

TUBULOINTERSTITIAL NEPHRITIS WITH UVEITIS (TINU SYNDROME). A CASE REPORT

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SUMMARY

In this case report, we describe the case of a 50-year-old woman referred by her general practitioner to a pulmonologist in order to investigate persistent fever and elevation of C-reactive protein despite antibiotic treatment following a respiratory infection. The patient was examined extensively, during which rheumatology, gastroenterology, nephrology, ophthalmology, laboratory and imaging tests were performed. Due to a rapid progression of renal insufficiency with active urinary sediment, the patient was referred for a renal biopsy, which confirmed tubulointerstitial nephritis, followed by a diagnosis of bilateral anterior uveitis two months later - genetic testing was also conducted, which confirmed the diagnosis of tubulointerstitial nephritis with uveitis syndrome. Steroid treatment brought about a gradual reduction of proteinuria and a stabilisation of renal function.

Key words: TINU syndrome, tubulointerstitial nephritis, uveitis, mCRP

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INTRODUCTION

Tubulointerstitial nephritis with uveitis syndrome (TINU) is a rare pathology, which refers to intraocular inflammation occurring in combination with tubulointerstitial nephritis (TIN), with an absence of other systemic disease. It is manifested in general flu-like symptoms, a deterioration of renal functions, while among ocular symptoms bilateral uveitis predominates, manifested in the majority of cases following inflammation of the kidneys, though it may also precede this condition or take place concurrently. The pathogenesis has not been entirely clarified; it is assumed that a role is played by antibodies acting against modified C-reactive protein (mCRP), and also by genetic influence. The epithelial cells of the renal tubules and ciliary body share similar functions, and most probably also contain related antigens, which explains the simultaneous affliction of both organs. The majority of patients are adolescents, with a predominance of the female sex. TINU syndrome can be treated very well and has a good prognosis,

corticosteroid treatment is associated with an improvement to complete restoration of renal function.

CASE REPORT

A fifty-year-old female patient was admitted to our department according to schedule in order to examine a case of renal insufficiency. The patient had no family history regarding pathologies of the kidneys or autoimmune disease. In her youth she had been generally healthy, and at the age of 45 years she was diagnosed with psoriasis. She had been taking chronic medication for a period of one year at the time of admittance for arterial hypertension (angiotensin II antagonist, Ca blocker). With regard to her epidemiological history, the patient had suffered from a respiratory disease two weeks previously, her travel history was negative. Due to her persistent febrile condition, accompanied with heavy fatigue, breathlessness after exertion and a dry cough, the patient was treated with a whole range of antibiotics, first of

all prescribed by her general practitioner and then later by a pulmonologist (Amoksiklav, Klacid, Biseptol, Ciplox, Cefazidime), but without any evident effect. From the laboratory examinations it was possible to observe a rise in the level of creatinine to 134 $\mu\text{mol/l}$, a slight rise in CRP (from 29 to 95) without leukocytosis, negative findings were determined for procalcitonin, haemoculture, routine cultivations including serological examinations (Chlamydia, Mycoplasmas, Mantoux, Influenza, Cytomegalovirus, Borrelia, Listeria, Antistreptolysin-O, serum ACE Saccharomyces), suspected anamnestic antibodies against herpes virus 1 and 2, and Epstein-Barr virus. A detailed immunological examination, focusing on autoantibodies demonstrated only the presence of lupus anticoagulants, while negative results were produced in the examinations for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigen antibodies (ENA), rheumatoid factor (RF), anti-nucleosome antibodies (ANUC), anti-Smith antibodies (anti-Sm), anti-topoisomerase antibodies (anti-Scl-70), anti-double-stranded DNA antibodies (anti-dsDNA), anti-ribonuclear protein antibodies (anti-RNP), anti-histidyl-tRNA-synthetase antibodies (anti-Jo.1), anticentromere antibodies (ACA), anti-histone antibodies (AHA), anti-glomerular basement membrane antibodies (anti-GBM), C3, IgA, IgM, IgG and IgE. Of tumour markers, a non-specific elevation of neopterin and beta-2-microglobulin was determined. Multiple imaging examinations were performed, the X-ray image of the paranasal sinuses showed a finding of mucosal hypertrophy, X-ray of the lungs was without manifest infiltration, CT of the lungs and abdomen also without pathology. Transoesophageal echocardiography did not identify vegetation, spirometry demonstrated ventilation to

be within the norm, gastroscopy showed a finding of pan-gastritis, due to which the patient was treated with proton pump inhibitors and prokinetics. Colonoscopy detected a minor polyp of a benign character. Following consultation with a rheumatologist, a PET/CT examination was conducted for the purpose of excluding systemic pathology or malignancy upon positivity of tumour markers, producing an uncharacteristic finding of diffuse increased deposition of fluorodeoxyglucose in the parenchyma of both kidneys. A subsequent CT examination demonstrated an expansion of the cortical part of the parenchyma of the kidneys and an eroded pyramid structure; glomerulonephritis was considered in differential diagnostics. As a secondary finding, indistinct signs of bone marrow activation and persistent filling of the right maxillary sinus were determined. The patient was subsequently referred to our centre in order to complete an ultrasound examination of the kidneys (Fig. 1), when due to rapid progression of renal insufficiency with proteinuria and active urinary sediment (creatinine 222 $\mu\text{mol/l}$, proteinuria 0.48 g/l, erythrocyturia 6/ μl , leukocyturia 45/ μl , squamous epithelium 61/ μl) the patient was indicated for a biopsy of the kidneys. The histological finding confirmed TIN with suspicion of drug-induced/parainfectious aetiology (Fig. 2 – A, B, C, D). An immunofluorescence examination of the biopsy material did not demonstrate deposits of IgA, IgG, IgM, kappa and lambda light chains, C3 or C1q. Due to persistent renal dysfunction (creatinine 252 $\mu\text{mol/l}$) the patient was prescribed a short course of steroids (prednisone 30 mg/day for a period of 14 days), producing a partial effect on the functional parameters of the kidneys (creatinine 193 $\mu\text{mol/l}$). Two months later the patient reported blurred vision, reddening and painful sensation in both eyes. She was

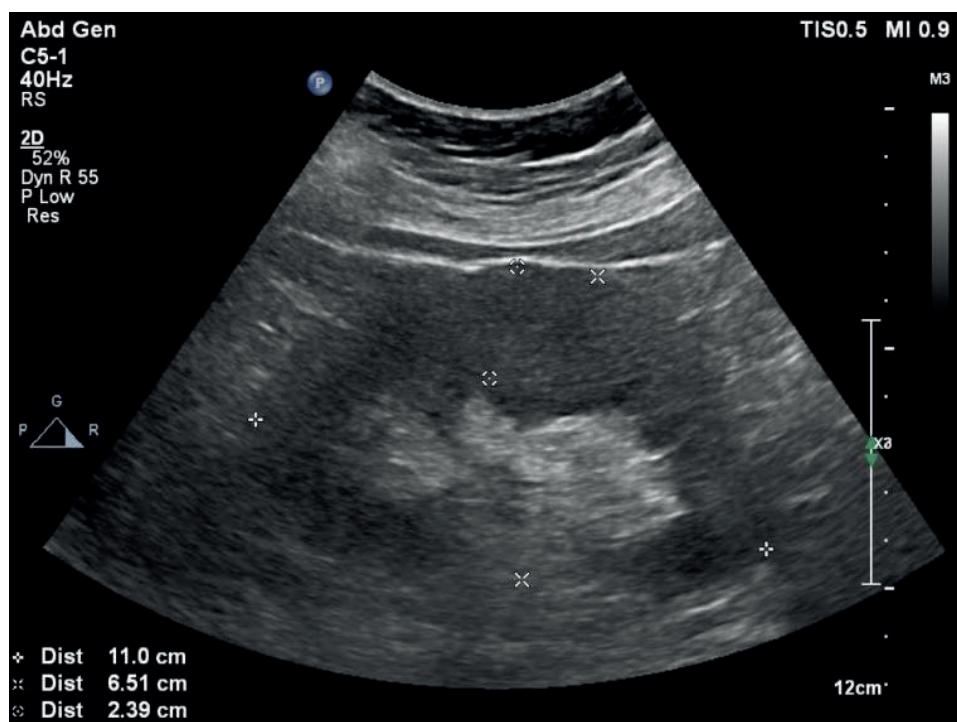


Figure 1. Renal ultrasound - kidneys manifesting borderline nephromegaly, parenchyma 24 mm bilaterally

diagnosed with bilateral anterior uveitis, which was treated locally with eye drops containing dexamethasone. Due to optical edema the patient was examined by a neurologist, the finding on the brain MRI was without pathology. A genetic examination was also conducted, which confirmed a possible association with TINU syndrome (HLA class II genotype DQB1*04*05). Our case study presents a rare syndrome, of which only 592 cases have been registered to date worldwide [1]. In accordance with recent recommendations, the patient treated with corticoids for a period of 6 months, with progressive detracton and a pronounced response of the pathology, achieving remission of the renal manifestations. With regard to ocular complications, bilateral uveitis persists.

DISCUSSION

TINU syndrome afflicts both children and adults. It was first recorded in 1975 (Dobrin et al.), and the most comprehensive overview to date (5/2022) states a total of 592 cases worldwide. The average age of patients is 17 years old, with a predominance of the female sex [1]. The mechanisms of origin are not well known, a genetic influence is presumed (strong association with HLA-DQA1*01, HLA-DQB1*05 and HLA-DQB1*01), as well as co-participation of various environmental triggers, including medications and microbial pathogens. In one case report an association with the Chi-

nese herb Goreisan was also described [2,3]. TINU is considered to be an immune-mediated process in connection with a humoral immunity disorder, and recurrence of TINU in a patient following a kidney transplant has also been recorded [4]. A role may be played in the pathogenesis by mCRP, which is an autoantigen for cells of the uvea and renal tubules. In the case of an altered pH (inflammatory micro-environment) it irreversibly dissociates from CRP. It is considered to be a tissue and cellular form of the acute phase protein. Expression of mCRP can be analysed immuno-histochemically in samples of renal biopsy in patients with TINU syndrome, examination of autoantibodies against mCRP is conducted using the ELISA method, with purified human C-reactive protein. In patients with acute interstitial nephritis, raised levels of antibodies against mCRP may be a predictor of the subsequent development of uveitis [4,5,6].

In addition to uveitis and TIN, TINU syndrome is manifested in systemic findings and general symptoms – fever, fatigue, arthralgia, myalgia, weight loss and loss of appetite. It may also be accompanied by arterial hypertension [7]. Patients with uveitis suffer from headaches, photophobia, reddening of the conjunctiva, swelling of the eyelids and deterioration of visual acuity [8]. Uveitis most often develops in association with affliction of the kidneys (52 %), and is mostly anterior (65 %) and bilateral (88 %). Recurrences of the disease are possible, more frequently in the ocular form, without a relapse of nephritis. Children are prone to more frequent ocular recu-

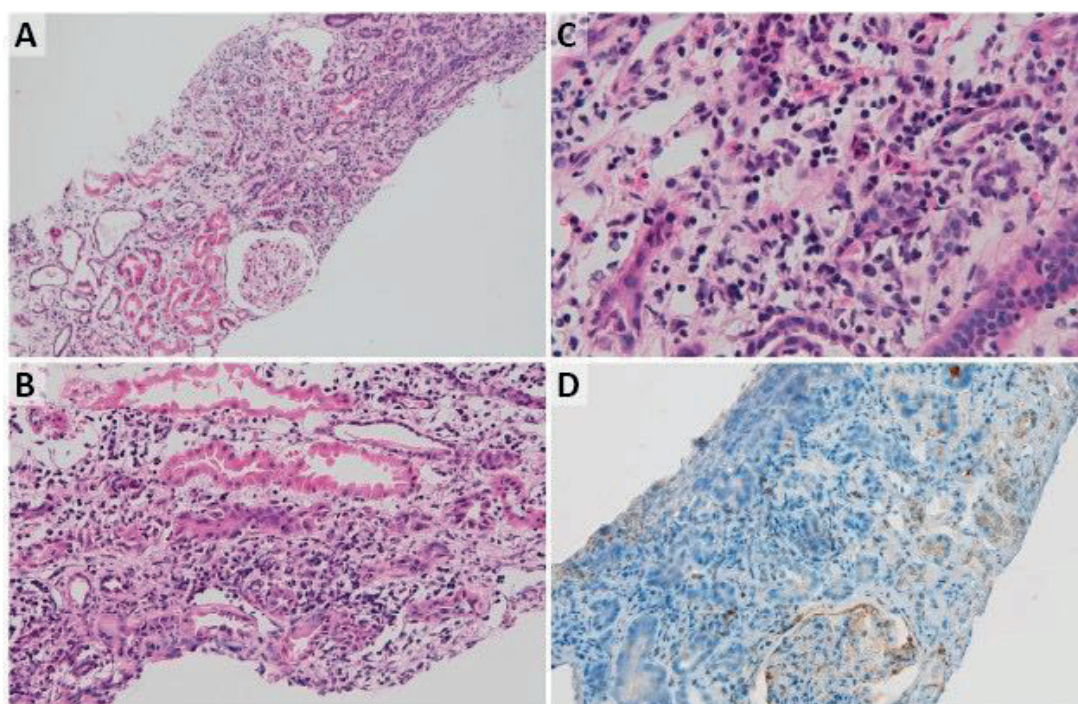


Figure 2. Puncture biopsy of patient's kidney. Histological picture with completely intact glomeruli without sclerotisation or crescents (A, haematoxylin-eosin, magnification 40x), with edema and inflammation of the interstitium and tubules, even leading to disintegration in places (B, haematoxylin-eosin, magnification 200x). The inflammatory infiltrate is predominantly lymphocytes, with focally numerous eosinophilic and neutrophilic granulocytes (C, haematoxylin-eosin, magnification 400x). Only isolated plasma cells were positive for IgG in immunohistochemistry (D, haematoxylin and DAB, magnification 100x)

rences, whereas by contrast they suffer less often than adults from acute renal damage and the development of chronic kidney disease (CKD). More advanced age in adults and the presence of posterior uveitis or panuveitis are associated with an increased risk of the development of CKD [1]. Manifestation of renal damage has characteristics that are typical of acute TIN. Laboratory changes may include leukocyturia, eosinophilia, anaemia, accelerated sedimentation of erythrocytes and rise in CRP. A raised value of beta2 microglobulin in urine may be the first sign of impaired tubular function, in the case of normal tubular function this protein is not present. Tubular affliction also results in glycosuria, phosphaturia and acidification defects [9].

The clinical diagnosis is determined on the basis of concurrent incidence of uveitis with TIN. It is necessary to exclude systemic diseases such as sarcoidosis, Sjögren's syndrome and systemic lupus erythematosus. Bone marrow granulomas may also be present [11]. Sonography may demonstrate pronounced parenchymal edema of the kidneys [2]. The presence of TIN is documented by means of a biopsy of the kidneys, in which the typical histopathological finding is an inflammatory infiltrate with a predominance of lymphocytes in the interstitium, and inflammation causing alteration and even destruction of the tubules. The character of the inflammatory infiltrate differs depending on the aetiology. In the case of a drug-induced reaction, eosinophilic granulocytes may be present to a greater degree. A larger proportion

of plasma cells attests to an autoimmune aetiology, and when in combination with a larger number of neutrophilic granulocytes this attests to a parainfectious aetiology [10]. The standard procedure is an immunohistochemical examination of IgG-positive plasma cells. However, the presence or absence of individual elements of inflammation is non-specific, and as a result the diagnosis and determination of the aetiology must always be the result of a clinical-pathological consensus. The histopathological diagnosis also includes an immunofluorescence analysis of IgA, IgG, IgM, kappa and lambda light chains, C3 and C1q, which serves to exclude the presence of deposits of immunocomplexes or antibodies against basement membranes of the tubules [12].

The first line of treatment for patients with progressive renal insufficiency is usually corticoids (prednisone) in a dose of 1 mg/kg per day for a period of three to six months, with progressive detracting, in which the length of treatment depends on the response. In the case of recurrence, the choice of second line treatment is further immunosuppressants such as methotrexate, mycophenolate, cyclosporin, azathioprine and cyclophosphamide. The optimum treatment for patients with uveitis includes timely referral and the guidance of the therapy by an ophthalmologist [1,9].

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