http://dx.doi.org/10.35630/2199-885X/2022/12/1.8

ACUTE TUBULOINTERSTITIAL NEPHRITIS WITH UNDERLYING UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE. A CLINICAL CASE STUDY

Received 19 November 2021;
Received in revised form 14 December 2021;
Accepted 15 December 2021

Darya Savitskaya ✉, ***Liubov Popova***, ***Anton Popov***, ***Olga Poselyugina***

Tver State Medical University, Tver, Russia

✉ *daryasavi98@yandex.ru*

ABSTRACT — Acute tubulointerstitial nephritis (ATIN) is an acute kidney disease that can develop under the influence of various exogenous and endogenous factors and is manifested by inflammatory changes in the tubulointerstitial tissue of the kidneys, often accompanied by the development of acute renal kidney damage (AKI). Approximately 3–19% of all AKI cases are due to ATIN nephrobiopsy data, which indicates a difficult non-invasive diagnosis of this disease. Complaints of patients with ATIN are few and are associated with manifestations of acute renal damage: a decrease in urine volume, an increase in blood pressure (BP). Important in the diagnosis of ATIN is urinary syndrome, manifested by proteinuria less than 1 gram per day, erythrocyturia, leukocyturia, including eosinophiluria. In patients with suspected ATIN, a full physical examination is performed, attention is drawn to the appearance of pain on palpation of the kidneys, blood pressure is measured, diuresis, and the presence of edema are assessed. In laboratory diagnostics, it is necessary to investigate the level of creatinine, blood urea, general urine analysis, with instrumental — ultrasound examination of the kidneys, if indicated, a kidney biopsy is performed.
Treatment is aimed at immediate cessation of the effect of the etiological factor, maintenance of water-electrolyte balance and correction of violations of acid-base balance, blood pressure. In this regard, it is possible to use crystalloid solutions, loop diuretics (furosemide, torasemide), antihypertensive drugs in accordance with the general principles of management of patients with AKI, immunosuppressive therapy for ATIN immune genesis, with ATIN drug genesis — glucocorticoids. In the presence of appropriate indications, renal replacement therapy is performed. The prognosis of the disease often depends on timely diagnosis and appropriate treatment.
The paper presents the clinical case of a female patient affected with acute tubulointerstitial nephritis.

KEYWORDS — acute tubulointerstitial nephritis, diagnosis, treatment, undifferentiated connective tissue disease.

INTRODUCTION

Acute tubulointerstitial nephritis (ATIN) is an acute kidney disease that occurs as a result of exposure to various exogenous and endogenous factors, manifests in the form inflammatory processes in the tubulointerstitial tissue and compromises the functioning of the organ [1]. Renal biopsy detects ATIN in 2.3% to 9% of all cases, whereas its chronic counterpart has a 1.8% to 2.5% occurrence rate. Given that no biopsy is taken in most clinical cases, we could assume medical professionals actually face this disease far more frequently in their work [2].

ATIN is mainly caused by bacterial or viral infections, medications, various metabolic disorders, systemic diseases, etc. [3]. Non-steroidal anti-inflammatory drugs (NSAIDs) cause 45% to 70% of all ATIN cases, with another 30% to 45% attributable to antibiotics [4].

Immune system response plays the key role in the mechanism of this disease. Direct exposure of tubule membranes and renal interstitium to the etiological factor triggers the production of antigenic complexes [5]. Immune complexes are produced in response and become fixed in the interstitium and in the tubule wall, which causes an inflammatory response and interstitial edema. This further causes renal tissue ischemia and epithelial dystrophy of the tubules and vessels. Clinical manifestations of the disease occur [6].

The core manifestations are headache, lumbar pain, arthralgia, rash, fever, drowsiness, adynamia, and nausea. Acute renal failure is common, manifesting as dysuric disorders, mainly as polyuria and nocturia; oliguria and anuria may occur as well, a sign of severe organ damage [7].

When diagnosing the disease, the focus is made on the intake of nephrotoxic substances in the history; a matching clinical picture; urinary syndrome signs in general urine test, which manifests as moderate proteinuria (< 1 g/day), aseptic leukocyturia, hematuria, cylindruria, and reduced relative density of the urine [8]. Blood biochemistry reveals increased creatinine, urea, and electrolyte disorders. Clinical blood tests show eosinophilia, leukocytosis, and increase ESR. Renal ultrasound detects enlarged kidneys with a more

echogenic parenchyma. In case the diagnosis is difficult, morphological study of the renal tissue is carried out [9].

Treatment seeks to address the cause, maintain water-electrolyte balance, and adjust the acid-base balance. Glucocorticosteroidscan be used especially effectively when treating ATIN associated with systemic diseases [10]. Renal replacement therapy is used if there are indications. Timely diagnosis and appropriate treatment affect the prognosis.

The goal hereof is to present a clinical case of acute tubulointerstitial nephritis with underlying undifferentiated connective tissue disease.

MATERIALS AND METHODS

The paper overviews state-of-the-art approaches to the diagnosis and treatment of ATIN as discussed in literature; it also analyzes the clinical case of a patient.

RESULTS

Patient G, 22, admitted to the Nephrology Unit of a public hospital in Tver Oblast, the Regional Clinical Hospital in Tver, with complaints of moderate asthenia, frequent headaches, pain in the ankle joints and calf muscles at rest, aggravated by exertion.

Medical history revealed that in June 2020, the patient had survived a laboratory-confirmed coronavirus infection complicated by moderate bilateral polysegmental pneumonia. The patient underwent inpatient treatment at a specialized clinic; her therapy consisted of 1000 mg of azithromycin per day for 7 days, 2.0 g of ceftriaxone per day for 7 days, 5 mg of apixaban per day for 2 weeks, and peroral paracetamol. Discharged from the hospital two weeks later, as X-ray confirmed full recovery from pneumonia.

For several months, she continued to exhibit moderate asthenia and subfebrile temperatures; pain spread across small joints in feet and calf muscles; the patient also reported all-body muscle tremor. For that reason, the patient visited a rheumatologist. The doctor initiated an examination to find a rheumatological disease. The patient was screened for markers of systemic lupus erythematosus, vasculites, rheumatoid arthritis, and other connective tissue diseases that could affect joints and muscles alike. However, all the laboratory markers only showed an increase in the antinuclear factor to 1:160. Thus, undifferentiated connective tissue disease was suspected. For primary therapy, the patient was prescribed 4 mg of methylprednisolone per day (she continues this treatment as of today), which had a positive effect as it alleviated joint pain and eliminated muscle tremor. Therapeutic plasmapheresis was recommended as well. To that end, the patient was admitted to an inpatient clinic.

Anamnesis vitæ showed the patient was a schoolteacher, had no concomitant chronic diseases, bad habits, or allergies to medicines. No burdened family history, no prior surgeries.

General condition was satisfactory as of the time of admission. Normal physique. Normally colored skin of normal humidity, the exposed mucous membranes pink. Peripheral lymph nodes not enlarged, not adhering to the adjacent tissue, palpation painless. Thyroid not enlarged, no peripheral edemas. No visible musculoskeletal pathologies. 18 respiratory movements per minute. Clear pulmonary sound in percussive testing above the lungs. Rattling-free vesicular breathing. The boundaries of relative cardiac dullness unchanged. 80 heartbeats per minute, satisfactory volume, rhythmic. Blood pressure of 130/80 mmHg. Rhythmic and sonorous heat tones. Soft abdomen, no palpation pain in any compartment. Peritoneal irritation symptoms negative. Liver and spleen not enlarged. Regular and formed stool. Kidneys are not palpable. 1.6 l diuresis. Hand joints not swollen, painless, fully motile. Hand strength sufficient. Transverse compression symptom negative. Muscle palpation painless, no muscle asthenia.

The patient went on to undergo inpatient examination. Clinical blood test results were as follows: leukocytes – $9.48 \cdot 10^9$/l (mild leukocytosis),erythrocytes — $4.04 \cdot 10^{12}$/l, hemoglobin — 122 g/l, erythrocyte sedimentation rate (Westergren) — 8 mm/h, leukocyte formula: 72.2% neutrophils, 22.4% lymphocytes, 4.3% monocytes, 0.4% eosinophils, 0.4% basophils, 0.3% immature granulocytes, total leukocytes: 100.0%; neutrophils — $6.84 \cdot 10^9$/l, lymphocytes — $2.12 \cdot 10^9$/l; monocytes — $0.41 \cdot 10^9$/ l, eosinophils — $0.04 \cdot 10^9$/l, basophils — $0.04 \cdot 10^9$/l; immature granulocytes — $0.03 \cdot 10^9$/l.

General urine test showed a low specific weight of 1004 g/cm^3, some turbidity, a light-yellow color, acidic reaction, 2–5 of squamous epithelium in the field of view, 0–1–2 leukocytes in the field of view.

Bacteriological urine testing for flora and antibiotic sensitivity (by seeding): negative.

Blood biochemistry returned normal readings: potassium — 4.00 mmol/l, sodium — 141.0 mmol/l, venous glucose — 5 mmol/l, total bilirubin — 12.0 μM, direct bilirubin — 1.0 μM, aspartate aminotransferase — 18.4 U/l, alanine aminotransferase — 25.0 U/l, total cholesterol — 4.77 mM, high-density lipoproteins — 1.39 mM, low-density lipoproteins — 2.78 mM, triglycerides — 0.67 mM, protein — 66 g/l, urea — 4.58 mM, creatinine — 74.4 μM, glomerular filtration rate of 99.55 ml/min, uric acid — 299 μM, albumin — 43 g/l, phosphorus — 2.27 mmol/l. The kidneys retained their nitrogen excretion function.

Zimnitsky urine test showed concentration failure (hyposthenuria, specific urine weight fluctuating between 1004 and 1009 g/cm^3), polyuria (3.6 l of daily diuresis), and nocturia.

Electrocardiography registered a sinus rhythm at 78 bpm, vertical electrical axis, and signs of sinistroventricular overload.

Kidney ultrasound showed the right kidney to be lowered, as its upper pole was projected 50–55 mm below the diaphragm in lateral recumbent position on the right side. Noteworthy is the increased kidney mobility when changing the body position. Kidney sized 127 mm in length, 43 mm in width. Kidney boundaries clear, with a smooth outline. Traceable 14 to 17 mm thick parenchyma of increased echogenicity. No renal cavity dilations, no concrements detected. Satisfactory acoustic access to the left kidney. Left kidney shape unaltered, lowered slightly less than the contralateral kidney. Kidney sized 128 mm in length, 46 mm in width. Kidney boundaries clear, with a smooth outline. Parenchyma of increased echogenicity and finely granular echostructure, 13 to 16 mm thick. Left-kidney cavities not dilated. No concrements found in the projection of the renal sinus.

Ankle joint X-ray revealed no pathologies. Due to the pandemic, examination by a rheumatologist in the inpatient setting was not an option. The patient was advised to visit the rheumatologist at an outpatient facility after discharge.

With this data in mind, the patient was diagnosed with: Mild tubulointerstitial nephritis as the primary diagnosis. Undifferentiated connective tissue as the secondary diagnosis. Dextral first-degree nephroptosis.

Based on the diagnosis, the patient started a therapy: four sessions of therapeutic plasmapheresis, 4 mg ofmethylprednisolone daily (oral intake), 20 mg of omeprazole twice daily 30 minutes before meals (oral intake).

Treatment continued for 10 days and had a positive effect on the patient: general asthenia decreased, headaches arrested, ankle-joint and calf-muscle pain eliminated. General urine tests showed relative density to have increased to 1018 g/cm^3, a sign of normalized concentration ability of the kidneys. The patient was discharged and advised to continue to take Canephron, an herbal medication, two pills thrice daily for a month (oral intake) and to be followed by outpatient nephrologist and rheumatologist.

DISCUSSION

In this clinical case, the patient likely survived ATIN caused by undifferentiated systemic connective tissue disease. This diagnosis was reinforced by the acute concentration disorder that the patient had on top of undifferentiated connective tissue disease without bacteriuria. Interestingly, the patient had no pronounced clinical manifestations of nephritis, and the nitrogen excretion function was preserved, i.e., creatinine and urea in blood were within the normal range. Besides, the patient had lower specific urine weight (hyposthenuria, nocturia), which is characteristic of ATIN, but no proteinuria, no altered urinary sediment in urine tests. We can assume that methylprednisolone intake as prescribed due to undifferentiated joint disease contributed to the absence of typical clinical signs of ATIN; moreover, the same medication is effective in pathogenetic ATIN treatment.

We cannot be certain, however, whether coronavirus and two courses of antibiotics that the patient had to take due to her bilateral pneumonia contributed to the damage of the renal tubulointerstitial system. Undoubtedly, the patient has to be thoroughly examined by a rheumatologist; dynamic follow-up and monitoring of test results are now crucial, as they might help differentiate the connective tissue disease.

In general, timely diagnosis and early treatment helped recover from ATIN. This clinical case is an example of atypical ATIN progression, and it shows how a concomitant pathology, and its treatment could affect the clinical signs of the kidney disease.

We assume this report to be of use for doctors in any field, especially for those in primary care.

REFERENCES

1. KDIGO, AKI. (2012). Work Group: KDIGO clinical practice guideline for acute kidney injury.Kidney IntSuppl 2.1, 1–200.
2. **Batyushin, M.M., et al.** (eds.). (2021). Clinical guidelines. Tubulointestitsial kidney diseases.Moscow. Retrieved from: https://rusnephrology.org/wp-content/uploads/2021/02/tubulointerstitial.pdf.
3. **Lewington, A&Kanagasundaram, S.** (2011). Renal association clinical practice guidelines on acute kidney injury.Nephron Clinical Practice, 118, Suppl. 1, c349–c390.
4. **Dennis, G. Moledina&Perazella,M.A.** (2018). Treatment of Drug-Induced Acute Tubulointerstitial Nephritis.Clinical Journal of the American Society of Nephrol, 13(12), 1785–1787. DOI: https://doi.org/10.2215/CJN.12001018
5. **Shilov, Ye.M., et al. (eds.).** (2016). Nephrology. Clinical guidelines.Moscow: GEOTAR-Media. Retrieved from: http://www.rosmedlib.ru/book/ISBN9785970437148.html.
6. **Li, C., Su, T., Chu, R., Li, X., &Li, Y.** (2014). Tubulointerstitial Nephritis with Uveitis in Chinese Adults.Clinical Journal of the American Society of Nephrol, 9(1), 21–28. DOI: https://doi.org/10.2215/CJN.02540313

7. **Joyce, E., Glasner, P., Ranganathan, S., &Swiatecka-Urban, A.** (2017). Tubulointerstitial nephritis: diagnosis, treatment, and monitoring. PediatrNephrol., 32(4), 577–587. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5099107/.

8. **Colvin MD,R.B.& Chang MD, A.** (2019). Diagnostic Pathology: Kidney Diseases, 3rd Edition. Philadelphia, Elsevier Publ., pp. c240–c280.

9. **Mukhin, N.A., et al. (eds.).** (2016). Nephrology: National Guidelines.Moscow: GEOTAR-Media.

10. **Rangan, G.K., Wang, Y., Tay, Y.C., &Harris, D.C.** (1999). Inhibition of nuclear factor-kappaB activation reduces cortical tubulointerstitial injury in proteinuric rats. Kidney Int., 56(1), 118–34. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/10411685/.