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CASE REPORT

Improvement in renal function after empirical steroid therapy in NSAID-induced acute kidney injury

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Abstract

We report a case of an 81-year-old woman, who developed acute kidney injury (AKI) during treatment of gout with naproxen. The patient's other comorbidities were chronic kidney disease grade G3b, chronic heart failure with permanent atrial fibrillation, arterial hypertension, osteoarthritis and osteoporosis. After excluding other causes of AKI, a presumptive diagnosis of NSAID-induced acute interstitial nephritis was established. Because of multiple comorbidities and anticoagulation, renal biopsy was not attempted. Since we observed no improvement after naproxen discontinuation, steroid-pulse therapy was initiated, with subsequent oral steroid follow-up. As a result, after several days we achieved improvement in renal function, with complete recovery after couple of months. In conclusion, we suggest that aggressive steroid therapy be considered for patients with presumptive diagnosis of NSAID-induced interstitial nephritis, especially when comorbidities and general state preclude invasive diagnostic measures.

Keywords: Interstitial nephritis, acute kidney injury, NSAID toxicity

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Introduction

Acute interstitial nephritis (AIN) is a common, but underdiagnosed cause of acute kidney injury (AKI), accounting for about 15-20% of all cases [1]. AIN can be hypersensitivity-related (most common), infective, secondary to connective tissue disease (CTD) or idiopathic [2-4]. The majority of AIN cases are drug-induced, of which non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics are the main culprits [1,5,6]. Patients with AIN may present with oliguria, maculopapular rash, hematuria, fever, arthralgia, peripheral edema, hypertension and costovertebral angle tenderness; laboratory studies often reveal proteinuria, erythrocyturia, eosinophilia, and abnormal renal function tests (RFTs). There is no single specific test for AIN and definitive diagnosis can only be made by renal biopsy [1,6,7]. As a result of unspecific nature of symptoms, ambiguous laboratory studies and lack of simple, safe, specific and available diagnostic measures, AIN can be easily overlooked as a cause of AKI [1]. Treatment modalities are mainly supportive in nature, with discontinuation of an offending drug as the most important measure; if renal dysfunction persists, initiation of steroids can be considered, [1,6,7] even though there is limited evidence on the effect of such a therapy [9]. Moreover, it is often stated that before initiating steroid therapy, renal biopsy should be obtained, despite its invasive nature and unfavorable risk profile (especially for patients with multiple comorbidities) [1,6,10]. AIN is usually expected to resolve and complete recovery of renal function is often observed, although some cases lead to progressive renal loss with subsequent end-stage renal failure [6,7].

Case presentation

An 81-year-old female presented to ED with weakness, edema and nycturia of five days' duration, which appeared six days after treatment with naproxen sodium (550 mg twice daily) for gouty arthritis of right first metatarsophalangeal joint. The patient's other medical history was notable for chronic kidney disease G3b (serum creatinine 1.4 mg/dl, eGFR 37.2 ml/min - on a stable level for the last 8 years; the earlier course of renal function was unknown due to lack of medical record from that time), chronic heart failure with preserved ejection fraction (HFpEF) with permanent atrial fibrillation, arterial hypertension, osteoporosis, osteoarthritis, mild obesity and breast cancer (successfully treated with mastectomy and radiotherapy 30 years ago). Except naproxen, her medication included: acenocoumarol 0.5 mg qd, torasemide 5 mg qd, metoprolol succinate 25 mg qd and lercanidipine 10 mg qd.

Upon admission the patient was afebrile, alert, fully oriented, without signs of distress. Her vital signs were normal (BP 130/90 mmHg, HR 80/min, SaO2 98%, normal capillary-refill time), physical examination was remarkable only for bilateral moderate lower leg pitting edema. Auscultation revealed normal breath sounds and normal heart sounds, there were no signs of arthritis, costovertebral angle tenderness was absent and except post-mastectomy right-sided scar, no rash was noticed.

Investigations

The patient's basic laboratory tests were significant for high RFTs (serum creatinine concentration – 3.0 mg/dl, urea concentration 176.8 mg/dl), moderate hyperkalemia (6.1 mmol/l), elevated ESR (65 mm/h) with near-normal CRP concentration (8.46 mg/l) and hyperuricemia (7.6 mg/dl). LFTs, other electrolyte concentrations (including sodium, calcium, chloride, bicarbonate and inorganic phosphorus), ABG and glucose were within normal limits. Blood morphology showed mild eosinophilia (0.52 G/l) and coagulation studies showed subtherapeutic INR of 1.41. ECG was performed, which revealed atrial fibrillation with ventricular response of 80/min, without signs of ischemia and without signs specific for hyperkalemia, including normal T waves. Requested urinalysis demonstrated moderate proteinuria (129.0 mg/dl), mild leukocyturia (10-20/hpf) and moderate erythrocyturia (60-100/hpf), with dysmorphic erythrocytes predominant. The laboratory work-up is presented in Table 1 and Table 2.

To precisely assess the urine output, Foley catheter was temporarily inserted. This revealed oliguria of 30 ml/h (0.32 ml/kg/h). Abdominal ultrasound was performed, which showed normal-sized kidneys with reduced corticomedullary differentiation without urine stasis, with few renal cysts. No other pathologies were noticed.

Differential Diagnosis

The clinical picture was consistent with diagnosis of acute kidney injury (AKI). Serum creatinine was 2.1 times baseline and moderate oliguria was present, which fulfilled 2012 KDIGO criteria of stage 2 acute kidney injury [11]. In order to find the cause of AKI, a list of possible (for this particular patient) differential diagnoses was made. This included prerenal causes of decompensated heart failure and intrinsic causes of urinary tract infection (UTI), acute glomerulonephritis and drug-induced interstitial nephritis. Postrenal causes of AKI were ruled out due to lack of urine stasis under ultrasound examination. The patient did not complain about worsening dyspnea. Besides, her ABG was normal, and no rales were noticed during physical examination. This made heart failure decompensation as a cause of AKI unlikely. Similarly, no signs of UTI (*e.g.*, dysuria, frequent urination, fever) were present. However, to exclude infection in face of leukocyturia and elevated inflammation parameters, urine cultures were obtained, which proved negative.

Acute glomerulonephritis and acute interstitial nephritis are other possible causes of AKI in this patient. To differentiate between them, 24h urine was collected, and daily proteinuria was assessed, which turned out to be 0.51 g/d. Such a mild proteinuria, together with blood eosinophilia and naproxen use (which can provoke allergic nephritis), support acute tubulointerstitial nephritis as a plausible cause of AKI in our patient. On the contrary, normal blood pressure, lack of severe proteinuria and no obvious, identifiable cause decreased the likelihood of acute glomerulonephritis. In order to make an unequivocal diagnosis, renal biopsy was considered. However, due to anticoagulation therapy, renal cysts, chronic heart failure, and chronic kidney disease, renal biopsy would have been associated with high risk

Table 1. Results of laboratory work-up – peripheral blood

Test	Result	Test	Result
WBC	10.52 G/l	**Serum Creatinine**	3.0 mg/dl
Hb Concentration	12.3 g/dl	**Serum Urea**	176.8 mg/dl
PMNs	6.13 G/l	**Serum Potassium**	6.1 mmol/l
Eosinophiles	0.52 G/l	**Serum Sodium**	137 mmol/l
Basophiles	0,11 G/l	**Serum Chloride**	102 mmol/l
Lymphocytes	3.23 G/l	**Serum Phosphorus**	3.7 mg/dl
Monocytes	0,53 G/l	**Serum Calcium**	8.6 mg/dl
CRP	8.46 mg/l	**Arterial pH**	7.36
ESR	65 mm/h	**Arterial Bicarbonate**	22 mmol/l
ALT	32 U/l	**Arterial pO_2**	91 mmHg
AST	27 U/l	**Arterial pCO_2**	39 mmHg
Serum Bilirubine	1.1 mg/dl	**Serum Uric Acid**	7.6 mg/dl
INR	1.41	**Serum Glucose**	95 mg/dl
Serum Albumin	3.7 g/dl	**Serum Protein**	6.4 g/dl

Table 2. Results of laboratory work-up - urinalysis (includes daily proteinuria)

Test	Result
pH	7.5
Specific Gravity	1.015 g/ml
Protein Concentration	129.9 mg/dl
Proteinuria	0.51 g/d
Glucose	Absent
Leukocytes	10-20 /hpf
Erythrocytes	60-100 /hpf

of potentially serious complications, including hemorrhage and renal failure exacerbation. Therefore, no renal biopsy was performed and presumptive diagnosis of NSAID-induced acute tubulointerstitial nephritis was established.

Other, less common, but theoretically possible diseases that were considered in this patient, included TINU (tubulointerstitial nephritis with uveitis), connective tissue disease-related renal failure (*e.g.*, lupus nephritis), sarcoidosis and amyloidosis. The patient did not have any symptoms regarding eye and vision (including photophobia and ocular pain), and during physical examination no signs, such as red eye or vision loss were present; therefore, the patient was not consulted with an ophthalmologist right away, but it was kept in mind that ocular problems might appear in the future. Similarly, no signs or symptoms indicating connective tissue disease (CTD) or sarcoidosis were present; isolated renal sarcoidosis is very rare (and diagnosis requires renal biopsy), while diagnosis of CTD generally requires other symptomatology than isolated renal disease. However, this is not the case with lupus nephritis, therefore, serum antinuclear antibodies test was taken, which proved negative (the ANA titer was below 1:80). As far as amyloidosis is concerned, serum protein electrophoresis with immunofixation was done and concentration of serum free light chains with kappa to lambda ratio was assessed. Both tests did not give evidence for monoclonal gammopathy, therefore, taking into consideration no chronic inflammatory condition and the clinical picture, amyloidosis was provisionally ruled out.

Treatment

Upon admission, naproxen was discontinued, and furosemide 40 mg/d intravenously was initiated in order to treat hypervolemia and hyperkalemia. Because of no signs of pulmonary edema, only moderate hyperkalemia without any corresponding ECG changes and no signs of encephalopathy, the patient was not a candidate for renal replacement therapy (*e.g.*, hemodialysis or hemofiltration) and a conservative approach was chosen. Pending urine culture and daily proteinuria results, renal function, urine output and serum electrolytes were monitored. After

Table 3. Serum creatinine [mg/dl] on each day of treatment. Naproxen was discontinued upon admission (day 0) and steroid therapy began on day 4

Day	0	2	3	4	5	6	7	8	9	10
Serum Creatinine [mg/dl]	3.0	2.4	2.4	2.4	2.5	2.9	2.7	2.2	2.1	1.7

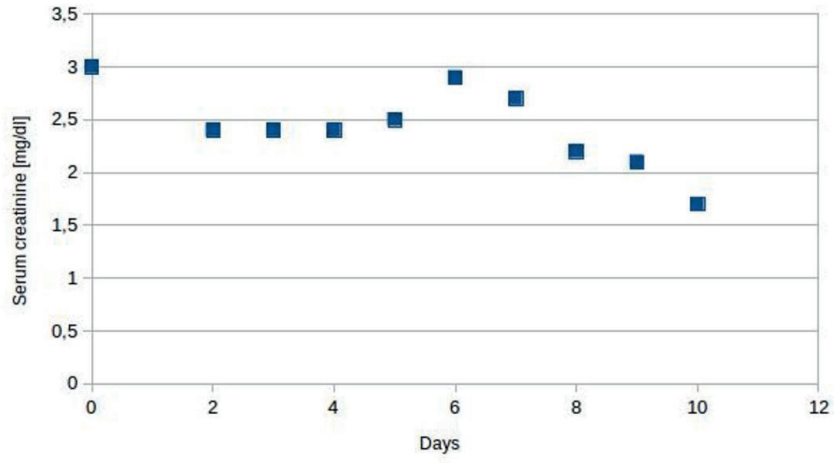

Figure 1. Serum creatinine [mg/dl] on each day of treatment presented on the graph. The baseline level of patient's renal function was 1.4 mg/dl. Naproxen was discontinued upon admission (day 0) and steroid therapy began on day 4

three days, no edema was present, oliguria was absent and serum potassium level was 4.6 mmol/l. Some improvement in renal function was noted, with serum creatinine being 2.4 mg/dl after two days and remaining stable from then on. Because of lack of further improvement, taking into consideration: 1) negative prognostic factors in this patient, including age and baseline diminished renal function, 2) benefits of early initiation of immunomodulatory therapy as opposed to delay in treatment [2], 3) risk of progression to end-stage kidney disease, after thorough discussion of pros and cons with the patient and obtaining informed consent, it was decided to initiate systemic steroid therapy on day fourth. This began with 0.5g of methylprednisolone qd intravenously for three days and was continued with prednisone 40 mg bid onwards, as in the prevailing Polish national guidelines [28]. On day fifth transient serum creatinine increase was noted (2.9 mg/dl) and then, gradual renal function improvement was observed. Serum creatinine concentrations in time are presented in Table 3 and Figure 1.

During systemic steroid therapy blood pressure, glucose levels and serum electrolyte concentrations were monitored. Glucose profile showed normal glucose levels with no signs of steroid-induced diabetes or pre-diabetes, while blood pressures were below 140/90 mmHg without any additional medication. However, serum potassium concentration decreased to 4.6 mmol/l after steroid therapy initiation, requiring oral supplementation of 20 mEq/day to be maintained at this level. Serum sodium concentrations remained within normal limits.

Apart from treatment of AKI, the patient's anticoagulation therapy needed to be revised. This was done with daily INR measurements, readjusting acenocoumarol doses accordingly. Furthermore, newly diagnosed hyperuricemia demanded appropriate management, because of its detrimental effect on patient's cardiovascular disease [12] as well as unfavorable influence on renal function [13]. Therefore, patient's diet was modified, allopurinol 100 mg qd was initiated and ambulatory serum uric acid measurement in 3 weeks recommended. Since acute kidney injury did not resolve rapidly enough, renin-angiotensin-aldosterone system (RAAS) blockade (*e.g.*, oral ACE inhibitor) was not administered. Such treatment was postponed after adequate renal function stabilization, despite its positive influence on chronic kidney disease (and patient's chronic heart failure), due to its potentially deleterious impact on AKI [14].

To prevent steroid-induced osteoporosis, calcium carbonate 500mg bid with cholecalciferol 5μg bid was started. Despite better efficacy of bisphosphonate in preventing steroid-induced osteoporosis [15], bisphosphonate potential nephrotoxicity precludes its use in the setting of AKI [16]. After renal function improvement, repeated urinalysis, blood morphology and inflammatory markers were obtained. These showed reduction of proteinuria, erythrocyturia and leukocyturia (55.2 mg/dl, 2-5/hpf and 1-2/hpf respectively), resolution of eosinophilia (to undetectable levels on automated analyzer) and restoration of CRP concentration to normal levels (5.48 mg/l; it was still too early to expect ESR decrease).

Outcome and Follow-up

On day 10th, the patient was discharged. Following medications were prescribed: prednisone 40 mg in the morning and 20 mg in the afternoon, potassium chloride 10 mEq bid, acenocoumarol 1 mg qd, metoprolol succinate 25 mg qd, lercanidipine 10 mg qd, torasemide 5 mg qd, esomeprazole 20 mg qd (gastric ulcer prevention), allopurinol 100 mg qd and calcium carbonate 500 mg bid with cholecalciferol 5 μg bid (because of relatively short time from AKI it was decided to postpone potential introduction of alfacalcidol after full assessment of Ca-P homeostasis (including iPTH and 25-OH-D3 concentration measurement) under conditions of stable recovery). The patient was advised to re-check serum creatinine, sodium and potassium levels in two weeks.

The patient appeared to her Primary Care Provider three weeks after discharge and serum creatinine, sodium and potassium were obtained. These showed serum creatinine 1.6 mg/dl, sodium 144 mmol/l and potassium 5.6 mmol/l. Improvement in renal function allowed further prednisone dose reduction, while potassium

supplementation was terminated due to mild hyperkalemia. In two months, serum creatinine was 1.4 mg/dl and steroid therapy was finished. RFTs, sodium and potassium levels remained stable after the next two months.

Discussion

Acute interstitial nephritis accounts for 15-20% of all cases of AKI and the majority of cases are caused by medication exposure [1,6,10]. Drug discontinuation is the mainstay of treatment [1,6,16-19,21] and if renal function fails to improve, systemic steroid administration should be considered [6,19-21]. However, no randomized controlled trials assessing steroids efficacy are available, [6,16,21] official evidence-based guidelines are lacking, and published studies give contradictory results, some in favor of steroid treatment [16,17] and others not supporting its use [14,20]. Similarly, as far as steroid dosing regimen is considered, generally two strategies are proposed, and there is no sound evidence that any of these is superior to the other: 1) prednisone 1 mg/kg/d for 4-6 weeks with dose tapering [17] or 2) methylprednisolone 0.5 g/d for 3 days and prednisone 1 mg/kg/d thereafter with dose tapering [28] (in the described case, second strategy was chosen because of prevailing Polish national guidelines [28] and experience). Therefore, it is generally thought that in the setting of suspected AIN not resolving after drug discontinuation, renal biopsy should be obtained [22,23]. This will document presence of AIN, exclude other causes of AKI (treated with medications other than steroids) and help to avoid side effects of unnecessarily-initiated steroid-based therapy [23]. Anyway, renal biopsy is an invasive procedure, which carry a risk of bleeding, infection and renal failure progression, complications being more common in the elderly [24,25]. Since end-stage kidney disease is related to profound worsening of life [26], a question arises what is the best approach to an older patient with likely AIN-caused AKI not satisfactorily improving after suspected drug discontinuation, provided that chronic diseases the patient suffers from, increase the risk of renal biopsy. Making a proper decision in such a scenario requires taking carefully into consideration all the known factors, pros and cons, and keeping the patient well-informed so that they could consciously agree and cooperate with the proposed or initiated treatment. In face of lacking randomized controlled trials and evidence-based guidelines, we tend to advocate for early consideration of steroid-based therapy in such situations, although we know that it cannot be clearly concluded from the case that it was the initiated steroid treatment that caused the renal function return to the baseline (for example, now it cannot be known if renal function would have improved if we had waited a bit longer after drug cessation, especially considering the reported refractoriness of NSAID-induced AIN to steroids). However, what the patient can gain is improvement of renal function (decreasing the likelihood of ESKD and related complications), even if the renal disease we treat turns out to be different than AIN, *e.g.*, acute glomerulonephritis (steroid-based therapy is frequently initiated in various acute diseases of a kidney [6]). Moreover, side effects of steroids are numerous [23], but many of them resolve after drug discontinuation; it should be reminded that in the setting of possible AIN they are used for a short time (4-8 weeks) [8,17]. At last, providing maximal comfort with minimally invasive measures, which impose the smallest possible treatment burden, is an important issue when dealing with multimorbidity of the elderly [27].

Learning Points

Acute interstitial nephritis is a common, often overlooked cause of acute kidney injury, mainly induced by allergic reaction to frequently taken drugs. When drug discontinuation does not result in renal function improvement and patient has many co-morbidities, making renal biopsy particularly risky, steroid therapy should be considered.

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Conflict of Interest

The author declare no conflict of interest.

Data Availability Statement

All presented data can be accessed.

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