Covid-19 Vaccine as a potential triggering factor for Anti-GBM disease, A case report and systematic review

Mohanad Ahmed[1], Sabah Mohamed[1], Rayan Sibira[1], Isra Eltazi[1], Hussein Al-hussein[1], and Ahmad Salih Abdulhadi[1]

[1]Hamad Medical Corporation

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Abstract

COVID-19 vaccine side effects are still a hot area under study, Many side effects have been identified, and others are still under study. Herein, we are reporting a patient who developed Rapidly Progressive Glomerulonephritis due to anti-GBM disease two days after receiving the COVI-19 vaccine.

Introduction:

The novel coronavirus 2019 (COVID-19) pandemic that has been causing striking worldwide extensive morbidity and mortality during the past two years was followed by heroic research and vaccine discoveries, altering the course of the illness in a more benign direction. The worldwide vaccination campaigns are of clear benefit. Still, adverse events that were not previously observed during clinical trials are now sprouting and should remain in focus and must be tracked and followed up vigilantly. Interestingly, there has been an upward trend in reporting cases of unmasking/reactivation of glomerular disease after receiving mRNA vaccines.

Antiglomerular basement membrane (anti-DBM) disease is an autoimmune vasculitis disease characterized by the production of autoantibodies against type IV collagen present in basement membranes affecting both kidneys and lungs. These autoantibodies cause capillaritis at the mentioned sites, and patients usually succumb to rapidly progressive glomerulonephritis and alveolar bleeding. Diagnosis is made by linking clinical data and serologic testing, though renal biopsy is required for confirmation [1]. Like most autoimmune diseases, anti-GBM disease occurs in genetically predisposed individuals after a specific insult such as an infection, drugs, environmental exposure, etc. [2].

During the COVID era, accelerated vaccine production has been observed. The different vaccines use different mechanisms to generate immunity. Pfizer BNT162b2 and Moderna mRNA-1273 use a pioneer mechanism, a lipid nanoparticle nucleoside-modified mRNA encodes SARS-CoV-2 spike (S) protein which medicates host attachment and viral entry. AstraZeneca uses a replication-deficient chimpanzee adenovirus vector containing the SARS-CoV-2 S protein. It has been shown recently that vaccines, specifically mRNA-based ones, are linked to the development of glomerular disease [3].

Case Report/Case Presentation

We are presenting a 26 years old male, previously healthy, working as a labor in a building company. The patient was sent on 16th August 2021 to our medical department from a field hospital complaining of cough, hemoptysis, shortness of breath, and feeling fatigued for seven days which increased in severity in the last two days. He mentioned no chest pain or fever. On further questioning, he said he received the COVID-19 vaccine (Moderna) second dose on 14th August, while the first was given on 17th July. Currently, he doesn't smoke,

consume alcohol, or take any medications. On examination, the patient looked in mild respiratory distress. His vital signs showed a respiratory rate of 23 cycles/min, pulse rate of 98 beats/min, and Blood pressure of 115/76 mmHg. He was afebrile, and his Oxygen saturation was 96% on room air. Chest examination was significant for diffuse bilateral crackles with scattered wheezes. Cardiovascular, abdomen, and neurologic exams were unremarkable. The patient was started on salbutamol nebulization while blood tests and chest X-rays were requested.

Initial lab results were significant for a Hemoglobin (Hb) of 5.6 gm/dl; platelets count was 231,000/mcl; blood urea was 15 mmol/l; creatinine was 641umol/l; potassium was 4.1 mmol/l, and bicarbonate was 18 mmol/l. The chest X-ray showed bilateral diffuse airspace opacity and patchy consolidative changes at both lung parenchyma with background lung nodular shadow (Figure 1).

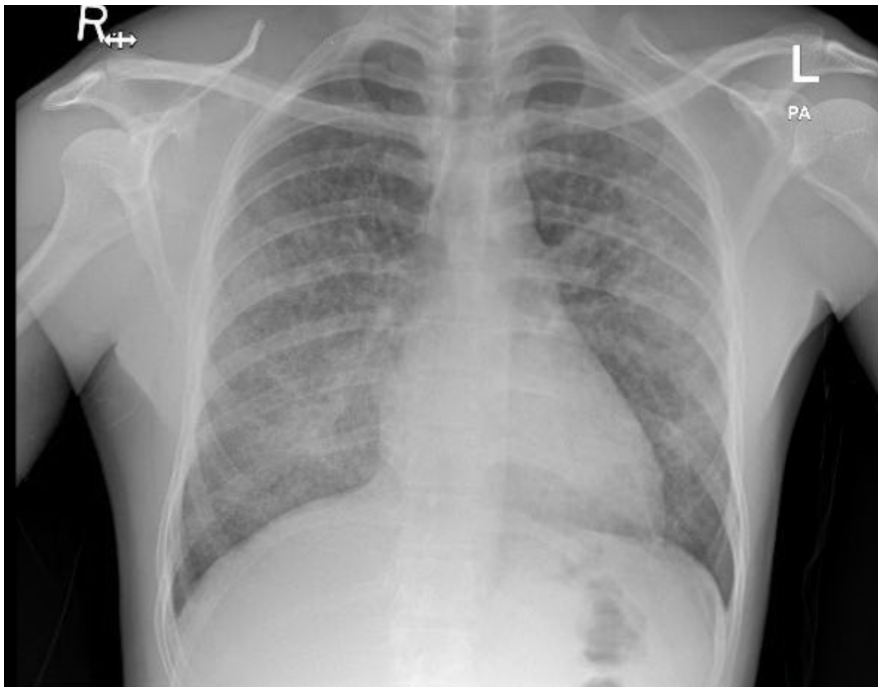

Figure1. Chest X-ray on initial presentation showed bilateral diffuse airspace opacity and patchy consolidative changes at both lung parenchyma.

Initial management included transfusion to two units of packed red blood cells, starting antibiotics to cover the possibility of community acquired pneumonia while the admission process was initiated.

Ultrasound scan of both kidneys showed normal size and no evidence of obstruction. The next day, the patient laboratory tests showed no improvement in his renal parameters, and he started to feel more shortness of breath. Computed tomography (CT) scan of the chest was done (figure 2), followed by bed Bedside bronchoscopy, and the presence of pulmonary hemorrhage was confirmed.

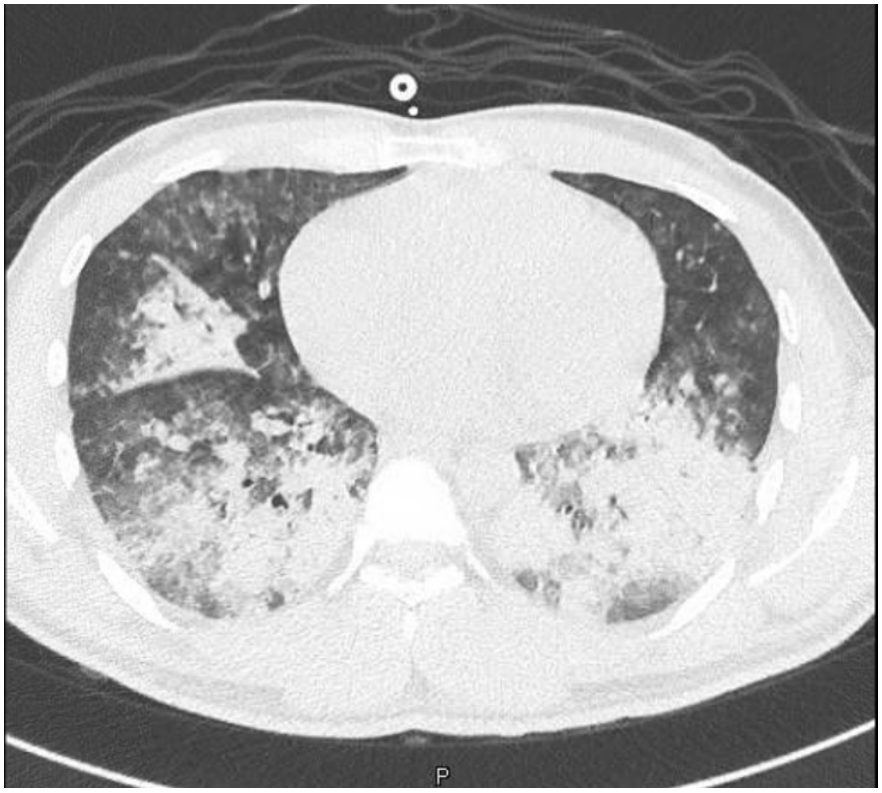

Figure 2. CT of the chest showing Bilateral diffuse consolidation with centrilobular nodules, in keeping with alveolar space disease

The patient was started on pulse steroids, and an anti-glomerular basement membrane antibodies test was sent. On 19th August 2021, echocardiography was done and reported as normal, followed by an ultrasound-guided kidney biopsy on the same day.

Although the patient was started on steroids, he continued to deteriorate. His oxygen requirement increased, Renal parameters worsened, and he developed lower limb edema, followed by decreased urine output. At this point, the patient was shifted to the intensive care unit, central line inserted and the nephrology team started him on regular hemodialysis. On 20th August, the report of anti-GBM antibody was released. It was positive (titter = 550.0 U/mL). Plasmapheresis started and planned to be continuous with weekly measuring the antibody titter till it becomes negative. In addition to that, the patient was started on Cyclophosphamide 100 mg daily, and the plan was to continue for a total of three months. On 23rd August, the biopsy result was reported as Crescentic glomerulonephritis, consistent with Anti-GBM disease (Figure 3).

Pathological Finding:

Kidney biopsy (Figure.3, A-C) showed 24 glomeruli, 23 glomeruli show extra capillary cellular crescents, but none show fibro cellular/fibrous crescents. The crescents are temporally homogenous at the same age and stage and fill the space delineated by Bowman's capsule (Figure.3, A-B), some show rupture of Bowman's capsule. Some glomeruli show active periglomerular inflammation (Figure.3, A). Mild tubular atrophy and interstitial fibrosis were also noted (10-15% of the cortical tissue), associated with moderate multifocal interstitial inflammatory infiltrate composed of lymphocytes and occasional eosinophils. Direct immunofluorescent microscopy showed linear staining of IgG (Figure.3, C), complement component C3, and light chains (kappa and lambda) along the glomerular basement membrane. These findings of Crescentic glomerulonephritis are consistent with Anti-Glomerular Basement Membrane (GBM) glomerulonephritis.

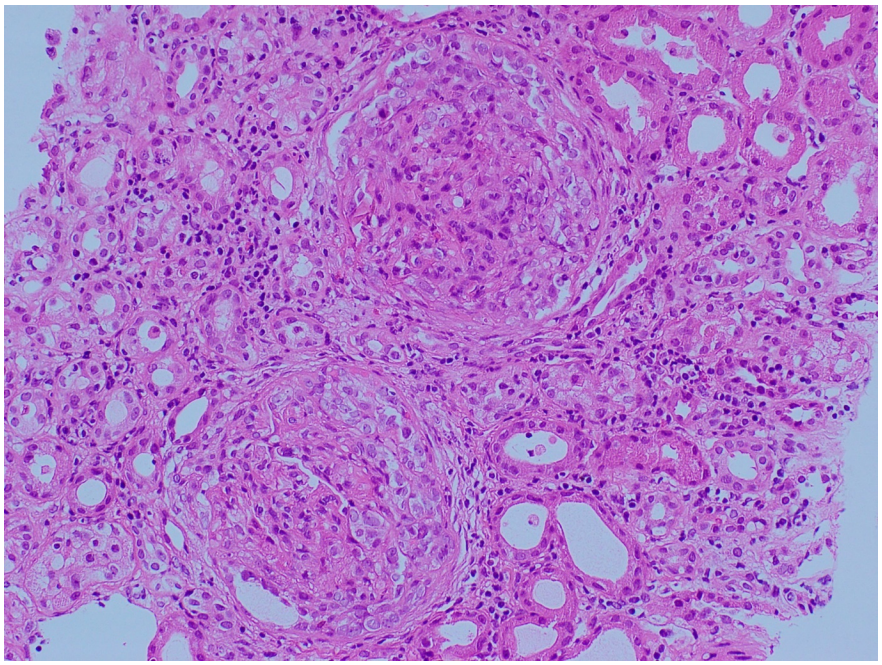

Figure 3 (A) Uniform cellular crescents with periglomerular inflammation (H&E, x200).

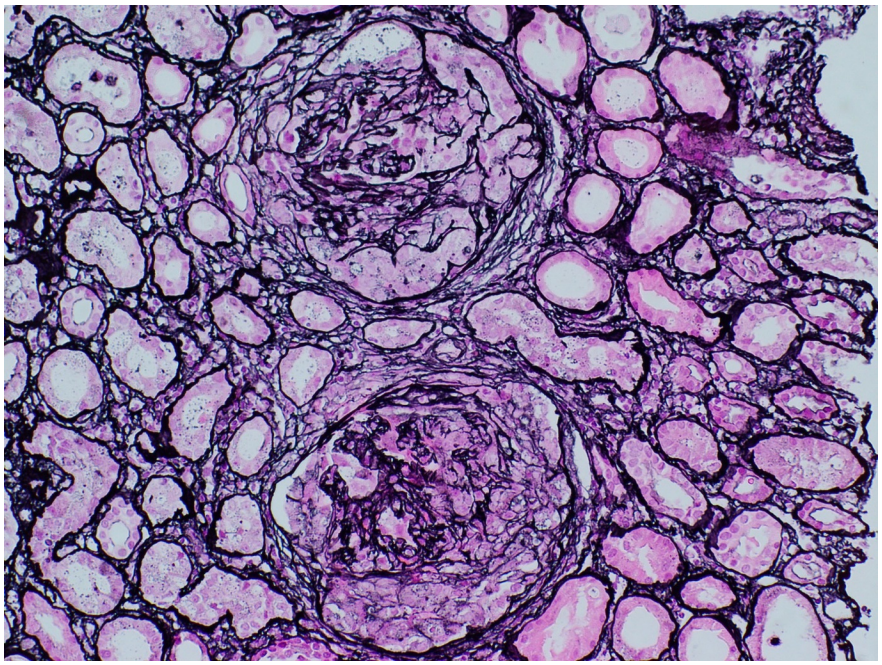

Figure 3 (B) Remnants of GBM surrounded by cellular crescents, which fill the space delineated by Bowman's capsule (Jones silver stain, x200).

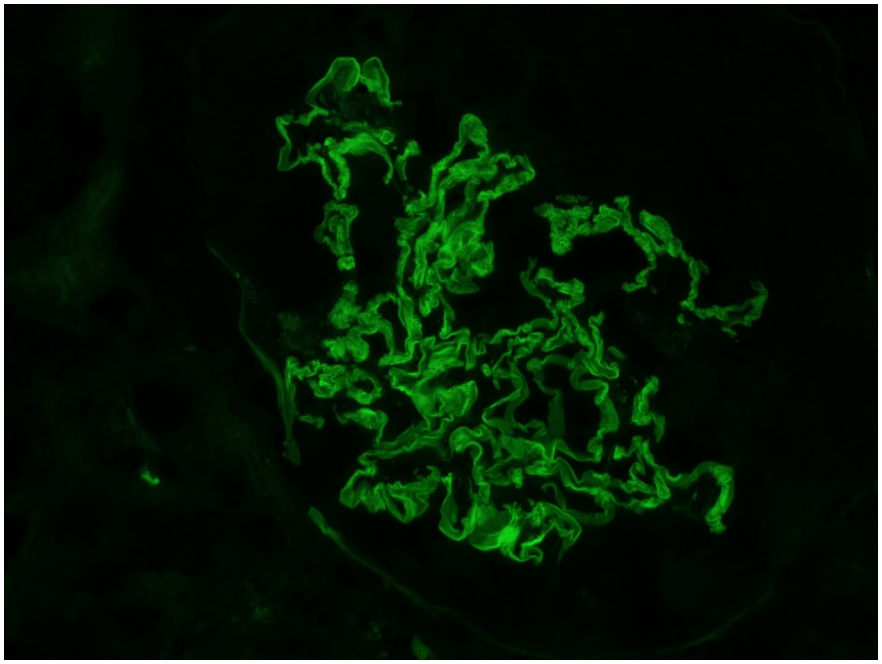

Figure 3 (C) Strong linear ribbon-like appearance IgG (2+) in the GBM, the glomerulus is compressed by a crescent, which does not stain (Direct immunofluorescence on frozen kidney tissue, x200).

The patient was kept on plasmapheresis, hemodialysis, Cyclophosphamide while steroids were switched to oral with tapering down after five days of intravenous pulse steroids.

A few days later, the patient showed significant improvement in his clinical condition and laboratory tests. His renal function improved, and symptoms were resolved, so hemodialysis frequency was reduced. His weekly titter of anti-GBM antibody was steadily declining with plasmapheresis. After three weeks, the measured titter dropped from 500 U/mL to 7 U/mL. Plasmapheresis was stopped while he was kept on regular hemodialysis three times per week in addition to Cyclophosphamide 100 mg daily.

Discussion:

Since the start of the covid-19 vaccination, the temporal association between the vaccine and the development of de novo or relapse of glomerular diseases, including anti-GBM, has been studied [4]. However, the pathogenesis of vaccine-associated glomerular disorders has not been fully elucidated. On checking the literature, we found a minimal number of reported cases of de novo anti-GBM disease following COVID-19 vaccine "in particular mRNA vaccines" [5,6,7].

Anti-GBM is a rare disease with a bimodal distribution. The majority of the young patients present with pulmonary manifestations, while most of the elderly patients present with renal involvement [8.9]. Comparing our patient to the previously reported cases, all reported cases were elderly females who presented with hematuria and acute kidney injury following the COVID-19 vaccine. However, our patient was a young male, presented with symptomatic pulmonary hemorrhage and renal impairment simultaneously.

The duration between exposure to the vaccine and the incidence of anti-GBM disease varied between days to weeks [5,6,7]. At the same time, its symptoms started two days after the second dose of Moderna vaccine in our reported patient. Although we were unable to find other triggers, they cannot be excluded entirely. All reported cases, including our patient, showed a negative association with Antineutrophil cytoplasmic antibodies (ANCA). In all patients, the symptoms started after the second dose of the vaccine, and they were all asymptomatic after the first dose.

The outcome of the reported cases showed no specific pattern. Despite receiving steroid cyclophosphamide and plasmapheresis, our patient's renal function did not improve, and he remained dialysis-dependent.

Table 1: Cases of De Novo Anti GBM disease post mRNA COVID-19 vaccines

	Report	Age/gender	Type of vaccine	Dose	Days from Vaccine to onset	De novo or relapse	Symptoms on presentation	ANCA association	Treatment	Other triggers
1	Japan	F, 70 YO	N/A	2nd	9 days	De Novo	AKI, Hematuria	-ve	S,PLX,IV CYP	Centipede bite
2	USA	F, older	Moderna	2nd	14 days	De Novo	AKI, hematuria	-ve	S,PLX,CYP	N/A
3	Singapore	F, 60 YO	Pfizer	2nd	1 day	De Novo	AKI, Hematuria, NRP	-ve	S,PLX,O CYP	N/A
4	Qatar	M, 26 YO	Moderna	2nd	2 days	De Novo	Hemoptysis, AKI	-ve	S,PLX,O CYP	N/A

** S: Steroid, PLX: plasmapheresis, CYP: cyclophosphamide, O:oral , IV: intravenous, AKI: Acute kidney injury, NRP : nephrotic range proteinuria

Conclusion;

This case report suggests that COVID-19 vaccines could be related to the development of anti-GMB disease. However, further information and studies are needed to establish and confirm this relation.

Statements

Statement of Ethics

The patient had given his written informed consent to publish her Case.

Disclosure Statement

All authors declared no conflict of interest.

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Author Contributions

1. Ahmed S Abdulhadi: Overall supervision and guiding.
2. Mohanad A E Ahmed: Corresponding author, Writing the case report, abstract and conclusion, language review and correcting language errors, submission to a journal.
3. Sabah E A Mohamed: writing the discussion.
4. Esra Z M Eltazi : writing the discussion.
5. Hussein N Al Hussein : writing the Introduction.
6. Rayan M Sibira : preparing pathology slides and writing pathology report.

References (Numerical)

1. McAdoo SP, Pusey CD. Antiglomerular Basement Membrane Disease. Semin Respir Crit Care Med. 2018 Aug;39(4):494-503. doi: 10.1055/s-0038-1669413. Epub 2018 Nov 7. PMID: 30404116.
2. DeVrieze BW, Hurley JA. Goodpasture Syndrome. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459291/.

3. Izzedine H, Bonilla M, Jhaveri KD. Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine: true association or circumstantial? *Nephrol Dial Transplant* . 2021;36(9):1565-1569. doi:10.1093/ndt/gfab215.
4. Li, Nicholas L., P. Toby Coates, and Brad H. Rovin. "COVID-19 Vaccination Followed by Activation of Glomerular Diseases Does Association Equal Causation?." *Kidney International* (2021).
5. Nagai, Kei, Mamiko Iwase, and Atsushi Ueda. "A case of anti-GBM nephritis following centipede bites and COVID-19 vaccination." *CEN Case Reports* (2021): 1-5.
6. Tan, Hui Zhuan, et al. "Is COVID-19 vaccination unmasking glomerulonephritis?." *Kidney international* (2021).
7. Sacker, Allan, Vanderlene Kung, and Nicole Andeen. "Anti-GBM nephritis with mesangial IgA deposits after SARS-CoV-2 mRNA vaccination." *Kidney international* 100.2 (2021): 471-472.
8. Savage, C. O., et al. "Antiglomerular basement membrane antibody mediated disease in the British Isles 1980-4." *Br Med J (Clin Res Ed)* 292.6516 (1986): 301-304.
9. Levy, Jeremy B., et al. "Long-term outcome of anti–glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression." *Annals of internal medicine* 134.11 (2001): 1033-1042.