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RESEARCH ARTICLE

Case History of Severe Toxicoallergic Dermatitis in Patient with Acute Leukemia

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Abstract

Adverse drug reactions are a serious problem in practical healthcare since they can have a significant impact on the patients' quality of life while the global prevalence of morbidity and mortality caused by drug after-effects is increasing every year. Among the most common adverse drug reactions are skin reactions. They have described a case history of severe furosemide-induced toxicoallergic dermatitis in a 62-year-old man with acute myeloid leukemia taking saluretic due to comorbid cardiac pathology. Furosemide was withdrawn due to of severe toxicoallergic dermatitis onset while the glucocorticosteroids therapy with a 40 mg qd dose of prednisolone was prescribed. Secondary to furosemide withdrawal and due to glucocorticosteroid therapy, the following amelioration was registered: there were no new lesions, bullae and anabrosis disappeared, edema decreased and the patient's general state of health improved. The described case of severe furosemide-induced toxicoallergic hemorrhagic vasculitis is associated not only with the direct allergenic action of the drug being the sensitization reaction trigger, but is also associated with the aberrant immunoreactive status of a particular patient due to his hematologic malignancies (acute myeloid leukemia). Such severe toxicoallergic reactions are rare enough, but it is extremely important to draw the clinicians' attention to this problem, since these are the timely diagnosis of mentioned conditions, the identification and elimination of the trigger drug, timely and adequate treatment that guarantee a favorable prognosis for patients. That is why clinicians should not only aim for the verification and treatment of the underlying disease, but also consider the patient's comorbid conditions.

Keywords: *Drug-induced dermatitis, furosemide-induced severe toxicoallergic dermatitis, Delayed-onset allergy, Toxicoallergic dermatitis in acute leukemia.*

Introduction

Due to the rapid development of medical science over the past decades doctors now have a wide range of technologies and medicines enabling a high-quality medical care for patients with dissimilar abnormalities of internals. However, the use of even the most advanced high-technology medicinal products does not guarantee the absence of drug side effects (SEs). Currently, adverse drug reactions (ADRs) are a serious challenge in practical healthcare, since they can have a considerable impact on the patients' quality of life, while the global prevalence of morbidity and mortality caused by drug after-effects (DAE) is increasing with every year [1, 3]. In particular, the studies have hown that the frequency of drug SEs is about 3.5% of the total number of hospital admissions [1, 2]; moreover, DAEs cause about 197.000 deaths in Europe every year [4]. In the vast majority of cases ADRs occur in older people [5, 3]. One of the studies showed that about 1.5% of emergency hospital admissions among eldery people in the United States involve SEs drug events. Moreover, a half of mentioned people were of 80 years old and older [6]. The phenomenon of polypragmasy as well as misprescriptions of certain drugs by general practice doctors is the reason of great prevalence of DAEs among the elderly [7, 9].Thus, the British large-scale retrospective study (6048 prescriptions for 1777 patients over a period of 12 months analyzed) found a 5% prescription errors rate in general practice [7]. Among the most frequent ADRs are skin reactions (drug-induced dermatoses (DIDs)) that can imitate other skin or systemic diseases. Clinicians should be aware of this when diagnosing various nosologies [10, 5]. As studies show, the prevalence of skin reactions to drugs varies within 10-30% of the total number of ADRs which is 0.6-3.0% of the total hospital admissions. Among the most common DIDs are urticaria, maculopapular and morbilliform rash [11, 12, 10]. However, serious conditions posing a serious threat to patients' life and health occur in DIDs: toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, acute exanthematous pustulosis, drug-induced lupus, drug-induced vasculitis, bullous pemphigoid, linear IgA bullous dermatosis, drug-induced neutrophilic dermatoses (erythema nodosum, pyoderma gangrenosum, Sweet syndrome), cutaneous lymphoma-like drug reactions, etc [13, 14, 5].

Among DIDs risk factors are age over 60, being a female, immune system abnormality, hepatocellular insufficiency, renal disease, and pregnancy [5, 7, 8, 9].The studies proved the antiepileptic agents, antidepressants, non-steroidal anti-inflammatory agents, sulfanilamide agents, and anticoagulants to be the drugs most often causing the DIDs [15, 17]. In one large-scale retrospective study conducted by the German Federal Institute for Drugs and Medical Devices 345 662 cases of DAEs within a period between 1978 and 2016 were analyzed. The analysis included

DAEs cases reported by general practice doctors, therapeutics, patients, and lawyers. The study showed that 23.1% (79.976) of DAEs were caused by drugs used for nervous system disorders therapy (anticonvulsants, antipsychotics, antidepressants), 13% (44.787) by drugs for cardiovascular disease therapy, 12.4% (43.006) by antineoplastic and immunomodulatory agents, 10.9% (37.661) by anticoagulants, blood substitutes, and antianemics and 10.5% (36.327) by antibiotics, antiviral medications and antifungal drugs [17].

Another DIDs-associated problem is that dermatoses are often difficult to reveal due to patients' comorbid abnormality which can also be accompanied by skin lesions. DIDs often imitate their autopathic analogues, besides it is not always possible to find a causal link between the dermatosis onsets and to use a particular drug [15, 16, 13].That is why it is necessary to focus the clinicians' attention on the need for careful monitoring and studying the ADRs in patients, which in its turn will increase the efficiency and safety of the therapy.

Case History

A 62-year-old patient M. Kh-ko stayed at the hematology department of the A. Ostroumov Clinic of Hospital Therapy, Sklifosovsky Clinical and Research Institute for Emergency Medicine of the I.M. Sechenov First Moscow State Medical University for the period from 06/27/19 to 07/25/19. According to his medical history, he underwent an examination for megalosplenia and altered haemogramma, morphologic assessment of the bone marrow, and molecular genetic analysis in 2017, which revealed the Jak2 V617F mutation. This checkup enabled the clinicians to diagnose a myeloproliferative disorder, commonly known as an agnogenic myeloid metaplasia (AMM).

Hydroxyurea (Hydrea) therapy (1500 mg qd) has been assigned. Until spring of 2019 the patient's general state remained satisfactory. On May 2019 the deterioration started: general weakness and increasing dyspnea appeared. Due to these symptoms the patient was admitted to the department of general practice according to the place of residence. The second examination revealed an atrial fibrillation with ventricular contraction rate (VCR) of 75-150 bpm and signs of left ventricular (LV) hypertrophy with abnormal LV diastolic function and pulmonary hypertension (in the medical history mentioned as COPD). A short course of therapy within the cardiac insufficiency gave a slight effect. Soon after the patient's discharge the symptoms of heart failure increased: orthopnea and swelling in legs and crurae developed. The patient was admitted to the cardiology department of the University Medical Center No. 4, I.M. Sechenov First Moscow State Medical University.

The echocardiogram showed asymmetric hypertrophy of the entire interventricular septum (29 mm during diastole) with obstructive component. The peak pressure gradient in the outflow tract was 21 mm Hg, dilatation of the left atrium was 19.4 cm^2, dilatation of the right atrium was 20 cm^2, right ventricular dilatation (with the diameter of 41 mm in the middle third), dilatation of pulmonary trunk (PT) was 31 mm, dilatation of inferior vena cava was up to 26 mm, systolic pressure in PT was 51 mm Hg, ejection fraction (EF) was 55%. There was also found a moderate amount of fluid in the pericardial cavity (up to 200-300 ml) and signs of a considerable pulmonary hypertension. Ultrasonography of the abdominal organs revealed hepatolienomegaly (spleen size was 250x110 mm) and signs of bilateral hydrothorax. Clinical blood analysis results are as follows: red blood cells −3.0×10^{12}/l, Hb−92 g/l, white blood cells−23×10^9/l (eos. - 1%, myeloblasts−24%, promyelocytes-4%, myelocytes−64%, immature neutrophils−7%, band neutrophils−5%, segmentonuclear neutrophils − 37%, lymphocytes − 10%, monocytes − 6%), platelets − 76×10^9/l, ESR − 27 mm/hour. The biochemical profile analysis showed: glucose−4.1 mmol/l, total bilirubin− 15.8 mcmol/l, thymol test − 2.75 singles, ALT− 19.4 u/l, AST − 21.2 u/l, alkaline phosphatase− 90.4 u/l, γ-glutamyltransferase−22, 1 u/l, LDH − 861 u/l, blood urea nitrogen− 4.9 mmol/l, creatinine−77.5 mmol/l. A sternal puncture was done with regard to peripheral blood values. It revealed 30.5% of blasts in the bone marrow. The patient was transferred to the hematology department with a diagnosis of blast crisis in agnogenic myeloid metaplasia.

Still the following therapy was started before the transfer: lasix 40-60 mg i.m. qd, clexane 0.4 mg s/c bid, verospiron 1capsule 100 mg qd, lisinopril ¼ of a tablet 1.25 mg qd, bisoprolol 2.5 mg ½ of a tablet qd, digoxin 0.125 mg 1/2 of a tablet qd. A few days after the beginning of the prescribed therapy, small skin changes including reddish maculopapular lesions (0.3-0.5 cm across) on both crurae due to swelling were newly diagnosed. Yet, these lesions had no specific characteristics and did not cause discomfort to the patient. In order to specificate the revealed blast transformation in the bone marrow the following investigative procedures were carried out in the hematology department: cytochemical analysis of blast cells (myeloperoxidase was positive in 30% of blast cells, PAS-reaction was in diffuse-granular form); standard cytogenetic assay (karyotype: 46, XY, i(18) (q10) [3] /48-50, XY, +?Y or mar, der (7)t(1;7) (q10;p10), +8, del(13) (q?21), ?der(16), i (18) (q10)[1], +21, +21[16] /46, XY[1]. Findings revealed a clone with subclone and complex changes in the karyotype: 7 derivative from translocation (1; 7) with q-loss 7; trisomy 8; tetrasomy 21; del with q-loss 13; 16 derivative?; i 18 on q; marker chromosome); immunophenotyping (blasts 24.2% (CD34+ CD38+ HLADR+ CD7+ MPO+ CD117+ CD13+ CD33+ CD15+ CD36+ CD64+ CD4-|+ CD14+ cytCD3-cytCD22-CD79a-.

Diagnostic Decision: immunophenotype of blast cells which correspods to myelomonocytic linear form).

Thus, the examinations enabled the clinicians to diagnose the patient with acute myeloid malignant leukemia due to chronic myeloproliferative disease Jak2+ (agnogenic myeloid metaplasia) with multiple cytogenetic abnormalities. Further clinical imaging revealed the following comorbidity: asymptomatic hypertrophic cardiomyopathy with left ventricular outflow tract obstruction; permanent tachysystolic atrial fibrillation; heart failure with preserved left ventricular ejection fraction, Killip class III, New York Heart Association Functional Classification IV; bilateral hydrothorax; hydropericardium; atherosclerosis of the aorta and coronary arteries; COPD, stage II, unstable remission phase; respiratory failure, stage II; pulmonary hypertension stage II; circulatory inefficiency, III phase.

Considering the patient's age, leukemia, and cardiac comorbidity, the treatment began with small doses of

cytosar 20 mg s/c bid along with the concomitant cardiac therapy (verospiron 100-200 mg qd, furosemide 100-140 mg iv bolus qd, lisinopril 1.25 mg qd, bisoprolol 2.5 mg qd, clexane 0.4 mg s/c bid), allopurinol 400 mg qd, pantoprazole 40 mg qd, panangin 20-40 mg ivfd qd. Secondary to the treatment, the left-sided hearing loss developed, which was regarded as a lasix after-effect. There was also an enhancement of pre-existing lesions on both crurae (Fig. 1): secondary to pre-existing maculopapular lesions, multiple round and oval bullae of 0.5-3.0 cm across appeared; bullae were separated from each other and randomly arranged. They burst after 3-5 days, discharging serosanguineous fluid and forming irregular-shaped and clearly outlined erosions followed by crusting. The patient had inflammatory cutaneous edema and lymphorrhea. Skin in the affected site had an intensively crimson colour.

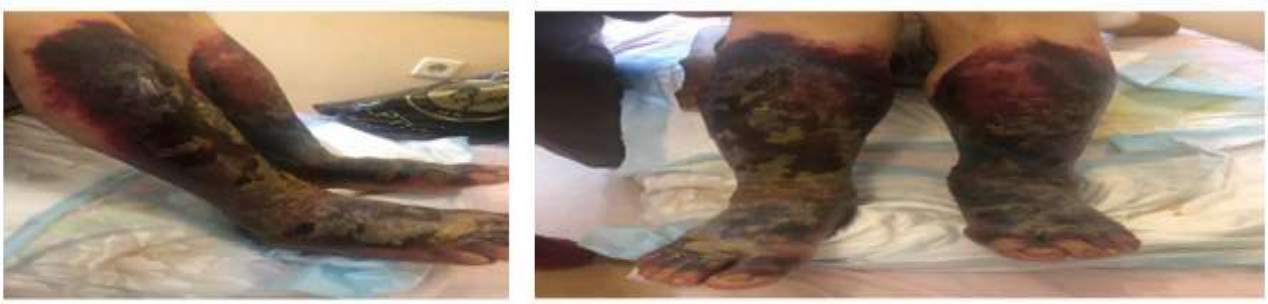

Figure 1: Toxicoallergic furosemide-induced dermatitis: multiple bullae with serosanguineous fluid, irregular-shaped and clearly outlined erosions and excoriation on both crurae

Dermatologist consulted the patient and diagnosed toxicoallergic dermatitis. Recommendations: to withdraw furosemide with replacing by prednisone 40 mg per os qd, to apply Dermoveit cream transdermally bid. Diuretic therapy was corrected (furosemide was withdrawn in the favor of diuver 20 mg qd), prednisolone thetment at a dose of 40 mg per os qd along with Amoxiclav 1000 mg 2 bid, and thromboconcentrate of erythrocyte suspension administration was started. Lorinden C was prescribed to apply transdermally 2 bid. This resulted in the following positive dynamics: dyspnea subsided, the patient started sleeping horizontally, edema considerably decreased, crurae skin gained (cutaneous edema amelioration, bullae, and lymphorrhea disappearance) while hemogramma showed blastosis depression in peripheral blood. The dermatologist's follow up showed a complete decurrence of swelling and the absence of new lesions due to the prescribed therapy. The patient was recommended to take 6 tablets of prednisolone at a dose of 30 mg qd for 2 weeks, followed by reducing in half a tablet q2w to 4 tablets qd.

In a month the drug must be reduced in half a tablet qwk to the complete withdrawal. Additionally, within the prednisolone active-treatment period 1 tablet of pantoprazole at a dose of 40 mg qd should be taken for the purpose of gastroprotection while the glycaemic control must be performed q2w. The patient was also prescribed to apply D-panthenol and Lorinden C transdermally. Two courses of low-dose chemotherapy with cytosar induced clinical and hematological remission. On glucocorticosteroids treatment completion the crurae skin health considerably improved and there were no lesions relapses within active-treatment period detected. Upon health improvement, the patient was discharged to be followed up by a hematologist, cardiologist, and dermatologist at the place of residence.

Discussion

Furosemide is among the most widely used loop quick-relief diuretics which results in rather intense but short-term diuretic effect [18, 20]. This drug has been actively used by clinicians for several decades to treat pulmonary edema, congestive heart failure, resistant hypertension and kidney disease as a quick-relief drug in patients suffering from cirrhosis with ascites [18, 19]. The furosemide mechanism of action involves blocking of Na^+-K^+-$2Cl^-$-cotransporter of basement membranes of cells of ascending limb of Henle's loop resulting in reabsorption of Na^+ and Cl^- in this portion of the nephron which determines the diuretic effect of the drug [19, 20]. The most common furosemide-induced SE is electrolyte disorder (hyponatremia and hypokalemia) and acid-base disturbance (hypochloremic alkalosis) [18, 20]. Yet, furosemide-induced skin reactions as well as responses to the intake of other "non-antibacterial" sulfanilamides (thiazide and loop diuretics, acetazolamide, sulfanilamide hypoglycemic agents, sulfosalazine and some of COX-2 inhibitors) occur much less frequently (approximately in 2.5-3.5% of cases) and only 3% of them are true hypersensitivity reactions. Normally, sulfonamides-induced cutaneous allergic reactions develop in 7-14 days after the onset of drug action and manifest as minor macular or papular rashes while pustular or bullous lesions are extremely rare [21, 19, 22, 23]. Among severe furosemide-induced dermatoses there have been recorded cases of bullous pemphigoid [21, 19, 23], polymorphic erythema, Sweet syndrome, cutaneous necrotizing vasculitis [24], acute generalised exanthematous pustulosis [25], DRESS-syndrome (Drug Reaction with Eosinilia Systemic Symptoms) [22]. Bullous pemphigoid (BP) develops most commonly in severe furosemide-induced dermatoses [21]. A British case-control retrospective study was conducted that compared medical histories of patients with (n=86) and without (n=134) PD randomized by age, gender and comorbid conditions. The aim of the study was to prove a cause-and-effect relationship between the intake of certain drugs and BP development. It was found that most patients with BP were treated with loop diuretics (furosemide, in particular) (OR = 2.4, 95% CI 1.2-5.0, p=0.02). Yet, the study did not show a considerable difference between patients taking other diuretics, non-steroidal anti-inflammatory agents, antidepressants, anticonvulsants and antihypertensive drugs before the BP onset. The findings revealed a frequent furosemide intake by patients with BP before its development regardless of gender, age and comorbid conditions.

They also directly implied furosemide to be the most probable cause of their BP start [26]. Another similar study conducted in France highlights the relationship between BP development and the intake of drug other than furosemide-spironolactone [27]. Obviously the decision to include a different drug to the investigation can be explained by the fact that spironolactone is used much more often in France. In particular, pironolactone was used by 7.4% of control patients in the French study and by 3.7% of controls in the British research [26]. In a recent retrospective study conducted in the United States, the cases of furosemide-induced DIDs were analyzed in patients with sulfa allergy, while perfoming the radionuclide renography.

The medical histories of 1403 patients over the period from 2009 to 2015 were analyzed. The mentioned patients underwent the radionuclide renography, 1103 of whom were examined with furosemide administrated at a dose of 23.2±6.5 mg. In the furosemide group, 83 patients had histories of sulfa allergy, and two had a slight rash. This suggests that the use of furosemide is associated with an extremely low risk of minor allergic reactions in patients with sulfa allergy [28]. The development mechanism of most mentioned severe furosemide-induced dermatoses is not exactly known which results in need for the study management in this area. Currently, it is believed that the pathogenesis of these conditions is based on the antigenic hapten action of furosemide as well as on the onset of immune dysregulation with dysfunction of regulatory T-cells and stimulation of B-lymphocyte clones recognizing autoantigens and inducing the production of autoantibodies [29, 26, 30, 31]. Moreover, no specific biomarkers of DIDs were noticed while the clinical manifestations and immunopathological changes were predominantly similar to those with idiopathic forms [21, 19]. Some scientists say that there is a genetic predisposition to severe DIDs induced by certain drugs, but no specific genetic mutation has yet been found [30]. In their case history furosemide was administered as a routine drug for the symptomatic treatment of heart failure along with a ß-blocker (bisoprolol), ACE inhibitor (lisinopril), cardiac glycoside (digoxin), anticoagulant (clexane) and aldosterone antagonist (verospiron).

A great number of studies showed that both furosemide and drugs for correcting the patient's cardiac pathology [12, 7, 8, 10, 9, 4] could cause DIDs. However, the patient has repeatedly taken all of the mentioned drugs earlier while furosemide was included to the treatment regimen just after the detection of heart failure. There is also a clear cause-effect relation between the beginning of furosemide intake and TAD development in the described case history. In this instance it is quite difficult to arrive at diagnosis of furosemide-induced TAD since skin lesions can also appear in underlying disease (acute myeloid leukemia) masking the saluretic ADR onset. Besides, the improvement of their patient's health condition due to withdrawal of furosemide proved this drug to be the ADR trigger.

Among all the drugs used in our patient's treatment, it is furosemide that is mentioned in literary sources as the drug most commonly causing the toxicoallergic dermatitis. The underlying cause of TAD in their patient is a delayed-onset allergy which is distinctively mediated by T-lymphocytes and delayed-onset hyperresponsiveness mediators, rather than antibodies like other types of allergic reactions are. Still, this type of reactions is not less antigen-specific than the antibody reactions are, since T-lymphocytes have receptors specifically binding to the antigen [32, 33]. These receptors are presented by truncated and T-lymphocyte membrane-integrated IgM antibodies, as well as by Medawar's antigens [34]. When an allergen first enters the body (here furosemide), T-helpers and T-killers fall under the antigen-dependent differentiation. The second penetration results in proliferation and maturation of a great number of T-killers interacting with the antigen which in its turn results in production of various cytokines possessing cell-killing effect [34, 33].

Thus, in this case, skin lesions developed in result of direct cytotoxic action to the target cells of T-lymphocytes, the cytotoxic action of lymphokines and macrophages, which resulted in acute inflammatory toxicoallergic lesions in our patient. It should be noted that in our case a considerable reason of TAD start were the changes in the patient's immunological status due to acute myeloid leukemia. Besides, the patient had been taking cytosar to treat the underlying disease. One of the mentioned drug effects is suppression of cell immunity and antibody-mediated protection. Due to the severe TAD furosemide was withdrawn with the following substitution to diuver (torasemide) at a dose of 20 mg qd.

In order to stop the severe toxicoallergic reaction, the patient was prescribed with prednisolone at a dose of 40 mg qd. Secondary to the furosemide withdrawal and glucocorticosteroid (GCS) therapy, amelioration was registered on day five (there were no new lesions, the bullae count decreased). On the 14th day of prednisolone therapy, the lesions had almost disappeared while edemas decreased, and the patient's general state improved. The timely recognized trigger (furosemide) and its effect elimination with the following prescription of the appropriate GCS (prednisone) treatment enabled clinicians to eliminate the start of severe TAD in a short period of time. According to the medical evidence, such cases of severe furosemide-induced toxicoallergic reactions have a favorable prognosis after the drug withdrawal and hormonotherapy prescription, which was observed in the described case history [25, 26, 21, 19, 22, 23].

Findings

The described case of severe furosemide-induced toxicoallergic hemorrhagic vasculitis is associated not only with the direct allergenic action of the drug being the sensitization reaction trigger, but is also with the aberrant immunoreactive status of a particular patient due to his hematologic malignancies (acute myeloid leukemia). Although severe toxicoallergic reactions are rare enough, it is extremely important to draw the clinicians' attention to this problem, since these are the timely diagnosis, the identification and amelioration of the trigger drug, timely and adequate treatment that guarantee a favorable prognosis for patients.

That is why clinicians should not only aim for the verification and treatment of the underlying disease but also consider the patient's comorbid conditions. The number of drug-induced dermatoses may increase with due time since every year new treatment methods and drugs appear. Therefore there is a need for studying the drugs causing the mentioned conditions, as well as patients prone to their development.

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