Increased Detection of Rickettsialpox in a New York City Hospital Following the Anthrax Outbreak of 2001

Use of Immunohistochemistry for the Rapid Confirmation of Cases in an Era of Bioterrorism

Tamara Koss, MD; Eric L. Carter, MD; Marc E. Grossman, MD; David N. Silvers, MD; Asher D. Rabinowitz, MD; Joseph Singleton, Jr, BS; Sherif R. Zaki, MD, PhD; Christopher D. Paddock, MD

Background: Rickettsialpox is a self-limited febrile illness with skin lesions that may be mistaken for signs of potentially more serious diseases, such as cutaneous anthrax or chickenpox. The cluster of cutaneous anthrax cases from bioterrorism in October 2001 likely heightened awareness of and concern for cutaneous eschars.

Objectives: To apply an immunohistochemical technique on paraffin-embedded skin biopsy specimens for diagnosing rickettsialpox, and to compare the reported incidence of rickettsialpox before, during, and after the cluster of cutaneous anthrax cases.

Design: Case series.

Setting: Dermatology department in a large tertiary care hospital in New York City.


Main Outcome Measures: Results of immunohistochemical testing of skin biopsy specimens and of serological testing.

Results: Immunohistochemical testing revealed spotted fever group rickettsiae in all 16 eschars and in 5 of the 9 papulovesicles tested. A 4-fold or greater increase in IgG antibody titers reactive with Rickettsia akari was observed in all 9 patients for whom acute and convalescent phase samples were available; 6 patients had single titers indicative of rickettsialpox infection (≥1:64). Of the 18 patients, 9 (50%) presented in the 5 months following the bioterrorism attacks.

Conclusions: Rickettsialpox remains endemic in New York City, and the bioterrorism attacks of October 2001 may have led to increased awareness and detection of this disease. Because rickettsialpox may be confused with more serious diseases, such as cutaneous anthrax or chickenpox, clinicians should be familiar with its clinical presentation and diagnostic features. Immunohistochemical staining of skin biopsy specimens, particularly from eschars, is a sensitive technique for confirming the clinical diagnosis.

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Rickettsialpox is an acute, self-limited, febrile illness caused by Rickettsia akari and transmitted by Liponyssoides sanguineus, a hematophagous mite that infests the common house mouse (Mus musculus). Rickettsialpox begins with the bite of an infected mite, which forms a black eschar. Patients subsequently develop the abrupt onset of high fever, headache, and systemic symptoms, followed by a sparse, disseminated, papulovesicular rash.

Rickettsia akari is a member of the spotted fever group of rickettsiae, which also includes Rickettsia rickettsii, the cause of Rocky Mountain spotted fever; Rickettsia conorii, the cause of boutonneuse fever; and Rickettsia africae, the cause of African tick bite fever. Rickettsialpox has been described primarily in New York City, but it has also been reported in large cities in the eastern United States (in Massachusetts, Connecticut, Maryland, Ohio, and Pennsylvania) and in rural North Carolina, Utah, Russia, Korea, and South Africa. The disease has been reported in patients ranging in age from 6 months to 72 years. In the past, the laboratory diagnosis of rickettsialpox was based on testing of paired serum samples to detect a 4-fold increase in antibodies reactive with R. akari, a process requiring several weeks. Because patients often do not return for follow-up after the resolution of their illness, convalescent phase serum samples are frequently unavailable for confirma-
We report a large series of 18 rickettsialpox cases from January 1, 2001, through February 28, 2003. The clinical features of the 18 patients diagnosed as having rickettsialpox are shown in Table 1. The presenting complaints for all patients were fever and rash. Of the 18 patients, 17 (94%) presented with the classic triad of an eschar (Figure 2A and B), fever, and papulovesicular rash (Figure 3A and B); all patients had a papulovesicular rash on the trunk and extremities. Only 2 patients (11%) complained of pruritus, and 4 patients (22%) had an enanthema, characterized by small erosions of the palate, tonsils, uvula, tongue, or pharynx. Patients’ self-reported fever ranged from 38.3°C to 40.6°C (median, 39.3°C). The duration of the rash before presentation ranged from 3 to 9 days (median, 7 days). When the eschar was pointed out to patients during the examination, most did not know how long their eschar had been present, and 5 (28%) were not aware of having an eschar until it was revealed during the physical examination. The most common location of the eschars was around the ankle, as seen in 5 patients (28%). Other locations included the calf, forearm, and back (2 patients, or 11%, for each location); and the chin, neck, chest, upper arm, abdomen, and thigh (1 patient, or 6%, for each location). Sixteen patients (89%) presented with a headache, and 7 (39%) complained of diffuse myalgias. Less common signs and symptoms were lymphadenopathy, gastrointestinal complaints, dizziness, anorexia, sore throat, and arthralgias.

Eighteen patients with laboratory-confirmed rickettsialpox (6 males and 12 females), who ranged in age from 15 months to 73 years, were examined during a 20-month period (Figure 1). The clinical features of the 18 patients diagnosed as having rickettsialpox include an eschar, fever, and papulovesicular rash. Of the 18 patients, 17 (94%) presented with the classic triad of an eschar (Figure 2A and B), fever, and papulovesicular rash (Figure 3A and B); all patients had a papulovesicular rash on the trunk and extremities. Only 2 patients (11%) complained of pruritus, and 4 patients (22%) had an enanthema, characterized by small erosions of the palate, tonsils, uvula, tongue, or pharynx. Patients’ self-reported fever ranged from 38.3°C to 40.6°C (median, 39.3°C). The duration of the rash before presentation ranged from 3 to 9 days (median, 7 days). When the eschar was pointed out to patients during the examination, most did not know how long their eschar had been present, and 5 (28%) were not aware of having an eschar until it was revealed during the physical examination. The most common location of the eschars was around the ankle, as seen in 5 patients (28%). Other locations included the calf, forearm, and back (2 patients, or 11%, for each location); and the chin, neck, chest, upper arm, abdomen, and thigh (1 patient, or 6%, for each location). Sixteen patients (89%) presented with a headache, and 7 (39%) complained of diffuse myalgias. Less common signs and symptoms were lymphadenopathy, gastrointestinal complaints, dizziness, anorexia, sore throat, and arthralgias.

Three patients were initially thought to have cutaneous anthrax. Other initial clinical diagnoses included herpesvirus infection, Lyme disease, syphilis, and viral exanthem. Thirteen patients underwent hematologic and
biochemical tests during their initial evaluation in the emergency department. Of these 13 patients, 4 (31%) had mild leukopenia, with a white blood cell count ranging from $2.9 \times 10^3/\mu L$ to $3.3 \times 10^3/\mu L$ (normal range, $3.54 \times 10^3/\mu L - 9.06 \times 10^3/\mu L$). Two patients (15%) had leukocytosis. One patient had a white blood cell count of $9.7 \times 10^3/\mu L$, with 6% bands. The 15-month-old child had a markedly elevated white blood cell count of $22.5 \times 10^3/\mu L$, with 60% neutrophils, and an erythrocyte sedimentation rate of 95 mm/h (normal rate, 0-20 mm/h). Three patients (23%) had mild thrombocytopenia, with a platelet count ranging from $133 \times 10^3/\mu L$ to $154 \times 10^3/\mu L$ (normal range, $165 \times 10^3/\mu L - 415 \times 10^3/\mu L$). One patient (8%) each had mild transaminase elevations (aspartate aminotransferase level, 63 U/L [normal, 12-38 U/L]; and alanine aminotransferase level, 128 U/L [normal, 7-41 U/L]), an elevated alkaline phosphatase level ($177 \ U/L$ [normal, 33-96 U/L]), and an elevated lactate dehydrogenase level ($415 \ U/L$ [normal, 115-221 U/L]).

Sixteen patients were diagnosed clinically as having rickettsialpox in the dermatology clinic, and were treated with a 7-day course of doxycycline ($100 \ mg$ orally twice a day). All but 1 of the patients seemed only mildly ill. One patient had a toxic appearance and vomited several times during her examination in the dermatology clinic; she was hospitalized and treated with intravenous doxycycline ($100 \ mg$ twice a day) for 3 days before being discharged and treated with oral doxycycline for 5 days. Another patient, the 15-month-old girl, was diagnosed clinically as having rickettsialpox vs an atypical viral exanthem. Because she had a markedly elevated white blood cell count and erythrocyte sedimentation rate, the attending pediatric rheumatologist requested an echocardiogram to rule out atypical mucocutaneous lymph node syndrome. The patient was hospitalized for 2 days and treated with a single dose of intravenous ceftriaxone sodium, $75 \ mg/kg$, and a 7-day course of oral erythromycin, $18 \ mg/kg$ per dose every 8 hours.

Fever and other systemic symptoms resolved after 24 to 48 hours of antibiotic therapy in all patients. In 12 (86%) of the 14 patients, the papulovesicular eruption had completely resolved by the follow-up visit 1 week after presentation, with only minimal postinflammatory hyperpigmentation. Eschars were seen in 17 of the 18 patients; these healed in 3 to 4 weeks, leaving a small depressed scar in 2 (50%) of the 4 patients seen at the 1-month follow-up visit.

A biopsy specimen was obtained from 16 of the 17 eschars. The histopathologic features of the eschars were characterized by variable degrees of epidermal and dermal necrosis (Figure 2C and D). There was a direct correlation between the amount of necrosis in the dermis and epidermis: the more significant the necrosis of the upper portion of the dermis, the greater the degree of epidermal necrosis with ulceration. Ulcerated lesions typically had neutrophils and thrombosed vessels in the ulcer base. The primary pattern of inflammation in all cases was that of a superficial and deep perivascular mononuclear cell infiltrate and/or a skin biopsy specimen of a papulovesicle showing a perivascularesmononuclear cell infiltrate and any degree of dermal edema.
ules (Table 2). Staining was identified predominantly within the macrophages and mononuclear cells of the perivascular infiltrates associated with these lesions (Figure 4). A 4-fold or greater increase in antibodies reactive with *R. akari* was detected in all 9 patients for whom paired acute and convalescent phase serum samples were available (Table 2). For 9 patients, only 1 serum specimen (acute or convalescent phase) was obtained. Six patients had single elevated titers reactive with *R. akari*.

One patient each had an acute phase titer of 1:64, 1:128, 1:256, 1:512, and 1:2048, and 1 patient had a single convalescent phase titer of 1:512.

**COMMENT**

The 18 rickettsialpox cases seen in our institution during the 20-month period are noteworthy, because this represents a 3-fold increase in our annual number of cases.
compared with the previous 5 years. Of our patients, 9 (50%) presented in the 5 months following media reports of the cutaneous anthrax cases in October 2001 (Figure 1). In contrast, there were only 3 rickettsialpox cases in the 5 months preceding the attacks, and we identified only 1 case of rickettsialpox during the corresponding period in 2002 to 2003. Immediately following the bioterrorism attacks, clinicians and patients were likely to be more observant and much more concerned about a cutaneous eschar.

Several researchers have suggested that rickettsialpox is probably underrecognized and underreported, perhaps because patients with mild disease do not seek medical attention or because clinicians may diagnose patients with rickettsialpox as having chickenpox or other diseases. Alternatively, the true incidence of rickettsialpox in our catchment area may be increasing because of environmental conditions favoring disease transmission (eg, more crowded housing, larger mouse populations, a change in the mite species infesting mice, or the presence of murine diseases that encourage mites to find alternative hosts, such as humans).

Our patients' clinical presentations are similar to those described in previous historical and contemporary reports (Table 1), with most patients (94%) presenting with the classic triad of fever, eschar, and rash. This presenta-
tion should alert clinicians to consider rickettsialpox. Headache was common (89%), and myalgias were seen in more than one third (39%) of our patients. An enanthema of the oral mucosa was present in one fifth (22%) of our patients. Although regional lymphadenopathy was commonly reported when rickettsialpox was first described in the mid to late 1940s, it was present in only 3 (17%) of our patients. Generalized lymphadenopathy, which was described in a few patients in earlier case series, was not seen in any of our patients (Table 1).

In general, routine laboratory test results do not contribute to the diagnosis of rickettsialpox. Mild leukopenia and mild thrombocytopenia have been described during the acute phase of the disease and were seen in approximately one third of the patients we examined. In our series, the most dramatic laboratory abnormalities (a markedly elevated white blood cell count and erythrocyte sedimentation rate) were seen in the youngest patient.

The disease most commonly confused with rickettsialpox is chickenpox. Patients with rickettsialpox generally have fewer lesions than patients with chickenpox, and the lesions do not appear in crops. Although rickettsialpox may be rarely associated with pruritus, the pruritus of chickenpox is usually much more severe. In addition, the classic “dew drop on a rose petal” lesion of

Table 2. Immunohistochemical Staining of Skin Biopsy Specimens and Anti–Rickettsia akari Serum Antibodies in 18 Patients With Rickettsialpox

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Date of Presentation</th>
<th>Immunohistochemical Staining</th>
<th>Phase</th>
<th>Anti–R. akari Antibody Titers (Determined by IFA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/24 y</td>
<td>2/23/01</td>
<td>Eschar Not identified</td>
<td>Acute</td>
<td>ND</td>
</tr>
<tr>
<td>2/F/60 y</td>
<td>5/5/01</td>
<td>Papule Negative</td>
<td>Convalescent</td>
<td>512</td>
</tr>
<tr>
<td>3/M/48 y</td>
<td>7/23/01</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>32</td>
</tr>
<tr>
<td>4/F/32 y</td>
<td>8/8/01</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>32</td>
</tr>
<tr>
<td>5/F/29 y</td>
<td>10/9/01</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>512</td>
</tr>
<tr>
<td>6/F/21 y</td>
<td>10/16/01</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>&lt;32</td>
</tr>
<tr>
<td>7/M/29 y</td>
<td>11/2/01</td>
<td>Eschar Positive</td>
<td>Convalescent</td>
<td>1024</td>
</tr>
<tr>
<td>8/F/51 y</td>
<td>11/13/01</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>32</td>
</tr>
<tr>
<td>9/F/15 mo</td>
<td>12/21/01</td>
<td>Papule Positive</td>
<td>Convalescent</td>
<td>1024</td>
</tr>
<tr>
<td>10/F/36 y</td>
<td>12/28/01</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>32</td>
</tr>
<tr>
<td>11/M/25 y</td>
<td>1/29/02</td>
<td>Papule Equivocal</td>
<td>Convalescent</td>
<td>256</td>
</tr>
<tr>
<td>12/F/55 y</td>
<td>2/5/02</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>128</td>
</tr>
<tr>
<td>13/F/42 y</td>
<td>2/20/02</td>
<td>Papule Positive</td>
<td>Convalescent</td>
<td>2048</td>
</tr>
<tr>
<td>14/F/25 y</td>
<td>2/23/02</td>
<td>Eschar Positive</td>
<td>Convalescent</td>
<td>ND</td>
</tr>
<tr>
<td>15/M/73 y</td>
<td>3/11/02</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>&lt;32</td>
</tr>
<tr>
<td>16/F/59 y</td>
<td>5/20/02</td>
<td>Papule Negative</td>
<td>Convalescent</td>
<td>ND</td>
</tr>
<tr>
<td>17/M/51 y</td>
<td>8/5/02</td>
<td>Eschar Positive</td>
<td>Acute</td>
<td>ND</td>
</tr>
<tr>
<td>18/F/59 y</td>
<td>10/31/02</td>
<td>Papule Positive</td>
<td>Acute</td>
<td>128</td>
</tr>
</tbody>
</table>

Abbreviations: IFA, immunofluorescence assay; ND, not done.

Figure 4. Abundant immunohistochemical staining of spotted fever group rickettsiae within the perivascular macrophages and mononuclear cells of an eschar, visualized by using a polyclonal rabbit anti–Rickettsia rickettsii antibody (immunoperoxidase with naphthol–fast red substrate and hematoxylin counterstain, original magnification ×158).
chickenpox is morphologically distinct from the erythematous papules, with or without a tiny central vesicle, seen in rickettsialpox. Skin lesions in various stages of evolution (papules, vesicles, and crusts) occur concomitantly in chickenpox, whereas the lesions of rickettsialpox are typically monomorphic. Perhaps the most useful distinguishing feature is the eschar, which is present in nearly all patients with rickettsialpox but not classically associated with chickenpox.

Numerous eschar-associated rickettsial diseases may resemble rickettsialpox, including Mediterranean spotted fever, African tick typhus, Queensland tick typhus, Siberian tick typhus, and scrub typhus. Rocky Mountain spotted fever is only rarely associated with an eschar. The geographic distributions of most of these diseases are helpful for establishing a diagnosis (Table 3). The differential diagnosis of a single necrotic eschar also includes cutaneous anthrax, aspergillosis, spider bite, ecthyma gangrenosum, factitial dermatitis, and trauma.

Cutaneous anthrax starts as a painless pruritic papule. The papule enlarges and develops a central vesicle or bulla, which may have satellite vesicles and which is surrounded by a striking brawny, nonpitting edema that is absent in rickettsialpox. The vesicle subsequently ulcerates and is covered by a single, painless, necrotic eschar. (The eschar of rickettsialpox is also painless and may occasionally be pruritic.) Low-grade fever, regional lymphadenopathy, and malaise are common findings, but a papulovesicular rash does not occur, which distinguishes this disease clinically from rickettsialpox. No specific histologic features definitively differentiate the eschars of anthrax from those of rickettsialpox, and both diseases share a spectrum of inflammatory changes and dermal and epidermal necrosis. However, marked edema and hemorrhage are generally identified with greater frequency in the lesions of cutaneous anthrax.

Other diseases that cause a sparse papulovesicular eruption and that may be confused with rickettsialpox include infectious mononucleosis, several enterovirus infections (such as echovirus types 9 and 16, coxsackievirus A types 9 and 16, and coxsackievirus B type 5), gonococcal, and eczema vaccinatum. Cutaneous anthrax is a mild self-limited illness that resolves in 6 to 10 days without treatment. To our knowledge, there are no relapses after infection with R. akari and there have been no reported fatalities.

Headache and lassitude may persist for up to 2 weeks after resolution of the fever. Symptoms during the acute illness can occasionally be severe, requiring hospitalization in a few patients. In our series, 3 patients (17%) were hospitalized. The treatment of choice for rickettsialpox is doxycycline, which can dramatically reduce the duration of systemic symptoms (and is also indicated for the treatment of cutaneous anthrax). The recommended dosage of doxycycline is 100 mg orally or intravenously twice a day for 7 days (vs 60 days for cutaneous anthrax associated with bioterrorism). Chloramphenicol may be given to patients who are younger than 8 years or allergic to doxycycline.

The histopathologic features of our patients’ eschars (epidermal and dermal necrosis, a superficial and deep perivascular mononuclear cell infiltrate, and blood vessel thrombosis or necrosis) and papulovesicles (variable papillary dermal edema and a superficial and mid-dermal perivascular mononuclear cell infiltrate) are similar to those described by Kass et al, although we do not use the term lymphocytic vasculitis. The histologic features of rickettsialpox are characteristic, but not diagnostic. Histopathologic analysis of a papulovesicle, however, can help exclude other diseases in the clinical differential diagnosis, such as herpesvirus infections and a tick bite reaction, characterized by multinucleated giant cells and (often) the presence of mouthparts, respectively.

In our series, IHC staining of skin biopsy specimens provided the most sensitive method of confirming the diagnosis. This assay was positive for the diagnosis in 21 (84%) of 25 biopsy specimens tested. Biopsy specimens of eschars provided the best sample for evaluation: all eschars were positive for rickettsialpox, compared with only 56% of the papulovesicles.

Rickettsialpox should be considered in the differential diagnosis of patients presenting with fever, an eschar, and a papulovesicular eruption, especially in areas where the disease is common, such as New York City. Cutaneous anthrax resulting from natural exposure or acts of bioterrorism is in the differential diagnosis of rickettsialpox; this underscores the importance of clinicians’ ability to promptly recognize and definitively diagnose rickettsialpox. During the acute phase of rickettsialpox, IHC testing of a skin biopsy specimen from the eschar is the best method for confirming the clinical diagnosis. This test is highly sensitive, requires only 1 patient visit, and may provide results in a few days. Although serological results can be useful in confirming the diagnosis of rickettsialpox, seroconversion may not occur for several weeks and at least 2 patient visits are necessary for the collection of serum samples. Early recognition of the clinical presentation of rickettsialpox and the availability of a sensitive confirmatory IHC test should lead to more rapid and accurate diagnosis and prompt institution of appropriate therapy.
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From the Department of Dermatology, Columbia University College of Physicians & Surgeons, New York, NY (Drs Koss, Carter, Grossman, Silvers, and Rabinowitz); and the Viral and Rickettsial Zoonoses Branch (Mr Singleton and Dr Paddock) and Infectious Disease Pathology Activity (Dr Zaki), the Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga. Dr Paddock is now with Infectious Disease Pathology Activity, the Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention.

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Corresponding author and reprints: Tamara Koss, MD, Department of Dermatology, Columbia University College of Physicians & Surgeons, 161 Fort Washington Ave, 12th Floor, New York, NY 10032 (e-mail: tamarakoss@yahoo.com).

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