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Exceptional Case

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# *De novo* and relapsing necrotizing vasculitis after COVID-19 vaccination

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## ABSTRACT

We describe five cases of severe necrotizing vasculitis following the RNA-based vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including four relapsing anti neutrophil cytoplasmic antibodies (ANCA) vasculitis, 27 days (1–60) after vaccination and one patient with quiescent chronic hepatitis B and *de novo* polyarteritis nodosa (PAN) 21 days after vaccination. Ten other cases were reported to the French national pharmacovigilance database: six patients with ANCA-associated vasculitis and four patients with PAN (first symptoms 19 days on average after vaccination). Five of these 10 patients developed kidney dysfunction. In conclusion, coronavirus disease 2019 (COVID-19) vaccines can be associated with *de novo* or recurrent ANCA vasculitis or PAN. Attention should be paid to patients with known ANCA vasculitis or patients with a history of hepatitis B infection.

**Keywords:** AKI, ANCA, crescentic glomerulonephritis, hepatitis B, immunology, kidney biopsy

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) vaccine is now considered as a best shield against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19 vaccines have shown an excellent efficacy and overall acceptable safety profile [1]. Recently, Barda *et al.* showed that the BNT162b2 vaccine was associated with an increased risk of myocarditis, lymphadenopathy and herpes zoster infection [2]. Furthermore, other reports indicated that minimal change disease [3, 4] and immunoglobulin A nephropathy [5, 6] could occur following vaccination for SARS-CoV-2.

In the present study, we report five cases of severe necrotizing vasculitis following the vaccine for SARS-CoV-2 developed from February 2021 to September 2021 in our ward [including four relapsing ANCA vasculitis and one *de novo* polyarteritis nodosa (PAN) with severe acute kidney injury] and compared them to cases reported from the French National Pharmacovigilance database.

## FOUR PATIENTS WITH ANCA VASCULITIS

Patients who developed relapsing ANCA vasculitis were aged from 75 to 85 years. Demographic and clinical data are shown in Table 1. None of these patients had presented COVID-19 primo infection before the vaccination. Relapsing ANCA occurred after the first dose for one patient and after the second dose for the

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Table 1. Demographic and clinical data from patients with relapsing vasculitis after COVID-19 vaccination

| Sex | Age (years) | Primo infection COVID-19 | Number of vaccine dose | Type of vaccine | Timing of first symptoms after vaccination | Creatinine serum level before vaccination (µmol/L) | Years of vasculities diagnosis | Extra renal symptoms | Creatinine serum level at diagnosis (µmol/L) | Proteinuria (g/day) | Hematuria | Immunology (UI/mL) | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F | 78 | No | 2 | BNT162b2 | 3 days | 106 | 2020 | Hypereosinophilia asthenia, arhtralgia | 150 | 0.03 | No | Anti-MPO (76) | Steroids |
| M | 78 | No | 2 | BNT162b2 | 60 days | 79 | 1995 | Arthralgia, anoraexia, asthenia, fever | 146 | 0.47 | Yes | Anti-PR3 (86) | Steroids + rituximab |
| M | 75 | No | 1 | BNT162b2 | 1 day | HD[a] | 2000 | Arthralgia, purpura | HD[a] | HD[a] | HD[a] | Anti-PR3 (39) | Steroids |
| M | 85 | No | 2 | BNT162b2 | 45 days | HD[a] | 2009 | Diffuse alveolar haemorrhage, asthenia, purpura | HD[a] | HD[a] | HD[a] | Anti-PR3 (156) | Steroids + rituximab |

Characteristics of the four patients from our centre with ANCA vasculitis. F, female; M, male.
[a]HD: haemodialyzed patient

three other patients. The mean delay between vaccination and first symptoms was 27 days (1–60 days).

Patient 1 was a 78-year-old woman, with ANCA vasculitis known from 2020, with kidney involvement. She developed eosinophilia, arthralgia and asthenia, 3 days after the second dose of vaccination, with increased serum creatinine level and a high rate of anti-myeloperoxidase (MPO) antibodies. Anti-MPO antibodies were negative before the vaccination. She was treated with steroids.

Patient 2 was a 78-year-old man, with known ANCA vasculitis since 1995, without kidney dysfunction. He developed asthenia, fever, anoraexia and arthralgia 60 days after the second dose of vaccination. Acute kidney injury was associated with proteinuria and haematuria. A kidney biopsy indicated crescentic glomerulonephritis. This patient had known ANCA antibodies prior to vaccination, and ANCA antibodies remained present despite treatment with methotrexate. We observed an important rise of antibodies ANCA titers after vaccination, from 12 µI/mL to 86 µI/mL. Kidney injury required treatment with steroids and rituximab therapy.

Patient 3 was a 75-year-old man who was on chronic haemodialysis due to known vasculitis since 2000. Haemodialysis was started in 2018. He developed asthaenia, arthralgia and purpura 1 day after his first vaccination, and was treated with oral steroids. ANCA antibodies titer was 39 µI/mL at the time of the vasculitis relapse. The last available level before vaccination was 18 µI/mL, the year prior to vaccination. He had not presented a recurrence for 18 months before vaccination.

Patient 4 was an 85-year-old man who was on chronic haemodialysis due to vasculitis since 2009. Haemodialysis was started in 2015. He presented severe acute respiratory syndrome related to diffuse alveolar haemorrhage, with asthenia and purpura necrotizing lesions, 45 days after the second dose of vaccine. Anti-proteinase-3 antibodies level was 153 µI/mL at the time of the vasculitis relapse versus 55 µI/mL before vaccination. He was successfully treated with oxygen therapy, steroid and rituximab therapy. He had not presented a recurrence for 10 months before vaccination.

Finally, in all of these four patients who had ANCA antibodies before vaccination, ANCA antibodies titers increased (both anti-PR3 and anti-MPO). Patients with severe necrotizing vasculitis including diffuse alveolar haemorrhage or crescentic glomerulonephritis were successfully treated with steroids and rituximab.

## ONE PATIENT WITH PAN

The 73-year-old male patient who developed PAN had a quiescent chronic hepatitis B, controlled with tenofovir treatment over 20 years and normal renal function (serum creatinine was 93 µmol/L 2 weeks before vaccination). The first symptoms including fever, arthralgia, purpura and orchitis occurred 21 days after the first dose of the vaccine. He developed a severe acute kidney requiring haemodialysis 32 days after the vaccination. Kidney biopsy showed necrotizing vasculitis preferentially targeting medium-sized arteries, with thrombosis and microaneurysms associated with acute tubular necrosis (Figure 1).

Hepatitis B virus PCR had been negative for 20 years and was still negative at the time of diagnosis. Anti-neutrophil cytoplasmic antibodies were negative. Tenofovir was withdrawn and replaced by entecavir because of the acute tubular lesions and possible Fanconi syndrome associated with glomerular lesions. Necrotizing vasculitis was treated with cyclophosphamide and steroids.

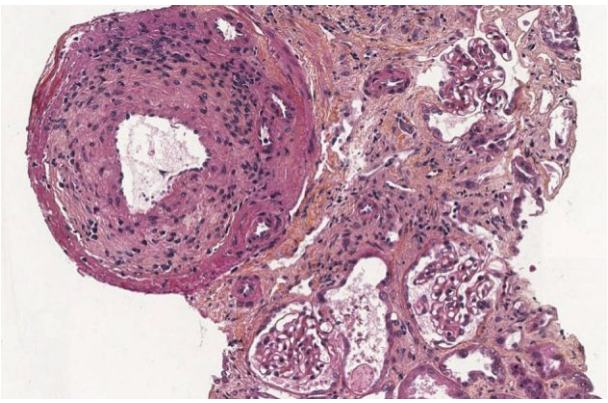

FIGURE 1: Kidney histology of a 73-year-old patient with quiescent hepatitis B, developing PAN following the second dose of COVID-19 vaccine.

## CASES OF ANCA-ASSOCIATED VASCULITIS AND PAN REPORTED TO THE FRENCH PHARMACOVIGILANCE CENTRES (NATIONAL DATABASE)

Up to 29 September 2021, six other cases of ANCA-associated vasculitis and four other cases of PAN were reported to French pharmacovigilance centres after COVID-19 vaccination. There were seven males and three females and the median (range) age was 61 years (38–72 years). Seven patients were vaccinated by adenovirus vaccines [JNJ-78436735 (Ad26.COV2.S) and AZD1222 (ChAdOx1)] and three by mRNA vaccines (BNT162b2 and mRNA-1273). Most of the patients developed symptoms after the first injection ($n = 7$; 70%). The median (range) time to onset was 19 days (2–31 days) after injection. All the four cases of PAN were *de novo* diagnosis. Among the six ANCA-associated vasculitis, four patients were positive for anti-PR3 antibodies and one patient for anti-MPO antibodies (not specified in the last case). One patient had a history of granulomatosis with polyangiitis and all the other cases were *de novo* diagnosis. Among these 10 patients, 5 developed kidney dysfunction (proteinuria, haematuria, increased serum creatinine level and/or kidney injury on biopsy). Nine patients were treated with corticosteroid and/or immunosuppressing medications.

## DISCUSSION

Although the overall efficacy of COVID-19 vaccination has been proven excellent and safety is considered acceptable in the vast majority of patients, some patients may develop auto-immune diseases [7]; our observations reveal that they could be a trigger for *de novo* or relapsing vasculitis and subsequent necrotizing vasculitis and PAN. To our knowledge, five other cases of ANCA-associated vasculitis following SARS-CoV-2 vaccination were recently reported [8, 9].

Because of the global scale of vaccination, other cases could emerge. Clinical descriptions should be helpful to understand the physiopathology and incriminate the SARS-CoV-2 vaccination. Nowadays the relationship between COVID-19 vaccination and development of auto-immune disease has been suggested. Immune mechanisms involved could be the activation of the NLRP3 inflammasome by vaccine-adjuvant [10] or molecular mimicry with immune cross-reaction [11].

The annual incidence rate of ANCA vasculitis is 20 per million habitants in Europe [12]. As the vaccination coverage in France is 88%, we observed during the 9-month observation period, a reported incidence of ANCA vasculitis flare-up, occurring after vaccination, for only 10 cases, i.e. a lower incidence than expected. It is therefore not possible at this time to estimate on a collective level the risk of developing ANCA vasculitis in the period following vaccination.

Our results suggest that ANCA antibody levels and clinical symptoms of relapse should be monitored in patients with ANCA vasculitis. Although general symptoms after COVID-19 vaccine may occur in some patients, they are usually developed within 72 h after vaccine, whereas symptoms associated with *de novo* or ANCA vasculitis relapse after COVID-19 vaccine seem to appear later.

The risk of *de novo* glomerular disease after COVID-19 vaccine remains lower than the risk of acute kidney injury or death after primo infection with SARS-CoV-2 [13–15], and a worldwide vaccination effort should be supported.

PAN is a rare cause of vasculitis targeting the medium-size arteries classically associated with hepatitis B infection. Recent cases of PAN after the COVID-19 vaccine in patients, without hepatitis B infection, have been described. Physiopathology remains unclear but inflammatory pathways activation, leading to diffuse vascular inflammation and ischaemia of affected organs, is suggested. Further descriptions are needed to clearly understand the pathophysiology.

PAN is currently uncommon because of the generalization of hepatitis B vaccination. Those recent observations suggested the implication of other triggers, and PAN diagnosis should be considered in patients with systemic vasculitis with negative ANCA antibodies.

In conclusion, although the efficacy and safety of the COVID-19 vaccine have been demonstrated, particular attention should be paid to patients with known autoimmune diseases and especially those with known ANCA vasculitis. Symptoms suggesting recurrence may occur rapidly after vaccination. In the lack of circulating antibodies, PAN could be considered, even without a history of contact with hepatitis B.

## PATIENT CONSENT

The patients gave informed consent to publish their case.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## REFERENCES

1. Walsh EE, Frenck RW, Falsey AR *et al*. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020; 383: 2439–2450
2. Barda N, Dagan N, Ben-Shlomo Y *et al*. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. *N Engl J Med* 2021; 385: 1078–1090
3. Mancianti N, Guarnieri A, Tripodi S *et al*. Minimal change disease following vaccination for SARS-CoV-2. *J Nephrol* 2021; 34: 1039–1040
4. Lebedev L, Sapojnikov M, Wechsler A *et al*. Minimal change disease following the Pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis* 2021; 78: 142–145
5. Rahim SEG, Lin JT, Wang JC. A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination. *Kidney Int* 2021; 100: 238
6. Bomback AS, Kudose S, D'Agati VD. De novo and relapsing glomerular diseases after COVID-19 vaccination:

what do we know so far? *Am J Kidney Dis* 2021; 78: 477–480
7. Ishay Y, Kenig A, Tsemach-Toren T *et al*. Autoimmune phenomena following SARS-CoV-2 vaccination. *Int Immunopharmacol* 2021; 99: 107970
8. Hassanzadeh S, Djamali A, Mostafavi L *et al*. Kidney complications following COVID-19 vaccination; a review of the literature. *J Nephropharmacol*, In press
9. Shakoor MT, Birkenbach MP, Lynch M. ANCA-associated vasculitis following the Pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis* 2021; 78: 611–613
10. Ndeupen S, Qin Z, Jacobsen S *et al*. The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *iScience*. 2021
11. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. *Cell Mol Immunol* 2018; 15: 586–594
12. Salvador F. ANCA associated vasculitis. *Eur J Intern Med* 2020; 74: 18–28
13. Shetty AA, Tawhari I, Safar-Boueri L *et al*. COVID-19-associated glomerular disease. *J Am Soc Nephrol* 2021; 32: 33–40
14. Kudose S, Batal I, Santoriello D *et al*. Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol* 2020; 31: 1959–1968
15. Prendecki M, Clarke C, Cairns T *et al*. Anti-glomerular basement membrane disease during the COVID-19 pandemic *Kidney Int* 2020; 98: 780–781