Internal and Emergency Medicine (2022) 17:2179–2183
https://doi.org/10.1007/s11739-022-03112-8

IM-POINT OF VIEW

Monkeypox outbreak: after COVID-19, another challenge for the hemostatic system?

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Received: 29 August 2022 / Accepted: 20 September 2022 / Published online: 4 October 2022

Keywords Monkeypox · Smallpox · COVID-19 · Bleeding · Viral hemorrhagic fever

The huge amount of studies published in the last two year on the thrust of the COVID-19 pandemic shed further light on the already known relationships between viral infections and the hemostatic system [1]. Indeed, the analysis of pathogenetic mechanisms behind the COVID-associated coagulopathy (CAC) greatly improved our knowledge of the framework linking viral infection with endothelial inflammation, prothrombotic transformation, and barrier dysfunction [2].

Moreover, the Vaccine-Induced Thrombosis and Thrombocytopenia syndrome (VITT) described in recipients of ChAdOx1 nCoV-19 and Ad26 raised the attention of the scientific community about the potential thrombotic and hemorrhagic risks of the use of adenovirus as vectors for vaccines and gene therapies [3–5].

The COVID-19 pandemic is still ongoing, but the unprecedented vaccination campaign and the availability of effective anti-viral treatments have greatly dampened its impact on social and economic aspects of everyday life, at best in high-income countries. However, just when people started to breathe a sigh of relief, the threat of a new pandemic appeared on the horizon.

Indeed, on July 23, 2022 Monkeypox (MPX) was declared a Public Health Emergency of International Concern (PHEIC) by WHO Director-General Tedros Adhanom Ghebreyesus [6].

Should the hemostasis and thrombosis community be worried about a massive engagement in this epidemic, similar to that occurred during the COVID pandemic?

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As the great scientist Niels Bohr said, "Prediction is very difficult, especially about the future". On these grounds, any forecast about the future developments of this disease is highly error-prone. Nevertheless, we can try to speculate if MPX infection is expected to impact either side of the hemostatic system in a similar way to that seen in other viral diseases, such as viral hemorrhagic fever or COVID-19 [1].

MPX virus is not new, as it was first isolated in 1958 from monkeys at the Statens Serum Institut in Copenhagen, Denmark; the natural host of this virus also includes rope squirrels, tree squirrels, Gambian pouched rats, and dormice. As with many zoonoses, MPX virus is transmitted incidentally to humans when they encounter infected animals. The first known human case of MPX was recorded in 1970 in the Democratic Republic of the Congo, where has been causing illness and death in large numbers for decades [7]. Prior to 2022, human cases outside Africa have been rarely observed, and like other viral infections such Ebola and Zika, MPX gained global attention only when started to hit high-income countries.

The pathology of MPX virus infection, like that of all poxviruses, is mainly characterized by a prominent injury of epithelial cells, with the development of intracytoplasmic eosinophilic inclusion, ballooning degeneration, keratinocyte necrosis, and hyperplasia. The dermis presents lymphocytic inflammation, and vasculitis is also present [8]. Of note, reports concerning histopathology of humans that died due to an MPX infection do not exist.

Illness typically begins with fever, followed by the development of multiple papular, vesiculopustular, and ulcerative lesions on the face and body and lymphadenopathy. Most often, monkeypox infection is self-limited, usually lasting 2–4 weeks,

However, complications such as pneumonitis, encephalitis, keratitis, and secondary bacterial infections may arise, leading to a mortality rate between 1 and 11%, mainly in

Table 1 Biological and clinical characteristics of Monkeypox, Smallpox and Viral Hemorrhagic Fevers. Modif. from Ref. [1, 17, 18]

	Monkeypox	Smallpox	Viral hemorrhagic fevers (disease)
Virus/disease	Monkeypox virus	Variola virus	• Filoviruses: Ebola and Marburg virus (Ebola HF, Marburg HF) • Arenaviruses (Lassa HF) • Hantaviruses (Hemorrhagic Fever with renal syndrome), Nairoviruses (Congo-Crimean HF), and Phenuiviruses (Rift Valley fever [RVF]) formerly included in the Bunyaviridae family • Flaviviruses (Dengue, Yellow Fever, Omsk Hemorrhagic Fever)
Transmission	Human–human transmission mainly via sexual contact	Human–human eradicated	• Filoviruses: human–human; also by exposure to sick or dead infected forest animals, or to infected bats • Arenaviruses: rodents exposure • Hantaviruses: rodents exposure • Nairoviruses: bite of infected tick/rarely human-human, mainly in hospital setting • Phenuiviruses: bite of infected mosquitos • Flaviviruses: bite of infected mosquitos
Reservoir	Rodents, prairie dogs, opossums, and several primates	Only humans	• Filoviruses: fruit bats and humans • Arenaviruses: rodents (mainly Mastomys natalensis) • Hantaviruses: rodents • Nairoviruses: *Ioxodidae* ticks; cattle, goats sheep amplifying hosts • Phenuiviruses: ruminants, rats in some areas, wild animals • Flaviviruses: primates/rodents
Symptoms	Fever Multiple papular, vesiculopustular, and ulcerative lesions on the face and body Lymphadenopathy In the current outbreak, anorectal pain, proctitis with bleeding, and penile edema with balanitis and phimosis	Severe headache, backache, and fever Enanthema over the tongue, mouth, and oropharynx, then cutaneous rash evolving in vesiculopustular and ulcerative lesions followed by umbilication and crusting (pockmarks) Rarely complicated by panophthalmitis and blindness from viral keratitis, encephalitis, pneumonia	Fever Increased vascular permeability with decreased plasma volume Coagulation abnormalities Varying degrees of hemorrhage, up to DIC
Fatality rate	1% (West African clade and reported cases outside Africa) 11% (Central Africa clade)	1% (Variola minor) >30% Hemorrhagic Smallpox (HSPX)	From less than 5% (Dengue) up to 90% (Ebola HF)
Hemorrhagic features	Described only in animal models	DIC (only in HSPX, ~3% of cases)	DIC

Table 1 (continued)

	Monkeypox	Smallpox	Viral hemorrhagic fevers (disease)
Mechanisms of coagulopathy	Not fully elucidated Extensive liver necrosis with loss of clotting factors Endothelial damage in affected tissues Thrombocytopenia	Not fully elucidated (Smallpox eradicated before availability of modern study methods) Cytokine-induced coagulation activation? Endothelial damage in affected tissues? Thrombocytopenia	Endotheliopathy Tissue factor-induced coagulopathy Complement system activation Cytokine release Vasculitis Capillary leakage

DIC disseminated intravascular coagulation with thrombocytopenia, consumption of clotting factors, increased levels of fibrin degradation products

low-income countries [8, 9]. Of note, the sequenced viral genome from several countries closely resembles that of the strain endemic in Western Africa, which displays a 1% mortality, about 10 times lower than that reported by the Central African clade [9]. This finding fits well with the favorable clinical outcomes of a recently published case series of 528 subjects across 16 high-income countries, with no deaths and only three serious complications reported [10].

Moreover, poxviruses are expected to have less impact on thromboinflammation process because of their ability to evade the recognition and targeting by the immune system of the host.

Indeed, MPX virus in vitro infection of primary fibroblast does not induce interferon-stimulated gene (ISG) expression and further suppresses Tumour Necrosis Factor alpha (TNF-α), Interleukin 1 alpha and beta (IL-1α and β), C–C Motif Chemokine Ligand 5 (CCL5) and Interleukin 6 (IL-6) activation, all factors also implied on the Cytokines storm observed in SARS-CoV2 infection [11, 12].

On these pathophysiological and clinical grounds, it is expected that the involvement of the hemostatic system in the monkeypox infection is not prominent, or even negligible, as demonstrated by the lack of either thrombotic or hemorrhagic complications reported in such patients.

This reassuring scenario can be slightly jeopardized by the remark that the Monkeypox virus is a very close relative of the DNA virus Variola major, that caused smallpox (SPX) [11].

Widespread vaccination programmes led to the global eradication of smallpox, which was certified by the World Health Organization (WHO), and, since 1978, there has been no case of smallpox anywhere in the world. However, going back several years, it should be remembered that a small fraction of SPX cases (less than 10%) may present as a severe hemorrhagic form characterized by lesions with bleeding diathesis and disseminated intravascular coagulation, with a case fatality rate of nearly 100% within the first week of illness [13].

Relevant to this, it should be observed that in 2009 Schultz and Colleagues described an animal model of MPX infection whose features most resembled the hemorrhagic/toxic SPX subtype and provided a more severe disease than other rodent models of human MPX disease [14]. The mechanism for such a severe hemorrhage course was not determined, although extensive liver necrosis with loss of clotting factors and endothelial damage in affected tissues have been supposed to contribute to the multiorgan hemorrhage [14]. Furthermore, a low-dose model of SPX and MPX was described in the common marmoset and associated with thrombocytopenia, hemorrhagic rash and lethality [15, 16].

This clinical picture, although restricted to a very peculiar animal model of MPX infection, strongly resemble also that of viral hemorrhagic fevers due to other viruses, such as

Ebola, Marburg, Dengue, Lass or Hanta viruses [1]. It has been hypothesized that in viral hemorrhagic fever infected dendritic cells and macrophages lose their ability to produce type I interferon (IFN) sufficiently and lymphocytes fall into cell death. Inappropriate dendritic cell function causes a perturbation in the innate immune system that leads to increased vascular permeability, further worsened by an unbridled production of cytokines from infected macrophages [17]. Moreover, the replicated viruses disseminate throughout the body and induce a variety of systemic reactions, such as dysfunction of the visceral parenchymal cells, platelet disability, and coagulopathy which lead to disseminated intravascular coagulation leading to uncontrolled hemorrhage.

Table 1 summarizes the biological and clinical characteristics of MPX, SPX and Viral Hemorrhagic Fevers.

Thank goodness, such a dramatic scenario has not been so far described in MPX patients, and it is unlikely that will be observed in the future.

However, the history of COVID-19 pandemic teaches us that it is very difficult to forecast the evolution of viral diseases, mainly zoonosis, because of the many conditioning factors, such as the rapid spread of international traveling across a globalized world climate and ecological changes. Although global warning has mainly been related to the emergence of fungal species, viruses may threaten humans, if jumping to mammals and acquiring the capability to replicate at higher temperatures [19].

Between 4 May and 12 July 2022, more than 10,000 new non-endemic MPX cases have been reported globally. This huge number, likely underestimated due to the limited access to MPX diagnostics in many regions, clearly shows that this zoonotic virus can efficiently spread between people and thus could pose a risk to global public health. Moreover, we cannot conceivably exclude that some MPX more aggressive variants can arise, with clinical features similar to those already described in animal models [14].

In conclusion, all the available data seems to exclude that MPX outbreak can have a relevant impact in terms of hemostatic, mainly hemorrhagic, disorders.

Nevertheless, the close relationship between viruses, inflammation and hemostasis should not be overlooked, and the recent achievements in the pathophysiology of virus-induced thromboinflammation should always be considered, in view of "preparing for another epidemic" [1].

Author contributions All the authors equally contributed to the idea and to the preparation of the paper.

Declarations

Conflict of interest The author(s) declare that they have no conflict of interest.

Human and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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