LETTER TO THE EDITOR

WILEY

Tubulointerstitial nephritis and uveitis syndrome post-COVID-19

To the editor:

The angiotensin-converting-enzyme-2 (ACE2) receptor is expressed in many extrapulmonary organs: eyes (conjunctival, corneal, and limbal epithelial cell, retina), nerves, vessels, small intestine enterocytes, kidney proximal tubules, with involvement by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and positive conjunctival swab tests.[1] The co-expression of ACE2 and the serine protease TMPRSS2 is in 6.6% of corneal epithelium and endothelium cells – less than that in lung and kidney tissues.[2] Coronavirus disease 19 (COVID-19)-related uveitis and optic neuritis were recently reported.[3] Furthermore, the inflammation of renal interstitial tissue and uveal tissue characterizes tubulointerstitial nephritis and uveitis (TINU) syndrome. However, the outcome of nephritis and uveitis can be different, making the diagnosis challenging. TINU syndrome usually shows bilateral anterior uveitis and may evolve into a chronic disease, or it recurs years after the first episode.[4] Renal disease shows an acute onset and resolves spontaneously with full recovery or evolves into chronic renal insufficiency.

We describe the case of a 7-year-old girl (stature 121 cm; weight: 23 kg; Tanner stage: PH1, B1), admitted, during the COVID-19 pandemic, for persistent fever and bilateral red eyes, photophobia, eye pain. The nasopharyngeal swab for SARS-CoV-2 was positive in two different swabs. The swab for other respiratory viruses was negative. The anamnestic records excluded previous kidney and ocular diseases. The ophthalmologist diagnosed bilateral, anterior uveitis and prescribed 0.1% dexamethasone eye drops, tapered over a 2-week period until the resolution. She showed nocturia, polyuria, and polydipsia. Fourteen days after the end of steroid treatment and a negative swab, she showed a relapse of uveitis, with a reduction of visual acuity in the right eye (4/10), ipsilateral conjunctival hyperemia, bilateral iris-capsular synechiae, papilledema and macular edema. The optical computerized tomography confirmed the diagnosis. The encephalic computerized axial tomography was negative, and the magnetic resonance showed a bilateral slight distension of the retrobulbar area peri-optic nerve sheath. Cerebrospinal fluid (CSF) analysis showed normal chemical-physical examination and cell count, negative PCR analysis for viruses and microbic agents, concordance between the CSF and serum bands, excluding an intrathecal production of immunoglobulin G (IgG). The human leukocyte antigens (HLA)-B27, -B51, -B57, lymphocyte subpopulation analysis, autoimmune tests, anti-N-methyl-D-aspartate receptor (NMDA), anti-myeline olygodendrocyte glycoprotein (MOG), anti-aquaporin-4 antibodies were negative. Anti-SARS-CoV-2 IgG were significantly increased (8080.7 AU/mL). She showed increased creatinine values, glycosuria, albuminuria, proteinuria, glomerular filtration rate of 60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, according to Schwartz's formula. The diagnosis of tubulointerstitial nephritis was confirmed by the increased serum and urinary levels of tubular enzymes β2-microglobulin (6.4 mg/L; normal 0–0.23 mg/L), α1-microglobulin (31.6 mg/L; normal 0–12 mg/L), α2-macroglobulin (20.4 mg/L; normal 0–9.4 mg/L). She was treated with prednisone ($1\ mg \cdot kg^{-1} \cdot d^{-1}$) for 1 month, a second course of topic 0.1% dexamethasone and mydriatics, with a gradual tapering.

During the follow-up, creatinine and glomerular filtration rate normalized with uveitis remission. Three months after the steroids discontinuation, she showed a relapse of bilateral uveitis, treated with steroids (prednisone: $0.75\ mg \cdot kg^{-1} \cdot d^{-1}$) for one month, with a gradual tapering. Two months later, for a further relapse, she started anti-TNF-α treatment (adalimumab) (20 mg × 14 d), with the complete uveitis remission. The diagnosis of TINU syndrome was suggested by the outcome, characterized by the remission of tubulointerstitial nephritis and the relapsing uveitis, only partially responding to steroids.

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The prevalence of TINU syndrome reported by uveitis centers, is 1.1%–2.3% in children,[4] with differences linked to several factors, including TINU recognition, frequently underdiagnosed. The epidemiological and etiological data do not permit the real definition of genetic, HLA haplotype, epigenetic and environmental factors (infections, drugs) involved in the pathogenesis.[5]

It is essential to exclude systemic diseases that can trigger an overlap of ocular and renal inflammation, including Behçet disease, systemic lupus erythematosus, Sjogren's syndrome, sarcoidosis, tuberculosis, atypical Kawasaki disease, COVID-19, and multisystem inflammatory syndrome in children (MIS-C).[6–11] Ocular symptoms in adults with COVID-19 are polymorphous.[3] Most of patients with MIS-C or with Kawasaki disease, show conjunctivitis, less frequently anterior uveitis or corneal punctate epitheliopathy.[7,10,11] COVID-19-related uveitis underlies multifactorial pathogenetic mechanisms, which may involve virus-induced direct cytopathic effect; eyes thrombotic vasculopathy; the antigen mimicry between virus and self-antigens of the eyes, especially in patients with HLA-B27; and increased cytokine secretion, especially of TNF-α, IL-1, IL-18.[12]

In a recent case series, 66.6% patients with TINU developed renal and ocular involvement simultaneously, most a bilateral anterior uveitis, rarely a bilateral pan uveitis. Treatment with topical and systemic corticosteroids allowed a significant improvement of uveitis, no evolution to chronic kidney disease.[13] A recent review on 592 TINU patients evidenced a females prevalence, with bilateral and anterior uveitis following nephritis. Children showed more uveitis relapses, less acute and chronic kidney disease, with a higher incidence of chronic kidney disease in posterior or pan uveitis.[14]

This case offered a diagnostic dilemma between a tubulointerstitial nephritis with relapsing uveitis secondary to SARS-CoV-2 infection, and TINU syndrome. The clinical course suggested TINU. The increased levels of β2-microglobulin could be secondary to the autoimmune pathogenesis of TINU. The prompt diagnosis and treatment of uveitis allowed to prevent ocular complications and visual impairment. This is one of the few pediatric cases of TINU syndrome, associated with SARS-CoV-2.[15] TINU syndrome has been reported in a few children with a strict contact with SARS-CoV-2 positive patients, or with positive SARS-CoV-2 nucleic acid or IgG. These data support that the pathogenesis of TINU is not secondary to virus-induced direct cytopathic effect but to the autoimmune response after SARS-CoV-2 infection. Autoantibodies are detected after COVID-19 and some patients develop autoimmune diseases. SARS-CoV-2 dysregulates self-tolerance and triggers autoimmune diseases, in part by the cross-reactivity of virus antigens with the host cells.[16] The SARS-CoV-2 spike protein shows a high-affinity superantigen-like sequence motif near the S1/S2 cleavage site, with a high binding affinity with T-cell receptors (TCRs).[17] An intriguing matter for study is whether SARS-CoV-2 induces transient or persistent autoimmunity and whether virus variants have different influences on autoimmunity. Cytokines secretion regulates the immune response, and acts as a trigger of autoimmune diseases secondary to COVID-19.[18] The role of cytokines and autoimmunity explains the response to adalimumab in our patient, allowing the remission.

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CONSENT FOR PUBLICATION

Written informed consent has been obtained from the patient.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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