Review

Cutaneous manifestations of filovirus infections

Dieudonné Nkoghe¹,², MD, Eric Maurice Leroy¹,³, VD, PhD, Médard Toung-Mve², MD, and Jean Paul Gonzalez¹, MD, PhD

¹Centre International de Recherches Médicales de Franceville (CIRMF), Franceville, Gabon, ²Ministry of Health, Libreville, Gabon, and ³MIVEGEC (IRD 224/CNRS 5290/UM1/UM2), Montpellier, France

Correspondence
Dr Dieudonné Nkoghe, MD
Infectious Diseases
CIRMF
BP 769 Franceville
Gabon
E-mail: dnkoghe@hotmail.com

Conflicts of interest: None

Abstract

Ebola virus and Marburg virus, two filoviruses belonging to the Filoviridae family, are among the most virulent pathogens for humans and non-human primates, causing outbreaks of fulminant hemorrhagic fever (HF) in Central African countries with case fatality rates of up to 90%. Fruit bats are the likely reservoir, and human infection occurs through contact with bats or infected large-animal carcasses or by person-to-person contact (through body fluids, medical care, and burial practices). Schematically, clinical manifestations occur in three successive phases and include general, gastrointestinal, and mucocutaneous disorders. Death usually results from hemorrhagic complications. Cutaneous manifestations rarely make a major contribution to disease severity but can assist with the diagnosis. Rash, the main cutaneous disorder, is nonspecific and cannot guide the differential diagnosis. Immunohistochemical examination of skin biopsy or necropsy specimens can confirm the diagnosis.

Introduction

Filoviruses belong to the Filoviridae family, order Mononegavirales, a large group of viruses with single-stranded RNA genomes of negative polarity.¹ The term “filovirus” refers to the elongated filamentous morphology of these pathogens on electron micrographs (Fig. 1). The other three major families of this order, which are genetically closely related to the filoviruses, are Paramyxoviridae (e.g. measles virus), Rhabdoviridae (e.g. rabies virus), and Bornaviridae (bornavirus). Filoviruses are divided into two genera: Marburg virus (MARV) and Ebolavirus (EBOV). MARV includes a single species (Lake Victoria Marburg virus), while EBOV is subdivided into five species: Zaire, Côte d’Ivoire, Sudan, Reston and Bundibugyo (recently discovered in Uganda).²

Filoviruses are among the most virulent and hazardous pathogens for humans and non-human primates and are classified as level 4 security agents. Filoviral infections have been described in Africa, Europe, USA, Russia, and Asia. Filoviruses cause outbreaks of fulminant hemorrhagic fever, mostly in equatorial Africa (Fig. 2) and more rarely in Europe. Since 1967, 23 Ebola outbreaks have been confirmed by virus isolation or by molecular and biological methods, and there have been nine documented outbreaks of Marburg fever.³ Ebolavirus pathogenicity depends on the species: Zaire ebolavirus is more virulent than the other species, with a case fatality rate of 80–90%, compared with 50–55% with Sudan ebolavirus and 36% with Bundibugyo ebolavirus. Côte d’Ivoire ebolavirus has caused only one documented, non-fatal human case, while Reston ebolavirus has only been described in Asia, in non-human primates. The human lethality of Marburg virus during the outbreak in Uige province, northern Angola, in 2004–2005, was close to that of Zaire ebolavirus.⁴,⁵

The reservoirs of these viruses are not fully known, but recent studies have identified four fruit bat species (Hypsignathus monstrosus, Epomops franqueti and Myonycteris torquata, and Rousettus aegyptiacus) as likely natural reservoir species for EBOV and MARV in Gabon.⁶,⁷

In appropriate physiological and environmental conditions, transmission to great apes (gorillas and chimpanzees) occurs by direct contact with female bat blood and/or placenta after delivery.⁸ Spread within these non-human primates is due to direct contact in the course of fighting and breastfeeding. Human infection can occur in three ways: (i) by direct contact with body fluids of infected non-human primates (during poaching for example) or while handling infected animal carcasses found in the forest;⁹ (ii) direct contact with reservoir species;⁸ and (iii) more rarely, by accidental transmission in laboratory facilities.¹⁰ Human–human transmission generally occurs...
through close physical contact with blood and other body fluids (feces, vomit, urine, saliva, and semen) during medical care (by family, healthcare workers, or traditional healers) or burial practices.\textsuperscript{11,12}

After a variable incubation period, victims develop high fever accompanied by gastrointestinal, respiratory, and cutaneous disorders followed, in severe cases, by shock with multivisceral hemorrhage and death within a few days. During outbreaks, laboratory diagnosis is based on detection of circulating viral antigens or genetic material by polymerase chain reaction (PCR).\textsuperscript{13,14} There is no specific treatment or vaccine, and treatment is solely supportive; isolation measures and aseptic burial are crucial.\textsuperscript{12,15}

**Clinical manifestations**

It is virtually impossible to distinguish between Ebola and Marburg fever on clinical grounds alone. Presumptive diagnosis during outbreaks is based on a combination of epidemiological information and clinical manifestations, which may differ from one viral species to another.

After an incubation period of 1–21 days,\textsuperscript{3} signs and symptoms evolve in three successive phases, which sometimes overlap. The first phase is characterized by non-specific symptoms; the second by multiple organ involvement; and the third, terminal phase, by recovery or death, depending on both host and viral factors.

**Phase I**

Symptoms typically begin with a flu-like syndrome with abrupt-onset fever (39–40°C), violent headache (primarily in the occipital region but spreading to the parietal and frontal regions), and generalized fatigue with myalgia and arthralgia (always present). Sometimes, myalgia with concomitant neck muscle tension occurs, mimicking meningitis. Marburg fever can be associated with prostration, malaise, ocular pressure sensitivity, photophobia, and vertigo.
Phase II
The second phase begins with severe visceral disorders, on day 2–4 after symptom onset, and lasts for 7–10 days. Severe abdominal pain, nausea, watery diarrhea, and loss of appetite lead to weight loss and marked dehydration. Patients have “a ghostly appearance” with deep-set eyes, an expressionless face, and extreme lethargy. Respiratory symptoms appear at the same time, with violent sore throat accompanied by chest pain and dry cough, resulting from pharyngeal damage; this is highly evocative of filovirus infection (patients describe having a “ball” in the throat). Swallowing is hindered, further aggravating nutritional status. A non-itchy rash appears between the second and seventh day, followed by fine scaling (see below). Bleeding is frequent, with petechiae at various sites, an ocular burning sensation, reddening, melena, hematemesis, hematuria, epistaxis, hemoptysis, and bleeding at puncture sites. Pregnant women often develop uterine bleeding that results in miscarriage. Ultimately, the nervous system can be involved, leading to behavioral disorders (aggressiveness, confusion, delirium), paresthesia, hyperesthesia, and seizures.

Phase III
The terminal phase results in recovery or death. Tachypnea may occur with hiccup, followed by anuria. Death occurs after 2–3 days due to plasmatic shock with capillary extravasation and multiorgan failure. Survivors experience a lengthy period (one month or more) of painful convalescence with intense fatigue, loss of appetite, profound prostration, weight loss, and migratory arthralgia. Some survivors are unable to recall the most severe period of illness. Bacterial infections and psychoses have been reported. Sequelae may include orchitis, recurrent hepatitis, transverse myelitis, and uveitis. Psychiatric sequelae include confusion, anxiety, and restless and aggressive behavior.

Mucocutaneous manifestations
Cutaneous manifestations of filovirus hemorrhagic fever syndrome (FHF) are not in themselves life threatening. They provide diagnostic pointers during early outbreaks, especially in light-skinned patients. Cutaneous manifestations usually appear in phase II, 4–5 days after initial symptom onset. They occur in more than half of patients. They are more frequent and more characteristic in MARV infection than EBOV infection.

Macular or maculopapular exanthema resembles a non-pruritic measles-like rash with flaking in dark-skinned patients (Fig. 3). Pinpoint dark-red papules are first observed around the hair roots, on the buttocks, the upper arms and legs, and the face, and then extend to the trunk and the rest of the body. In some cases, exanthema extends in centripetal fashion from the arms and legs to the trunk. Around day 8, dark, livid, diffuse cutaneous erythema occurs over the entire body in most cases, sometimes accompanied by cyanosis. Exanthema may be associated with various stages of erythema and disappears within a few days in survivors. Patients experience peeling of the affected skin, lasting from a few days to two weeks. It is most severe on the palms of the hands, soles of the feet, and the extremities.

Mucosal lesions are also common, affecting the eyes, mouth, and pharynx; about 50% of patients have bilateral conjunctival congestion with photophobia, which can signal the onset of more severe hemorrhagic manifestations. Cold sore-like lesions, gingivitis, and glossitis accompanied by fissuring have also been described. Sore throat and dysphagia are the result of pharyngitis. Such inflammation appears as a dry erythema, with a grayish exudate often accompanied by
small whitish clear lesions resembling “tapioca granules” on the soft palate.\textsuperscript{3,19,20,27} Enanthema can also extend to the tonsils and palatal floor.\textsuperscript{18,24} All these mucosal lesions can bleed.\textsuperscript{17}

In addition to these manifestations, survivors may experience hair loss at the end of convalescence.\textsuperscript{3,16,24}

**Differential diagnosis**

Fever is the common denominator of FHF, while bleeding may be discreet or absent. Diagnosis is difficult in isolated (sporadic) cases, at the beginning of outbreaks,\textsuperscript{29} and in imported cases.\textsuperscript{30}

In endemic areas, the diagnosis is based on the case definition, itself based on clinical and biological signs. Five categories of case definition have been proposed: alert; suspected (for non-medical staff); probable; confirmed cases; and contact case (if evaluated by a physician).\textsuperscript{12}

Malaria, typhoid, shigellosis, other enteric bacterial infections, viral hepatitis, leptospirosis, and other forms of HF (yellow fever, Lassa, Crimean-Congo, Dengue and Chikungunya) are early differential diagnoses (Table 1).

The first Ebola outbreak in Nzara, Sudan, was initially confused with bacterial dysentery,\textsuperscript{19} and the initial outbreak in Gabon in 1994 was confused with yellow fever.\textsuperscript{31,32} Outbreaks of typhoid fever and shigella occurred simultaneously with Ebola hemorrhagic fever in western Kasai (Democratic Republic of Congo) in 2007.\textsuperscript{33}

During the Ebola outbreak in Yambio (southern Sudan) in 2004, most cases involved children, and there was a concurrent measles outbreak.\textsuperscript{34}

**Histopathology**

Filoviruses can be detected by immunohistochemistry on skin samples by the CDC Molecular Pathology unit. Formalin-preserved skin biopsy samples are not infectious and can safely be sent abroad to specialized laboratories for histological analysis, serology, and electron microscopy. However, histopathology shows nonspecific skin alterations, restricted to endothelial cells and fibroblasts of the dermis and epidermis. Lesions appear uniform, with varying degrees of swelling and necrosis. Large amounts of viral antigens can be detected by ELISA, and viral inclusions can be identified by electron microscopy, within the cytoplasm and in the extracellular matrix, around the sweat glands (Fig. 4).\textsuperscript{35} Note that these features support the possibility of virus transmission through the skin.

**Outbreak response**

There is no specific treatment or vaccine for FHF. This chapter does not discuss global outbreak containment (import and export controls and enhanced disease surveillance) but focuses on patient management in African countries. During the last decade, the outbreak response has been organized at the local level. Many recommendations have been issued on case definitions and surveillance, case management and isolation, social mobilization, education, communication and medical anthropology, and logistics (including funding). It is important to realize the important role played by medical anthropologists in understanding local people’s perceptions, feelings, and responses to disease, and in identifying features of clinical care and intervention that are culturally insensitive or inappropriate.\textsuperscript{38}

**Patient management**

Outbreaks are managed by multidisciplinary international teams, placing the emphasis on rapid isolation of suspected cases in order to avoid transmission in the hospital setting. Patients should also be isolated with insect-proof screens. Convalescent patients are separated from acute patients. Hospital personnel must be informed of the nature of the disease and its transmission routes. They should wear gowns, gloves, masks, and goggles. Special care is needed for certain procedures, such as setting up a perfusion and handling blood, secretions, and any other

---

Table 1 Differential diagnosis of infectious diseases in tropical African countries based on cutaneous manifestations

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Clinical manifestations</th>
<th>Mucocutaneous findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola and Marburg</td>
<td>Hemorrhagic fever with gastrointestinal and respiratory symptoms</td>
<td>Maculopapular rash, pharyngitis</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>Hemorrhagic fever</td>
<td>Facial edema, pharyngitis</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>Arthralgic fever</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>Arthralgic fever</td>
<td>Papular rash</td>
</tr>
<tr>
<td>West Nile fever</td>
<td>Fever with neurological disorders</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Fever, nasal congestion, cough, conjunctivitis</td>
<td>Maculopapular exanthema, enanthema</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>Fever with gastrointestinal symptoms</td>
<td>Rash (rose spots)</td>
</tr>
</tbody>
</table>
potentially infected biological materials or devices (catheters, suction devices). Guidelines on disinfection of the skin and medical materials and destruction of bedding and waste must be strictly enforced to prevent nosocomial transmission.

Nonspecific treatment

Treatment is essentially symptomatic. Because of the risk of bleeding, oral medications should be preferred to injections (IV or IM), and paracetamol should be preferred to aspirin. Dehydration due to fever, vomiting, and diarrhea must be treated, by the oral route when possible, and seriously ill patients must be placed in an intensive care unit.

Specific treatments are being developed along two lines: direct inhibition of viral replication; and host protection. A promising anticoagulant (rNAPc2) has been tested in experimentally infected primates, with improved survival associated with attenuation of coagulation and inflammatory responses.

At least two candidate vaccines are being tested in experimental studies: VZVΔG/ZEBOVGP and VZVΔG/MARVGP (live attenuated recombinants of vesicular stomatitis virus expressing either the EBOV or MARV glycoprotein); and ADV-GP/NP (an inactivated recombinant adenovirus expressing the Ebola virus glycoprotein and nucleoprotein). Both have been shown to protect experimentally infected animals (guinea pigs and rhesus macaques) and seem to be well tolerated.

Conclusion

Mucocutaneous manifestations of FHF are frequent, nonspecific and non-life-threatening. Generally, they occur between the 2nd and 7th day after initial symptom onset and may be present during convalescence. They contribute to differential diagnosis of tropical viral diseases associated with skin lesions.

Skin biopsy can be useful for diagnostic confirmation, through the detection of viral antigens and viral inclusions by electron microscopy. The possibility that filoviruses may be transmitted by skin contact must be kept in mind.

Acknowledgments

CIRMF is supported by the Gabonese Government, Total Gabon and Ministère Français de la Coopération.

References


