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Acute kidney injury during DRESS syndrome: a case report and literature review

Abstract

The article presents a case of a 46-year-old woman hospitalized in the Nephrology Department due to acute kidney injury with concomitant cutaneous manifestations. The patient had a history of deep vein thrombosis, resulting in intestinal resection and ileostomy 6 months before the hospitalization. On admission, the patient presented a widespread erythematous and papular eruption with pruritus, burning sensation, and scaling, involving her whole body and most pronounced on her face. The laboratory tests showed increased levels of liver and cardiac injury markers, as well as kidney dysfunction requiring temporary hemodialysis. A skin biopsy revealed chronic inflammation with abundant eosinophils. Based on these findings, the patient was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, likely induced by allopurinol. The article highlights the significance of prompt identification of clinical DRESS features, the variety of which can hinder timely diagnosis and management.

Key word: drug hypersensitivity syndrome, allopurinol/adverse effects, acute kidney injury/etiology, skin diseases/etiology

INTRODUCTION

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) is a rare, systemic drug reaction with a severe clinical course accompanied by peripheral blood eosinophilia. The number of new cases is estimated at about 2/100,000 per year [1] with a slight predominance in women (ratio 5/4) [2]. The incidence of the syndrome varies between 0.01 and 0.1% of cases of exposure, depending on the drug used [3]. The symptoms of the syndrome occur with a delay, typically from 2 to 6 weeks after exposure to the causative agent (drug) [4] and may persist even after its discontinuation. In most cases, initially nonspecific general symptoms appear such as weakness, fever (38–40°C), skin itching and lymphadenopathy. Later, skin changes are observed: extensive maculopapular rash with subsequent scaling and erythroderma. In the course of the disease, internal organs may be involved, most often the liver, kidneys, lungs and heart. The varied clinical course makes diagnosis difficult and delays the initiation of proper treatment [5]. Nowadays, the scale according to RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples) (Tab. 1) [2, 5] is most commonly used to assess the probability of clinical DRESS. The offending agent can be identified in about 80% of cases, and in about 20% it remains unknown. The vast majority (75%) of cases are observed after exposure to a small group of drugs: allopurinol, aromatic antiepileptic drugs, sulfonamides, vancomycin, minocycline, as well as anti-tuberculosis antibiotics: rifampicin, isoniazid and ethambutol [5]. Sporadically, DRESS syndrome has also been reported after exposure to some non-steroidal anti-inflammatory drugs (ibuprofen, celecoxib), beta-lactam antibiotics (amoxicillin, piperacillin), kinase inhibitors (imatinib), antiviral drugs, omeprazole [4–6]. Kidney involvement (interstitial nephritis) occurs in 10–30% of patients; it is particularly characteristic of DRESS induced by allopurinol and may manifest in many ways from isolated proteinuria to acute kidney injury (AKI) requiring temporary or chronic renal replacement therapy (3%)

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Table 1. Criteria for diagnosing DRESS syndrome: < 2 — excluded, 2–3 — possible, 4–5 — probable, > 5 — definite according to RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples) and symptoms present in the presented case

Clinical parameters	No	Yes	Unknown	Presented case
Fever ≥ 101.3°F (38.5°C)	–1	0	–1	0
Lymphadenopathy	0	1	0	0
Atypical lymphocytes	0	1	0	0
Eosinophilia				
700–1499 cells/μL or 10–19,9%	0	1	0	1
≥ 1500 cells/μL or ≥ 20%	0	2	0	0
Skin rash				
Rash suggestive of DRESS (Suggestive features: ≥ 2 facial edemas, purpura, infiltration, desquamation)	-1	1	0	1
Extent ≥ 50% of BSA	0	1	0	1
Skin biopsy suggestive of DRESS	–1	0	0	0
OOrgan involvement (1 point for each organ involvement, maximum score: 2)				
1	0	1	0	1
2	0	2	0	0
Disease duration ≥ 15 days	–1	0	–1	0
Exclusion of other causes (1 point if 3 of the following tests are performed and are negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture)	0	1	0	1
Total score				5

and occurring in about 8% of patients. AKI is defined according to the KDIGO guidelines as an increase in serum creatinine concentration by ≥ 0.3 mg/dL (26.5 μmol/L) within 48 hours or ≥ 1.5 times within 7 days, or a decrease in urine output < 0.5 mL/kg/h for 6 h [7]. In this article we present a case of a patient who was diagnosed with allopurinol-induced DRESS syndrome manifesting with typical skin changes accompanied by acute kidney injury.

CASE REPORT

A 46-year-old female patient with no previous nephrological history presented to the Emergency Department with weakness and accompanying skin rash. On admission, the patient complained of persistent itching and burning of the skin and numerous skin changes of the type of erythematous-pustular rash with scaling (Fig. 1, 2). These symptoms appeared about 72 hours before admission to the hospital. Initially, the skin changes involved only the face, then the whole body; at the same time, there was general weakness. The patient was initially treated in the Night and Holiday Medical Assistance Unit, where she received single doses of dexamethasone and clemastine — without effect. In her history, the patient reported (having had a) thrombosis of the superior mesenteric, splenic and portal veins 6 months earlier, complicated by acute mesenteric ischemia with subsequent resection of the ileum and creation of ileostomy; without changes in the arterial vessels (aorta, renal arteries). Due to the unclear etiology of thrombosis, the patient remained in the course of vascular and hematological diagnostics. In her history, she also reported a weight loss of 27 kg since the resection of the intestine. History for previous kidney diseases, hypertension, diabetes — negative. No abnormalities in the character and amount of urine output were found. The patient regularly received only rivaroxaban (20 mg/day) and folic acid (15 mg/day). Two weeks before admission to the Nephrology Department, due to hyperuricemia detected in a single measurement (serum uric acid level 16 mg/dL; without symptoms of gout) in primary health care conditions, allopurinol treatment (300 mg/day) was started.

The tests performed in the Emergency Department showed a significantly impaired renal excretory function with serum concentrations of creatinine 12 mg/dL (N: 0.5–1.1 mg/dL), urea 323 mg/dl N: 15–40 mg/dL)

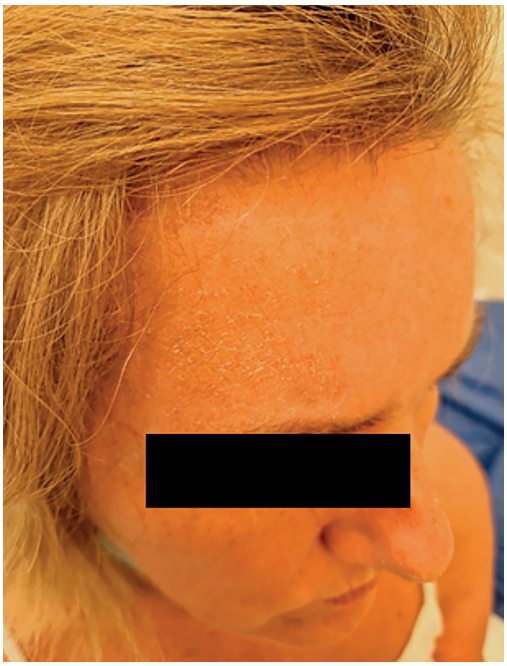

Figure 1. Skin lesions on admission — scaling

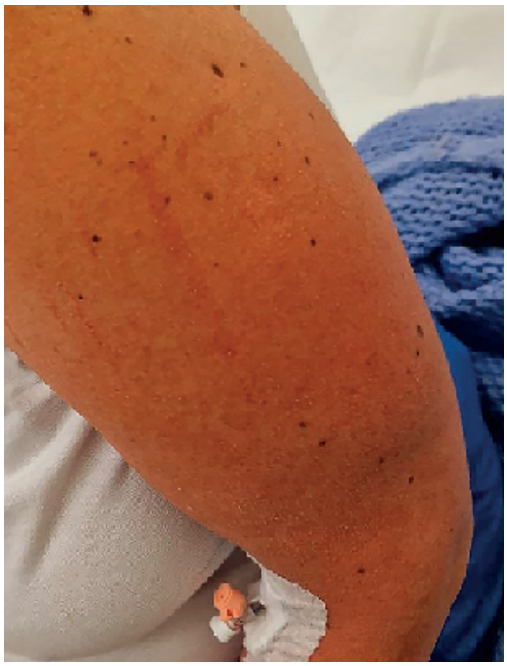

Figure 2. Skin lesions on admission — erythematous-pustular rash; excoriations

with coexisting compensated non-respiratory acidosis (pH 7.44 with pCO_2 24.5 mmHg and HCO3- concentration 16.5 mmol/L), without hyperkalemia. In addition, in the peripheral blood morphology, mild anemia (Hgb 11.9; N: 12–16 g/dL), leukocytosis 17.1 thousand/μL with eosinophilia 890/μL (5.2%) and normal platelet count 309 thousand/μL were observed. Notable were also increased concentration of inflammatory markers (CRP 87.8 mg/L; N: 0–5 mg/L) and markers of cardiac muscle damage (cTNI 17 ng/L; N: < 14 ng/L), increased activity of liver enzymes (AST 48 U/L, N: < 40 U/L; ALT 54 U/L, N: < 32 U/L; with normal level of total bilirubin 0.89 mg/dL, N: 0.2–1.1 mg/dL) and coagulation disturbances (APTT 45.1 s, N: 26–40 s; PT 34.5 s, N: 12–16 s).

Hyponatremia was also observed: Na+ — 115 mmol/l, and hypoproteinemia: TP — 55.3 g/L (possible complication after resection of the small intestine). Serum uric acid level was 2.8 mg/dl (N: 4–5 mg/dL). The urine test revealed proteinuria 0.56 g/L with active sediment (15 fresh red blood cells, without leached cells; N: 0–2; 15 white blood cells, N: 0–4; numerous bacteria in the field of view). The results of laboratory tests at admission, during hospitalization and after its completion are presented in Table 2.

In computed tomography, kidneys of 100 and 115 mm in size without signs of congestion, with increased echogenicity and signs of weaker contrast enhancement in the arterial and venous phase were visualized. Renal parenchymal layers of 18 mm thickness; in the upper pole of the right kidney, a 14 mm cyst with high-protein content (suspicion of blood content) was found, and in the calyx of the left kidney a 6 mm calculus. In Doppler ultrasound examination, high-resistance arterial flows were found in the cortical-medullary area of the kidneys — RI (Resistive Index): 0.78–0.82 (N: < 0.7). In imaging studies of the lungs, no significant deviations from the norm were found, no focal changes. Due to the history, characteristic skin changes, peripheral blood eosinophilia, signs of acute kidney, liver and cardiac muscle damage, a tentative diagnosis of DRESS in reaction to allopurinol was made. On the first day of hospitalization, allopurinol administration was discontinued, pulses of methylprednisolone were initiated (total dose of 1125 mg over 5 days), followed by conversion to oral prednisone (60 mg/d). Due to the symptoms of uremia, a temporary vascular access for hemodialysis was implanted and renal replacement therapy was started; 3 hemodialysis sessions were performed within 4 days.

Based on the clinical picture and additional tests performed (HIV Combo antigen test, HBs antigen concentration, anti-HBc and anti-HCV antibody titers, serum protein electrophoretic separation, ANA and ANCA titers, C3 and C4 complement components concentrations), other than DRESS possible

Table 2. Laboratory tests at admission, during hospitalization, and in the 2-month follow-up period

Parameter unit (reference value)	At admission	During hospitalization	Before discharge	2 months later
Hemoglobin g/dL (N: ♀ 12–16)	11.9 ↓	9.5 ↓	9 ↓	10.9 ↓
Leukocytes thousand/μL (N: 4–6)	17.1 ↑	7	8.9	13.4 ↑
Eosinophils cells/μL (N: 50–500)	890 ↑	600 ↑	400	–
Platelets thousand/μL (N: 150–400)	309	128 ↓	81 ↓	163
Creatinine mg/dL (N: ♀ 0.5–1.1)	12 ↑	2.94 ↑	1.45 ↑	1.08
Urea mg/dL (N: 15–40)	323 ↑	174 ↑	94 ↑	48 ↑
Uric acid mg/dL (N: ♀ 4–5)	2.8	7.7 ↑	6.5 ↑	4.4
Na^+ mmol/L (N: 145–145)	115 ↓	137	135	–
K^+ mmol/L (N: 3.5–5.1)	4.9	4.1	3.6	3.8
AST U/L (N: 5–40)	48 ↑	21	23	–
ALT U/L (N: 35–40)	54 ↑	39	45 ↑	–
cTNI ng/L (N: < 14)	17 ↑ → 13.4	–	–	–
CRP mg/dL (N: < 5)	87.8 ↑	2	5.7	–
Total protein (serum) g/L (N: 60–80)	55.3 ↓	–	–	–
Albumins g/L (N: 35–55)	38.3	32.1 ↓	–	–
Total protein (urine) ng/L (N: none)	0.56 ↑	–	0.49 ↑	–
APTT s (N: 25–40)	45.1 ↑	25.4	24.6	–
PT s (N: 12–16)	34.5 ↑	19.9 ↑	15.6	–
D-dimer ng/mL (N: 500)	890 ↑	< 270	–	–

causes of AKI were excluded, including viral infections, lymphatic system malignancies, acute cutaneous lupus erythematosus and vasculitis. Due to the lack of mucosal involvement, Stevens-Johnson syndrome was excluded. A biopsy of the pathologically altered skin was taken — the histopathological picture showed foci of chronic inflammation with numerous eosinophils; the result was obtained on the 3rd day of hospitalization. In the following days, a gradual improvement of the clinical condition was observed, with a reduction of skin changes with transient patchy peeling of the epidermis of the whole body. With the return of diuresis and observed improvement of renal excretory function, further procedures were discontinued. Due to the history of thrombosis and progressive decrease in platelet count (reduction to 81 thousand/μL, within 12 days of low molecular weight heparin administration), the diagnostics for hemostatic disorders were extended and increased activity of factor VIII and presence of antibodies against heparin-PF4 complex were found. In view of the above, anticoagulant therapy was modified again to rivaroxaban. Due to increasing anemia, 1 unit of irradiated leukocyte-poor red blood cell concentrate was transfused, obtaining stabilization of red blood cell parameters. Due to significant weight loss, signs of malnutrition (hypoproteinemia) and coexisting electrolyte disturbances, oral nutritional treatment was administered. After 21 days of hospitalization, the patient was discharged home in good general condition. On the day of discharge, slightly impaired renal excretory function persisted (serum creatinine concentration 1.16 mg/dL; eGFR according to CKD EPI formula 43 mL/min/1.73 m^2). Continuation of oral prednisone treatment at a dose of 1 mg/kg/day with gradual dose reduction by 5 mg every 2 weeks was recommended. In addition, rivaroxaban treatment (15 mg/d) was continued. Pantoprazole 40 mg/d was added. For the significant weight loss, oral treatment with a high-energy nutritional preparation was recommended.

DISCUSSION

DRESS syndrome is a rare acute drug reaction characterized by extensive rash with concomitant involvement of internal organs, lymphadenopathy and peripheral blood eosinophilia. Symptoms develop with a delay relative to the causative agent, typically from 2 to 6 weeks after exposure [4]. The risk of DRESS syndrome increases proportionally to the dose of the drug (causative agent). There is also an increased risk in patients with impaired renal

function and consequently impaired excretion of drugs; this applies especially to people treated with allopurinol, phenytoin and minocycline [8–10]. In the presented patient, the occurrence of DRESS syndrome may have been related to the administration of too high an initial dose of allopurinol (300 mg). The starting dose of allopurinol should be 100 mg/day or less, especially in patients with kidney failure. Gradual dose escalation is the key to minimizing the risk of adverse effects, such as DRESS syndrome. Predisposition to the development of DRESS for individual HLA polymorphisms and dependence on the polymorphism of genes encoding metabolizing enzymes (cytochrome P, N-acetyltransferase) have also been demonstrated [8–13]. Another interesting phenomenon described in the course of DRESS syndrome is reactivation of viruses from the Herpes viridae family (Epstein-Barr, cytomegalovirus, HHV-6, HHV-7); it occurs in up to 75% of patients, and its role in the pathogenesis of DRESS is unclear [14–18]. The first symptoms of DRESS are most often fever (75–90%), malaise and lymphadenopathy (54–65%). The characteristic skin reaction appears with a delay of 2 to 6 weeks; it occurs in 97% of cases and facilitates diagnosis. In almost 80% of cases, skin changes involve more than half of the body surface. The lesions are most often maculopapular (60%), less frequently generalized erythema (54%) may occur. A typical symptom is also facial edema (70%). In half of the cases, mucosal involvement of a mild course was observed. The occurrence of blisters, pustules and peeling of the epidermis was also described [5, 19]. In the presented patient, numerous erythematous-pustular changes were found — initially on the facial skin — then on the whole body, merging into generalized erythema. After a few days, patchy peeling of the epidermis occurred in the area of changes. The most common abnormalities in the laboratory tests are eosinophilia (82–95%), leukocytosis (95%), neutrophilia (78%), lymphocytosis (25–52%), monocytosis (69%) and presence of atypical lymphocytes (35–67%). In the described case, leukocytosis 17.1 thousand/μL, with neutrophilia 15.1 thousand/μl and eosinophilia 890/μL were observed. Involvement of at least one internal organ occurs in 90% of cases. About 35% of patients may have involvement of 2 organs, and involvement of at least 3 occurs in 20% of cases. Liver damage is the most common visceral manifestation of DRESS syndrome, occurring in 53–90% of cases. Pulmonary involvement symptoms occur in 30% of patients. Cardiac involvement occurring in 2–20% is associated with poor prognosis. Involvement of the central and peripheral nervous system is described in 2–8% of patients. In the discussed clinical situation, the patient suffered the involvement of two organs: skin and kidneys.

Relapses occur in 25% of patients, usually a few weeks/months after the symptoms have subsided. They are especially common in cases with rapid reduction of corticosteroid dose, therefore a gradual dose reduction is recommended for the patient. They may be induced by drugs other than the drug initially causing the symptoms. In patients who have had DRESS, an increased risk of developing autoimmune diseases, including autoimmune thyroiditis, vitiligo, systemic lupus erythematosus and type 1 diabetes, has also been reported, so patients should be closely monitored for the occurrence of these diseases in subsequent years [20–23]. Due to the great heterogeneity of clinical symptoms of DRESS, the decision on the intensity of treatment is based on the assessment of skin and internal organ involvement. Patients without clinical, laboratory or imaging evidence of organ involvement may be treated symptomatically with topical corticosteroids. Additionally, to alleviate symptoms, antihistamines and emollients may be considered in treatment. In case of the presence of organ changes, oral preparations of prednisone are used, until clinical improvement and normalization of laboratory parameters are achieved, at an initial dose of 0.5 to 1 mg/kg per day, gradually reduced over 8–12 weeks. In severe cases, intravenous methylprednisolone (250 to 500 mg per day for two to four days) is recommended, followed by conversion to oral steroid [24]. Most patients with DRESS syndrome return to full health within a few weeks to a few months after discontinuation of the drug. Also in the described case, renal function recovery was observed (serum creatinine concentration after 2 months — 1.08 mg/dL, eGFR 64 mL/min/1.73 m^2), and serum uric acid concentration remained in the range of 4–5 mg/dL. In the described case, hypouricemic treatment was not continued; in patients requiring further treatment, due to exclusion of allopurinol from further use other drugs lowering the uric acid level can be considered, e.g. febuxostat (liver metabolism), especially in patients with impaired renal function [25]. According to the ACR 2020 guidelines (American College of

Rheumatology), treatment can be extended with uricosuric drugs - probenecid, benzbromarone, sulfinpyrazone, which however require preserved renal excretory function and which, unfortunately, are not available in Poland. In the next step, in case of their ineffectiveness, pegloticase can be included. Flozins and some sartans (losartan, irbesartan) [26] used for nephroprotection in patients with chronic kidney disease with albuminuria also have hypouricemic potential. Drugs that should be avoided, i.e. those increasing uric acid level, are acetylsalicylic acid and loop and thiazide diuretics.

According to a recent systematic review regarding DRESS syndrome with kidney manifestations, most of 71 cases identified in the literature were associated with antibiotics (34%) — most commonly vancomycin (24%) — xanthine oxidase inhibitors (15%) and anticonvulsants (11%). The kidneys were the only visceral organ affected in 21% of cases, while both liver and kidneys were involved in 54% of patients. AKI was the predominant kidney manifestation, occurring in 96% of cases, with anuria in 4% of cases, and need for temporary renal replacement therapy in 30% of cases. Isolated proteinuria or hematuria were found only in 4% of patients. However, almost all patients recovered full kidney function, confirming an overall favorable prognosis despite the initial severity of the disease. Mortality in described cohort was 13%, which is higher than previously reported, and was negatively associated with female sex (22.6% *vs.* 5%). Factors such as class of medication taken, latency period or pre-existing kidney disease did not correlate with higher mortality rates [27].

CONCLUSIONS

DRESS syndrome is a rare but potentially fatal hypersensitivity reaction that requires rapid diagnosis and early treatment. In the diagnosis, a detailed medical history is essential, in which the first thing to pay attention to is the dynamics of the symptoms and their temporal correlation with the introduction of a new, syndrome inducing drug. Characteristic skin changes with accompanying peripheral blood eosinophilia are particularly helpful in making the diagnosis. In the described case, typical symptoms: fever, extensive skin changes with eosinophilia, increased liver enzyme activity, biochemical signs of kidney damage and the correlation between symptoms and initiation of allopurinol treatment allowed for a quick diagnosis (5 points on the RegiSCAR scale), initiation of proper treatment and achievement of complete remission.

Conflict of interest

The authors declare no conflict of interest.

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