Case study

COVID-19 and hyperinflammation: Role of steroid in mild disease

Abstract

Current COVID-19 has become a major public health problem because of its pandemicity, with wide spectrum of disease manifestation. SARS-COV-2 can have a varied clinical manifestation ranging from asymptomatic, mild symptomatic to severe disease like acute respiratory distress syndrome, cytokine storm, and multiorgan dysfunction. It has been described in literature that cytokine storm/hyperinflammation arises as result of dysregulated immune response leading to excessive release of various cytokines which causes multiorgan dysfunction. But there is paucity of literature describing the immune response and hyperinflammation in mild disease which may cause unremitting symptoms. Here we describe a case series of three patients with mild disease, who had persistent symptoms beyond 1 week and managed with low dose steroid after confirming it to be hyperinflammation. So it is imperative to detect the hyperinflammatory phase to halt the disease progression. Also we have discussed the role of immune system and role of steroid in COVID-19.

Key words: COVID-19, Mild disease, Immune system, Hyperinflammation

Introduction

COVID 19 has been a major health problem causing significant morbidity and mortality. It is a respiratory viral illness, with presentation ranging from asymptomatic infection to symptomatic illness of varying severity of mild to severe disease including acute respiratory distress syndrome (ARDS).[1]

It has similar symptom like SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), and influenza. Many cases of mild to moderate disease have shown uncontrolled immune exacerbation resulting from excessive release of various cytokine,

culminating in a cascade of inflammatory event with involvement of vital organs resulting in ARDS, multiple organ dysfunction syndrome (MODS) which are the primary reason of increased mortality among ICU patients.[2]

There is paucity of literature describing the prevalence and intensity of inflammation in mild disease which may show deterioration in late phase of illness or during recovery phase that might land up in cytokine storm. Here, we have described case series of hyperinflammation in mild case during late phase of disease.

Cases Presentation

Case 1

A 47 year, female admitted with complaints of fever, sore throat, body ache for 1 day. She had no other past medical illness. Her general and systemic examination were normal. She was tested positive for COVID RT-PCR on same day. Preliminary blood investigation was normal along with sterile blood and urine culture sensitivity. Chest X-ray was normal. Fever was persisting in spite of usual care including hydroxychloroquine (HCQ) along with antibiotic coverage. She was found to have low leukocyte count (3.3×10^9/L), raised inflammatory marker like erythrocyte sedimentation rate (ESR)-170mm in 1st hour, C-reactive protein (CRP)-143mg/dl on day 9th of hospitalisation. Low dose dexamethasone (0.1mg/kg) was started, which resulted in subsidence of fever over next 1 day and ESR, CRP dropped down drastically to lower level after 2 days (ESR-85mm in 1st hr, CRP-18 mg/dl). Steroid was continued for 4 days. She was then discharged after 3 days of asymptomatic period.

Case 2

A 53yr, male COVID positive (RT-PCR) patient admitted with complaints of fever, headache, body ache for 3 days. He was a known diabetic, and was on oral hypoglycaemic agents (OHA) with controlled blood sugar. General and systemic examination were unremarkable. Initial laboratory parameter showed low leukocytes count(1.9×10^9/L), mild transaminitis, high ESR & CRP (ESR-170mm in 1st hr, CRP-66mg/dl) with sterile blood and urine culture. Chest X-ray was normal. He was managed with standard care with HCQ, antibiotics. He continued to have fever,

so low dose dexamethasone 0.1mg/kg/day was started on day 11th of hospitalisation in view of persistent fever and high inflammatory state, and continued for 3 days. He remained symptom free after starting of steroid till discharge with settling down of inflammatory marker to lower level over 2 days (ESR-70mm in 1st hour, CRP-10 mg/dl).

Case 3

A 57yr, female, who was a diabetic patient admitted as asymptomatic COVID with uncontrolled blood sugar. She neither had other comorbidity nor any addiction history. Her systemic examination was normal. Routine baseline blood investigation was normal except high random blood sugar which was managed and controlled with OHA and insulin. She started having low grade daily fever associated with headache from day 7th of hospitalisation. Repeat blood investigation showed low leukocytes count (3.59×10^{9}/L), high inflammatory marker (ESR-162mm in 1st hour, CRP-57mg/dl), negative serology for dengue and malaria, sterile blood and urine culture. Chest X-ray was normal. Low dose dexamethasone (6mg/day) was started on day 8th of admission and continued for 3 days. She remained afebrile from next day till discharge with normalisation of CRP-8mg/dl and lowering down of ESR to 35mm/1st hour.

Case 1 and 2, both had positive RT-PCR on day 9th of illness with persistent systemic symptom whereas case 3 had onset of febrile period at the end of 1st week with negative RT-PCR on 12th day. All the cases were mild disease with persistent systemic symptoms without respiratory sign/symptoms beyond 1st week and showed drastic response to short course low dose steroid, and all were seemed to be saved from sequelae of hyperinflammation.

Discussion

SARS-CoV-2 is a respiratory viral infection presenting predominantly as fever (88.7%), cough (67.8%) with or without other symptoms like headache, fatigue, breathlessness which may subsequently progress to pneumonia, ARDS or rapidly develop cytokine storm resulting in MODS (multiple organ dysfunction syndrome).[1] The data from China during initial phase of pandemic revealed that mild to moderate disease constitutes 81% of total cases where as 14% case, 5% cases had severe disease and critical illness respectively.[3] Here, we have encountered 3 cases with mild symptoms mainly fever with other constitutional symptoms which persisted beyond 1st week.

Some studies have described the natural history of SARS-CoV infection in three phases. First phase start with one or more symptoms like fever, dry cough, myalgia, headache and other systemic manifestation due to viral replication and viremia. Second phase start with the appearance of immunoglobulin along with diminished viral replication which may sometimes shows worsening of symptoms to severe disease (Pneumonia with or without hypoxemia) with few patients having fatal course. Around 50% patients start showing seroconversion at the end of 1st week and rest join the race by 2nd week. Most of the cases recover by second week but one third cases may progress to third phase (hyper inflammation phase) which is characterised by severe lung inflammation causing ARDS, sepsis, coagulopathy, MODS, shock, cardiac failure, suggesting cytokine storm. So worsening of disease in 2nd week is perhaps unrelated to viral replication, rather suggest immune-pathological phenomena.[4-6]

It is also evident that viral replication differ in both SARS-CoV-1 and COVID-19. The maximum viral shedding in COVID-19 start at disease onset and decline slowly to recovery phase at 2nd week where as in SARS-CoV-1, viral shedding steadily increases to attain the peak at 2nd week.[7,8]

SARS-CoV-2 is acquired by inhalation of microdroplets of infected individuals or through fomites from a contaminated surface. The virus gain access to lung parenchyma through its gateway receptor type-II ACE2+ pneumocytes of the alveolar epithelium and releases large number of virions after replication and subsequently proceed to viremia phase.[9] The severe disease is thought to be due to dysregulated immune system, imbalance of ACE2/ACE levels in COVID-19 and the dysregulated angiotensin-II /AT1R axis of the renin-angiotensin-aldosterone system (RAAS) that culminate in hyperinflammation, cytokine storm and the resulting severe pulmonary damage, sepsis, shock.[10] Role of various cytokines have been implicated in the pathogenesis of severe disease as studied by Qin et al**.** in 452 patients. It showed that inflammatory cytokines like IL-6, IL-8, IL-10, and TNF-α were elevated in severe disease.[11]

COVID-19, immune system and inflammation

COVID-19 has the tendency to attack our immune system unusually involving secondary lymphoid tissues as revealed in an autopsy study. All reported cases have shown splenic atrophy with reduced number of lymphocytes, macrophage phagocytosis, focal necrosis and also decrease lymph node number with lymph node atrophy. There is evidence of low lymphocyte

count, low lymphocyte to neutrophil count, low to undetectable NK cell in patients of COVID-19.[11]

Lymphocytopenia has been found in majority of severe COVID-19 patients as evident from a study comprising 123 patients. CD8+ T cell and NK cells were affected mostly and were reduced to a very low level. CD8 + T cells were reduced by 28.43% in mild disease whereas reduced by 61.9% in severe disease. NK cells were reduced by 34.31% and 47.62% respectively, in mild and severe groups. Level of serum IL-6 were significantly higher in severe group as compared to mild group.[12] So possible destruction of immune system in COVID-19 might be due to direct attack of virus or indirectly by cytokines. It is also a fact that lymphocytes don't express ACE2. So it is presumed that the destruction of lymphocytes are programmed and executed by cytokines.[11]

Till date no studies have been conducted in asymptomatic/ mild symptomatic infected individual to study the immune response to COVID-19 infection.

Abnormal laboratory parameter in COVID-19 patients may include lymphopenia, raised acute phase reactants, elevated levels of C-reactive protein, ferritin, and d-dimer.[13] Meta-analysis of numerous studies showed significant increase in inflammatory markers in the severe disease as compared to non-severe disease. The weighted mean difference (WMD) of inflammatory markers between severe and non-severe group were; ESR (WMD = 27.67 mm/h), CRP (WMD = 36.61 mg/L), LDH (WMD = 102.15U/L), Procalcitonin (WMD = 0.03 ng/Ml).[14] All our cases had low leukocyte count during 1st week, also had raised inflammatory marker in the form of high ESR and CRP after 1st week of illness.

Role of immunosuppression

Corticosteroids suppress immune system initially impairing innate immunity. Hence its use was discouraged because of apprehension of viral replication and disease propagation. But there have not been any severe disease or fatal pneumonia in those patients on long immunosuppression by low dose steroid.[15] Corticosteroids have primary role in suppressing immune system to halt the cytokine storm and its consequences like ARDS, disseminated intravascular coagulation, hypotension, shock and death. So it should be used at the notch of infection and inflammation so

as to terminate the cascade event of cytokine storm which is usually happens after 1st week of illness.[16]

The questionable role of steroid reflected a ray of hope after the RECOVERY trial which was conducted in 176 NHS hospitals with 6425 patients with dexamethasone arm (2104 patients) received 6mg per day for 10 days and 4321 patients with usual care. There was significant reduction in mortality by 35% among invasive mechanical ventilation and 20% reduction in mortality among patients on oxygen therapy with or without non-invasive ventilation. There was no benefit in mild or moderate cases. It was also observed that dexamethasone reduced the period of hospitalisation as compared to usual care.[17]

Steroid should be started when following features are noticed - 1. Sign of hypoxemia 2.rapid worsening of chest imaging 3.excessive inflammatory response. It should be used for short period preferably 3-5 days and the recommended dose should not exceed equivalent to methylprednisolone 1–2 mg/kg/day.[18] We have used low dose steroid (Dexamethasone 0.1mg/kg) for all three patients for 3-5 days which resulted in subsidence of all symptoms including fever with drastically lowering down of inflammatory markers.

Conclusion

Mild disease can have persistent symptoms beyond 1st week which may be due to hyperinflammation, so detecting the initiation of hyperinflammation is crucial point to manage the patients so that morbidity and mortality can be minimised. Hence it need further research to validate the role of hyperinflammation in mild disease.

Comment [V1]: Include the effect of low dose of steroid in conclusion

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui D, et al.; China Medical Treatment 16 Expert Group for Covid-19. Clinical characteristics of 17 coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720.

2. Wu R, Wang L, Kuo HD, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z, Poiani GJ, Amorosa L, Brunetti L, Kong AN. An Update on Current Therapeutic Drugs Treating COVID-19. Curr Pharmacol Rep. 2020 May 11:1-15.

3. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control an Prevention. *JAMA.* 2020;323(13):1239–1242.

4. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361(9371):1767-1772.

5. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-469.

6. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405-407.

7. Cheng PK, Wong DA, Tong LK, et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet. 2004;363(9422):1699-1700.

8. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020;20(5):565-574.

9. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-879.

10. Bm H. COVID-19 induced Renin-Angiotensin System (RAS) imbalance may drive acute lung injury: the evidence and therapeutic options. BMJ. 2020;368.

11. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-768.

12. Wan S, Yi Q, Fan S, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). medRxiv; 2020.

13. Lippi, G., & Plebani, M. (2020). Laboratory abnormalities in patients with COVID-2019 infection, *Clinical Chemistry and Laboratory Medicine (CCLM)*, *58*(7), 1131-1134.

14. Ghahramani S, Tabrizi R, Lankarani KB, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res. 2020;25(1):30. Published 2020 Aug 3.

15. Isidori AM, Arnaldi G, Boscaro M, Falorni A, Giordano C, Giordano R, Pivonello R, Pofi R, Hasenmajer V, Venneri MA, Sbardella E. COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency. Journal of Endocrinological Investigation. 2020 Apr 25:1.

16. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19 [published online ahead of print, 2020 May 19]. Clin Infect Dis. 2020;ciaa601.

17. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. N Engl J Med. 2020;NEJMoa2021436.

18. Qin YY, Zhou YH, Lu YQ, et al. Effectiveness of glucocorticoid therapy in patients with severe coronavirus disease 2019: protocol of a randomized controlled trial. Chin Med J (Engl). 2020;133(9):1080-1086.