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C-Reactive Protein As Bioinflammatory Markers In Covid Management Is More Than Prognostic Indicator: A Case Series

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Abstract:
SARS COVID-19 is known to cause wide spectra of illness varying from asymptomatic to mild, moderate, severe pneumonia and even death Considerable number of people infected with COVID-19 infection are presenting with features of fatiguability, myalgia, low grade fever, insomnia and persistent vague complaints in the late phase of infection which is unrelated with severity of disease. We are presenting series of cases with post-acute COVID-19 having symptoms of myalgia, depression, fever and fatiguability arthralgia with raised CRP. C-reactive protein, the first acute phase protein to be described, is a sensitive marker of inflammation and tissue damage is an important regulator of inflammatory process and not just a marker of inflammation or infection. Treating these patients reduces morbidity.

Key words: *Arthralgia; CRP; post- acute COVID-19*

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I. Introduction

SARS COVID-19 is known to cause wide spectra of illness varying from asymptomatic to mild, moderate, severe pneumonia and even death. This variability in presentation is being attributed to the degree of dysregulated immune response of body to the viral antigen varying from development of no antibodies to hyperstimulation syndrome to severe cytokine storms. Since the pandemic has evolved. It has been seen that the various chemokines released as the response to the viral antigen like CRP, IL-6, procalcitonin, D-dimer, ferritin have a definite role in determining the progression of disease and their assessment have prognostic significance. But these bio-inflammatory markers beside having prognostic significance if co related with clinical presentation play important role in deciding the management of patients who present to us once the acute viral illness phase is over that is beyond 14 days. C-reactive protein, the first acute phase protein to be described, is a sensitive marker of inflammation and tissue damage. Precise response and ease of assay have made an ideal marker of inflammation [1]. Evidence suggests that CRP is an important regulator of inflammatory process and not just a marker of inflammation or infection. A considerable number of people infected with COVID-19 infection are presenting with features of fatiguability, myalgia, low grade fever, insomnia and persistent vague complaints in the late phase of infection. These presentations are not related with the severity of disease. Here we are discussing a series of cases who presented to us with similar complaints, once acute phase of COVID-19 illness was over and their management in co- relation of their symptoms and blood inflammatory markers.

CASE 1 –

A male of 62 years was admitted as a case of moderate COVID-19 pneumonia 21st November 2020. Patient improved and became asymptomatic after almost 14 days of treatment as per protocol guidelines of the hospital. Patient was discharged. Patient developed fever 10 days later. Blood investigations showed: TLC = 10000, Polymorph = 80%, CRP = 25.9. Considering post viral secondary infection, Patient was started on short course of antibiotics for 5 days. Patient became afebrile after 5 days. CRP was normal.

CASE 2:

A female of 57 years presented in OPD as a case of mild COVID-19 infection on 23rd November. Patient was treated as per protocol. She became asymptomatic after 21 days. She started complaining of resurge of myalgia after 28 days. Blood investigation 22nd December showed TLC = 7790 with 80 % polymorphs and CRP = 18.4. Patient was treated with HCQS. Her symptom resolved after 10 days completely and her CRP levels reached to baseline.

CASE 3:

A diabetic male aged 58 years presented as a case of moderate COVID-19 pneumonia on 27 August and admitted as his spo2 was 88% and breathlessness was disturbing. Patient was managed as per protocol. He was discharged after 21 days on 18th September with spo2 of 96 % at room air and his CRP levels was 3.45 Patient was readmitted on 28th September (after 10 days) with complaints of fever, and falling spo2, cough with a non-homogenous opacity in right upper zone on X- ray. His TLC was 12800 with 86 % polymorphs and CRP 135.8 and IL-6 128.5. Patient was treated with antibiotics with no resolution on x ray and no relief of symptoms. Patient sputum was sent for fungal detection and culture and it turned out to be positive for candida species. Patient was treated on antifungal agents as per sensitivity and his symptoms started relieving and also his x ray showed clearing after 1 week. His blood investigations as on 2nd October showed CRP as 33.6 and also IL-6 as 30.4 and patient was able to maintain Spo2 94% at room air and was thus discharged with advice to continue with antifungals for 2 months.

CASE 4:

A 71-year-old male patient, non-diabetic, non-hypertensive from hilly region developed symptoms of fever, cough and cold with backache on 29th October 2020. His sample was tested positive for COVID19 and patient was treated as per protocol. Patient was afebrile after 10days.However his backache persisted and he maintained his spo2 at room air around 98 %. After 11 days, his blood report showed TLC = 8800 with 72% polymorph and CRP = 27.2. HCQS was given 15 days. On 17th November (18 days) he was asymptomatic. His repeat blood investigation showed TLC = 11000 with 69% polymorph and CRP 1.9. On telephonic follow up, after 15 days he had no further complaints.

CASE 5:

A 46 years old diabetic female presented with complain of sore throat, nasal symptoms for 3 days and she had positive RT-PCR on 21st November. Her blood investigation was TLC = 7000 with 59 % polymorphs and CRP = 46 and HbA1C = 9.2. She was treated with as per protocol and injection insulin. Patient recovered after 11 days (2nd of December) and TLC = 10,270, polymorphs = 76 % and CRP = 14.2 but myalgia persisted. HCQS was continued for next 15 days. Her symptoms relieved by another 15 days, and TLC = 10780 (p = 67 %) and CRP 32.6.

Case 6:

A male 64 years old, nondiabetic, hypertensive presented to emergency department on 3rd December with history of symptoms of fever, cough for last 4 days and diagnosed as mild COVID-19. Treatment as per protocol was given. (TLC= 13,000 with 79% polymorphs, CRP = 7.0 and IL-6 = 37. Patient was started with intravenous antibiotics, HCQS and steroid. He was discharged on after 13 days (on 16th December). He had myalgia and CRP was 25. HCQS was given and after 15 days, he was asymptomatic completely features.

CASE 7:

A male 55 years presented with fever, body ache and cough on 8th November and fever persisted for 10 days with negative RT-PCR COVID-19 done twice. His fever panel test was also negative. Patient was treated with steroids along with doxycycline and ivermectin. His fever subsided in two days. His reports of 23rd November revealed raised WBC count of 13,000 with 94 % polymorphs and CRP value 3.1. His liver enzymes were also raised more than 5 times of normal (SGOT/SGPT-272/542). He also developed bradycardia. Bradycardia responded to reduction of steroid dose. HCQS was continued. With treatment of antibiotics, he was asymptomatic in 15 days. Bradycardia was gone after stoppage of steroid. LFT and CRP came to normal.

CASE 8:

A 46-years old presented to our hospital on 23rd August a case of COVID-19 pneumonitis. He was treated with antibiotics, LMWH, steroid and HCQS. After 15 days, he was asymptomatic and after 15 days, patient again developed rise in temperature. His blood investigations of the day revealed TLC = 6000 with polymorph = 71 %, lymphocytes = 16 %and CRP 13.4. Salmonella typhi dot was positive and he was treated with ceftriaxone for 10 days. He was asymptomatic and CRP was 1.5.

II. Discussion

Presentation of variable symptoms is a common feature of Post-acute COVID-19 infection. The common presenting features are myalgia, leg pains, easy fatiguability, low grade fever, insomnia, mental-fogging, loss of concentration, depression, and lack of drive to initiate activities. CRP is an acute phase protein and a nonspecific biochemical marker of chronic inflammation. It is a surrogate of another inflammatory cytokine such as IL -6, IL-8. The positive relationship between the CRP and IL6 during inflammation is well

established [2]. It is produced in hepatocytes and adipose tissues in response to increase level of pro-inflammatory cytokines in peripheral circulation. It rises within 48 hours of inflammation and rapidly decreases within hours of stimulus absence (half-life is 18 hours [3]. Its increased levels are seen in infection, inflammation, diabetes, depression and atherosclerosis. Moderate level of rise in CRP levels associated with viral upper respiratory infection is a common finding in initial days of infection (day 2 to day 5 in influenza) and settles to base line within 7 days. As per observation any rise in CRP beyond 7 days need to be treated with antibiotics in case of these viral illnesses [4]. The highest concentration of CRP has been found to be associated with some bacterial infection [5]**.** Dan coster et al in their study have proposed for an approach of using the kinetics [6]. of CRP in patients whose first CRP measurement is low for assistance in differential diagnosis between acute viral and acute bacterial respiratory infections [A highly significant diagnostic contribution of adding ESR and CRP to history and physical examination, particularly when the illness had lasted one week or more was demonstrated in a study by H.Melbye et al. Fatigue is highly prevalent and cause disruption in quality of life. Although the underlying biological mechanism is unknown, increases in inflammation had been implicated. In a study by Hyong Jin, Cho et al [7], a prospective association was demonstrated between an inflammatory marker and fatigue in general population. An association was found between low grade systemic inflammation and fatigue which seemed primarily driven by a persistent immune activation irrespective of presence or development of comorbidity. Human studies have shown the development of cytokine induced fatigue in healthy individuals administered with proinflammatory cytokine IL-6 and interferon-alpha and is associated with depression [8]**.** The mentioned study made an observation that fatigue and pain are 2 symptoms frequently present not only in acute or chronic high grade inflammatory disease or cancers, but also in low grade inflammatory disease such as chronic fatigue syndrome. These symptoms are often associated with depression. In all these diseases proinflammatory markers have been highlighted [9]. Moderately elevated blood levels of proinflammatory cytokines including C-RP have been found in patients presenting with fatigue in number of case control studies and meta-analysis [10] Wittenberg G M, Stylianou A, Zhang Y et al had concluded that anti-inflammatory drugs can have therapeutic effects on psychological symptoms of depression associated with inflammatory disease, that are not entirely attributable to treatment effect on physical health [11]. A strong correlation is found between high CRP levels and new onset diabetes later [12,13]. Inflammatory marker such as CRP have been related to the development of insulin resistance and type- 2 diabetes. The main implication of these findings is that inflammation may not only be implicated in the development of diabetes, but also on-going levels of hyperglycemia once diabetes is established [14,15]. High CRP levels have been correlated to increase thrombotic events and cardiovascular diseases [16,17]. Increased CRP level is typically associated with disease, but liver failure is one condition observed to impair the CRP production. Very few drugs reduce elevated CRP unless they treat the underlying pathology, that is causing acute phase stimulus. Hydroxy chloroquine and chloroquine are antimalarial drugs that have been successfully used in treatment of autoimmune diseases. Low doses appear to have minimal effect on pH but can prevent activation of PRRS to modulate downstream innate immune responses [18]. Post chikungunya presenting with rheumatic myalgia up to 2 weeks has also been attributed to chronic low-grade inflammation and have been recommended treatment with, steroids (low doses), NSAID and HCQS [19]. Studies on the use of chloroquine phosphate (CQ) and hydroxychloroquine (HCQ) in the acute phase have shown inconsistent effects, though some benefit cannot be ruled out [20]. Brazilian guidelines advise use of HCQ for persistent symptoms (>3–4 weeks) in the dosages of 5 mg/kg/day. WHO guidelines also support using HCQ 200 mg once daily or CQ 300 mg daily for 4 weeks for resistant musculoskeletal symptoms [21]. What emerges on analysis of these case series is that patients presenting with COVID-19 symptoms and abnormal blood reports and bio inflammatory markers may be suffering from secondary infections, post viral rheumatic arthralgia or precipitation of type 2 diabetes. They were treated with appropriate antibiotics, antifungal as per diagnosis. Also, one of the cases responded well to his symptoms when treated with HCQS referring the post chikungunya myalgia. A female patient had her symptoms well relieved with sugar control and infection with antibiotics. Thus, we observe that the treatment of COVID-19 if approached on individual basis in correlation with blood investigation and CRP have positive outcome and prevents the late morbidity of the disease.

III. Conclusion

Post-acute COVID-19 persistence of symptoms are a common presentation which needs to be thoroughly investigated and appropriately treated irrespective of severity of disease. This may lead to decrease morbidity and mortality post COVID-19 and decrease losses of active days of patients.

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