherited forms of the condition are often a component of phenotypes with extracutaneous manifestations such as cardiomyopathy or deafness. Acquired PPK can be drug-induced or associated with cancer (lung, breast, colon, kidney, stomach, or genitourinary tract cancers). Acquired PPK can develop in association with hypothyroidism [36].

Erythromelalgia is a rare disorder characterized by an intense, intermittent burning pain with redness and swelling, most commonly in the extremities. This pain is intensified by high ambient temperatures and relieved by cooling the affected area, a pattern which is opposite of Raynaud's phenomenon. Attacks last several minutes to days. While in children a primary form with autosomal dominant pattern is observed, in adults it is more commonly a manifestation of an underlying disease such as myeloproliferative disorders, systemic lupus erythematosus, or cancers [37].

Cowden disease (Multiple Hamartoma Syndrome) is a rare autosomal dominant disorder, characterized by multiple small, noncancerous growths that are most commonly found on the skin and mucous membranes (such as the lining of the mouth and nose), but can also occur in the intestinal tract and other parts of the body. Patients have increased risk of breast, thyroid, and uterine cancer. Patients have mutations in PTEN gene (a tumor suppressor gene in 80% of patients). Some patients have palmar keratotic lesions [38].

Primary dermatologic conditions associated with rash involving palms and soles

Psoriasis is a chronic inflammatory skin disease characterized by scaly, hyperkeratotic, papules and plaques involving any part of the body. Palmoplantar psoriasis is a variant of psoriasis which is seen with or without psoriasis elsewhere on the body. It is mostly characterized by well-demarcated, erythematous, scaly plaques of the palms and/or soles. Lesions can be pustular, involve nails, and create painful fissures and hyperkeratotic plaques on the palms and soles [39]. For primary care providers, differentiation from lesions of secondary syphilis is important. Referral to dermatologist experienced in treatment of psoriasis is indicated.

Lichen planus is a relatively common, pruritic, inflammatory disease of the skin, mucous membranes, and hair follicles. It typically affects adults, with peak age 40 and 70 yr in those of European origin. Race may affect the age of presentation and the prevalence of the disease. Lesions are pruritic, small, flat-topped, polygonal papules, initially erythematous and later violaceous and hyperpigmented. On

the surface, gray or white puncta or streaks (Wickham striae) cross the lesions. Rash has a predilection for the flexor wrists, trunk, medial thighs, shins, dorsal hands, and glans penis. The palms and soles may be affected with small papules or hyperkeratotic plaques [40]. In addition, LP of the palms and soles can occur as an isolated rash without involvement of the rest of the skin. Lesions on the palms and soles at times are larger and symptoms can be severe and resistant to treatment [41].

Pompholyx is an eczematous skin condition presenting as symmetric vesicular hand and foot dermatitis. The lesions start as vesicles on palms and sides of the fingers on erythematous and perspiring palms and evolve into scaly ring lesions 1 mm to 3 mm in about 3 to 4 weeks. Chronic eczematous changes with erythema, scaling, and lichenification may follow. Pain rather than itching is often the complaint. Allergic contact, idiopathic and exposures to cosmetic and hygiene products are the most common etiologies. However, other diagnosis, outlined in this article such as mycosis fungoides and pustular psoriasis, need to be considered [42].

Palmoplantar eccrine hidradenitis is closely related to neutrophilic eccrine hidradenitis. It was originally described in children presenting with tender, erythematous plantar nodules (idiopathic plantar hidradenitis); patients with palmoplantar involvement and exclusive palmar involvement have since been reported. The lesions usually resolve in 2 to 4 weeks without treatment; recurrences and longer duration of the lesions have been reported [43].

Conclusion

Skin rash involving palms and soles can be associated with several systemic conditions. Some of these conditions require rapid recognition, as delay in diagnosis can have life-threatening consequences (Table 1). Others require early diagnosis because of potential transmission to others and public health implications (Table 1). Finally, sometimes palm and sole rash may be associated with underlying conditions, such as inflammatory, hematologic, or oncologic conditions. Primary care clinicians familiar with these conditions will be able to initiate appropriate work up, and refer to appropriate consultants, to allow for timely diagnosis of underlying conditions. In addition, being familiar with the conditions that cause palm and sole rash will result in minimizing unnecessary testing and patient morbidity.

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