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CORRESPONDENCE

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The pressing need for study on the effects of Mpox on the progression of vascular inflammation: A well-timed call

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Abstract

Background: This article explored the possibility that the Mpox virus (MPXV) may initiate or stimulate the consequences of vascular inflammation. In 1970, it was discovered that Macaca cynomolgus primates infected with MPXV also infected humans in the Democratic Republic of the Congo.

Discussion: The study demonstrates that MPXV invades host cells via viral proteins and surface receptors, initiating the release of diverse inflammatory mediators such as IL-1, IL-6, TNF-α, CCL2, CXCL2, CXCL8, CXCL10, and so forth probably through endothelial dysfunction by reactive oxygen species production. In general, these mediators have been found to contribute to vascular inflammation and the formation of atherosclerotic plaque at a later stage, which may contribute to the onset of vascular inflammation.

Conclusion: The discussed association between vascular inflammation and Mpox has the potential to be an important finding in the field of vascular biology research.

KEYWORDS

atherosclerosis, cardiovascular diseases, endothelial dysfunction, Mpox, oxidative stress, vascular inflammation

Dear Editor,

Mpox (previously known as monkeypox) is a contagious viral disease caused by the Mpox virus (MPXV), belonging to the *Orthopoxvirus* genus, *Poxviridae* family, and *Chordopoxvirinae* subfamily.[1,2] According to the US Center for Disease Control and Prevention (CDC), there were more than 57,995 confirmed cases in 100 countries and territories by September 13, 2022.[3] Inflammatory mediators such as interleukin (IL)−1, IL-6, C-C motif ligand 2 (CCL2), CXC motif chemokine ligand 8 (CXCL8), Interferon regulatory factor 3 (IRF3), CXCL10, tumor necrosis factor-alpha (TNF-α) and so forth through inflammatory signaling pathways such as nuclear factor-kappa B (NF-κB) are generated during infection and are responsible for causing inflammation and boosting the immune system, according to the literature. Inflammatory cytokines and chemokines may enhance the immune response and inflammation by drawing immune cells to infection sites.[4,5] The effects of Mpox infection have not been studied heretofore with a focus on how it may initiate or exacerbate pre-existing vascular inflammation. The purpose of this paper was to establish the hypothesis that Mpox is linked to vascular inflammation.

The MPXV with a double-stranded DNA genome, encodes more than 200 proteins crucial for virus replication and spread.[6] Immune cells like macrophages and dendritic cells are the primary targets of MPXV infection. MPXV utilizes a multistep process to enter host cells, involving viral proteins and cell surface receptors. The viral

envelope glycoprotein initiates attachment to specific receptors (glycosaminoglycans) like heparan sulfate (HS), laminin, and integrins, although the precise receptors remain incompletely understood.[7] The ciliated simple epithelium contains club cells that have glycosaminoglycan receptors. HS is made up of glycosaminoglycans (GAG), such as syndecan and perlecan, and a core protein.[8]

An infection with the human monkeypox virus causes a wide range of cardiac symptoms.[9,10] There is a need for thorough examination and care due to the virus's influence on the vascular system, which includes endothelial dysfunction and thrombotic events. It is unclear what pathophysiology underlies the vascular inflammation linked to MPXV infection. On the basis of research, observations, and studies on viral infections generally as well as some results particular to MPXV, a number of processes have been put forth. MPXV mostly affects mucous membranes and the skin, resulting in recognizable skin lesions.[11] Studies, however, indicate that the virus may also be able to infiltrate endothelial cells, which line blood arteries and are essential for normal vascular function.[12] When MPXV directly invades endothelial cells, it can interfere with their regular physiological processes, resulting in endothelial dysfunction and atherosclerosis subsequently.[13]

Several signal transduction pathways, including TLR-4, NF-kB, and MAPK, can activate several pro-inflammatory cytokines and macrophages during MPXV infection.[14] Pro-inflammatory cytokines such as TNF-α, can also be secreted by activated macrophages.[15] These signal transduction pathways also stimulate endothelial dysfunction and cardiovascular inflammation subsequently.[14,16] Within endothelial cells, the mentioned signal transduction pathways may result in an increase in reactive oxygen species (ROS) and oxidative stress. Thus, like other viral infections, such as COVID-19, MPXV may lead to an elevation in the production of ROS and harm to antioxidant systems, potentially weakening the immune system.[17–19] To far, however, there is no proof that MPXV infection increases cellular oxidative stress. It is known that oxidative stress plays a role in the development of vascular endothelial dysfunction.[14] Therefore, we can infer that MPXV may contribute to adhesion molecule expression.

Endothelial dysfunction may result from excessive ROS damaging endothelial cells and reducing their ability to function.[14] Pro-inflammatory cytokines trigger endothelial cell activation, which results in the endothelium expressing cell-surface adhesion molecules necessary for inflammatory cells to adhere and recruit across the endothelium of post-capillary venules.[20] The most significant groups of cell adhesion molecules (CAMs) expressed in endothelium and inflammatory immune cells and implicated in leukocyte transmigration include the selectin family, integrin family, and immunoglobulin (Ig) superfamily.[20] The first cells to reach the inflammatory site are neutrophils, and endothelial connections allow neutrophils to extravasate over the endothelial junctions.[5,21] There are six consecutive steps in the process by which leukocytes transmigrate over endothelial barriers: rolling, activation of endothelium, adhesion to the endothelial cells, crawling towards endothelial junctions, transendothelial migration, and diapedesis.[22,23] CAMs such as CD54 and CD106 are arranged in transmigratory cups in endothelial junctions, which resemble microvilli and hold neutrophils in place while promoting their transmigration. According to several studies, oxidative stress controls leukocyte extravasation in response to inflammatory stimuli, perhaps via redox-sensitive transcription factors including NF-κB and activator protein 1 (AP-1) as well as direct activation of CAMs produced by endothelial cells.[20] The oxidative alteration of lipoproteins, especially LDL, in the artery wall is one of the first stages of vascular inflammation, associated with the endothelial production of adhesion molecules.[24] These all together lead to endothelial dysfunction which may result in vascular inflammation.

The entry of MPXV into host cells involves multiple entry viral proteins (Figure 1), leading to replication in the cytoplasm and the production of viral proteins such as immunomodulators through transcription and translation of the viral genome.[25] Released infectious virions can then infect neighboring cells. MPXV infection triggers immune responses involving macrophages, dendritic cells, T cells, and B cells.

During an inflammatory response, ROS can be generated in a variety of cells and tissues, including endothelial cells, macrophages, and smooth muscle cells leading to oxidative stress and dysfunction in the endothelial cells when present in excess levels.[26] Generally, ROS and inflammatory mediators including cytokines or chemokines, cause injury to the endothelial wall of blood vessels, leading to endothelial dysfunction, vasodilation and increased blood flow to the affected area.[27] Endothelial cells become receptive to these mediators and increase their permeability. Developed endothelial dysfunction regulates leukocyte adhesion and migration during inflammation. Rolling, adhesion, and migration of neutrophils, monocytes, and macrophages occur through interactions with adhesion molecules (selectins, integrins, ICAMs/CD54, VCAMs/CD106) (Figure 1). transmigration, contributing to the development of vascular inflammation, and formation of atherosclerotic plaques at a later stage.[23]

The potential aftereffects of viral infections other than MPXV are endothelial dysfunction, increased risk of atherosclerosis, thrombosis, vasculitis, and persistent inflammatory state.[28] Endothelial cells including lymphocytic infiltration are the source of endotheliitis caused by SARS-CoV-2. Widespread endothelial dysfunction and damage have resulted in apoptosis and a loss of microcirculatory regulation, an essential function of the endothelium. This is consistent with the theory that the pathophysiology of COVID-19 symptoms is mostly vascular inflammation.[29] While the precise mechanism by which other viruses, including influenza virus, induce atherosclerosis remains unknown, it appears that inflammation and coagulopathy play significant roles. The mechanisms involved could be as follows: (1) antigenic cross-reactivity; (2) increased levels of pro-inflammatory and prothrombotic cytokines, such as IL-2, IL-6, IL-10, and IL-18; (3) pro-inflammatory cytokine expression by infected monocytes and decreased clotting time; (4) increased macrophage trafficking into

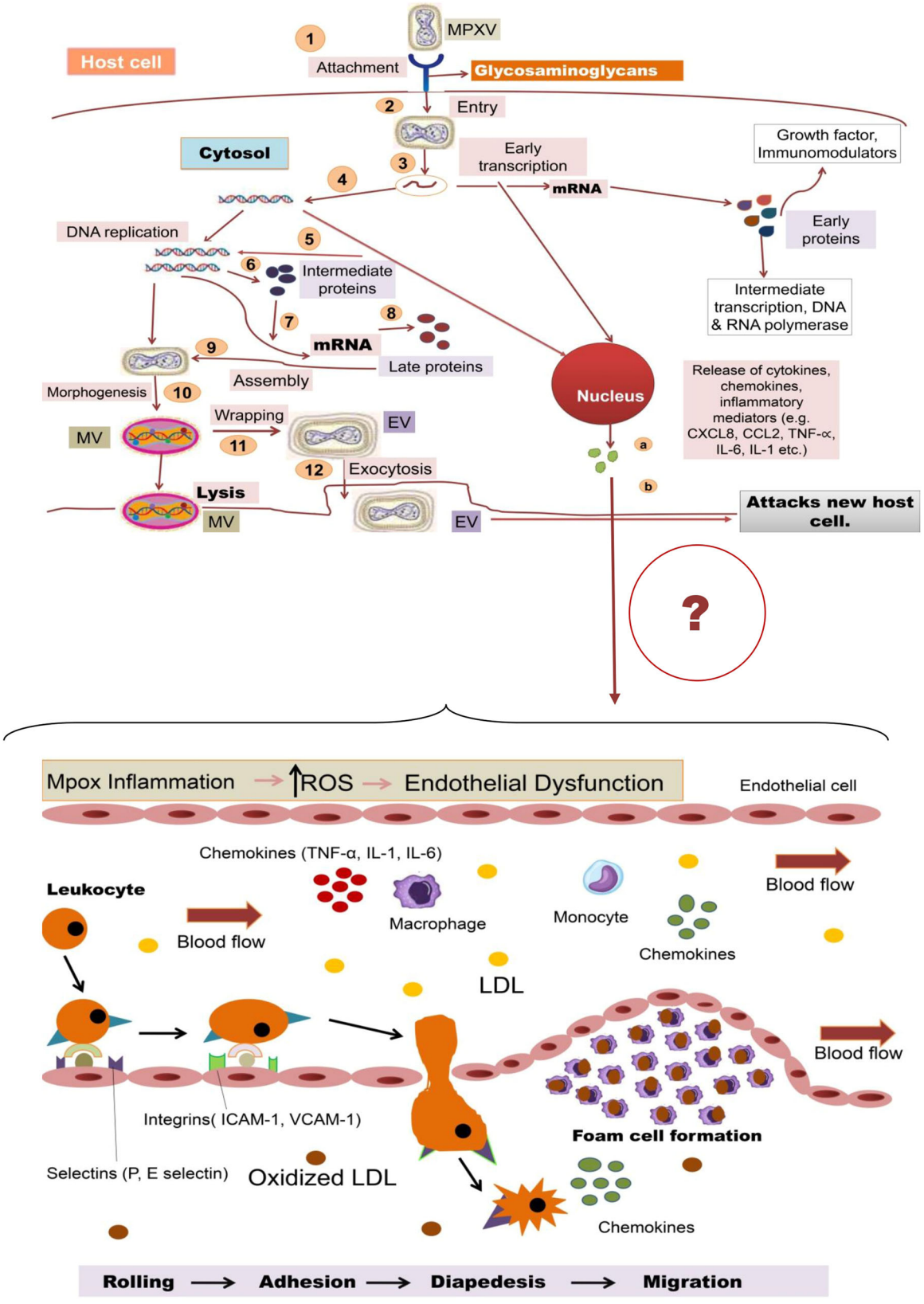

FIGURE 1 (See caption on next page).

the arterial wall; and (5) induction of procoagulant activity in infected endothelial cells, decreased clotting time, and increased expression of tissue factor.[30] Recurrent influenza virus infection has the potential to damage vascular endothelial cells and trigger the inflammatory response necessary to hasten and exacerbate atherosclerosis formation leading to vascular inflammation. Atherosclerosis incidence may also rise due to Herpes Simplex Virus (HSV).[31] The major receptor protein for oxidized low-density lipoprotein (ox-LDL), lectin-like oxidized LDL receptor-1 (LOX-1) is upregulated by HSV.[32] As a consequence, endothelial cells exhibit heightened ox-LDL uptake, lipid accumulation, and metabolism that are stimulated via the increased acquisition of saturated cholesteryl esters and triacylglycerols, coronary artery calcium accumulates, and thrombosis develops; all of these processes are associated with the progression of vascular inflammation and subsequent atherosclerosis.[22] Besides, there is a strong association between atherosclerosis and human immunodeficiency virus (HIV) infection, as those who are HIV-positive have a higher occurrence of atherosclerosis compared to those who are HIV-negative.[33] It is noteworthy that the particular impacts of viral infections on vascular inflammation may differ based on the kind of virus, the host's immune system, and underlying medical problems.

We are suggesting that there may be a crucial connection between the induction of vascular inflammation or the stimulation of existing inflammation to turn it from acute to chronic form during Mpox or as a post-Mpox effect; because different pro-inflammatory mediators are expressed from endothelium, leukocytes, and other cell types. A cytokine storm that occurs during human Mpox sickness is positively correlated with disease severity, according to a study of nineteen confirmed instances of MPXV infection.[34] The MPXV infection-induced cytokine storm is linked to a strong Th2 immune response, which is typified by increased serum levels of IL-4, IL-6, IL-5, and IL-10, and a decrease in Th1-associated cytokines, including TNF-α, IL-2, IL-12, IFN-α, and IFN-γ.[34] For instance, they can trigger leukocytic pro-inflammatory signaling pathways activation such as NF-κB, MAP kinases, STATs, and so forth that control the expression of many pro-inflammatory genes.[19] Inflammatory cytokines, adhesion molecules, and chemokines are produced as a result of those signaling activations. Leukocyte recruitment to vascular inflammatory sites hinges significantly on the critical stage of leukocyte rolling. The MPXV may induce inflammation, as it triggers an inflammatory response in the host's body as a defense mechanism against potential threats.[35] Patients with a history of obesity or smoking, for example, are more likely to experience vascular inflammation in the future if they have an MPXV infection. We urge further research into the potential link between Mpox and vascular inflammation, such as atherosclerosis, because the virus is linked to all the risk factors for these complications, including increased production of pro-inflammatory cytokines through pro-inflammatory signaling pathways. During inflammation, blood vessels in the affected region undergo vasodilation, accompanied by increased vascular wall permeability. Additionally, circulating leukocytes, such as neutrophils and monocytes, feature selectin-interacting receptors on their surfaces. These receptors enable leukocytes to initiate rolling along the vascular wall when they encounter selectins expressed on endothelial cells.[35] Subsequently, cytokines/chemokines like CCL2, TNF-α, CXCL2, CXCL8, CXCL10, IL-1, and IL-6 and so forth produced by the inflamed tissues, further enhance leukocyte adherence to endothelial cells and activate them.[19] After the initial rolling phase, leukocytes firmly adhere to endothelial cells through the interaction of integrins on their surface with adhesion molecules (e.g., ICAM-1/CD54 and VCAM-1/CD106) on endothelial cell surfaces.[36] This firm attachment is crucial for the subsequent migration of leukocytes from the bloodstream into the inflamed tissue. This migration, known as diapedesis, involves leukocytes squeezing between endothelial cells and entering the inflamed tissue. Generally, leukocytes then follow chemotactic gradients towards the origin of the inflammation, contributing to the formation of atherosclerotic plaques within blood vessels and thereby exacerbating vascular inflammation.[5] In addition, LDL particles may be subject to oxidative alteration when ROS are present. LDLs are oxidized during this process. Ox-LDL is engulfed by macrophages in the site of endothelial dysfunction, which causes foam cells to develop.[22] This may initiate acute vascular inflammation and may turn into chronic at a later stage developing foam cell formation,[5] which is a property of early atherosclerotic plaques. Figure 1 shows how MPXV enters cells and how this may be linked to vascular inflammation.

It is reasonable to infer from the above that the Mpox virus may have been associated with cellular dysfunction and vascular inflammation, which might lead to various cardiovascular disorders. Relatively little research has been done on how human Mpox affects the cardiovascular system, despite the fact that its respiratory and cutaneous symptoms have been well examined. Therefore, vigorous

FIGURE 1 A schematic representation of an MPXV life cycle and possible association with vascular inflammation. 1 and 2. Cellular entry. 3. Viral core uncoating. 4. Viral DNA release. 5. mRNA expression followed by early transcription and DNA replication. 6. Synthesis of intermediate proteins facilitating mRNA development. 7and 8. Synthesis of late proteins. 9. Assemble of viral particles. 10. Maturation of viruses through morphogenesis. 11. Enveloped virus (EV) formation from MV by wrapping. 12. Attacking new host cell either by lysis or by exocytosis. Besides, from the nucleus, (A) possiblerelease of inflammatory mediators while transcription and replicationtake place during the inflammation and (B) inflammatory mediators entering into the bloodstream. Due to the inflammatory mediators, rolling, adherence, diapedesis/chemotaxis of the leukocytes specially monocytes and macrophagesmay take placethatmay develop foam cells resulting in vascular inflammation.

study is suggested to fully understand the mechanisms and consequences for clinical care and public health of the link between Mpox and vascular inflammation.

AUTHOR CONTRIBUTIONS

Sara Shahid Meem: Conceptualization; visualization; writing—original draft. **Amrin Yeasin Proma**: Conceptualization; visualization. **Mohiuddin Ahmed Bhuiyan**: Writing—review and editing. **Syed Masudur Rahman Dewan**: Conceptualization; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHIC STATEMENT

Not applicable.

TRANSPARENCY STATEMENT

The lead author Syed Masudur Rahman Dewan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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