COVID-19- induced Granulomatosis with Polyangiitis:a Case Report and Literature Review

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Abstract

Objective To report a case of Granulomatosis with Polyangiitis (GPA)with Diffuse alveolar hemorrhage(DAH)that developed following Coronavirus disease 2019 (COVID-19) in an adolescent boy, and perform a literature review to better understand this disorder.Methods Retrospectively analyze the data of a case of GPA following COVID-19 infection, to summarize the clinical characteristics of GPA following COVID-19 infection by searching the database (PubMed,Wanfang Data,CNKI) and comprehensively analyze the literature results. Results 9 cases were reported,combined with our case,there were 10 cases of GPA following COVID-19 infection,including 4 males and 6 females,with an average age of(40.6±18.6)years,and the time interval between COVID-19 and diagnosis of GPA ranged from 1 day to 3 months for all 10 cases. The rate of mortality was 10.0%(1/10).Commonly seen clinical manifestations were cough(70.0%),dyspnea(50.0%),and Arthralgia/Myalgia(40.0%). CT scans showed ground-glass opacities,multifocal pulmonary nodules.Of all these patients, c-ANCA and PR3-antibody positivity were found .Conclusion COVID-19 pneumonia and COVID-19- induced new-onset GPA share many clinical and radiological features, making it challenging for clinicians to distinguish between the two. Our study also provided some clues about the diagnostic challenge of GPA induced by COVID-19.

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【**Key words**】 Coronavirus disease 2019;granulomatosis with polyangiitis;Case report;Literature Review

Background Granulomatosis with Polyangiitis (GPA) is a potentially fatal multisystem disease marked by necrotising granulomatous vasculitis of the minor arteries and veins. This condition mostly affects the lungs, upper respiratory tract and kidney.Although the processes behind the development of GPA are unknown, several factors such as infection, medications, and environmental exposure may play a role in the

disease's pathophysiology by inducing autoimmunity[1, 2] .Since the advent of the Coronavirus disease 2019 (COVID-19)pandemic, several reports have described AAV(anca associated systemtc vasculitis) occurrence after COVID-19 , indicating the potential of COVID-19 to trigger the development of GPA .We herein present a case of new-onset GPA with DAH(diffuse alveolar hemorrhage) that developed following COVID-19 infection in an adolescent patient,this is the first case of GPA with DAH in an adolescent in Hunan province of China, which developed shortly after COVID-19 infection, and we review the literature of GPA following COVID-19 infection by searching the database,to summarize the clinical characteristics of GPA following COVID-19.

Case Presentation

A 16-year-old boy with no past medical history presented to our Hospital with a 1-month history of fever,cough and shortness of breath, accompanying symptoms were epistaxis and tinnitus.One month prior to the onset of illness, the patient was exposed to a COVID-19 positive sick contact, so at the onset of symptoms, our patient was tested and returned positive for COVID-19 nucleic acid test.Before coming to our hospital, the patient was given active anti-infective treatment in a local hospital, but the symptoms were still not controlled, and the O2 saturation(SPO2) gradually decreased. So he went to the superior hospital for further diagnosis and treatment.

On admission, he was fever (37.6 C) with tachycardia (105 bpm), blood pressure 97/60 mm Hg, respiratory rate 25 beats per minute, and SPO2 90% on ambient air. He had saddle nose and bleeded from the bulbar conjunctiva.Wet rales could be heard on auscultation of the lung.

Blood tests were remarkable for: leukocytosis (20.8X10ˆ9/L,normal value 4-10.0X10ˆ9/L) with neutrophils (17.48X10ˆ9/L, normal value 1.5-8.0X10ˆ9/L),thrombocytosis (700X10ˆ9/L,normal value 100-300X10ˆ9/L) . PCT (0.88ng/L, normal value0-0.05 ng/ml),ESR(112 mm/ h, normal value 0˜15 mm/ h), C-reactive protein (80mg/dL, normal value 0-8 mg/L) and hypoalbuminemia with albumin 26.9g/L(normal value 35-55g/L) .Renal,liver functions and coagulation function were normal, and serum c-ANCAs ,PR3- antibody were positivity. COVID-19 nucleic acid test was negative.

On pulmonary CT showed multiple nodules and cavities in both lungs,creating"an island in the lung"(Fig. 1). Paranasal sinus CT scan showed bilateral maxillary sinus and left frontal sinusitis.No pathogenic bacteria were found in 2 rounds of alveolar lavage fluid mNGS (Metagenomic next-generation sequencing).

Pathological examination of the puncture specimen of the left lung mass showed that a small amount of lung tissue was examined, and fibrous tissue was significantly proliferated in some areas, with a large number of inflammatory cells infiltration.

The patients were identified as having GPA and met the 2022 classification criteria for GPA established by the American College of Rheumatology and European Association of Rheumatology[3]. He started receiving pulsed intravenous methylprednisolone(0.5 g/day for 3 days). Cyclophosphamide was not administered because of its negative effects, particularly on sperm function. Rituximab 500 mg was provided twice, spaced by two weeks, in place of cyclophosphamide.

During the course of treatment, the patient developed massive hemoptysis, and the oxygenation index further decreased.Diffuse hemorrhage in the airway was observed under bronchoscopy, and GPA combined with DAH was considered. After endotracheal intubation and plasma exchange, hemoptysis stopped and fever improved, but the patient eventually died from acute pulmonary embolism.

Search strategy and literature review

As of June 2023, We did a systematic literature review using a combination of the MeSH search keywords "COVID-19" or "Coronavirus disease 2019" with "Granulomatosis with polyangiitis" or "GPA" or "ANCA associated vasculitis" in the database (PubMed,Wanfang Data,CNKI). Three writers (RJ, ZJZ, and HBZ) independently evaluated the titles and complete texts of all pertinent papers. The three authors analyzed the search results and agreed on which articles to include. The authors collected data on age, gender, clinical

symptoms, laboratory and imaging findings, diagnosis and therapy, and prognosis of GPA after COVID-19 infection from each article.

Results from the literature review

By June 2023 (searching PubMed,CNKI and Wanfang Data), a total of 9 English cases of GPA following COVID-19 infection involvement and no Chinese case were found by searching literature[4-12]. Combined with our case,there were 10 cases of GPA following COVID-19 infection. (Table 1).The disorder often occurs in females aged 16 to 71 years , and the time interval between COVID-19 and diagnosis of GPA ranged from 1 day to 3 months .Of the ten patients (including ours), seven patients had no prior comorbidities while two had prior comorbidities of diabetes and rhinitis .Immunological tests showed positive PR3 antibody(100%) and C-ANCA (100%) are common. Commonly seen clinical manifestations were cough(70.0%),dyspnea(50.0%),and Arthralgia/Myalgia(40.0%).Pulmonary imaging studies showed multifocal cavitary pulmonary nodules in three patients ; ground-glass opacities in three patients;diffuse alveolar hemorrhage in two patients ; pleural effusions in one patients . The rate of mortality was 10%(1/10). All ten patients were treated with glucocorticoids which are the standard of care for vasculitis . Seven patients received rituximab therapy and two patients received plasmapheresis.All 9 patients had symptomatic and radiographic improve-ment at follow up (Table 2) .

Discussion

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 coronavirus, has infiltrated our planet during the last three years, generating one of the deadliest pandemics in history. Granulomatosis with polyangiitis (GPA) is a systemic disease that produces vasculitis in multiple organs. It primarily affects white persons between the ages of 40 and 65, affecting around one in every 100,000 people each year[13].GPA and COVID-19 both have a high rate of pulmonary involvement. GPA has a wide range of clinical symptoms, and diagnosis is sometimes overlooked or delayed.The development of GPA after COVID-19 infection is extremely rare[14].

We herein report a case of GPA that developed following COVID-19 in an adolescent boy. This is the first reported case of GPA with DAH in an adolescent boy in Hunan proveince of China, which developed shortly after COVID-19 infection,presented with pneumonia and DAH, directly responded to steroids,rituximab and plasmapheresis.We summarize the clinical characteristics of new-onset GPA following COVID-19 infection by searching the database (PubMed,Wanfang Data,CNKI) and comprehensively analyze the literature results.Results show commonly seen clinical manifestations were cough,dyspnea,and Arthralgia/Myalgia,the rare symptoms are gastrointestinal bleeding and DAH, and renal involvement is rare, which is different from other causes of GAP. Of these patients, c-ANCA and PR-3 antibody were all positivity.The CT findings of GPA were various, including consolidation, multiple nodules, mass shadows, ground glass opacities and cavitary nodules, but multiple nodules and ground glass opacities were the most common. Most patients were treated with methylprednisolone and rituximab, and the prognosis was good with early diagnosis and treatment.

Clinicians may struggle to differentiate GPA from COVID-19 pneumonia because they share many clinical and radiological characteristics. Previous case reports have shown that individuals with undetected GPA who are treated as COVID-19 pneumonia improve with steroid therapy, obscuring the true diagnosis[10]. This means that, especially during epidemics, new-onset GPA can be readily misinterpreted as pneumonia.The COVID-19 epidemic has made it more difficult to diagnose newly diagnosed GPA. As a result, clinical data and serologic tests are advised to differentiate COVID-19 infection from underlying GPA.Granulomatous polyangiitis (GPA) is an anti-neutrophil cytoplasmic antibody(ANCA)-related vasculitis (AAV) with a wide range of clinical, imaging, and laboratory manifestations[15].Although the mechanism of GPA development remains unknown, numerous causes such as genetic factors, drugs,infections, and environmental exposures, may be involved in the pathogenesis of the disease by triggering autoimmunity[1, 2].

Since the COVID-19 pandemic, several reports have described the occurrence of AAV after COVID-19 [8, 16], suggesting that COVID-19 has the potential to trigger the development of AAV.In susceptible individu-

als, autoimmunity may be generated by a combination of genetic, hormonal, and environmental factors[17]. One such environmental factor is viral disease.Studies have shown that there is a causal relationship between viral infection and the pathogenesis of autoimmune diseases. Epstein-barr virus, cytomegalovirus and human immunodeficiency virus are viruses that have been clearly associated with a variety of autoimmune diseases[18].Since the COVID-19 pandemic, several reports have described cases of GPA after COVID-19,and there have been many mechanistic analyses of the development of GPA after COVID-19. Increasing evidence suggests that SARS-CoV-2 is another virus that can induce dysregulation of the immune system and the development of autoimmune diseases in adults [19].

There are currently two conjectures about the mechanism of COVID-19 inducing GPA:

The first speculation:autopsies have revealed that patients affected with SARS-CoV-2 can develop small, medium and large vessel vasculitis within multiple organ systems [20],there are some speculations that the virus could be a direct invader of endothelial cells,and may cause vasculitis.

The second speculationIn:the debate between COVID-19 and GPA, the possibility that SARS-CoV-2 infection could be a "trigger" for vasculitis is an intriguing topic and a preferred speculation. Firstly, the time relationship between COVID-19 infection and the symptoms of GPA suggests that there may be a causal relationship between them. As described by Garlapati et al[21], many viruses have been shown to reveal potential GPA propensity by increasing serum levels of inflammatory mediators. We also know that SARS-CoV-2 increases levels of the same mediators, some of which play a role in the pathogenesis of GPA. Thus, it is conceivable that the presence of an excess of inflammatory mediators provides a substrate for neutrophil priming and ANCA-induced degranulation, leading to the development of GPA in patients.

Following vaccination with SARS-CoV-2 mRNA vaccines, AA V has been the subject of numerous reports[22, 23]. The finding of AA V following SARS-CoV-2 infection and vaccination further supports the theory that an immune response to SARS-CoV-2 may serve as a catalyst for the onset of GPA.

The immunological etiology of GPA is complicated, with roughly 80% of GPA patients producing PR3-ANCA[24]. Although positive ANCA is not required for the clinical diagnosis of GPA, it is pathogenic and plays a crucial role in the disease's etiology. ANCA titers rose with COVID-19, according to several publications. Lee et al. measured serum myeloperoxidase (MPO)-ANCA and PR3-ANCA levels in 178 SARS-CoV-2 patients[22]. There were 22 cases of MPOANCA (12.4%) and 14 cases of PR3-ANCA (7.9%). GPA was diagnosed in 12 patients (6.7%). They came to the conclusion that SARS-CoV-2 infection could increase ANCA positivity. Because the prevalence of ANCA positivity in the general population is 0.9%, the prevalence of ANCA in COVID-19 patients is much higher.

In COVID-19, SARS-CoV2 binds to angiotensin-converting enzyme 2, invades endothelial cells and causes microvasculitis. Because inflammatory cytokines and coagulation markers are elevated during and even after infection, the persistent inflammatory response and hypercoagulable state are associated with the development of vascular disease and other complications[8]. In AAV,increased inflammation caused by cytokines and macrophages leads to microvasculitis and endothelial damage, and some studies also speculate that there is cross-reaction between SARS-CoV-2 antigen and autoantibodies in autoimmune diseases[23] . These studies suggest a causal relationship between SARS-CoV-2 infection and vasculitis.

It is worth considering the role of SARS-CoV-2-induced alterations in the nasopharyngeal and pulmonary microbiota in the performance of GPA in patients after covid-19. There is good evidence that SARS-CoV-2 alters the microbiome and that microbial dysbiosis is significantly associated with increased TNF-α, which is a key mediator of granulomatous lesion formation.

Conclusion

We present a case of GPA with DAH, which developed shortly after COVID-19 infection. COVID-19 and COVID-19- induced new-onset GPA share many clinical and radiological features, making it challenging for clinicians to distinguish between the two. Our study also provided some clues about the diagnostic challenge

of GPA induced by COVID-19. The limited number of cases and retrospective evaluation are the limitations of this review.The retrospective study based on this case could provide useful information regarding the evaluation of clinical symptoms, diagnostic methods, and management of this confusing condition.In addition, the pathophysiology and mechanism of GPA induced by COVID-19 have not been fully elucidated and still need to be further studied.The possibility of a common immune mechanism for the development of vasculitis during SARS-CoV-2 infection and immunization warrants further investigation, which could provide important information about the pathogenesis of GPA and immune reactivity to COVID-19, and is crucial for the diagnosis and treatment of GPA.

Table1 Summary of clinical findings, demographics, and treatment strategies of GPA after COVID-19 infection

Case	**Age(years)**	**Sex**	**Past medical history**	**Chronology with COVID-19**	**GPA treatment**	**Outcomes**
Nakamura Y et al	17	Female	None	1.5 months	MPZ+RTX	Good prognosis
Weynand M et al	51	Female	diabetes, hypertension, osteoarthritis,and chronic nonallergic rhinitis	3 months	MPZ+RTX	Good prognosis
Selvarj.V et al	60	Female	dietcontrolled diabetes mellitus, allergic rhinitis	1 month	MPZ+RTX+PEX	Good prognosis
Lind E.A et al	40	Male	None	2 months	MPZ+RTX	Good prognosis
Izci D.T et al	36	Female	None	A few weeks	MPZ+CYC	Good prognosis
Bryant M.C et al	16	Female	asthma	1 week	MPZ+MMF	Good prognosis
Qurratulain et al	71	Female	None	2 weeks	MPZ+CTX	Good prognosis
Bressler m.Y et al	46	Male	None	2 weeks	MPZ+RTX	Good prognosis
Giles T et al	28	Male	None	1 day	MPZ+RTX	Good prognosis
Our case	16	Male	None	1 month	MPZ+RTX+PEX	Die

RTX: Rituximab, MPZ: Methylprednisolone, PEX: Plasmapheresis, CYC: Cyclophosphamide, MMF: Mycophenolate mofetil

Table2 Clinical characteristics,laboratory and chest roentgenogram features of COVID-19 induced GPA case

Features	**Total(n=10)**
Symptom, n (%)	
Fever	3(30)
Cough	7(70)

Dyspnea	5(50)
Bleeding(Dyspnea/alimentary tract hemorrhage)	3(30)
rash	2(20)
Arthralgia/Myalgia	4(40)
Laboratory Features,n (%)	
C-reactive protein—	6(60)
C-ANCA(+)	10(100)
PR3-antibody(+)	10(100)
Roentgenogram Features,n (%)	
Ground glass opacities in thorax	3(30)
multifocal pulmonary nodules	3(30)
diffuse alveolar hemorrhage	2(20)
pleural effusions	2(20)
Need for O2 support	3(30)
Kidney involvement at presentation	4(40)
Mortality, n (%)	1(10)

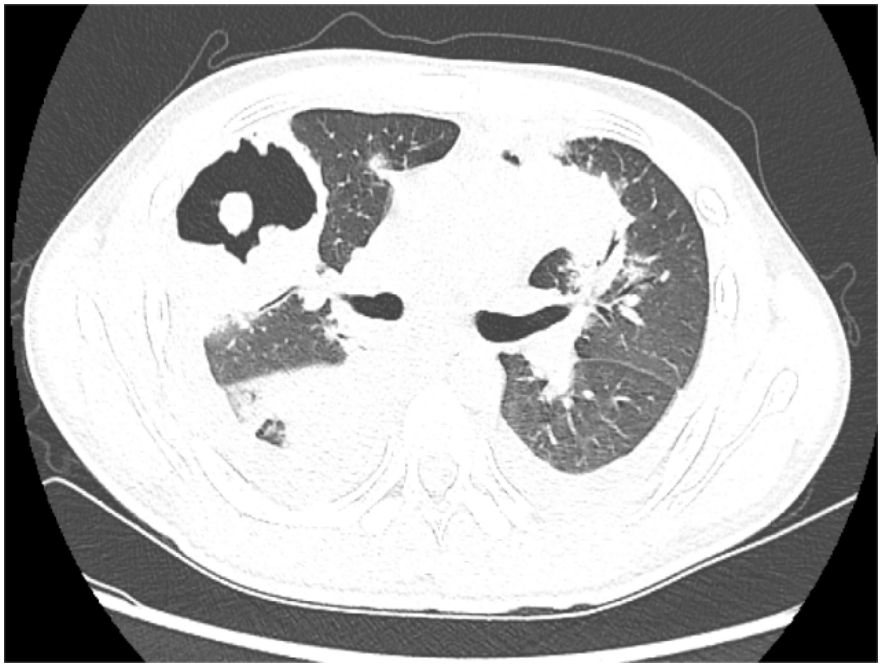

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Figure 1 . Chest computed tomography on admission. Chest computed tomography on admission showed multiple nodular shadows and cavities ,creating "an island in the lung".

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Jiaxiang Ma

Subject matter of photograph or article: *Chest computed tomography on admission. Chest computed tomography on admission showed multiple nodular shadows and cavities ,creating "an island in the lung".*

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