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Adult-Onset IgA Vasculitis Associated With Pulmonary-Renal Syndrome Following COVID-19 Infection: A Case Report and Literature Review

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Abstract

Immunoglobulin A (IgA) vasculitis, also known as Henoch-Schönlein purpura (HSP), is an immune complex-mediated inflammation of small blood vessels that leads to tissue destruction with or without organ damage. We described a case of a 41-year-old otherwise healthy female who presented with an ascending rash distributed on both lower extremities and arthralgia. Blood testing revealed high blood urea nitrogen (BUN), creatinine, and inflammatory markers, as well as a negative autoimmune panel. Urinalysis revealed proteinuria and hematuria. A kidney biopsy was performed, which revealed abnormalities. She was started on intravenous (IV) methylprednisolone pulse therapy. Suddenly, she complained of epistaxis and became desaturated. Computed tomography revealed bilateral pleural effusion, and she was transferred to the ICU. Bronchoalveolar lavage was performed and was consistent with an increasing bloodier return. Plasma exchange was performed. The rash and clinical symptoms improved dramatically. This study reports a case of IgA vasculitis based on The European Alliance of Associations for Rheumatology/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria associated with pulmonary-renal syndrome following a case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Categories: Internal Medicine, Infectious Disease, Rheumatology

Keywords: adult iga vasculitis, henoch-schönlein purpura (iga vasculitis), pulmonary-renal syndrome, sars-cov-2, covid-19

Introduction

Immunoglobulin A (IgA) vasculitis, also known as Henoch-Schönlein purpura (HSP), is an immune complex-mediated inflammation of small blood vessels, leading to tissue destruction with or without organ damage [1]. The disease affects both adults and children; however, it is rarely reported among adults [2]. It is the most prevalent kind of systemic vasculitis in children, occurring at a rate of three to 26 cases per 100,000 children each year while adults have a lower incidence of the condition, with an annual incidence of 0.1 to 1.8 per 100,000 individuals [2,3]. Males are 1.5 times more likely to get the disease than females [3].

The etiology of IgA vasculitis is unknown; however, it is thought that the condition usually occurs after a recent infection or medication use, leading to a deposition of IgA-antibody immune complexes in the small vessels (typically capillaries) of the skin, joints, kidneys, and gastrointestinal tract. Consequently, this leads to a hyper-inflammatory response [4]. The disease's presentation and progression are primarily determined by the organ involved; however, IgA vasculitis is frequently a self-limiting illness with a favorable prognosis in those who do not have renal involvement [4].

Since the emergence of COVID-19 in Wuhan, China, in 2020, the disease has been linked to several health, economic, and social complications [5]. Major health concerns have been raised over the post-coronavirus disease 2019 (COVID-19) infection, including pulmonary and extrapulmonary complications that are, in many cases, related to the hyperinflammation and cytokine storm of the disease [6]. A previous systematic review presented the clinical and laboratory factors associated with coronavirus disease based on its severity [7]. The best marker for severeness was decreased oxygen saturation (SpO2) [7]. Regarding symptoms, dyspnea, chest pain, and anorexia were relatively ominous for the seriousness of the disease and mortality [7]. Also, the study showed that critical and non-survivor groups tend to have an increase in creatine kinase (CK), C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), urea, creatinine, D-dimer, prothrombin time (PT), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), neutrophils, and total white blood cells (WBCs) and a decrease in arterial oxygen partial pressure/fractional inspired oxygen (pO2/FiO2), pO2, lymphocyte, and platelet (PLT) values when compared to other groups [7].

COVID-19-induced IgA vasculitis has been described in prior case reports [8-26]. However, these case reports were mainly in pediatrics or the very old age group [8-26]. In this report, we describe a case of a

healthy adult Saudi female patient who was diagnosed with IgA vasculitis manifesting with pulmonary-renal syndrome following a recent infection with COVID-19. To our knowledge, this is the first case report of COVID-19-induced IgA vasculitis associated with pulmonary-renal syndrome among the adult age group in Saudi Arabia.

Case Presentation

A 41-year-old, medically free, married Saudi female came to the emergency department complaining of a skin rash that started in the lower extremities three days before presenting to the hospital with an ascending progression associated with bilateral knee and ankle pain. She had a history of COVID-19 infection two weeks prior to her presentation, with upper respiratory tract symptoms and a polymerase chain reaction (PCR)-confirmed diagnosis, which was treated supportively without the need for anti-viral therapy or dexamethasone. On examination, the patient was normal despite a palpable, non-blanching, pruritic rash distributed on both lower extremities. The patient was admitted for close observation.

On admission, investigations revealed a normal blood count, an elevated creatinine ratio (CRE2), and blood urea nitrogen (BUN) values of 680.8 umol/L and 39.6 mmol/L, respectively. They also revealed elevated alanine transaminase (ALT) and aspartate aminotransferase (AST) of 72 U/L and 80 U/L, respectively, a decreased serum albumin of 25 g/L, elevated inflammatory markers, an erythrocyte sedimentation rate (ESR) of 36 mm/hour, and a C-reactive protein (CRP) of 12 mg/L. Anti-nuclear antibodies (ANA), antineutrophil cytoplasmic autoantibodies (ANCA), anti-double-stranded DNA (anti-dsDNA), lupus anticoagulant, anti-glomerular basement membrane antibody (anti-GBM), hepatitis B and hepatitis C serologies, and human immunodeficiency viruses (HIV) were all negative. Immunoglobulin levels were within normal ranges, except the IgA level was elevated at 487 mg/dL. The complement level decreased, as C3 was 20.6 mg/dL and C4 was 5.43 mg/dL. Urinalysis demonstrated the presence of hematuria and massive proteinuria. Ultrasound (U/S) of the abdomen showed normal-sized kidneys with a preserved corticomedullary junction.

A kidney biopsy was performed, and it revealed a sufficient number of glomeruli (13), with no signs of segmental or global sclerosis. There was no glomerular hypercellularity or visible leukocyte infiltrate, but two glomeruli displayed minor segmental fibrinoid necrosis with karyorrhexis and the production of cellular crescents. Mild acute tubular damage without atrophy was visible in the tubules. There was edema in the interstitium but no inflammation or fibrosis. The blood vessels were unremarkable (Figures 1-2). The patient met the Henoch-Scholen purpura criteria and the European Alliance of Associations for Rheumatology/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria.

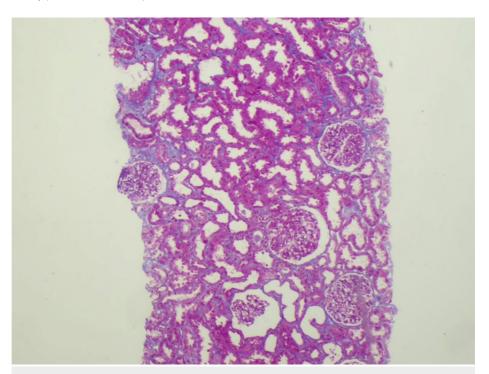


FIGURE 1: Kidney biopsy (20X, Masson trichrome stain)

The tubules show mild acute tubular injury with intratubular casts. No tubular atrophy, interstitial fibrosis, or inflammation is seen

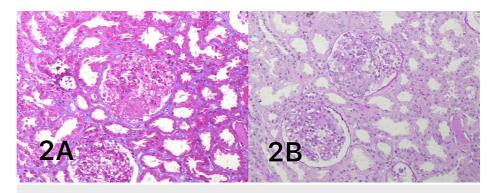


FIGURE 2: Kidney biopsy (20X, 2A: Masson trichrome stain, and 2B: periodic acid Schiff)

Images of one glomerulus showing segmental karyorrhexis, fibrinoid necrosis, and cellular crescents formation

The patient was started on intravenous (IV) steroid pulse therapy methylprednisolone 1000 mg daily for three days and then switched to oral 60 mg daily. Oral hydroxychloroquine 200 mg twice daily for three days and oral calcium carbonate 600 mg twice daily for seven days were given.

A few days later, she complained of epistaxis and hemoptysis. Upon examination, she had a blood pressure of 125/65 mmHg, a temperature of 37.2 °C, a regular heart rate of 105 bpm, oxygen saturation of 85% on room air, and responded to 5 l/min of supplemental oxygen via a nasal cannula, reaching 92-93%. Investigations reveal a low hemoglobin level (8.3 g/L) compared to her baseline of 12.3 g/L, low red blood cell count (3.01 x 10^12/L), low hematocrit (25.5%), and normal platelet count (320 x 10^9/L). The coagulation profile was normal, with a decreased fibrinogen level of 1.7 g/L and an elevated D-dimer level of 4.61 mg/L. An X-ray of the chest revealed bilateral pleural effusion (Figure 3). A computed tomography (CT) scan of the chest was relevant for bilateral diffuse ground-glass opacities mainly in the central area, with scattered areas of consolidation at the lower basal segments bilaterally, with bilateral pleural effusion greater on the right side (Figure 4). The patient was transferred to the intensive care unit (ICU), and bronchoalveolar lavage was performed, which was consistent with an increasing bloody return in keeping with active diffuse alveolar hemorrhage. Echocardiography revealed normal bi-ventricular systolic function, normal left ventricular diastolic function, and no hemodynamically significant valvular lesions.

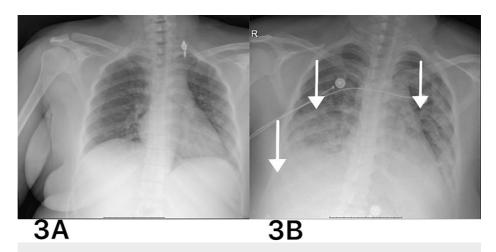


FIGURE 3: Chest X-ray

3A: Initial chest X-ray was grossly unremarkable. 3B: Repeat imaging was abnormal with evidence of bilateral hazy appearance involving the mid and lower lungs and blunting of the right costophrenic angle.

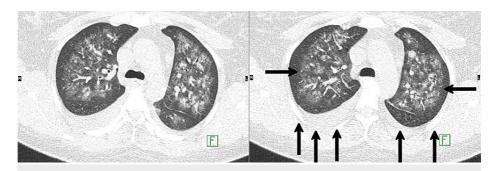


FIGURE 4: Computed tomography (CT) scan of the chest

Axial CT chest at the level of the carina demonstrated extensive ground glass opacities bilaterally with subpleural sparing and small-sized pleural effusion bilaterally right greater than the left.

The patient was started empirically on intravenous (IV) piperacillin-tazobactam while awaiting the final cultures. As discussed with the nephrologist, the patient was given two doses of intravenous immunoglobulin (IVIG), and plasma exchange was performed. The rash and clinical symptoms improved dramatically. Creatinine was reduced to 117.21 umol/L, blood urea nitrogen was normalized at 4.8 mmol/L, and hemoglobin was increased to 10.7 g/dL. The patient was discharged on a tapering schedule of oral prednisolone, and follow-up appointments have been scheduled.

Discussion

In this case report, we describe a case of a 41-year-old female, otherwise healthy, who had a typical presentation of IgA vasculitis based on EULAR/PRINTO/PRES criteria in the context of a recent COVID-19 infection, which is thought to be the provoking factor.

The pathophysiology of IgA vasculitis is not well-understood. However, several theories arise from the fact that the disease originally occurred following environmental exposure to an infection or a medication [27]. COVID-19 is a highly contagious viral infection caused by the coronavirus 2 (SARS-CoV-2) [28]. Although SARS-CoV-2 primarily affects the respiratory system, it may also impact the gastrointestinal tract (GI) and hepatobiliary, cardiovascular, renal, and nervous systems [29]. The key mechanism is the virus's high affinity for angiotensin-converting enzyme 2 (ACE2) receptors, which are extensively expressed in most human cells and induce the direct pathway of endothelial cell damage [30,31]. The indirect pathway is produced by dysregulation of the immune response and the elevation of several inflammatory mediators and proinflammatory cytokines [30,31]. SARS-CoV-2 promotes an immune reaction mediated by IgA, resulting in the deposition of this IgA immune complex in multiple organs and vessels, resulting in tissue destruction with or without organ damage [5].

Patients with IgA vasculitis are treated differently based on the severity of their illness and the presence of systemic involvement [3]. Rest and analgesics are used to treat non-necrotic, non-severe purpura or arthralgias [3]. Angiotensin-converting enzyme (ACE) inhibitors are used in mild-to-moderate proteinuria and hypertension cases. In cases with systemic involvement or life-threatening manifestations, glucocorticoids alone or combined therapy with immunosuppressive drugs are used [3].

Twenty-one cases of IgA vasculitis were reported following the COVID-19 infection, as summarized in Table 1. Fourteen total pediatric cases and seven total adult cases. Two cases from the pediatric age group were reported with isolated skin manifestations that were successfully treated conservatively. Eight cases were reported with only skin and gastrointestinal tract involvement; all cases were from the pediatric age group except one; all cases treated with steroid monotherapy except one from the pediatric age group were treated conservatively with excellent outcomes. Eight cases were reported with kidney involvement but no lung involvement; all pediatric and three adult cases were treated successfully with steroid therapy. Two of the adults were given a combination of steroids and immunosuppressive therapy. Three cases were reported with combined lung and kidney involvement: two of them from the pediatric age group died from respiratory failure, and one adult was treated successfully with steroid monotherapy. Not all cases were diagnosed by biopsy, but their clinical and laboratory results met established diagnostic criteria.

Study	Age/Gender	Country	Covid-19 infection onset	Organs involved	Biopsy	Criteria	Treatment	Outcome
Mousavi & Jafari., 2020	6-year- old/Male	Iran	Negative at admission/clinically diagnosed	Skin, kidney, lungs, GI	Not performed	Not mentioned	Methylprednisolone Hydroxychloroquine.	The patient died of respiratory

Marie Mari				tract				failure
	Allez et al., 2020 [9]	France	Positive at admission		neutrophils and lymphocytes. DIF: leukocytoclasia, and C3 and IgA deposits in	Not mentioned	Methylprednisolone	Not mentioned
House of Lamber of Services and Lamber of Ser	Gurzu et al., 2020 [10]	Romania	not confirmed with	and	type II alveolocytes and intra-alveolar macrophages. The bronchial epithelium was focally damaged with positive IgA deposition Kidneys: enlargement of the	Not mentioned	Supportive care	the sudden respiratory compromise (desquamative interstitial
	Suso et al., 2020 [11]	Spain	admission/ symptoms start to appear three weeks after Covid-19			Not mentioned	Methylprednisolone Rituximab	creatinine but persisted proteinuria and
Correct of Ayroan Port Porting Port Positive at administration and state of the Agriculture and Section 1973 Financial of Section 1974 Financial of Section	Huang et al., 2020 [12]	China	Positive at admission	and			Methylprednisolone	Improvement of the symptoms and renal function
Notified at al. 2021 101 101 101 101 101 101 101 101 10	Nakandakari Gomez et al., 2021 [13]	Peru	Positive at admission		Not performed	Not mentioned		
Sandhu st 22-year- al. 2021 18 22-year- al. 2021 22-year- al. 2021 18 22	Hoskins et al., 2021	States of	Positive at admission			Not mentioned		resolution of skin findings and abdominal
Alchaozi & 4-year- old/Male Bahrain start to appear 37 days after Covid-19 infection Skin and Joints Skin and Joints Skin and Joints Skin and Joints Joints Skin and Joints Joints Skin and Joints Joint Joints Joint Joints Joint Joints Joint Joints Joints Joints Joints Joints	Sandhu et al., 2021 [15]	India	Positive at admission	joints,	necrotizing, mesangial, and focal endocapillary proliferative IgA nephropathy with	Not mentioned	Prednisolone Mycophenolate	lesions, joint involvement, and abdominal symptoms
Jacobi et al., 3-year- 2021 [17] old/Male Israel Positive at admission Gl tract Not performed Not mentioned Prednisone Skin and Gl tract Skin biopsy: Neutrophil-rich small-vessel vasculitis, suggestive of leukocytoclastic old/Male old/Male Positive at admission Kidney, and Gl necrotizing IgA with focal endocapillary hypercellularity Falou et al., 8-year- 2021 [19] old/Male Desitive at admission Positive at admission Falou et al., B-year- 2021 [19] old/Male Positive at admission Positive at admission Resolution of paracetamol purpuric rash Skin and Gl necrotizing IgA with focal endocapillary hypercellularity Not mentioned Prednisone Prednisone Prednisone Prednisone Falou et al., 8-year- 2021 [19] old/Male Positive at admission Positive at admission Resolution of paracetamol purpuric rash Not performed Prednisone Skin and Not performed Positive at admission Positive at admission Resolution of paracetamol rash and joints Not mentioned Prednisone Prednisone Prednisone Prednisone Prednisone Resolution of paracetamol Prednisone Falou et al., 8-year- 2021 [19] old/Male Positive at admission Resolution of paracetamol rash and joints	AlGhoozi & AlKhayyat., 2021 [16]	Bahrain	admission/symptoms start to appear 37 days after Covid-19		Not performed	EULAR/PRINTO/PRES	Paracetamol	resolved Rash was still present
Li et al., 2021 [18] Old/Male Canada Positive at admission Skin, joints, Skin biopsy: Neutrophil-rich small-vessel vasculitis, suggestive of leukocytoclastic vasculitis. DIF: negative Kidney biopsy: Focally crescentic and segmentally necrotizing IgA with focal endocapillary hypercellularity Falou et al., 8-year- 2021 [19] Old/Male Positive at admission Positive at admission Positive at admission Skin and Not performed Skin and Old Positive at admission Positive at admission Positive at admission Not performed Positive at admission Not performed Positive at admission Not performed Positive at admission Positi	Jacobi et al., 2021 [17]	Israel	Positive at admission		Not performed	Not mentioned	Methylprednisolone	
Falou et al., 8-year- Skin and resolution of EULAR/PRINTO/PRES paracetamol rash and joints	Li et al., 2021 [18]	Canada	Positive at admission	joints, Kidney, and GI	vasculitis. DIF: negative Kidney biopsy: Focally crescentic and segmentally	Not mentioned	Prednisone	abdominal, and joint pain. Improvement of urinalysis
	Falou et al., 2021 [19]	Lebanon	Positive at admission		Not performed	EULAR/PRINTO/PRES		resolution of rash and joint

Barbetta et al., 2021 [20]	62-year- old/Male	Italy	Positive at admission	Skin, Kidneys, and GI tract	Skin biopsy: Perivascular and interstitial lymphocytic infiltrate mainly distributed in the upper dermis, together with extravasated red blood cells, ectasia capillary vessels, and endothelial cells with signs of swelling without atypia. DIF: intense IgA vascular deposits	Not mentioned	Methylprednisolone	Improvement of renal function, abdominal pain, and skin rash.
Kumar et al., 2021 [21]	13-year- old/Male	United States of America	Negative at admission/ symptoms start to appear 4 weeks after Covid-19 infection	Skin and kidneys	Skin biopsy: Small vessel neutrophilic vasculitis. Non-specific, patchy deposition of fibrinogens present in the superficial dermis only. DIF: negative	Not mentioned	Prednisolone	Gradually
el Hasbani et al., 2021 [22]	16-year- old/Male	Lebanon	Positive at admission	Skin, kidneys, and GI tract	Not performed	EULAR/PRINTO/PRES	Prednisolone	Improvement of the rash and urinalysis
Borocco et al., 2021 [23]	13-year- old/Female	France	Positive at admission	Skin and GI tract	Not performed	EULAR/PRINTO/PRES	Pain relievers	No complications
Jedlowski & Jedlowski., 2022 [24]	70-year- old/Male	United States of America	Positive at admission	Skin, kidneys, and GI tract	Skin biopsy: Leukocytoclastic vasculitis DIF: strong signal granular IgA deposition Kidney biopsy: Mesangial hypercellularity, focal/mild endocapillary hypercellularity, tubular atrophy, interstitial fibrosis, and lymphocytic tubulitis, without crescents. DIF: granular mesangial deposition of IgA (2+), with identification of patchy effacement of podocytes	Not mentioned	Methylprednisolone Prednisone	Resolution of abdominal pain, rash, and renal function.
Ziyara et al., 2022 [25]	12-year- old/Male	United Kingdom	Positive at admission	Skin, joints, and GI tract	Not performed	Royal College of Pediatrics and Child Health Guidelines 2020	Prednisolone	Improvement of skin rashes Developed self- limited abdominal pain with painful swellings of the small joints in the hands bilaterally with normal investigations
	4-year- old/Male	Saudi Arabia	Positive at admission	Skin, joints, and kidney	Not performed	Not mentioned	Prednisolone	Improvement of skin rashes and joint pain
Asiriet al., 2022 [26]	23-month- old/Male		Positive at admission	Skin, joints, and GI tract	Not performed	Not mentioned	Prednisolone	Improvement of the GI symptoms, joint pain, and skin rash
	4-year- old/Male		Positive at admission	Skin, joints, and GI tract	Not performed	Not mentioned	Prednisolone	Improvement of the GI symptoms, joint pain

TABLE 1: Reported cases with IgA vasculitis induced by COVID-19 infection

IgA: immunoglobulin A

Our patient was diagnosed with IgA vasculitis based on the EULAR/PRINTO/PRES criteria associated with pulmonary-renal syndrome following a COVID-19 infection. Initially, the patient was treated with steroids to reduce the risk of developing persistent kidney disease because urine protein levels were significantly elevated. However, these alone did not provide the effectiveness desired, and she was later successfully treated with plasma exchange and intravenous immunoglobulin (IVIG).

As COVID-19 is a novel disease and its pathogenic mechanism of causing IgA vasculitis is not well understood, every patient who is infected with or recently recovered from COVID-19 and presents with a skin rash or arthralgia should have baseline blood and urine tests done and should be treated promptly to avoid the emergence of irreversible consequences.

It's vital to remember that case reports are descriptive and can't be utilized to prove a cause-and-effect link. On the other hand, the efficacy of current therapeutic regimens is debatable since the majority of available research has been conducted on children, with findings that have been generalized to adults. As a result, we recommend further studies be done to be able to determine the role of SARS-CoV-2 in the pathogenesis of IgA vasculitis and the efficacy of the available therapeutic interventions on adults.

Conclusions

In conclusion, our study showed that COVID-19 could serve as an indirect trigger of IgA vasculitis through the hyperinflammatory response and cytokine storm. Adult-onset IgA vasculitis may be efficiently treated with plasma exchange and intravenous immunoglobulin. We present the first case of IgA vasculitis based on the EULAR/PRINTO/PRES criteria associated with pulmonary-renal syndrome after a SARS-CoV-2 infection that was effectively treated with intravenous immunoglobulin (IVIG) and plasma exchange and showed an impressive response.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Biomedical Research Ethics Committee, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia issued approval HAPO-02-K-012-2022-05-1094. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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