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Post COVID immune phenomena: Expanded role of the Nephrologist

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Abstract
Aims and objectives: To describe the diagnosis, management and outcomes of 5 cases of post COVID immune disorders that needed intervention from the Department of Nephrology in a single center.
Materials and Methods: Five cases of post COVID immune disease detected at VPS Lakeshore Hospital and Research Centre, Kochi have been described. All cases were diagnosed with an RT-PCR assay. Their management and final outcomes also were analyzed.
Results: 2 cases of post COVID diffuse alveolar hemorrhage, 2 cases of post COVID systemic lupus erythematous (SLE) and 1 case of post COVID macrophage activation syndrome with ANA and APLA positivity have been described. The two patients of diffuse alveolar hemorrhage required plasma exchange and immunosuppression and made a full recovery. One patient with SLE made a full recovery and underwent a kidney transplant. The other patient with SLE succumbed to bacterial meningitis 10 months after starting treatment. One patient with post COVID macrophage activation syndrome with ANA and APLA positivity responded to high dose steroids and intravenous immunoglobulin and made a complete recovery
Conclusions: Post COVID immune phenomena may present in multiple ways such as diffuse alveolar hemorrhage, skin vasculitis, macrophage activation syndrome and new onset systemic lupus erythematous. These conditions may present in atypical age groups and in varying combinations. A high index of suspicion and quick diagnosis is imperative in the management of these rare conditions.

Keywords: COVID, Skin biopsy, vasculitis, steroids, skin lesions, fever, joint pain, lung infection

Introduction
The COVID 19 pandemic has not only caused devastating loss of life and multiple morbidities, but has also caused a number of immune phenomena that have posed diagnostic and therapeutic challenges. As Nephrologists, our involvement extends beyond direct COVID related renal diseases, and an idea of novel immune phenomena that occur, both in our traditional set of patients and also in patients with no renal dysfunction, who need our intervention is essential. The attempt of this case series is to illustrate our center's experiences with post COVID immune phenomena and their management.

Case 1
A 51 year old diabetic and hypertensive male was diagnosed with COVID 19 with Category B symptoms. He had been vaccinated with two doses of Vero cell inactivated vaccine. His baseline parameters were as follows: Hb: 13.6 g/dl, TC: 8770 cells/mm^3, S. Creatinine: 0.7mg/dl, CRP: 58.5. Ferritin 400 mcg/l, d-dimer – 0.8. Liver functions were normal. He was treated with remdesivir, a short course of steroids and other supportive measures and medications. Four months after recovery he developed vesiculobullous lesions all over the body (Fig 1), mild fever, hemoptysis, cough and breathlessness with type-1 respiratory failure. Chest X ray showed bilateral infiltrates (Fig 2) and a CT chest revealed diffuse alveolar hemorrhage (Fig 3). He required ventilation with HFNC. A Skin biopsy showed florid vasculitis reaction in small and medium vessels with prominent leucocytoclasia (Fig 4). Autoimmune workup was as follows: ANA -negative, dsDNA-negative, ANCA-negative, c3, c4-normal, APLA (IgG, IgM)-negative.

He was offered plasma exchange along with immunosuppression by the departments of Nephrology and Immunology. A total of 10 sessions of plasma exchange with intervening CT thorax assessments of the alveolar hemorrhage were carried out (removal- 40 ml/kg; replacement with fresh frozen plasma, albumin and normal saline). He was also administered intravenous methylprednisolone 250 mg for 3 days followed by oral prednisolone and rituximab 500 mg 2 doses one week apart. With these measures, the patient improved and alveolar hemorrhage resolved. He was discharged in a healthy stable state. Patient continued oral steroids which are being gradually tapered at the time of writing.

Case 2

A 35 year old normotensive and euglycemic male was diagnosed with COVID 19 Category B symptoms. He had been vaccinated with two doses of ChAdOx1n CoV 19 recombinant vaccine. His baseline parameters were as follows: Hb: 14.3 gm/dl, TC: 18940 cells/mm^3, S. Creatinine: 0.8 mg/dl, d-Dimer: 4.13, CRP: 23, liver functions were normal. He was treated with remdesivir, short course of steroids, anticoagulants and other supportive measures. Three weeks after COVID infection he developed hemorrhagic purpuric/bullous lesions all over the body, abdominal pain, hematemesis, breathlessness and hemoptysis. Chest X ray showed diffuse bilateral infiltrates and a CT chest revealed diffuse alveolar hemorrhage. An Upper GI endoscopy revealed multiple ulcerations in duodenum and jejunum. A Biopsy of gastrointestinal mucosa showed ischemic necrosis and skin biopsy showed leucocytoclastic vasculitis. Autoimmune workup was as follows: ANA-negative, ANCA-negative, c3, c4-normal, APLA (IgG, IgM)-negative

A Nephrology opinion was sought and plasma exchange was advised. In addition, he was administered methyl prednisolone 250 mg for three days, and 2 doses of rituximab. After 5 sessions of plasma exchange (removal- 40 ml/kg; replacement with fresh frozen plasma, albumin and normal saline) the patient improved and alveolar hemorrhage resolved. He was discharged in a healthy stable hemodynamic state on tapering doses of oral steroids.

Case 3

A 79 year old gentleman, a case of chronic kidney disease stage VD, suffered from autosomal dominant polycystic kidney disease. He was diagnosed with COVID 19 category B symptoms. He had been vaccinated with two doses of ChAdOx1 n CoV 19 recombinant vaccine. His baseline parameters were as follows: Hb: 7.3 gm/dl, TC: 6290 cells/mm^3, ESR-75 mm/hr, Ferritin: 1487, d-Dimer: 1.06, CRP: 100, liver functions were normal. He was treated with remdesivir, anti-coagulants and other supportive measures. Seven months after diagnosis of covid he developed polyarthralgia of large joints along with oral ulcers. There were no other manifestations involving other organs. Immunological workup revealed positive ANA and anti-ds DNA positive. ANCA-negative, c3, c4-normal, APLA-negative

Management

The patient was begun on oral steroids and hydroxychloroquine. He became symptomatically better and was discharged. He needed a small dose of maintenance steroid to combat arthralgias. The patient succumbed to bacterial meningitis months 10 months after starting immunosuppression.

Case 4

A 51 year old female, a case of chronic kidney disease stage VD, with diabetic kidney disease was diagnosed with COVID 19 (cat B symptoms). She had taken one dose of ChAdOx1 n CoV 19 recombinant vaccine. Her parameters at diagnosis were as follows: Hb: 9.8 gm/dl, TC: 8450 Cells/mm^3, ESR: 95 mm/hr, Ferritin > 2000, CRP: 34 d-dimer 1.2. She was treated with remdesivir, anticoagulants and other supportive measures. Five months later, she presented with polyarthralgia of the large and small joints. Autoimmune workup was as follows: ANA-positive, anti-ds DNA: negative, Rheumatoid Factor: Positive, ANCA-negative, c3, c4-normal, APLA (IgG, IgM)-negative, anti CCP negative.

She was begun on oral steroids and hydroxychloroquine, following which she became symptomatically better. She is now on tapering doses of steroids and after completing 15 months of treatment, underwent a kidney transplantation with basiliximab induction and triple immunosuppression consisting of a calcineurin inhibitor, mycophenolate mofetil and oral steroids. She has had an uncomplicated post-transplant course at the time of writing.

Case 5

A 54 year old gentleman, who was a known case of chronic kidney disease on conservative management, with diabetic kidney disease, (S. Creatinine 2 mg/dl) presented with sudden worsening of renal functions (S. Creatinine 11 mg/dl) associated with a left ureteric calculus, an obstructed left urinary system and pyelonephritis. He was started on hemodialysis and posted for a urological corrective procedure. On the eve of his surgery, he tested positive for SARS CoV 2. He had been vaccinated against covid with two doses of an unknown vaccine (details unavailable). His baseline parameters were as follows: Hb: 8.5 g/dl, TC: 12400 cells/mm^3, Ferritin: 509, d-Dimer: 2, CRP: 13, Liver functions were normal. A CT Chest showed no pneumonia. He was managed conservatively and did not require immunosuppression for COVID. He tested negative after a week and was posted for a left ureteroscopy and DJ stenting. The procedure revealed significant pyonephrosis and the calculus was pulverized with laser. He showed good improvement after surgery. Throughout the course of his illness, he was covered with broad spectrum antibiotics. Blood and urine cultures had been sterile. 10 days after testing positive for SARS CoV2 and 2 days after the urological procedure, the patient developed fever and severe thrombocytopenia (Platelet count 2.5 lakhs to 3000 in 2 days). The other cell lines were initially normal and there was no coagulopathy (PT/INR, apt values). Antibiotics were hiked suspecting sepsis and he was given multiple platelet transfusions. However platelet count continued to fall despite these measures. A peripheral smear showed no abnormal cells, LDH was marginally elevated and there were no signs of hemolysis. (No schistocytes, indirect hyperbilirubinemia or anemia). Evaluation for sudden unexplained thrombocytopenia revealed positive ANA and anti-DS DNA negative, and strongly positive IgG APLA. C3, C4, and ANCA were negative. Within 2 days, the patient also became significantly neutropenic (TC 700).

Inflammatory markers were low and cultures sterile. S. Ferritin was reported as > 2000. An urgent bone marrow aspiration and biopsy was done (Fig 5) to show evidence of macrophage activation syndrome with significant lymphocytes. He was started on a combination of high dose steroids (dexamethasone 8mg thrice a day), which was gradually tapered and intravenous immunoglobulin (2 g/kg). He responded well to this treatment and counts stabilized. He recovered and it was possible to wean him off dialysis. 3 months after the episode, he continues to remain stable with maintained counts. He is on low dose steroids for arthralgias that he had developed during the time of diagnosis. He was also given low dose aspirin for a month, which was later discontinued.

Tables 1, 2 and 3 depict the demographics, presenting features and management respectively.

Discussion

Patients who have recovered from the initial SARS CoV2 infection can develop long-term symptomatology. Five individuals with no personal or family history of autoimmunity, presented with features of vasculitis in our centre. There was a temporal association between COVID infection and the development of clinical manifestations with no other intercurrent inciting events.

Diffuse alveolar haemorrhage following COVID 19 has been described in a variety of scenarios. Pertinent to the case described in this article, are the cases described by Fares *et al.* [1] where a patient presented with concomitant microscopic polyangitis and COVID 19. ANCA vasculitis presenting as diffuse alveolar haemorrhage has been described in association with COVID 19 at varying time periods following contraction of SARS CoV2 from concomitant presentation [2] to 2 months following COVID [2]. Cases 1 and 2 in our series also presented with life threatening diffuse alveolar haemorrhage. Neither developed renal failure, but had other clues of vasculitic activity like cutaneous vasculitic changes in both cases. Although both cases had negative basic auto-immune serology, the presence of skin vasculitis and sudden unprovoked diffuse alveolar hemorrhage unrelated to active COVID infection both leant themselves to a likely auto-immune etiology. Both cases were started on plasma exchange and immunosuppression in consultation with the department of Immunology. These interventions proved lifesaving and there was complete resolution of the illness. Early intervention in such cases may thus prove important in avoiding mortality.

Reports have described increasing cases of COVID related cutaneous manifestations, either in the early stage of the infection or as a late-onset manifestation. Leucocytoclastic vasculitis is a small vessel vasculitis characterised by immune complex aggregates in the postcapillary venules, infiltration of polymorphonuclears cells, fibrinoid necrosis and leukocytoclasis. SARS-CoV- 2 antigens may promote the development of antibodies, forming antigen– antibody complexes that target the vascular endothelium of the skin. Cutaneous leucocytoclastic vasculitis could be associated with a wide spectrum of pathologies (infections, drugs, malignancies and autoimmune disorders). The presence of positive PCR in skin biopsy is a reliable tool to ensure the association between COVID infections and cutaneous manifestations.

The first case of post COVID-19 systemic lupus erythematosus (SLE) in the United States of America was reported by Ramachandran *et al.* [3]. Their case was diagnosed with a collapsing glomerulopathy along with positive ANA titres which showed at least partial response to immunosuppression. In addition there have been around 10 published cases of new onset systemic lupus erythrematosus that was triggered by COVID 19. The reader is referred to table 1 in the article published by Assar *et al.* [4] where a detailed analysis of each case has been presented. Pulmonary involvement and acute kidney injury formed the majority of SLE presentations among these cases. 3 out of the 4 cases of acute renal injury showed recovery with immunosuppression. To our knowledge, Cases 3 and 4 represent the first described cases of SLE presenting in a population of chronic kidney disease on maintenance dialysis. Case 3 was a case of autosomal dominant polycystic kidney disease (ADPKD), thus confirming new onset lupus, and in Case 4, the native kidney disease was consistent with diabetic kidney disease. Both patients developed significant arthralgic symptoms which necessitated immunosuppression. Case 3 developed a fatal meningitis 10 months after starting immunosuppression. Case 3 is also notable with respect to the advanced age for the first presentation of lupus, not to mention male gender. These two factors are also notable in Case 5.

There also seems to be little correlation between severity of COVID and the development of autoimmune disease. Literature suggests little if no correlation between rheumatic disease and COVID-19 disease severity in hospitalized patients [5-7]. In our case series, cases 3 and 4 had high initial S. ferritin values, however severe disease as in cases 1 and 2 did not. Vaccination status also seemed not to be a concern in these patients developing serious complications related to autoimmunity. B cell activation, even with mild COVID disease has been proposed as the causative factor for the production of various antibody secreting cells [8] including presumably, anti-nuclear antibody (ANA). In our case series as well, the three patients who tested positive for ANA post COVID had varying levels of COVID disease activity as measured by S. Ferritin, d-dimer, LDH.

The decision to immunosuppress is a tricky one, one that will have to be made on a case by case basis. Strategies for immunosuppression in post COVID rheumatological disease are vague at present since the exact pathogenesis is unclear. Various mechanisms for COVID induced autoimmunity include endothelitis induced thrombosis, persistence of the virus in dormant form causing prolonged innate immunity activation, and NETosis [9]. Various strategies including rituximab, steroids [9] and combinations of high dose methylprednisolone and mycophenolate mofetil [10] have been used depending on the severity of symptoms, in essentially clinical decisions made to treat SLE post COVID. In our series, Cases 3 and 4 needed immunosuppression in view of the severity of their symptoms, and were started on steroids and hydroxychloroquine. More powerful immunosuppressants like cyclophosphamide were avoided in view of their general high risk of sepsis and septic events. Case 3 developed a fatal meningitis 10 months after immunosuppression. Case 4 showed good symptomatic relief with these measures. She has since undergone a kidney transplant and is doing well at the time of writing, on the usual triple immunosuppression strategy (Steroid, mycophenolate mofetil and calcineurin inhibitor). Case 5, a

case of diabetic kidney disease had thrombocytopenia and arthralgia as the main problems post COVID, which, on workup revealed not only ANA but also APLA positivity. He was started on a small dose of oral steroids, low dose aspirin along with hydroxychloroquine and is asymptomatic for three months at the time of writing with stable renal functions.

The phenomenon of APLA positivity in COVID 19 is a curious one, one that needs further study. In a case series/study published by Guerra *et al*. [11], the levels of antiphospholipid antibodies (APLA), both those included in criteria for antiphospholipid syndrome, and others were much higher in patients with COVID than a control group of non covid individuals. The presence of coexisting thrombotic disorders like pulmonary thromboembolism was insufficient to assign a causal relationship with these antibodies or markers like elevated ferritin or d-dimer. The authors concluded that although the high prevalence of various anti phospholipid antibodies in the setting of severe COVID was pertinent, their causal role even in thrombotic or bleeding complications was unclear due to different pathophysiological processes in catastrophic APLA and COVID. In our case, Case 5, we discontinued low dose aspirin after a month of follow up. Repeat levels of APLA are yet to be measured.

On the other hand, the manifestations of thrombocytopenia and hemophagocytosis in and post COVID 19, as occurring in Case 5, are better described. Proposed mechanisms of COVID induced thrombocytopenia include inhibition of platelet synthesis due to direct infection of the bone marrow cells or platelets by the virus, virus-mediated liver damage leading to decreased thrombopoietin production, pulmonary endothelial damage followed by platelet aggregation and consumption in the lungs, and an immune mediated destruction [12].

Macrophage activation syndrome (MAS) following COVID has been described in a few cases and is frequently associated with and presents concomitantly with COVID pneumonia [13, 14]. Delayed presentation after recovery from COVID pneumonia has also been described [13]. Isolated refractory thrombocytopenia may be an early clue to the development of macrophage activation syndrome, in the appropriate clinical context [15]. There have been atypical presentations of macrophage activation syndrome in the context of COVID, including one case where the presenting feature of COVID 19 was MAS, in the absence of pneumonia [16]. Case 5 in our series appears to be the second such case of MAS occurring in the context of COVID without documented pneumonia. Macrophage activation may also complicate prolonged infections with COVID and occur upto a month after the onset of disease [17]. Early diagnosis is key, as criteria for diagnosis of MAS may not be satisfied in early stages. Therapeutic strategies are varied, ranging from tocilizumab [18]. To intravenous immunoglobulin [19]. We used a combination of steroids and intravenous immunoglobulin, to which the patient showed good response. The potential relationship between these two entities is postulated to be due to the cytokine storm induced by COVID 19. Without therapeutic intervention, this inflammation results in severe tissue injury and death.

In addition to its role in heralding hemophagocytosis, transfusion resistant thrombocytopenia in the context of COVID may also indicate immune thrombocytopenia (ITP). ITP is a diagnosis of exclusion, after ruling out sepsis, disseminated intravascular coagulation, autoimmunity and drug induced thrombocytopenias. A systematic review of literature published by Bhattacharjee *et al*. [12]. Showed that ITP in patients with COVID is an entity to be seriously considered in the appropriate clinical context. Bleeding manifestations were not as much as expected in this category of patients, even with severe thrombocytopenia. Onset of ITP was more common in the second and third week after COVID. Onset of COVID-19 illness. Treatment strategies include high dose steroids and intravenous immunoglobulin, both of which are effective. Thrombopoietin receptor agonists can be used as second-line agents. The same strategies were used in Case 5 of our series, albeit for a different diagnosis.

Limitations: The treatment protocol for COVID in our patients was not standardised for the simple reason that these cases were diagnosed at various points in the pandemic, when treatment strategies were dynamic and ever changing. Long term follow up is also essential.

Conclusion

COVID-19 infection can be a trigger for a de-novo autoimmune response. Unusual manifestations like new onset systemic lupus erethematosus, macrophage activation and diffuse alveolar hemmorhage may present even a few months after COVID. A high index of suspicion of these symptoms, prompt intervention and long term follow up is required in such cases.

Table 1: Demographic characteristics

Demographic data	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5
Age (Years)	51	35	79	51	54
Gender	Male	Male	Male	Female	Male
Duration since Covid (Months)	4	1	7	8	1 week
Vaccination status (Doses)	2	2	2	2	2
Comorbidities					
Diabetes	Yes	No	No	No	Yes
Hypertension	Yes	No	Yes	No	Yes
DLP	Yes	No	No	N0	Yes
CKD	No	No	Yes	Yes	Yes

Table 2: Presenting features

Symptoms	Patient-1	Patient-2	Patient-3	Patient-4	Patient -5
Skin lesions	Yes	Yes	No	No	No
Arthritis	No	No	Yes	Yes	No
Hemoptysis	Yes	Yes	No	Yes	No

Oral ulcer	Yes	No	Yes	N0	No
Systemic involvement other than lungs	No	Yes	No	No	No
ESR	Increased	Increased	Increased	Normal	increased
ANA	Negative	Negative	Positive	Positive	positive
dsDNA	Negative	Negative	Positive	Negative	negative
ANCA	Negative	Negative	Negative	Negative	negative
Renal function	Normal	Normal	CKD on MHD	CKD on MHD	CKD STAGE 3
Skin biopsy	Leucocytoclastic vasculitis	Leucocytoclastic vasculitis	Not done	Not done	Not done
Bone marrow biopsy					Macrophage activation with excessive lymphocytes

Table 3: Management

Symptoms	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5
Pulse steroids	Yes	Yes	No	No	No
PLEX	Yes	Yes	No	No	No
RITUXIMAB	Yes	Yes	No	No	No
HCQ	No	No	Yes	Yes	No
Iv /Oral steroids	Yes	Yes	Yes	Yes	Yes
IVIG	No	No	No	No	Yes

Statement of Ethics: Ethical approval is not required for this study in accordance with local or national guidelines.

From all cases 1 to 5: Written informed consent was obtained from each patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement: No conflict of Interest

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Author Contributions

Jayaram JK: Curating Case histories.
Kartik Ganesh: Corresponding Author and writing of Manuscript.
Abi Abraham M: Correction of Manuscript and overall supervision of manuscript creation.
Jithin S Kumar, Sunita Simon: Description of cases.
Jayasree Govindan: Provision and description of histopathology images.
Govind Gangadharan: Contribution in details and references of macrophage activation syndrome.
Mishaal Halid: Provision and description of radiology images.
Mohammed Iqbal KM: Supervision of manuscript.
All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author."

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