Rocky Mountain spotted fever is still the most lethal tick-vectored illness in the United States. We examine the dilemmas facing the clinician who is evaluating the patient with possible Rocky Mountain spotted fever, with particular attention to the following 8 pitfalls in diagnosis and treatment: (1) waiting for a petechial rash to develop before diagnosis; (2) misdiagnosing as gastroenteritis; (3) discounting a diagnosis when there is no history of a tick bite; (4) using an inappropriate geographic exclusion; (5) using an inappropriate seasonal exclusion; (6) failing to treat on clinical suspicion; (7) failing to elicit an appropriate history; and (8) failing to treat with doxycycline. Early diagnosis and proper treatment save lives.

Rocky Mountain spotted fever (RMSF), a tick-vectored disease that was first described in the Rocky Mountain region of the United States in the late 1800s, is caused by the obligate, intracellular cocccobacillus Rickettsia rickettsii. Rickettsia rickettsii elicits a moderately severe to life-threatening systemic illness in its host by infecting endothelial cells lining small vessels of all major tissues and organ systems. Lethal and irreversible damage to endothelium in the dermis, lungs, heart, kidneys, gastrointestinal tract, brain, skeletal muscle, and other sites results in protein and often severe clinical manifestations associated with untreated disease. These pathophysiologic events are responsible for the rash, headache, myalgias, and gastrointestinal symptoms that are commonly associated with RMSF, and can lead to more devastating manifestations, including gangrene, pulmonary hemorrhage and edema, acute respiratory distress syndrome, myocarditis, acute renal failure, meningoencephalitis, and cerebral edema.

For older clinicians, RMSF was perhaps the primary, if not only, tick-borne illness emphasized in medical school curricula before the early 1980s. Within the last 20 years, RMSF has been relatively overshadowed by the discoveries of, and subsequent attentions devoted to, an expanding and diverse collection of other tick-transmitted diseases in the United States, including Lyme disease, Lyme-like illnesses in the South (Masters disease or southern tick-associated rash illness), the ehrlichioses (human monocytic ehrlichiosis, human granulocytic ehrlichiosis, and Ehrlichia ewingii ehrlichiosis), and several distinct babesioses. Despite the recent recognition of these various novel illnesses, RMSF remains the most lethal tick-borne infection in the United States. The case-fatality ratio of untreated RMSF across all age groups combined approaches 25%, and the disease continues to kill patients throughout the United States each year: 224 deaths caused by RMSF were reported to the Centers for Disease Control and Prevention during 1983 through 1998, although this number underestimates the true magnitude of mortality attributable to this infection. Rocky Mountain spotted fever is something of a misnomer, as the disease has been reported in all the contiguous United States.
except for Maine and Vermont\(^1\) (Figure 1). During the last several decades, relatively few reports of RMSF have originated from the Rocky Mountain states. The greatest number of cases are reported from southeastern and midwestern states, with North Carolina, Oklahoma, Tennessee, Arkansas, South Carolina, Maryland, and Virginia consistently among the top 10 states in contemporary national surveillance summaries of RMSF.\(^{33,36}\) During 1996 through 2000, approximately 2700 cases of RMSF were reported to the Centers for Disease Control and Prevention (cases per year: mean, 536; range, 365-831).\(^{37,38}\) The disease is transmitted by the American dog tick (Dermacentor variabilis), a relatively common and broadly distributed tick in the eastern United States, and by the wood tick (Dermacentor andersoni) in the Rocky Mountain states.\(^{33,39,40}\) A clear spring-summer distribution of cases is an immutable feature of this illness and attests to the association of RMSF with peak occurrences of Dermacentor tick bites. During 1993 through 1996, 92% of confirmed cases of RMSF occurred from April through September, with 43% occurring in May and June. Confirmed cases may occur during every month of the year, but episodes of RMSF are unusual during fall and winter, and these generally originate from southern states.\(^{35}\)

Although a history of recent tick bite can be extremely helpful in establishing a presumptive diagnosis of RMSF, the absence of this feature should not dissuade a clinician from considering this diagnosis if clinical or epidemiologic suspicion for the disease is otherwise high. In this context, a definite recollection of a tick bite within the 14 days before the occurrence of symptoms has been reported in approximately 60% of confirmed cases in several patient series.\(^{35,36}\) An early diagnosis of RMSF remains a clinical dilemma and represents an often difficult challenge, even to physicians who are acquainted with the disease. The broad yet sporadic distribution of RMSF, coupled with the relatively nonspecific signs and symptoms early in the illness, compounds the diagnostic difficulty for physicians who are unfamiliar with the epidemiological and clinical features of this disease. Periodic reinforcement of RMSF in the differential diagnoses of tick-borne illnesses is important because a delayed or missed diagnosis can be catastrophic.\(^{31-45}\)

We report 2 cases of RMSF to illustrate the diagnosis. The second case, which was diagnosed later in the course of the illness, demonstrates the difficulties that can be encountered in reaching the correct diagnosis.

CASE 1

A 5-year-old female resident of Cape Girardeau County, Missouri, presented to an emergency department and was evaluated by one of us (S.J.W.) on June 1, 2001, with a 1-week history of intermittent fever, with temperatures as high as 40°C. Three days after the onset of fever, she developed a maculopapular erythematous rash on her extremities, including her palms and soles, that moved centripetally to involve her trunk. Her parents reported tick exposure around their rural residence, but no definite antecedent tick bite. The family did not own a dog. The patient’s additional symptoms at presentation included mild nausea the previous week, headache, and a “scratchy” sore throat. Other than rash, the findings of the physical examination were unremarkable. The patient’s temperature was 40.6°C. Significant laboratory results included a white blood cell count of 8800 \(\times\) 10\(^3/\mu L\), with 5% band cells, 70% neutrophils, 17% lymphocytes, and 8% monocytes. The platelet count was 192 \(\times\) 10\(^3/\mu L\). The serum glutamic pyruvic transaminase and glutamic oxaloacetic transaminase levels were elevated (60 \(\mu L\) and 80 \(\mu L\), respectively). Serologic tests were negative for *Ehrlichia chaffeensis*. A 2-week course of oral doxycycline was prescribed.

The patient’s fever abated on June 3, and she reported feeling much better the following day. Her fading rash was still visible (Figure 2 and Figure 3). She had an increased appetite and, according to her mother, was again becoming playful. Serum samples collected on days 7 and 35 of the illness were tested with an indirect immunofluorescence assay, which demonstrated rising IgG antibody titers that were reactive with *Rickettsia* titrates at dilutions of 1:32 and 1:2048, respectively).

CASE 2

An 11-year-old white female resident of Cape Girardeau County presented in late May with a low-grade fever at home (in-office temperature, 38.3°C), frontal headache,
stomachache, and an erythematous maculopapular rash on her arms, legs, and trunk that had spread to her palms and soles. There were no oral lesions. The diagnosis of Coxsackievirus hand-foot-and-mouth disease was made, and the patient was sent home. Her fever, rash, and headache persisted. Two days later, nausea and vomiting developed. The patient was evaluated in the emergency department, diagnosed as having viral gastroenteritis, treated with intravenous fluids, and discharged with promethazine suppositories. Four days later, she was treated by a chiropractor for neck and back pain, without relief. The next day she was hospitalized for further evaluation and treatment. On admission, she had petechiae in some areas and blanching erythematos papules in others, but no palpable purpura. It was unclear when her rash had developed petechial characteristics. She was hemodynamically stable throughout her illness, and the headache, vomiting, fever (temperatures as high as 40°C), and rash were her predominant complaints. There was no recollection of a tick bite. The family did own a healthy dog. The patient denied photophobia on admission, but developed it later in the hospitalization. She had no meningismus. She had been treated for attention deficit disorder and gave a history of having had migrainelike headaches. A review of systems revealed no other abnormalities.

On admission, the patient underwent a spinal fluid examination (negative results) because of the fever, neck pain, vomiting, and petechial rash. A complete blood cell count demonstrated a white blood cell count of $12 \times 10^3/\mu$L (5% band cells, 43% segmented neutrophils, 40% lymphocytes, 10% monocytes, and 1% reactive lymphocytes). The hemoglobin level was 12.1 g/dL, and the platelet count was $379 \times 10^3/\mu$L. A comprehensive metabolic profile showed a normal sodium level (138 mEq/L) and elevated levels of aspartate aminotransferase (51 U/L) and alanine aminotransferase (95 U/L). Other laboratory test results were normal. The leading diagnosis at this time was still a viral syndrome, and the patient was treated with ceftriaxone pending culture results.

Two days into her hospitalization, one of the authors (S.J.W.) was consulted, and a prophylactic regimen of doxycycline was initiated pending titer results. The patient’s fever abated less than 2 days later, with resolution of her headache and vomiting. Two days later, she was discharged, with the rash beginning to fade on her extremities. At discharge, her RMSF IgG serology drawn during hospitalization was negative, with the IgM positive at $>1:2048$. She was treated with doxycycline for 14 days and had no reported sequelae.

**COMMENT**

**DIAGNOSIS**

Rocky Mountain spotted fever has a mean incubation time of 7 days after the bite of an infecting tick.41 We need to remember that ticks can be very small; can attach on the body in places that are difficult to observe, such as the scalp, back, axillae, and inguinal regions; usually have a painless bite; and commonly go unnoticed. Diagnosis of RMSF can be difficult, particularly in the early stages of the illness. In a recent series of approximately 1000 cases of confirmed RMSF that occurred during 1993 to 1996, the triad of rash, fever, and headache was present in only 44% of the cases at any time during the illness. The occurrence of this classic triad at initial presentation, however, is less frequent, and the rash, which in the initial phases is macular rather than petechial, with the macules blanching with pressure, is generally not apparent until 3 to 4 days after the onset of the disease. Occasionally, RMSF may be “spotless” or “almost spotless.”42 Of importance, early in the illness, more than 50% of the patients have nausea or vomiting, and infection of the gastrointestinal tract is a common misdiagnosis.23 Photophobia and myalgias, especially bilateral calf pain, can also be present.47,48 In addition, IgM and IgG antibodies reactive with *R rickettsii* may be undetectable during the first week of the illness.49 Tick-borne illnesses need to be considered by physicians during the evaluation of fever of unknown origin, especially in the spring and summer. However, cases have been reported in all 12
months. Other tick-borne diseases, including ehrlichioses, Lyme disease, and babesioses, can also pose diagnostic challenges to a clinician who is presented with a febrile patient with nonspecific symptoms such as headache, fever, and myalgias. Leukopenia, thrombocytopenia, or elevated liver enzyme levels may occur in patients with RMSF as well as other tick-borne diseases, such as the ehrlichioses.28,46,52 A good history is essential to the diagnosis.

TREATMENT

The treatment of choice for RMSF is doxycycline therapy for at least 7 days.45,53 Doxycycline is preferred because it has a broader spectrum of coverage for other tick-borne illnesses, including the ehrlichioses and other rickettsial infections, which are frequently in the differential diagnosis. These infections collectively have been described as “doxycycline deficiency diseases.”31 Chloramphenicol is also active against R. rickettsii; however, this drug should only be used in situations in which doxycycline therapy is contraindicated, such as pregnancy. Treatment with chloramphenicol is associated with a higher percentage of fatal outcomes than treatment with tetracyclines.32,34 Moreover, gray baby syndrome and aplastic anemia that is unrelated to dosage, both rare but potentially fatal complications, have been reported with the use of chloramphenicol.23,34 Also, the efficacy of chloramphenicol in the treatment of other tick-borne illnesses that may mimic RMSF is uncertain.23 We particularly remember a 2-year-old patient from southern Missouri who was initially diagnosed as having RMSF. Examination revealed an extremely ill child with a petechial centripetal rash and fever. She did not respond to chloramphenicol therapy but did respond to treatment with doxycycline. Polymerase chain reaction analysis subsequently led to a diagnosis of infection with E. chaffeensis. The rash in ehrlichiosis, compared with the rash in RMSF, occurs less frequently, may be more transient, has a later onset, and is less often petechial.20

Doxycycline therapy is indicated, even in children, whenever RMSF or an ehrlichiosis is suspected. The risk of tooth staining is not significant for short-term therapy and is definitely subordinated to the prospect of a potentially lethal illness.53,55-59 In one study in which tooth discoloration in children receiving tetracycline was evaluated, it was observed that cosmetically perceptible staining occurred primarily only in those patients who received 5 or more multiday courses of this antibiotic.56 Also, doxycycline binds less strongly to calcium than do other tetracyclines.60 The American Academy of Pediatrics and the Centers for Disease Control and Prevention recommend doxycycline as the treatment of choice for RMSF and the ehrlichioses in children of any age.55,57

In febrile patients with a history of a tick bite in the preceding 14 days, we recommend empiric treatment with doxycycline on clinical suspicion. For adults, the dosage is 200 mg/d or 3 mg/kg of body weight, whichever is higher. In children who weigh less than 45 kg, the dosage of doxycycline is 4.4 mg/kg.61 This treatment covers RMSF as well as other tick-borne diseases, such as the ehrlichioses, relapsing fevers, Lyme disease, Lyme-like illness (also known as Masters disease), and tularemia. At least one of these other diseases is likely to be in the differential diagnosis. Coinfection with more than one of these pathogens is also a possibility.64,71 An argument has been made that hospitalized patients with suspected RMSF should also receive a third-generation cephalosporin that is active against Neisseria meningitidis because of the overlapping signs and symptoms and the disastrous consequences of missing either diagnosis.51,72 In our evaluations, we routinely request a complete blood cell count, measure aspartate aminotransferase and/or alanine aminotransferase levels, and obtain extra serum samples, saving the samples in a refrigerator for possible future tests. There are no serologic tests that can provide a reliable and accurate early diagnosis of any of the tick-borne illnesses, and treatment decisions should never hinge on a confirmatory assay. The greatest therapeutic response can be seen in the first 2 to 3 days of these illnesses. The saved initial serum sample can be useful when paired with a convalescent-phase serum sample in proving a diagnosis. Polymerase chain reaction technology is being used increasingly to sort out agents of various tick-borne diseases.

In dogs, as in humans, the symptoms of RMSF and the ehrlichioses can overlap. While one of the authors (E.J.M.) was involved in a prospective study of human monocytotropic ehrlichiosis,28 an experienced veterinarian called and offered a blood sample for culturing from a dog that he thought had canine monocytic ehrlichiosis. The culture yielded R. rickettsii, the agent of RMSF. Thus, in dogs, as in humans, the signs of RMSF and the ehrlichioses can be clinically similar. There are even reports of concurrent RMSF in dogs and their owners.73

EIGHT PITFALLS IN THE DIAGNOSIS AND TREATMENT OF RMSF

1. Waiting for a petechial rash on the palms and soles before making a diagnosis. Patients usually present for care on day 2 or 3, whereas the rash usually appears on day 3 or 4. The rash generally begins as a macular or maculopapular eruption on the wrists or ankles that only later involves the palms and soles and becomes petechial.41 Some patients have no rash or a very subtle or focal rash.46,47

2. Misdiagnosing gastroenteritis. Nausea and vomiting early in the illness occur in more than 50% of patients with RMSF.23 Gastrointestinal symptoms can also be a prominent early feature of other tick-vectored illnesses, such as the ehrlichioses.20

3. No history of a tick bite. Approximately 40% of patients with RMSF do not report an antecedent tick bite.32,35,36,43,47,54 In this context, absence of tick bite should never dissuade a clinician from considering RMSF.

4. Geographic exclusion. Rocky Mountain spotted fever has been reported in 46 states. It is more common in the lower midwestern and southeastern states, but it does occur elsewhere and should be con-
sidered endemic in the contiguous United States.53
5. Seasonal exclusion. Although 90% of cases occur during April through September, one needs to have an index of suspicion all year. Confirmed cases have been reported during every calendar month.36 Wintertime cases are more likely to occur in the southern states.36
6. Failure to treat early on clinical suspicion. Dependent on the patient’s age, untreated RMSF has a 10% to 25% case-fatality ratio.32,54 Delayed treatment after day 5 is associated with a significantly higher morbidity and mortality.55,56 Fifty percent of all deaths occur on or before day 8.62
7. Failure to elicit appropriate history. The nonspecific signs and symptoms of early RMSF, coupled with a general lack of awareness of this disease, conspire to make RMSF an elusive initial diagnosis. A good history that elicits exposure to ticks or tick-infested habitats or concurrent illness in household pets (especially dogs) or in similarly exposed family members can be extremely helpful to establish a presumptive diagnosis.
8. Failure to treat children with doxycycline. Doxycycline therapy is recommended by the American Academy of Pediatrics and by Centers for Disease Control and Prevention as the treatment of choice for all rickettsial diseases, including RMSF and the ehrlichioses, in children of all ages.53,54 It has the best outcome,6,54 and the risk of cosmetically perceptible tooth staining appears to be insignificant for a single course of treatment.55-59

CONCLUSIONS

Be aware of the tick-borne illnesses, including RMSF, especially in the spring and summer, when ticks are most active. A history of a definite tick bite may not be present, and with the increase in travel, geography should not be used to exclude a disease diagnosis. It is entirely appropriate to empirically treat on suspicion because of the potential for rapid disease progression, with significant concomitant morbidity and mortality. Doxycycline is the antibiotic of choice, even for children. Early diagnosis and treatment can save lives.

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