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Microscopy in Bioresponse Preparedness and Detection of Pathogens of Public Health Importance

Sherif R. Zaki and Cynthia S. Goldsmith

Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia 30333

After the intentional release of *Bacillus anthracis* in October 2001, the world changed dramatically as the threat of bioterrorism (BT) became a reality, prompting widespread concern about the deliberate use of smallpox, Ebola, tularemia, and other BT-related diseases. In response, there have been efforts to further strengthen the ability to provide diagnostic confirmation of these diseases and of similar illnesses for which they may be mistaken.[1] Rapid diagnosis of an etiologic agent can lead to reduced morbidity and mortality by allowing public health officials to respond promptly to an outbreak and prevent further spread of the infectious agent involved. Pathologic studies are indispensable to help focus and guide further laboratory testing, and therefore play a critical role in outbreak investigations. In particular, electron microscopic (EM), histopathologic, and immunohistochemical (IHC) techniques are essential to defining the morphological features of BT agents and providing crucial diagnostic information for investigators.

For potential smallpox infections, EM plays a primary role in diagnostics and in ruling out look-alike causes of rash illness.[2] The negative stain EM technique is rapid and is an excellent screening tool in that whichever virus is found within a specimen can be definitively diagnosed to a specific virus family. The infectious agents most commonly confused with poxvirus infection are the herpesviruses, and poxviruses and herpesviruses are easily distinguished by EM (Figs. 1, 2). Furthermore, immunogold labeling with pan-orthopox antibodies can help resolve equivocal diagnoses (Fig. 3); smallpox-specific monoclonal antibodies are being developed to enable EM to provide a definitive diagnosis for a smallpox infection.

During the anthrax incidents in the fall of 2001, a sustained laboratory investigation was mounted, with IHC results providing a rapid diagnosis of suspected anthrax cases while ruling out other etiologic agents[3] (Fig. 4). This response firmly established the front-line role of pathology in rapidly identifying BT agents and providing direction for clinical case management and epidemiological investigation. For pathogens of public health importance, the clinical history of the patient, pathologic examination of tissues, and correlation with other molecular test results can often provide important clues needed to ascertain the infectious agent involved. Histopathologic changes in tissues suggest specific IHC testing, which can confirm or rule out specific agents. A syndromic approach has been developed for the differential diagnosis of various potential BT agents, such as those causing viral hemorrhagic fever (Fig. 5, 6, 7), plague, and tularemia, as well as other pathogens of public health importance.

References

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3. J. A. Jernigan et al., Emerging Infectious Diseases 7 (2001) 933.

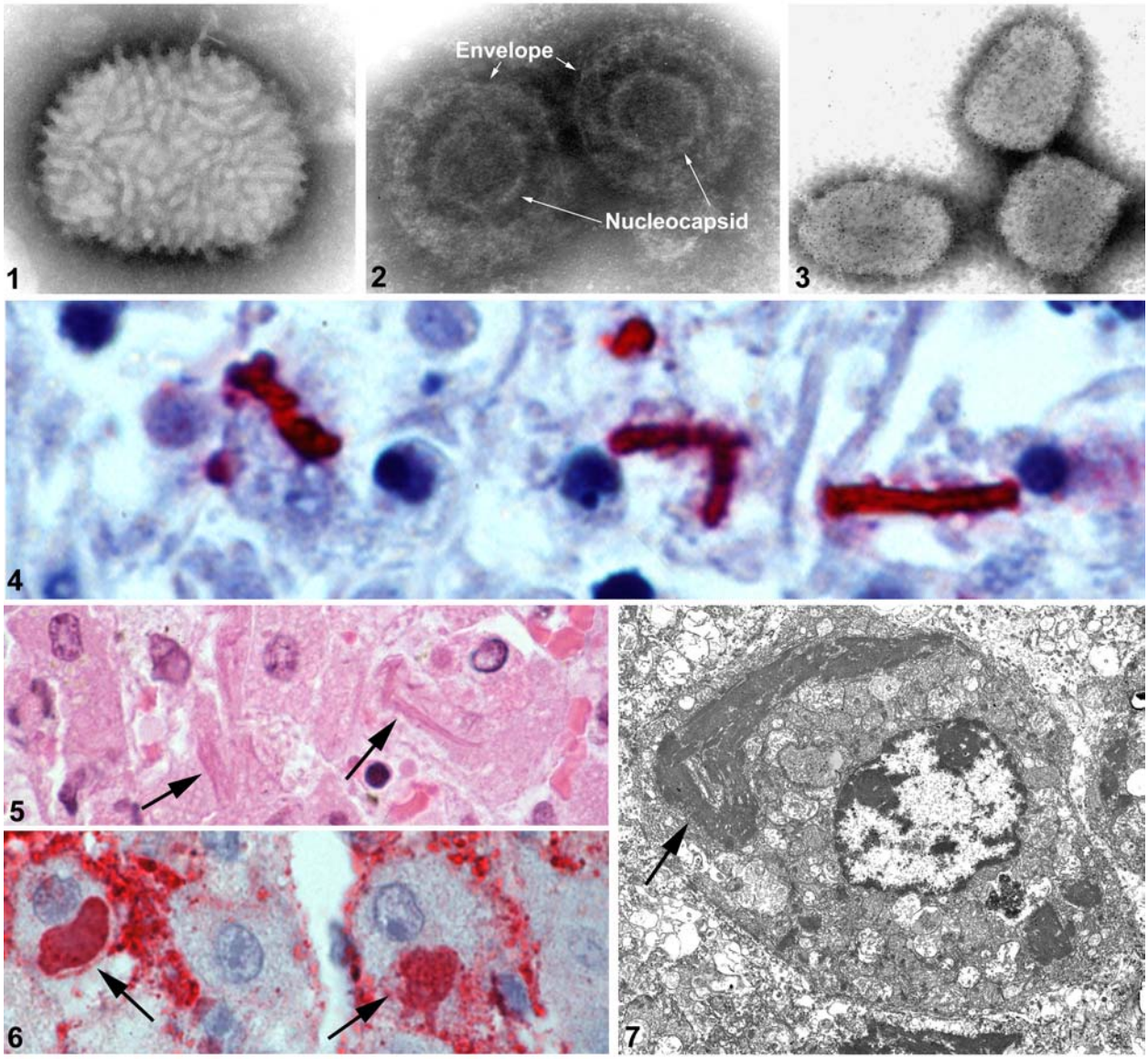

Figure Legends

1) Negative stain EM image of vaccinia virus isolate, showing the virion surface covered by whorled filaments. 2) Negative stain EM image of the herpesvirus varicella zoster, from a vesicular fluid specimen. 3) Immunogold labeling of vaccinia virus isolate. 4) IHC stain of tissue from a patient with *Bacillus anthracis*, showing large rod-shaped and fragmented bacilli. 5) Necrotic area in liver from a patient with Ebola hemorrhagic fever, showing filamentous, intracytoplasmic inclusions (arrows) in hepatocytes. 6) IHC staining of Ebola virus inclusions (arrows) and viral antigens within sinusoids of hepatic tissue. 7) Thin section EM of Ebola virus inclusion (arrow) within an hepatocyte. (4, 6- immunoalkaline phosphatase staining, naphthol fast red substrate with light hematoxylin counterstain.)

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