Diagnosing Rickettsia: Crimps, Complications, and Coups

To the Editor—The recent publication by Denison et al [1] conducted a study on the detection of the 3 most common spotted fever group rickettsia (SFGR) species endemic to the United States: *Rickettsia rickettsii*, *Rickettsia parkeri*, and *Rickettsia akari*. When patients present with fever and rash and SFGR is in the diagnosis, serology and skin biopsy are often done. Serology can be negative early, so skin biopsies are performed.

Both immunohistochemical stain (IHC) and nested polymerase chain reaction (PCR) remain the standard tests. There are potential problems with IHC in a skin biopsy: (1) The rickettsial antigens are unevenly scattered in tissue so it can be missed, (2) the depth and size of the tissue may affect retrieval of the organisms, (3) the air or fixation method can affect the quality and amount of nucleic acid or PCR amplicons, and (4) the timing of the biopsy in a patient's presentation and whether antimicrobial therapy were given can impact results [1].

Formalin-fixed, paraffin-embedded (FFPE) specimens are sent for the conventional nested PCR assays to the *ompA* gene and the 17-kDa antigen. The large segment gene targets take >8 hours to complete and are dependent on sampling and obtaining a sufficient number of organisms. Denison states that species-specific identification is difficult with FFPE specimens, so her team developed a multiplex PCR test that takes <3 hours, works on samples with fewer organisms, and can be performed on swabs and other sites as well on patients who have been treated with antibiotics [1].

In their study, there were 11 cases of rickettsialpox, 10 from New York. All tested positive with the multiplex test; none were positive with the nested PCR. In essence, rickettsialpox would not have been recognized given the current testing.

In 2006, Paddock et al [2] described the culture and initial characterization of 5 isolates of *R. akari* from eschar biopsy specimens from New York City patients with rickettsialpox. In this study, fresh cutaneous biopsy specimens were obtained from 7 patients suspected of having rickettsialpox, presenting with eschar-associated febrile illnesses. SFGR were identified by IHC staining in eschar biopsy specimens of all patients; segment of the rickettsial 17-kD antigen gene of
R. akari was only amplified from 5 of 7 patients via nested PCR. The failed attempts to isolate rickettsiae from 2 of the 7 patients involved biopsy specimens that were refrigerated at 4°C for 4 and 17 days, respectively, after the biopsy procedure. It is postulated that digestion of rickettsial nucleic acids by host tissue endonucleases, particularly in the specimen refrigerated for >2 weeks, barred the amplification of rickettsial DNA [2], which highlights the importance of timing of the biopsy.

We recently took care of a patient in Flushing, Queens, who presented with 2 eschars on each lower extremity, a diffuse truncal macular rash, and fevers >40°C. One week later, the rash became more papular. He worked in a restaurant and denied any rodent exposure. No one in his family was sick. Serology was initially negative. FFPE was sent to the Centers for Disease Control and Prevention, and IHC was positive along with nested PCR (in Dr Paddock’s laboratory). The nested PCR had 2 successive runs—the second amplified a secondary product and was placed in a blast search with a species-specific sequence for R. akari when, compared to the database sequences, it was determined to be positive. Subsequent serology became positive.

In 1946, an outbreak of 124 people presented with similar rashes resembling chickenpox to their local physicians in Kew Gardens, Queens. Rickettsialpox was the disease and it was caused by R. akari, transmitted by the mouse mite in a cosmopolitan location. Most people do not recall bites, and >90% have eschars. Doxycycline is the treatment of choice, and health authorities need to address rodent control.

Since then, there have been about 800 nonfatal cases. The New York City Department of Health typically reports 12–15 cases annually. The triad of symptoms include initial eschar, fever, and a papulovesicular rash. If serology is negative, skin biopsy may help with IHC and nested PCR. Denison et al found the multiplex PCR to be more specific than the current nested PCR [1]. Rickettsialpox is an underdiagnosed disease, but with the advent of this new testing modality, future cases will be identified more quickly.

Notes

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