LESSONS FOR THE CLINICAL NEPHROLOGIST

Biopsy-proven acute interstitial nephritis after SARS-CoV-2 mRNA vaccination—adverse vaccine side effect or unrelated complication from self-medication? Lessons for the clinical nephrologist

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The case

A 25-year-old man was referred to us in December 2021 with bilateral flank pain and increasing kidney values. After a SARS-CoV-2 infection in April 2021, he was vaccinated with BNT162b2 on 8 October. Due to tingling on the left side of his face, he presented as an outpatient at the Neurological University Clinic Heidelberg on 23 October, however, no cause was found. Cranial magnetic resonance imaging (MRI) was unremarkable. Serum creatinine at that time was 1.0 mg/dl (estimated glomerular filtration rate [eGFR] 107 ml/min) and urine dipstick was normal. An elevated serum-creatinine level of 1.32 mg/dl (eGFR 77 ml/min) was first measured on November 4, when he complained of seemingly food-related abdominal cramps. He was sent to an outside hospital on November 19. On admission, serum creatinine was 1.84 mg/dl (eGFR 52 ml/min) accompanied by elevated C-reactive protein (CRP) of 89 mg/l (normal < 5). Gastroscopy revealed mild type C gastritis. Duodenal biopsies were unremarkable. Colonoscopy, including inspection of the terminal ileum, was macroscopically inconspicuous. Histology revealed a normal mucosa without inflammation. His gastrointestinal symptoms then resolved spontaneously.

At referral, he had blood pressure of 140/80 mmHg, slightly painful kidneys but no oedema. There were no signs of infectious disease. Laboratory findings showed CRP of 38 mg/l, haemoglobin 12.0 g/dl, serum creatinine 3.02 mg/dl, eGFR 28 ml/min, while urine sediment was unremarkable and proteinuria was 247 mg/g creatinine (normal < 100). On ultrasound, kidneys were of normal size and shape. Kidney biopsy showed focally accentuated active mononuclear interstitial nephritis with some eosinophils and tubulitis (Fig. 1). There was no increase in IgG4-positive plasma cells. Focal tubular atrophy (5–10%) with interstitial fibrosis of varying degrees suggested long-standing inflammation in agreement with the history and laboratory data (Fig. 2). Autoimmune serology, including antinuclear antibodies (ANAs) and extractable nuclear antigen antibodies (ENAs), was negative. Angiotensin converting enzyme (ACE) in serum was normal. Chest x-ray did not find hilar lymphadenopathy or signs of interstitial lung disease. Our patient initially denied taking any medication. After receiving the biopsy results, he stated that he had been applying a pain relief gel containing diclofenac (23.2 mg/g) to a large area of his neck over 3 weeks since the end of October because of tension when sitting at his computer workstation. We initiated treatment with oral prednisolone 0.5 mg/kg tapering off over 6 weeks. Proteinuria completely resolved. Kidney function improved but did not completely recover. Creatinine clearance was 75 ml/min/1.73 m² on 25 March, 2022.

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Lessons for the clinical nephrologist

In the course of growing vaccination administration worldwide, there are increasing reports of side effects including acute immune-mediated kidney diseases that have occurred after SARS-CoV-2 vaccination. However, causal confirmation of the relationship with vaccination remains challenging and is not always beyond doubt. Acute interstitial nephritis (AIN) has also recently been linked to SARS-CoV-2 vaccination [1–4]. Of note, in the largest series of 5 cases published to date, two patients with severely elevated serum creatinine levels of 268 and 355 µmol/l had evidence of concurrent focal segmental glomerulosclerosis on biopsy just 3 days and "a few days", respectively, after vaccination, suggesting that renal disease was likely pre-existing. Two additional patients had mesangial IgA deposits on electron microscopy, in one patient with crescents [1]. Tubulointerstitial injury is also common in IgA nephritis. One of the latter patients with a very mild clinical course of AIN diagnosed 1 month following vaccination had concomitant ulcerative colitis. It could not be ruled out that AIN was related to inflammatory bowel disease [1].

Fig. 1 Renal histology showing active, predominantly mononuclear interstitial nephritis with tubulitis. Periodic acid-Schiff (PAS) stain

Fig. 2 Trajectory of renal function and disease activity. CRP C-reactive protein, eGFR estimated glomerular filtration rate according to the Chronic Kidney Disease Collaboration (CKD-EPI) equation. BNT162b2 Pfizer-BioNTech BNT162b2 vaccine

Another patient, described by Wu et al., developed a relapse of AIN after steroid taper, which reversed only after withdrawal of concomitant treatment with paroxetine [2]. Thus, in several of these well-documented published cases, it ultimately remained unclear to what extent the cause and magnitude of subsequent renal function impairment were clearly related to vaccination despite the detection of AIN in the biopsy. Notably, complete recovery of renal function did not occur after steroid treatment in all three patients with concurrent glomerular lesions, whereas it normalized in the two patients with unremarkable glomerular capillaries on histology and on electron microscopy [1]. Nevertheless, there is general agreement that AIN occurring in temporal association with vaccination should be considered a possible adverse event, especially if it cannot be otherwise explained. AIN was also recently described in two adolescent patients after a second dose of SARS-CoV-2 mRNA vaccination. Neither had evidence of other renal disease or drug exposure. Renal function recovered spontaneously in one patient, and in the other after treatment with methylprednisolone pulses [3]. Another 14-year-old boy in whom AIN was accompanied by severe nephrotic syndrome required haemodialysis as early as 8 days after an initial injection of SARS-CoV-2 BNT162b2 mRNA vaccine. Renal histology showed inconspicuous glomeruli by light microscopy but diffuse foot process effacement by electron microscopy indicating minimal change disease. It was suggested that the T-cell-mediated immune response to the SARS-CoV-2 vaccine was a trigger of the podocytopathy. Unlike the two cases described above, only partial remission was achieved after 5 weeks of treatment with corticosteroids [4].

The immunologic reaction in AIN is a cell-mediated process that usually manifests 7–10 days after exposure to the culprit substance [5]. Therefore, some reluctance to establish a causal relationship between the involved substance and the development of AIN is warranted when it occurs outside this time window. In our patient, we were able to rule out renal disease 15 days after vaccination because laboratory values were available by chance. An increased serum creatinine of 1.32 mg/dl was not noticed before 4 November 2021, when the family doctor took a blood sample because of gastrointestinal complaints. Thus, because of the long interval between vaccination and the
onset of kidney disease, a vaccine-related side effect is unlikely.

It is known that non-steroidal anti-inflammatory drugs (NSAIDs) can induce pseudo-allergic reactions in the kidneys regardless of the dose [5]. Because of their wide over-the-counter availability and rapid analgesic effect, NSAIDs are among the most common causes of drug-induced AIN, even though the risk is small in absolute terms. Although no figures are available on this, NSAIDs are also likely to be used sporadically in self-medication to relieve transient harmless symptoms, such as headache, muscle pain, or fever, that may be relatively common immediately after SARS-CoV-2 vaccination. Though reaching lower systemic concentrations compared with oral dosage forms, topical NSAIDs are absorbed through the skin and can cause renal disease [6]. AIN following transdermal topical application has been documented in isolated cases [7, 8]. Therefore, based on the temporal association of exposure and incident renal function impairment (Fig. 2) causal relationship was likely in our patient, especially since there was no evidence of infectious or autoimmune disease, particularly renal sarcoidosis or IgG4-related nephritis.

CRP has been shown to correlate with inflammatory activity even in drug-induced AIN [9]. Interestingly, CRP initially increased in parallel with rising renal retention values but spontaneously decreased after our patient discontinued the pain gel following hospitalization in mid-November 2021. Therefore, in the absence of other pathologies, the CRP trajectory outlined in Fig. 2 further supports the likelihood that tubulointerstitial inflammation was driven by transdermal absorption of diclofenac. Consequently, our patient will have to avoid NSAIDs for life and to use other classes of analgesics when needed to prevent recurrence of AIN.

In summary, causality of vaccine side effects, which are being increasingly reported during the SARS-CoV-2 pandemic, is not always clear and should not lead us to question the fundamental benefits of vaccination. Our case report provides an example of challenging a putative vaccine side effect. Clinical workup of AIN requires determining the period between exposure and onset as accurately as possible, but this is not always feasible, an accurate history of concomitant medication, and exclusion of other autoimmune or infectious diseases. Coincidental availability of normal renal values 15 days after vaccination and the temporal medication history, including self-medication, suggested that AIN in our patient was a rare drug-related complication due to extensive topical use of diclofenac and not a vaccine side effect.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical statement Patient consent was obtained for anonymous use of clinical and laboratory data and biopsy images.

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