Rickettsial Infection

Rocky Mountain spotted fever (RMSF) is a potentially life-threatening disease caused by Rickettsia rickettsii, an obligate, intracellular bacterium that is spread to human beings by infected ticks. The disease is the most common tick-borne rickettsial disease in the United States and can be fatal.[1] R. rickettsii is a fastidious, small, pleomorphic Gram-negative coccobacillus that primarily infects vascular endothelial cells.[1,2] In the United States, multiple tick species are vectors for R. rickettsii transmission. The tick species that is most frequently associated with R. rickettsii transmission is the American dog tick found in the eastern, central, and Pacific Coastal United States and is active from spring through autumn, with peak activity during late spring through early summer.[2] Consequently, 90% of RMSF cases occur between April and September and 40% occur in May and June.[3]

Initial clinical signs and symptoms are similar to those observed in other tick-borne rickettsial diseases; thus, diagnosing the disease in the early phase is difficult.[1] Symptoms typically appear 3 to 12 days after the bite of an infected tick.[2] Initial symptoms include sudden onset of fever, headache, chills, malaise, and myalgia, nausea, vomiting, abdominal pain, and anorexia.[3] A rash typically appears 2–4 days after the onset of fever; however, most patients seek health care before a rash develops and a rash may not develop in approximately 9% of cases.[1,2] During the first 3 days, the classic clinical triad of fever, headache, and rash is observed in a minority of patients, but the triad is observed in approximately 60% of patients within 2 weeks.[1,4] The rash classically begins as small, blanching, pink macules on the ankles, wrists, or forearms that spread to the palms, soles, arms, legs, and trunk. The face is spared. Over several days, the rash typically becomes maculopapular, sometimes with central petechiae.[1,2] Vasculitis may result in damage of the brain, heart, kidney, and spleen.[1] Severe late-stage manifestations of RMSF include meningoencephalitis, acute renal failure, acute respiratory distress syndrome, cutaneous necrosis, arrhythmia, and seizure.[2]
In the U.S., RMSF is the most frequently fatal rickettsial illness. Delays in diagnosis and treatment are the most important factor associated with increased likelihood of fatality. Without treatment, RMSF progresses rapidly, and the fatality rate is approximately 25%. With treatment, the fatality rate drops to 5%–10% depending on when the antibiotics were initiated. Infections treated after the 5th day are more likely to be fatal than those treated earlier. Additional risk factors for fatality include advanced age, male gender, and alcohol abuse. Glucose-6-phosphate dehydrogenase deficiency is a risk factor for fulminant RMSF, with death occurring in about 5 days. Although children are affected more commonly than adults, RMSF is more fatal in the elderly population.

The diagnosis of RMSF is based on physical examination of the patient and epidemiological data. Rapid diagnosis can be achieved through frozen section of a punch biopsy. Making a clinical diagnosis is difficult because the initial signs and symptoms are usually nonspecific. The indirect immunofluorescence assay is >90% sensitive and is the most commonly employed serological test for evaluation of R. rickettsii infection. However, antibodies may not be present until after 10–14 days of the illness. Because fatal cases of RMSF are often associated with delayed diagnosis and treatment, the decision to treat should never be delayed by laboratory confirmation. Biopsy of cutaneous lesions reveals leukocytoclastic vasculitis of varying severity, i.e., lymphohistiocytic and occasionally neutrophilic infiltration into the walls of capillaries and postcapillary venules with scattered karyorrhectic nuclear debris.

**Eczema Herpeticum**

Eczema herpeticum (EH) is a rare, secondary infection of a chronic skin disease with herpes simplex virus (HSV). It is most commonly found in patients with atopic dermatitis (AD). EH presents as an eruption of rapidly spreading disseminated vesicles that are monomorphic and dome-shaped and associated with cutaneous pain. The rash starts in areas affected by the underlying dermatitis, and it can spread to involve normal skin in three to 10 days. Systemic symptoms are often present and include fever, malaise, and lymphadenopathy. Three to six percent of patients with AD develop EH. EH is a difficult clinical diagnosis, and it is commonly misdiagnosed as a flare of the underlying chronic skin condition.

Skin biopsy of EH shows viral inclusions and multinuclear epidermal cells. Viral stains for HSV are positive. Heavy neutrophil infiltrate and early breakdown of the vesicles are usually seen. The diagnosis is mostly clinical.

Risk factors in patients with AD that predispose them to EH include severe AD, early-onset AD, prior *Staphylococcus aureus* skin infection, high total serum IgE/peripheral eosinophils, and the presence of other allergic diseases. EH is often caused or exacerbated by immunosuppressive agents being used to treat the primary dermatitis. Staphylococcal colonization of the skin may be associated with EH. In some cases, EH becomes secondarily infected with *S. aureus*, which can lead to septic shock. In other cases, it appears that *S. aureus* can predispose a patient to develop EH or increase its severity. It has been shown that *S. aureus* toxins modulate the host response to HSV in normal human keratinocytes, and staphylococcal alpha-toxin increases viral loads of HSV in keratinocytes by forming pores and promoting viral entry into epithelial cells.

The pathogenesis of EH is related to the balance of CD4+ and CD8+ T cells. There is a subset of patients with AD who are susceptible to disseminated viral infections from secondarily infected AD. Susceptibility has been linked to genes in peripheral blood mononuclear cells that have been shown to cause a different immune response following HSV exposure when compared to atopics who do not develop EH after HSV exposure. In a study of 792 genes, interferon genes were the most downregulated in EH patients, as well as several interferon regulatory genes. Skin barrier defects associated with mutations of the FLG gene, claudin-1, and tight junction proteins are also associated with the EH subset of patients with AD.

EH is a life-threatening disease that initially presents with seemingly benign dermatological findings. If untreated, EH can lead to a systemic viral infection involving multiple organ systems. Sequelae of viremia include fever, keratoconjunctivitis, encephalitis, meningitis, multiorgan failure, and septic shock. Six to ten percent of EH cases in immunocompetent and up to 50% of cases in immunocompromised patients are fatal. The cause of death is usually related to viremia, multiorgan involvement, and bacterial superinfection and septic shock. In children, disseminated HSV can be accompanied by bone marrow suppression and disseminated intravascular coagulation. If EH is misdiagnosed as an exacerbation of the underlying dermatitis and corticosteroids are administered, the viral infection can worsen.

**Situational Emergencies**

**Porphyria cutanea tarda**

Porphyria cutanea tarda (PCT) is the most common cutaneous porphyria in most populations and results from inhibition of the fifth enzyme in the heme synthesis pathway and uroporphyrinogen decarboxylase (UROD). UROD catalyzes the decarboxylation of uroporphyrinogen III to coproporphyrinogen III. PCT is predominantly a disease of adulthood with an estimated prevalence of one per 25,000. The three major forms of PCT are sporadic, familial, and toxic. PCT occurs as an acquired sporadic condition in 75% of patients, usually in association with liver disease and alcohol abuse, occurring in midlife. The remaining 25% inherit PCT as an autosomal dominant condition with low penetrance; its onset is usually earlier than that of the sporadic form. Conditions associated with UROD inhibition include hepatitis C infection, excessive alcohol intake, prescribed estrogen, HIV infection,
and iron overload. Decreased UROD activity increases production of symptom-causing carboxylic porphyrins.\[^{21}\] The toxic form of PCT results from exposure to polychlorinated aromatic hydrocarbons.\[^{22,23}\]

Cutaneous findings include skin fragility, bullae [Figure 1], erosions, vesicles, crusts, milia, hypo and hyperpigmentation, and hypertrichosis. Minor trauma results in skin erosions and blisters, which can become secondarily infected, forming crusts and scarring.\[^{21}\] Hepatomegaly is common in PCT, and cirrhosis is found in 30%–40% of patients. Urine is often discolored with a red-brown tinge.\[^{21}\] Following treatment, most patients remain in remission. However, approximately 30% of PCT cases can relapse during long-term follow up, especially if they continue to be exposed to risk factors. PCT is easily treatable and nonfatal. Life expectancy in PCT is normal in the absence of comorbidities, such as advanced liver disease.

Patients with PCT remain at risk for development of liver disease including hepatocellular carcinoma, irrespective of associated susceptibility factors.\[^{24}\] The incidence of hepatocellular carcinoma is approximately 3.5 times higher in PCT compared with matched chronic liver disease controls.\[^{18}\] Emphasis on discontinuing exposure to environmental triggers and counseling patients regarding the treatment plan is of utmost importance.

**Birt–Hogg–Dubé Syndrome**

A n a u t o s o m a l d o m i n a n t g e n o d e r m a t o s i s, Birt–Hogg–Dubé syndrome (BHD), is characterized by cutaneous fibrofolliculomas\[^{25}\] and an increased propensity for developing renal tumors,\[^{26}\] multiple pulmonary cysts,\[^{27}\] and spontaneous pneumothorax.\[^{28,29}\] Mutations in the *FLCN* (BHD) gene on chromosome 17p11.2, which encodes the protein folliculin, is responsible for the syndrome.\[^{30}\] Folliculin is expressed in the kidneys, lung, and skin.\[^{31}\] Although fibrofolliculomas, trichodiscomas, and acrochordons were initially described as the three distinct cutaneous tumors of BHD; these three lesions are now believed to represent only one of these tumors, the fibrofolliculoma.\[^{32}\] Similarly, the perifollicular fibroma is also considered a fibrofolliculoma.\[^{29}\] Some or all patients with Hornstein–Knickenberg syndrome, which features perifollicular fibromas, may actually have BHD.\[^{32-34}\]

Fibrofolliculomas and trichodiscomas are clinically indistinguishable, as both are hair follicle hamartomas, appearing as small, white, dome-shaped papules on the upper trunk, neck, and face.\[^{35}\] Histologically, fibrofolliculomas consist of strands of epithelial cells, two to four cells wide, emanating from a follicular structure with infundibular features [Figure 2]. The strands may rejoin the infundibulum at many points, and the infundibulum may be filled with keratin and dilated. Within the epithelial cords may be one or more sebocytes, possibly forming tiny lobules. Sebaceous ducts may also be identified. A well-circumscribed proliferation of loose connective tissue, made of fine fibers with some intervening mucin, may be detected around the epithelial cords. Elastic fibers may be sparse or absent.\[^{29}\] On the other hand, trichodiscomas also radiate from hair follicles and are typically nonencapsulated and well-demarcated tumors.\[^{29,36}\] They are fibrous tumors made of thin-walled blood vessels and often have peripherally situated sebaceous lobules.\[^{36}\] Other cutaneous lesions which may be found in patients with BHD include lipomas, facial angiofibromas, oral mucosal fibromas, and angioliopomas.\[^{37}\]

Patients with BHD are 7 times more likely to develop renal tumors compared to unaffected siblings. The tumors are diagnosed at a mean age of 50 years and are often bilateral or multifocal.\[^{38,39}\] Colorectal polyps, colorectal cancer, parotid gland tumors, breast cancer, and melanoma have also been documented in patients with BHD.\[^{31,39}\] Over 80% of adult patients with BHD have multiple lung cysts, often in the lung bases. As a result, they have a 50-fold increased risk of spontaneous pneumothorax compared to an unaffected sibling.\[^{35}\] Therefore, the diagnosis of BHD requires educating the patient about the risk of developing the associated conditions and seeking screening to avoid progression of possible occult malignancies.
Muir–Torre Syndrome

Muir–Torre syndrome (MTS) is an autosomal dominant genodermatosis characterized by the development of sebaceous tumors, often multiple, and in association with visceral neoplasms. The visceral neoplasms tend to be gastrointestinal carcinomas. Colonic polyps, epidermal cysts, and keratoacanthomas may also be present. Although the sebaceous tumors may be difficult to classify, they mostly resemble sebaceomas and sebaceous adenomas and occasionally carcinomas [Figure 3]. Despite sebaceous hyperplasia possibly being present, it is not considered an indicator of MTS. Multiple sebaceous tumors, especially when they occur before the age of 50 years, are strongly indicative of MTS.

Tumors tend to be in the gastrointestinal tract, especially polyps or adenocarcinomas of the colon. In addition, tumors may also be found in the larynx, ovary, uterus, and in the genitourinary system of men. Lymphoma has also been reported. The tumors may display microsatellite instability. MTS is considered an allelic variant of Lynch syndrome and represents about 9% of individual cases of Lynch syndrome. Immunosuppression may reveal latent MTS, especially in transplant patients. The tumors may display microsatellite instability. MTS is considered an allelic variant of Lynch syndrome and represents about 9% of individual cases of Lynch syndrome. Immunosuppression may reveal latent MTS, especially in transplant patients. A recent study suggests that solid organ transplant recipients mainly develop sebaceous carcinomas in an extraorbital distribution and that both wide local excision and Mohs micrographic surgery are equally effective treatment options. There were no recurrences after either procedure.

The sebaceous tumors of MTS may demonstrate sheets of basaloid cells in lobules or an intermingling of these cells with sebaceous cells in no particular order. These atypical features of the sebaceous tumors of MTS may be predictive of malignant transformation if not completely excised. Occasionally, the tumors may resemble basal cell carcinomas with focal sebaceous differentiation. Cystic areas and mucin may be detected. Some tumors may join with the surface and possess a central debris-filled crater, almost resembling a keratoacanthoma. All sebaceous tumors should be screened for MLH-1, PMS-2, MSH-2, and MSH-6 and their respective gene products. MTS is diagnosed when nuclear staining for the designated gene product is absent in the tumors. False-negative and false-positive results are uncommon. Alternatively, immunohistochemical or both immunohistochemical and genetic testing of neoplasms may be used to confirm the diagnosis of MTS.

The diagnosis of MTS is made when there is at least one sebaceous neoplasm and at least one internal organ cancer at some point in the patient’s life, excluding contributing factors such as AIDS or radiotherapy. The diagnosis is also suggested in a patient with a family history of MTS and a personal history of multiple keratoacanthomas or keratoacanthomas in areas not exposed to sunlight. Similar to BHD, cancer surveillance of patients with BHD should be conducted to prevent the progression of occult malignancy and includes annual examination of the testicles and prostate in men, examination of the breast and pelvis in women, colonoscopy starting as early as age 18 years depending on the genetic subtype of MTS, measurement of tumor markers, complete blood cell count, fecal occult blood test, and urinalysis.

Ochronosis

Alkaptonuria is the endogenous form of ochronosis and results from dysfunction of homogentisate 1,2-dioxygenase (HGD) leading to the accumulation of homogentisic acid (HGA) in connective tissue. Exogenous ochronosis results in a similar clinical picture but results from the topical application of agents such as hydroquinone, phenol, resorcinol, mercury, and picric acid. It can also result after oral or parenteral administration of antimalarial drugs. Like alkaptonuria, exogenous ochronosis causes the inhibition of HGD and accumulation of HGA.

HGA is partially excreted in the urine and partially accumulated in the body. Accumulation of HGA due to HGD defects can be identified because HGA undergoes spontaneous oxidation to benzoquinone-2-acetic acid (BQA). BQA forms an unknown melanin-like polymer that turns the urine black. The blackening of urine is a pathognomonic sign of the disease. The HGA that accumulates in the body also undergoes oxidation into BQA and subsequent polymerization into the melanin-like compound [Figure 4]. The oxidation and polymerization occurs in nonmineralized connective tissues of the skeletal, integumentary, ocular, and cardiovascular systems, leading to a pathological bluish-black discoloration. This phenomenon is known as “ochronosis.”

The development of ochronotic arthropathy is the result of deposition of the unknown melanin-like polymer within hyaline articular cartilage. Pigmentation is widespread, with all tissues of the joint affected. The affected tissues often become weak, brittle, and prone to chipping, fracturing, and cracking, causing rapid joint degeneration. Ligaments and tendons can also rupture. Consequently, patients can be left profoundly disabled. Patients with ochronotic arthropathy usually present with lumbar pain as the initial joint manifestation. Larger weight-bearing joints tend to be affected later in the progression of the condition.
CONCLUSION
Dermatologic emergencies, although uncommon, may present in a number of ways. It is incumbent on physicians to be vigilant for both the clinical and pathologic signs of these diseases to avoid serious, and sometimes deadly, consequences. We herein describe several such conditions which warrant emergent intervention. This list is not exhaustive but is meant to describe some of the more common pathologies, how to diagnose them, and an overview of appropriate management.

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