CASE REPORT

Granulomatosis with Polyangiitis (GPA) and COVID-19 Co-infection: A Case Report

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ABSTRACT
SARS-CoV-2 viral disease is transmitted primarily by release of respiratory droplets from infected persons in asymptomaticor symptomatic stages of illness.[1]COVID-19 has wide-ranging presentations with the hazard of adverse outcomes such as respiratory failure and sepsis.[1] Radiological findings of COVID-19 pneumonia on high-resolution computed tomography (HRCT) include peripherally placed ground glass opacities with or without consolidation.[2] These imaging features overlap with radiologic signs of autoimmune illnesses that afflict the lungs. Considering that 596,873,121 cases of COVID-19 infection were reported in 2022, diagnostic challenges in discerning the viral ailment from relatively rarer autoimmune conditions has resulted in misdiagnosis, missed diagnosis and delayed diagnosis, with consequential deleterious sequels of co-occurring conditions such as irreversible end-organ damage.[3,4] This case report is concerned with distinguishing undiagnosed GPA from co-occurring COVID-19 infection to underscore the importance of discriminating conditions with similar radiologic presentations to promptly shrink the risk of unabated activation of autoimmune mechanisms.

Key words: Granulomatosis with Polyangiitis, Wegener's granulomatosis, autoimmune granulomatous vasculitis, COVID-19 pneumonia

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INTRODUCTION

Wegener's granulomatosis is a necrotizing autoimmune granulomatous vasculitis with a predilection for small and medium sized vessels.[5] The multisystem disorder belongs to a group of anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis syndromes.[5] The eponym Wegener's granulomatosis has been replaced with a term that is more descriptive of the condition's scientific mechanism namely Granulomatosis with Polyangiitis (GPA), in consonance with the determination made by several reputable medical societies.[6] GPA is a rare disease with rates of biopsy confirmed vasculitis of 9.8 per million people per year; most frequently affecting persons of Northern European descent; and commonly observed in the age group of 40-65 years.[7,8] Men tend to develop the condition in a slightly higher frequency than women.[7,8] Two recognizable forms of GPA have been documented namely the limited form localized to the airways with no impending endangerment to life and the severe form with diffuse involvement that can lead to critical illness requiring salvage therapies.[9] Women tend to manifest the limited form more frequently than men.[7-9] The condition usually presents with a mix of non-specific symptoms of systemic illness as well as specific manifestations, if present, of ongoing respiratory tract, renal, ocular, dermatologic, neurologic and cardiac pathology.[10] Considering that the pauci-immune vasculitis can relapse and fulminate, a holistic assessment is necessary to map the degree of severity, corroborate with established diagnostic criteria and identify active damage to organ systems.[10]

CASE REPORT

A previously healthy 39-year-old East Indian male with a history of smoking for the past 5 years

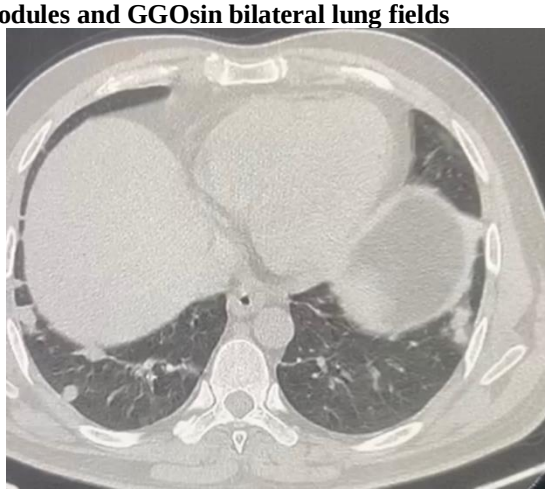
presented to the emergency department (ED) with 2 months of hemoptysis and progressively worsening dyspnea during the month prior to presentation. He endorsed a history of chronic nasal congestion and daily persistent headaches. He also complained of new onset pain in his left calf for the past 4 days. He has no history of deep vein thrombosis (DVT) or hypercoagulable disorder. On vital signs assessment, the patient was afebrile with a pulse rate of 100 beats/min, blood pressure of 120/80 mm Hg, and oxygenation of 95% on room air. Physical exam revealed multiple oral ulcers; and ocular exam was suggestive of episcleritis with findings of edematous sclera and injected superficial vessels(figure 1).

Figure 1: Clinical photo showing scleral edema suggestive of episcleritis

Laboratory tests revealed normal electrolytes and liver function. Renal function tests indicated a creatinine of 3.4, BUN of 40 and GFR of 45. Microscopic urinalysis was significant for albuminuria (3+) and 4-6 red blood cells per high power field. C-Reactive protein (CRP) was 185 mg/dl. D dimer was elevated at 2250 ng/ml. Urine studies revealed a mixed pre-renal and renal pathology. COVID-19 RT-PCR (reverse transcription-polymerase chain reaction) was positive. Considering the abnormalities on initial diagnostic tests, a need for further evaluation was discussed with the patient and he consented for hospitalization. Imaging studies were pursued which included ultrasonography (U/S) of the abdomen, venous doppler of bilateral lower extremities, HRCT of the lungs and Computed Tomography (CT) of the paranasal sinuses. Cardiac evaluation was performed with an electrocardiogram (EKG) and 2D echocardiogram (ECHO). The results were as follows:

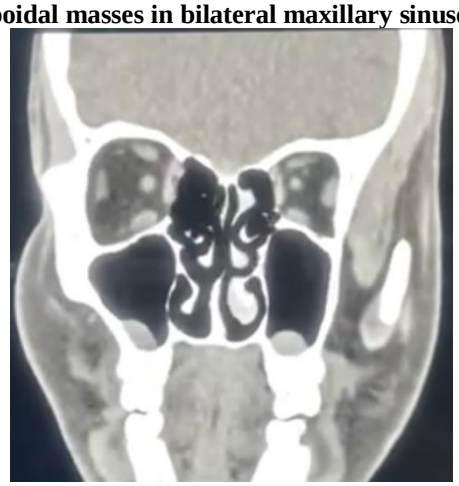
- U/S abdomen complete: grade-I medical renal disease with normal renal doppler values
- Venous doppler bilateral lower extremities: DVT of the left popliteal vein and bilateral soleal veins
- HRCT lungs: soft tissue nodules with adjacent ground glass opacities (GGOs) in bilateral lung fields with no obvious cavitary lesions (figure 2)

Figure 2: HRCT of the lungs showing soft tissue nodules and GGOsin bilateral lung fields



- EKG, 12 lead: features of pericarditis with minor concave ST elevations and PR depressions
- 2D ECHO: mild pericardial effusion with features of pericarditis
- CT, paranasal sinuses: multiple polypoidal masses in both the maxillary sinuses(figure 3)

Figure 3: CT of the paranasal sinuses revealing polypoidal masses in bilateral maxillary sinuses



Iron studies showed elevated ferritin and low iron. 24-hour urine output amounted to 350 cc. Biopsy was performed of the middle turbinate which showed features of granulomatous inflammation with no evidence of caseous necrosis and dense perivascular angio-destructive infiltrate of neutrophils. Sputum culture was negative including for acid fast bacilli. The anti-proteinase 3 anti-neutrophil cytoplasmic antibodies (ANCA-Pr3) was positive.

Clinico-radio-pathologic correlation, allowed for a diagnosis of GPA with concomitant COVID-19 infection. The potentiality of the infection to induce an autoimmune flare was strongly considered. Pursuing a comprehensive evaluation avoided attribution of the clinical symptoms solely to COVID-19 infection and discernment of the underlying autoimmune process. A treatment plan was then formulated to mechanistically address the dual pathologies. Inpatient rheumatology, pulmonology

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and nephrology were consulted who provided their recommendations to the primary care team regarding the treatment plan.

In accordance with the European League Against Rheumatism (EULAR) recommendations for management of autoimmune ANCA syndromes, the patient was started on the remission protocol pulse therapy of cyclophosphamide and methylprednisolone for a total of three days.[11] To limit toxicity secondary to cyclophosphamide, the maximum daily dose was limited to 200 mg.[11] For maintenance the patient was placed on 1 mg/kg/day of methylprednisolone which was further tapered to 5 mg daily and concomitantly started on 50 mg/day of azathioprine.

For the co-occurring COVID-19 infection, the patient was managed symptomatically as he was saturating adequately on room air and due to unclear timeline of symptom onset. Despite our worry of starting a patient with active viral illness on steroid therapy for GPA, our patient's pulmonary status responded well to the immunosuppressive treatment as it likely helped decrease systemic inflammation from the viral illness. Empiric antibiotic coverage for community acquired pneumonia with azithromycin was discontinued when sputum cultures resulted negative.

Hypercoagulability as a known consequence of COVID-19 infection could have affected the formation of DVTs in the left popliteal vein and bilateral soleal veins.[1,12,13] Patient was commenced on therapeutic anticoagulation during the hospital stay with low molecular weight heparin for a creatinine clearance of >30 ml/min in accordance with available clinical practice guidelines.[7,12]

From a renal standpoint, considering that ANCA-Pr3 was positive, and the patient fit the clinical picture of pulmonary renal syndrome of GPA, a decision to treat with the remission protocol and perform renal biopsy only if renal parameters do not improve was made.

Hematuria and proteinuria resolved, and renal function returned to baseline in a week. and the patient regained his appetite within a few days of institution of therapy. Dyspnea and hemoptysis improved on day 5 of treatment. Inflammatory markers returned to normal range on day 3 of treatment. Patient regained his appetite and was able to engage in physical therapy by day 2 of treatment.

Patient was discharged home in stable condition on maintenance doses of immunosuppressive agents, vitamin D, calcium, and trimethoprim sulfamethoxazole for pneumocystis pneumonia prophylaxis. Decision regarding not pursuing thromboprophylaxis after discharge was made in accordance with National Institutes of Health's (NIH) COVID-19 treatment guidelines.[13] This can be elucidated by a Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Venous Thromboembolism (VTE) abbreviated as the MIV score, totaling to zero and not meeting at least one of 5 criteria set forth by the NIH.[13] Discharge counseling regarding contact and isolation precautions as well as transitional care management were provided.

DISCUSSION

GPA is a form of necrotizing ANCA vasculitis characterized by the paucity of immune deposits and predominant involvement of small caliber vessels.[14] The ANCA antibodies are directed against proteinase 3 (Pr3) and hence indirect immunofluorescence demonstrates a cytoplasmic staining pattern.[15]

The etiopathogenesis of GPA is unknown.[16] Host and genetic factors are thought to affect susceptibility mediated by abnormalities in adaptive and innate immune responses.[16] The 2022 American College of Rheumatology (ACR)/ EULAR criteria for classifying ANCA vasculitis as granulomatosis with polyangiitis requires a score of 5 points or greater.[17,18] Similar to the vascular inflammation seen in GPA, SARS-COV-2 can cause vasculitis due to its high affinity for angiotensin-converting enzyme 2 or ACE2 receptors.[17]

Chest CT findings suggestive of GPA include nodules/masses that could cavitate, areas of consolidation, GGOs and segmental or subsegmental thickening of the bronchi.[19] Large and bilateral GGOs can signify alveolar hemorrhage from pathological inflammatory damage to pulmonary capillaries in the active phase of the disease.[19] However, these findings are largely nonspecific and are reported in other inflammatory and infectious entities such as acute pulmonary lupus, pneumocystis pneumonia and COVID-19 pneumonia.[17]

In terms of renal manifestations, 40% of the patients with COVID-19 infection develop hematuria and proteinuria from renal cellular injury likely consequent to viral binding to the ACE2 receptors in the proximal tubular brush border cells.[20] This clinical picture is comparable to the necrotizing glomerular inflammation seen in diffuse GPA.[19]

Taking into account the obvolution of clinical and radiological presentations between GPA and COVID-19, diagnosing the presence of dual pathologies can be difficult.[21] Diagnosis of GPA singly, is often delayed due to rarity of the clinical condition and the fact that patients attend several specialty consults prior to diagnostic confirmation.[22] Thus, when the diagnosis of COVID-19 is suspected, considering its transmission frequency and prevalence in the context of the global pandemic, it could potentially shroud the presence of co-occurring autoimmune respiratory conditions such as GPA.[21]

Review of available published cases of patients was conducted to learn diagnostic approaches in different case studies and strengthen our report's propositions. Qurratulain et al., describe an elderly woman with pulmonary symptoms who tested negative on two serial COVID-19 tests.[23] Since imaging revealed worsening consolidation, steroid treatment was commenced for COVID-19 infection regardless of the negative test results.[23] The treatment could have

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indirectly led to symptomatic improvement of undiagnosed GPA, which was eventually identified when tests for vasculitis resulted positive.[23] Bressler et al., report a middle aged man hospitalized for possible pneumonia with three negative serial COVID-19 PCR tests.[24] He was subsequently found to be positive for coronavirus IGM antibody which likely demonstrates a recent but prior unrelated infection.[24] Renal and skin biopsies provided pathological confirmation of GPA as the underlying condition.[24] Selvaraj et.al., describe a similar report of a patient with undiagnosed GPA and a history of COVID-19 infection 4 weeks prior to presentation.[18] GPA was diagnosed on account of ANCA-Pr3 positivity and renal biopsy that showed severe necrotizing and crescenteric glomerular inflammation.[18] The authors theorized that COVID-19 infection could have likely flared the clinically quiescent GPA.[18] Raeeskarami et al., describe an adolescent with symptoms of respiratory tract infection, negative COVID-19 PCR and IGM antibody, but positive IGG antibody to the virus.[25] A comprehensive evaluation revealed a severe manifestation of GPA that turned fatal.[25] The authors explain that the autoimmune mechanism seen in GPA triggered by pathogens such as staphylococcus aureus, entamoeba histolytica and Ross River virus infections due to similarity in the pathogens' peptides to Pr3, is similar to the T cell mediated response noted to human cell antigens in COVID-19 infection as a consequence of their molecular indistinguishability from the viral proteins.[25] Dysfunctional vascular endothelium secondary to inflammation from viral binding to the ACE2 receptors and if present, a concurrent COVID-19 hyperinflammatory cytokine storm can lead to the formation of neutrophil extracellular traps (NETs) that could induce the production of ANCA.[25] This could trigger existing GPA or cause new onset disease in a person with no prior history of autoimmune vasculitis.[25]

Our case is unique in that it describes active COVID-19 infection concurrent with a flare of GPA in a previously undiagnosed patient. This combination has a high potential to steer clinicians away from the diagnosis of GPA and focus solely on COVID-19 infection, particularly in the context of a pandemic. Since C-reactive protein and ferritin were elevated in our patient, it is possible that he had manifested the cytokine storm syndrome (CSS) which can trigger ANCA production to Pr3 and hence a flare of undiagnosed baseline GPA symptoms.[25] We also describe the challenges that most physicians face when starting the patient with an active viral illness on immunosuppressive regimen, and how in this patient's case, he was likely concomitantly manifesting a hyperinflammatory response to COVID-19 and hence improved with the remission protocol for ANCA syndromes. We offered renal biopsy to the patient to clarify whether the vasculitis was already there as pathology can reveal the amount of chronic damage to the renal parenchyma or if it was triggered by COVID-19 infection. However, the patient declined the procedure considering it's invasive nature and opted for close monitoring by outpatient rheumatology, nephrology, pulmonology, and primary care.

CONCLUSION

It is imperative for primary care providers to be informed of this co-presentation as an untreated flare of GPA is associated with a mortality of 80%.[26] Further epidemiologic analysis can reveal if this high mortality rate is further exacerbated by co-infection with COVID-19. It would be useful if larger studies can tally the number of cases with a missed diagnosis of GPA during the pandemic, particularly when severe or fatal outcomes occurred, to bridge gaps in current knowledge. An early interdisciplinary approach and employing a broad differential strategy when encountered with atypical presentations of respiratory illnesses can hasten detection and treatment of GPA. Also, a comparison of treatment plans employed for the co-presentation, in terms of staged versus concomitant introduction of therapeutics could benefit from further investigation to optimize treatment strategies. Lastly, education across curricular disciplines will allow generalists to familiarize themselves with rare disease entities that require timely diagnosis. This is more so relevant to safeguard vulnerable populations enduring regional gradients of rationing and privations from socioeconomic costs and avoidable morbidity and mortality.[3]

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DISCLAIMER

The views expressed herein are those of the authors alone.

FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

None to disclose

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