EXCEPTIONAL CASE

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

| Number | Primoinfection COVID-19 age (years) | Sex | Type of vaccine | Timing of first symptoms after vaccination | Years of vasculitis diagnosis | Creatinine serum level at diagnosis (μmol/L) | Type of renal symptoms | Proteinuria (g/day) | Hematuria | Anti-MPO (UI/mL) | Anti-PR3 (UI/mL) | Treatment |
|--------|---------------------------------|-----|----------------|-------------------------------------------|------------------------------|-------------------------------------------|-----------------------|-----------------|-----------|----------------|----------------|-----------|
| 1      | F 78                            | No 2 | BNT162b2       | 3 days                                    | 2020                         | 106                                       | Hypereosinophilia, asthenia, arthralgia, anorexia | 0.03             | Yes       | Anti-MPO (76) | Anti-PR3 (86) | Steroids  |
| 2      | M 78                            | No 2 | BNT162b2       | 60 days                                    | 1995                         | 79                                        | Arthralgia, anorexia, asthenia, fever             | 0.47             | Yes       | Anti-PR3 (86) | Anti-PR3 (86) | Steroids + rituximab |
| 3      | M 75                            | No 1 | BNT162b2       | 1 day                                      | 2000                         | 146                                       | Arthralgia, purpura                              | HD              | Yes       | Anti-PR3 (39) | Anti-PR3 (39) | Steroids + rituximab |
| 4      | M 85                            | No 2 | BNT162b2       | 45 days                                    | 2009                         | 150                                       | Diffuse alveolar hemorrhage, haemorrhage, purpura| HD              | Yes       | Anti-PR3 (156) |                | Steroids + rituximab |

Characteristics of the four patients from our centre with ANCA vasculitides. F, female; M, male.

### Discussion

In the context of COVID-19 vaccination, we report the clinical features of four patients with ANCA vasculitis who developed symptoms within 60 days of vaccination. Three patients had previously known ANCA vasculitis, while one patient had PAN.

#### Patient 1
Patient 1 was a 78-year-old female with known ANCA vasculitis. She developed eosinophilia, arthralgia, and asthenia 3 days after vaccination. Anti-MPO antibodies were negative before vaccination. She was treated with steroids.

#### Patient 2
Patient 2 was a 78-year-old male with known ANCA vasculitis. He developed asthenia, fever, anorexia, and arthralgia 60 days after 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.

#### Patient 3
Patient 3 was a 75-year-old male who was on chronic haemodialysis due to known vasculitis since 2000. Haemodialysis was started in 2018. He developed asthenia, fever, anorexia, and arthralgia 60 days after 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.

#### Patient 4
Patient 4 was an 85-year-old male 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. The last available level before vaccination was 18 μI/mL, the year prior to vaccination. 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.
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deviation of auto-immune disease has been suggested.

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associated vasculitis following SARS-CoV-2 vaccination were re-
vasculitis and PAN. To our knowledge, five other cases of ANCA-
diagnosis. Among the six ANCA-associated vasculi-
tis, 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 in-
jury 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 re-
cently 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 vaccina-
tion. 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 ex-
pected. 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 vac-
cine 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 re-
mains unclear but inflammatory pathways activation, leading to
diffuse vascular inflammation and ischaemia of affected organs,
is suggested. Further descriptions are needed to clearly un-
derstand 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 con-
sidered 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 espe-
cially 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.

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