Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. IgAN with minor histomorphologic alterations on light microscopy. (**A**) Representative glomerulus showing mild mesangial matrix expansion without mesangial hypercellularity on periodic acid–Schiff stain, original magnification ×40. (**B**) Immunofluorescence microscopy with 3+ granular mesangial reactivity for IgA, original magnification ×10. Bar = 20 μm (**A**) and 50 μm (**B**).

Figure S2. IgAN with cellular glomerular crescents. (**A**) Moderate interstitial fibrosis is evident on the trichrome stain. (**B**) The glomerulus on the left shows a segmental cellular crescent, and the glomerulus on the right shows segmental mesangial hypercellularity with mild mesangial matrix expansion on periodic acid–Schiff stain. (**C**) Immunofluorescence staining shows 2+ granular mesangial staining for IgA. (**D**) Electron microscopy shows electron-dense deposits in mesangium. Bar = 600 μm (**A**), 60 μm (**B,C**), and 1 μm (**D**).

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Granulomatous vasculitis after the AstraZeneca anti–SARS-CoV-2 vaccine

To the editor: Several reports of newly diagnosed or relapses of immune-mediated renal diseases following vaccination with anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA and AstraZeneca vaccines recently emerged in the litterature.[1,2]

We report the case of a 77-year-old man who developed an acute granulomatous nephritis associated with vasculitis after the first dose of the AstraZeneca vaccine. The patient had no significant medical history, and serum creatinine (SCr) was 1.2 mg/dl a month before vaccination with a protein-to-creatinine ratio at 0.07 g/g (N = 0.15) of creatinine. Four weeks after injection, the patient presented with fever, night sweating, and anorexia. He was not taking any medication. Laboratory tests revealed acute kidney injury (SCr, 2.7 mg/dl), normal proteinuria, no hematuria, and a C-reactive protein (CRP) level of 200 mg/L. Nasopharyngeal swab for SARS-CoV-2 was negative by polymerase chain reaction, as were anti–SARS-CoV-2 and anti-neutrophil cytoplasmic antibodies (repeated twice 15 days apart). Fluorine-18-fluorodeoxyglucose positron emission tomography scan showed diffuse hypermetabolism of medium vessels, suggesting vasculitis. The kidney biopsy revealed diffuse interstitial edema with noncaseating nonnecrotizing granulomas around small vessels (Figure 1); one showed fibrinoid necrosis. There were no immune deposits. Serum QuantiFERON for tuberculosis was negative, and there were no radiological or biological findings suggestive of sarcoidosis. The patient was started on methylprednisolone, with normalization of SCr and CRP levels within 4 weeks. Interestingly, the patient eventually mounted a humoral response 8 weeks after vaccination.

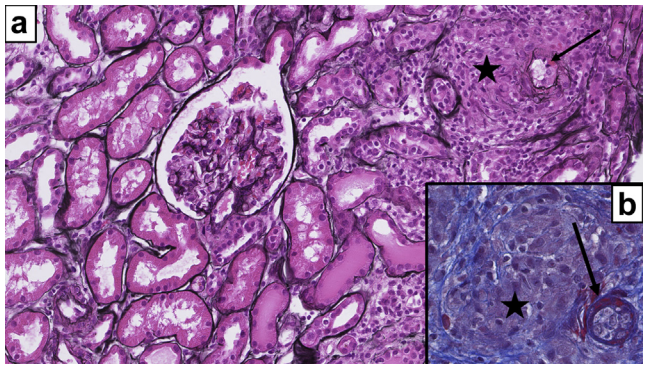

Figure 1 | (a,b) On light microscopy, the renal parenchyma is infiltrated by chronic interstitial inflammatory cells and poorly formed granulomas (stars). Some of these granulomas surrounded small vessels, which rarely showed segmental fibrinoid necrosis (arrows). Glomeruli are normal. (**a**) Jones silver stain, original magnification ×20; (**b**) Masson trichrome stain, original magnification ×40.

The association of vasculitis with *influenza* and *pertussis* vaccines has already been described but without granulomatous pattern.[3] Although causality between the renal lesions and the AstraZeneca vaccine cannot be definitively proven, the timing—and the absence of other causes—makes the link between the 2 plausible.[4]

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Fumarate in membranous nephropathy: more questions than answers

To the editor: A recent metabolomics study of urine in membranous nephropathy (MN) reports significant changes in 14 of 71 metabolites quantified by nuclear magnetic resonance, including 2-fold higher urinary fumarate in phospholipase A2 receptor–associated MN versus healthy controls.[1] This increase in urinary fumarate is attributed to the downregulation in podocytes of fumarate hydrase—the enzyme converting fumarate to malate—followed by a buildup in fumarate levels. However, alternative interpretations are possible. Supporting evidence from patients is limited to decreased fumarate hydrase staining in glomeruli from phospholipase A2 receptor–associated MN. However, net changes in fumarate levels also depend on other reactions producing or consuming this metabolite, not investigated in this study. Fumarate reacts with cysteine residues via Michael addition, forming a covalent adduct, 2-succinocysteine, that can be detected immunohistochemically. Aberrant protein succination provides a robust biomarker for high fumarate levels in fumarate hydrase deficiency.[2] Immunostaining for 2-succinocysteine, which could have probed for high fumarate levels in podocytes from MN patients, was not performed.

Notwithstanding fumarate excretion by podocytes, the urine composition is fine-tuned by tubular reabsorption. The transporter responsible for fumarate uptake from the tubular filtrate is the sodium dicarboxylate cotransporter-1 (NaDC1), expressed in kidneys at the brush border of proximal tubular cells.[3] NaDC1-knockout mice excrete significantly higher amounts of Krebs cycle intermediates in urine, including fumarate (see Figure 2 in the study by Ho *et al.*).[4] Furthermore, tubular NaDC1 is downregulated after renal ischemia reperfusion injury or obstructive nephropathy.[5,6] Excessive amounts of protein in the glomerular filtrate are also known to injure proximal tubular epithelial cells, which may likewise downregulate tubular NaDC1. In conclusion, more studies are needed to distinguish whether the increased urinary fumarate excretion is due to podocyte or tubular dysfunction or both. Presently, it seems premature to conclude that fumarate mediates podocyte injury in phospholipase A2 receptor–associated MN.

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The authors reply: We appreciate the thoughtful letter from Dr. Borza.[1] We agree with the critique that 2-succinocysteine staining would be informative to identify the source of the increased urinary fumarate in patients with phospholipase A2 receptor (PLA2R)–associated membranous nephropathy (MN). We also speculate that this increase might not entirely originate from the podocytes. However, we showed that the fumarate hydratase (FH) expression in the podocytes of patients with PLA2R-associated MN was attenuated compared with that of healthy and disease controls.[2] We also demonstrated that treatment of podocytes *in vitro* with purified IgG from MN patients attenuated FH expression, accompanied by an increase in fumarate levels. These changes were coupled with an increase in podocyte injury markers. Furthermore, FH overexpression ameliorated these alterations, whereas FH knockdown exhibited synergistic effects with IgG from MN patients.[2] In our study, we did not aim to elucidate the origin of increased urinary fumarate. We intended to evaluate the clinical usefulness of urinary fumarate as a predictive biomarker and its role in podocyte injury following PLA2R autoimmunity.