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Viral Inflammation: The Good, the Bad, and the Ugly

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Abstract

Viral inflammation although rare, is not a well-known entity, nor it is studied as well as bacterial inflammation. Nevertheless, an understanding of viral inflammation leads to the application of appropriate management principles. Viral inflammation can present either as a local or regional and systemic manifestation. Local or regional manifestation is exemplified by viral incursion of different individual organs whereas viremia represents systemic spread of a virus. A brief description of viral inflammation would help clinicians to understand the scope of the problem and helps to formulate a management strategy. The article focuses on the occurrence of local and systemic manifestation of viral inflammation.

Keywords: Respiratory Viruses, Inflammation, Systemic Inflammatory Response (SIR), Cytokines, Pattern Recognizing Receptors (PRRs), Proinflammation, Antiinflammation, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Introduction

Inflammation is not a common presentation of viral infection. However, it may occasionally be seen by clinicians from time to time as a virus encounters human tissue. It occurs as an immune response to limit the spread of viral infection. At times such a response rarely may spin out of control and cause serious consequences for human health. Viral inflammation may either be local/regional confined to an organ or systemic. Virus causing inflammation in about 1% of human population include influenza, respiratory syncytial virus (RSV), human immunodeficiency virus (HIV), severe acute respiratory syndrome corona virus (SARS-CoV), middle east respiratory syndrome (MERS-CoV), SARS-COV-2, rabies, smallpox, ebola, marburg, nipah, and hanta. Only less than 0.1% of infected individuals suffer from serious life-threatening infection [1].

Pathophysiology

As previously noted, a virus can present as a local or regional inflammation confined to an organ or systemic inflammation following viremia. Viral infection alone is inadequate to induce an inflammatory response in most instances and therefore the presence of inherited or acquired immunodeficiency e.g., HIV, immune deficiency from immunosuppressive drugs plays a role in inducing an inflammation.

Local or Regional Inflammatory Response

Respiratory viruses such as RSV, influenza A (IAV), and corona infect respiratory tract and cause inflammation. Viral particles as they enter the respiratory system confront sentinel local alveolar macrophages (AM) in the lung epithelium [2]. This results in freeing up of alveolar macrophages from lung epithelium leading to effector function, phagocytosis, release of chemokines, proinflammatory cytokines [3], and type-1 inteferon-ɣ (IFN-ɣ). Alveolar macrophages express toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene I (RIG-1) like receptors, and these sense viral protein and release proinflammatory cytokines, IFN-ɣ, and activate nuclear factor kapa beta (NF-κβ) pathway [4]. Innate immune response is initiated by encounter of a virus with AM leading to infiltration of neutrophils, monocytes, and activation of IFN-ɣ pathway [3]. Excessive proinflammatory cytokine release leads to severe disease although AMs play an essential role in the resolution of viral infection [4].

Inflammasome is an innate immune system sensor or receptor that is expressed by AMs and Dendritic Cells (DCs). Inflammasome is involved in the activation of NF-κβ, up-regulation of interleukin 1 beta (IL-1β), and secretion of its active form. It is also involved in caspase activation which control inflammation and cell death [5]. Caspase helps in the release of IL-1β. DCs

released inflammasome plays an important role in healing and immune response to infection [6].

Viruses activate inflammasomes such as nucleotide-binding domain and leucine-rich repeat containing protein 1(NLRP1), NLRP3, and interferon-inducible protein absent in melanoma 2 (AIM2). The latter two are involved in viral infection enhancement as well as viral clearing [7, 8]. NLRP3 is activated by respiratory viruses such as IAV, RSV, and corona virus. NLP3 expression and activation following IAV is important for innate and adaptive immune responses. NLP3 activation is essential for reducing mortality and morbidity following respiratory viral infection [7]. Inflammasome may also be responsible for initiation and resolution of lung inflammation following respiratory viral infection.

Systemic Inflammatory Response (SIR)

SIR develops in response to viremia. Any virus may be responsible for SIR including but not limited to rhinovirus, parainfluenza virus types 1–3, RSV, adenovirus, coronavirus, and cytomegalovirus as well as dengue, hanta, rota, and bocavirus. The innate immune system of the host through pattern recognizing receptors (PRRs) such as TLRs, RIG-1, NLRs, and C-type lectin receptors recognize pathogen-associated molecular patterns (PAMPs) [9]. This leads to the elimination of viral pathogens with the help of the release of proinflammatory cytokines and chemokines as well as recruitment of phagocytes and activation of coagulation and complement systems [10]. A balanced pro and anti-inflammation response help to eliminate viral pathogens. However, a loss of homeostasis can lead to a severe proinflammatory response resulting in damage to tissues or overwhelming anti-inflammation response leading to immunosuppression.

Severe proinflammatory response involves in the release of proinflammatory cytokines by the parenchymal cells and leukocytes. These cells release damage associated molecular patterns (DAMPs) which are recognized by PRRs resulting in their activation leading to further damage to the tissues [11]. It is further exacerbated by the activation of coagulation system, complement, and the endothelium.

Antiinflammatory response results from apoptosis of T cells, B cells, DCs, the exhaustion of T cells, expansion of T regulatory cells (Tregs), and the appearance of myeloid derived suppressor cells [12]. Antigen presenting cell (APC) dysfunction results in reduced capacity to generate proinflammatory cytokines [13]. The prolonged presence of neutrophils because of delayed program cell death and the increased number of immature neutrophils which are incapable of scavenging viral pathogens further exacerbates immunosuppressive effect.

SARS-COV-2

It is an example of a virus that triggers both systemic and local or regional inflammatory response. Immune mediated systemic inflammatory response involving different organs include the following.

Lungs

Acute Respiratory Distress Syndrome from severe inflammation mediated by interleukin-6 (IL-6) [14].

Multi System Inflammatory Syndrome (MIS-C)

It is seen in children older than 5 years of age mostly in non-white ethnic group affecting gastrointestinal tract, cardiovascular, respiratory system, and mucocutaneous lesions. It presents 25-45 days following SARS-COV-2 with a mortality rate of 1.7%. It is due to post-viral immune related complication [15].

Hemophagocytic lymphohistiocytosis (HLH)

HLH is seen in adults and the incidence is low. An evaluation of HLH is indicated in those who have cytopenia involving at least two cell lines in peripheral blood including low platelets, high blood ferritin levels (>2000ng/ml), and hypofibrinogenemia [16].

Antiphospholipid Syndrome

Anti-phospholipid (aPL) antibodies are not uncommonly detected in COVID-19 patients. COVID-19 doesn't play a prominent role in triggering antiphospholipid syndrome [17].

Generalized Vasculitis

Involves the skin, the central nervous system, the lungs, and the gastrointestinal tract 2 weeks after initial presentation of symptoms following COVID-19 [17].

Muscle Inflammation

Muscle involvement is seen in 3-11% of patients mostly in adult males with COVID-19. It is present in the 1st week of infection [18].

Joint Involvement

Joint involvement presents itself with or without inflammation. Inflammation may involve one or more joints predominantly in older adults.

Autoimmunity

Autoimmune diseases such as systemic lupus erythematosus, Sjogren syndrome, and rarely sarcoidosis have been reported in COVID-19 [19].

Local or Regional Response

Immune related local or regional responses are described below.

Skin

Skin lesions include urticarial lesions or maculopapular rash in about 5% individuals. Young patients may experience itchy or painful erythematous or violaceous lesions [20]. Other miscellaneous skin lesions have been described such as erythema multiforme, purpura, and acrocyanosis.

Hematological Manifestations

Anemia, thrombocytopenia, and lymphopenia are seen as asymptomatic presentation. Symptomatic appearance includes im-

mune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, and autoimmune hemolytic anemia.

Central Nervous System Manifestation (CNS)

CNS presentation includes cerebrovascular damage, encephalitis, encephalopathy, and Guillain-Barre syndrome (GBS) [21] from neuro assault of the SARS-COV-2 virus. CNS involvement occurs 2 weeks after the onset of viral infection. In addition to myelitis immune mediated CNS manifestations include myasthenia gravis, optic neuritis, and cranial nerve involvement [18].

Lung Lesions

The following pulmonary complications have been observed in infection with COVID-19 such as diffuse alveolar disease, pneumonia, organizing pneumonia, interstitial lung disease, pulmonary fibrosis, and pleural involvement consisting of pleural effusion [22].

Cardiac Lesions

COVID-19 related cardiac issues include myocardial injury, acute myocarditis more commonly in men affecting young adult to older individuals [23]. Pericardial effusion was also noted evolving into cardiac tamponade in a small percentage of patients.

Nephrological Complications

Renal issues seen include involvement of glomeruli and proximal tubule of the kidney. Glomerular disease presents as glomerular nephritis which may be minimal change disease or focal segmental glomerular sclerosis. Many of these patients develop renal failure requiring dialysis.

Endocrine Dysfunction

It includes hyperthyroidism and hypothyroidism. More individuals have hyperthyroidism when compared to hypothyroidism [24]. Adrenal gland lesions include adrenal bleeding, adrenal infarction, and rarely adrenal failure [25].

Acute pancreatitis is seen mostly in women and is seen in all age groups [26].

Eye Findings

Anterior uveitis and conjunctivitis have been reported [27].

Conclusion

Inflammatory response from viral infection, although uncommon, can be confined to an organ or can spill into systemic circulation causing generalized spread of inflammation. A balanced pro and antiinflammatory response lead to clearance of viral pathogen and a good outcome. However, either a hyperinflammatory response or an immunosuppressive response can result in poor outcome either due to multi organ dysfunction or an immunodeficiency state exhibiting the bad and ugly side of viral inflammation.

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References

1. Casanova JL, Abel L (2021) Mechanisms of viral inflammation and disease in humans. Science 374: 1080-1086.
2. Guilliams M, De Kleer I, Henri S, Post S, Vanhoutte L, et al. (2013) Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. Journal of Experiments Medicine 210: 1977-92.
3. Peiro´ T, Patel DF, Akthar S, Gregory LG, Pyle CJ, et al. (2018) Neutrophils drive alveolar macrophage IL-1β release during respiratory viral infection. Thorax 73: 546-556.
4. Juarez E, Nuñez C, Sada E, Ellner JJ, Schwander SK et al. (2010) Differential expression of Toll-like receptors on human alveolar macrophages and autologous peripheral monocytes. Respiratory Research 11: 2.
5. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, et.al. (2004) NALP3 forms an IL-1betaprocessing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity 20: 319-325.
6. Ji J, Hou J, Xia Y, Xiang Z, Han X (2021) NLRP3 inflammasome activation in alveolar epithelial cells promotes myofibroblast differentiation of lung-resident mesenchymal stem cells during pulmonary fibrogenesis. Biochimica et Biophysica Acta Molecular Basis of Disease 1867 :166077.
7. Tate MD, Ong JDH, Dowling JK, McAuley JL, Robertson AB, et al. (2016) Reassessing the role of the NLRP3 inflammasome during pathogenic influenza A virus infection via temporal inhibition. Scientific Reports 6: 27912.
8. Zhang H, Luo J, Alcorn JF, Chen K, et al. (2017) AIM2 Inflammasome Is Critical for Influenza-Induced Lung Injury and Mortality. Journal of Immunology 198: 4383-4393.
9. Boyd JH, Russell JA, Fjell CD (2014) The meta-genome of sepsis: host genetics, pathogens, and the acute immune response. Journal of Innate Immunity 6: 272-283.
10. Takeuchi O, Akira S (2010) Pattern recognition receptors and inflammation. Cell 140: 805-820.
11. Chan JK, Roth J, Oppenheim JJ, Tracey KJ, Vogl T et al. (2012) Alarmins: awaiting a clinical response. Journal of Clinical Investigation122: 2711-2719.
12. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, et al. (2011) Immunosuppression in patients who die of sepsis and multiple organ failure. Journal of American Medical Association 306: 2594-2605.
13. Liu TF, Yoza BK, El Gazzar M, Vachharajani MT, McCall EC (2011) NAD+-dependent SIRT1 deacetylase participates in epigenetic reprogramming during endotoxin tolerance. Journal of Biological Chemistry 286: 9856-9864.
14. McElvaney O, Natalie J, McEvoy L, McElvaney OF, Carrol TP, et al. (2020) Characterization of the inflammatory response to severe COVID-19 illness. American Journal of Respiratory Critical Care Medicine 202: 812-821.
15. Martinez OM, Bridges ND, Goldmuntz E, Pascual V (2020) The immune roadmap for understanding multi- system inflammatory syndrome in children: opportunities and challenges. Nature Medicine 26: 1819-1824.

16. Ramos- Casals M, Brito- Zerón P, López- Guillermo A, Khamashta M A, Bosch X (2014) Adult haemophagocytic syndrome. Lancet 383: 1503-1516.
17. Ramos-Casals M, Brito-Zerón P, Mariette X (2021) Systemic and organ-specific immune-related manifestations of COVID-19. Nature Reviews Rheumatology 17: 315-332.
18. Mao, L, Jin H, Wang M, Hu Y, Chenet S, et al. (2019) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. Journal of American Medical Association Neurology 77: 1-9.
19. Mantovani Cardoso E, Hundal J, Feterman D, Magaldi J (2020) Concomitant new diagnosis of systemic lupus erythematosus and COVID-19 with possible antiphospholipid syndrome. Just a coincidence? A case report and review of intertwining pathophysiology. Clinical Rheumatology 39: 2811-2815.
20. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C (2020) Pernio- like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. Journal of American Academy of Dermatology 83: 486-492.
21. Yachou Y, El Idrissi A, Belapasov V, Ait Benali S (2020) Neuroinvasion, neurotropic, and neuroinflammatory events of SARS- CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurological Sciences 41: 2657-2669.
22. Liu D, Zhang W, Pan F, Li L, Yang L, et al. (2020) The pulmonary sequalae in discharged patients with COVID-19: a short- term observational study. Respiratory Research 21: 125.
23. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, et al. (2020) Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. Journal of the American College of Cardiology 76: 533-546.
24. Chen M, Zhou W, Xu W (2021) Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid 3: 8-11.
25. Heidarpour M, Vakhshoori M, Abbasi S, Shafie D, Rezaei N (2020) Adrenal insufficiency in coronavirus disease 2019: a case report. Journal of Medical Case Reports 14:134.
26. Dirweesh A, Li Y, Trikudanathan G, Mallery JS, Freeman ML, et al. (2020) Clinical outcomes of acute pancreatitis in patients with coronavirus disease 2019. Gastroenterology 159: 1972-1974.
27. Ozturker Z K (2021) Conjunctivitis as sole symptom of COVID-19: a case report and review of literature. European Journal of Ophthalmology 93: 139-140.