DRESS SYNDROME WITH MILD MANIFESTATIONS AS A DIAGNOSTIC AND THERAPEUTIC PROBLEM: CASE REPORT

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SUMMARY – The group of severe cutaneous drug reactions with systemic symptoms includes several syndromes: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms (DRESS). These reactions occur several days to six weeks after introducing the incriminating drug. The skin and internal organs (liver, kidneys, lungs, etc.) are usually involved. A great possibility of lethal outcome is a critical characteristic of these syndromes. A patient with pyelonephritis diagnosed during emergency room workup is described. Ciprofloxacin was prescribed and the patient was discharged. After ten days, the patient came back with worsening condition, general inflammatory response, skin changes, liver and kidney damage, and eosinophilia. DRESS syndrome was diagnosed based on clinical and other findings. The diagnosis and treatment of severe drug reactions with cutaneous and systemic symptoms pose a medical challenge.

Key words: *Drug hypersensitivity – prevention and control; Drug eruptions – etiology; Drug eruptions – diagnosis; Drug eruptions – therapy*

Introduction

Severe forms of cutaneous drug reactions associated with systemic symptoms are one of the biggest diagnostic and treatment challenges in allergology. Such reactions usually start several days to six weeks after drug introduction. They occur in the form of changes on the skin and internal organs (liver, kidneys, lungs, etc.). Among severe cutaneous drug reactions with systemic symptoms, toxic epidermal necrolysis (TEN) is emphasized because of the highest mortality rate (30%-35%). There also are Stevens-Johnson syndrome (SJS) and transitional forms, all similar to TEN, but less extensively affecting the skin and thus having lower mortality (5%-15%). On the other hand, reaction called drug reaction with eosinophilia and systemic symptoms (DRESS), which is a form of hypersensitivity syndrome, has a mortality of about 10%[1]. One more syndrome should also be mentioned, i.e. acute generalized exanthematous pustulosis (AGEP) caused by medication. Unless properly treated, it is associated with a mortality of up to 5%. AGEP is characterized specifically by hundreds or even thousands of sterile, non-follicular pustules[2,3].

The SJS-TEN is usually induced by a medication. Nevertheless, other etiologies should also be taken into consideration, e.g., graft versus host disease. There are reports on several cases of SJS-TEN association with infections (*Mycoplasma pneumoniae*), while in some cases the etiology remained unexplained[1]. The SJS-TEN is most commonly associated with the

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usage of certain drugs, e.g., sulfonamides, anticonvulsants, some nonsteroidal anti-inflammatory drugs (NSAIDs) and allopurinol[1]. Rarely, SJS-TEN is described as a consequence of antiresorptive therapy, particularly alendronate. Also, there is a significantly increased risk for the development of this syndrome in HIV infection and autoimmune diseases (e.g., systemic lupus erythematosus)[1,4].

When it comes to AGEP and the incriminating drugs, the main cause of AGEP are antibiotics, in particular beta-lactams and macrolides; however, other etiologies are possible, such as viruses (B19 and enterovirus), mercury, bite of a spider, or other medications[3].

DRESS syndrome is also known as a drug induced hypersensitivity syndrome (DIHS). Generally, it is a reaction to the medication. DRESS is clinically defined by a triad of symptoms including fever, skin rash, and internal organ involvement that can be symptomatic or asymptomatic. The most common organs involved are the liver, kidneys and lungs[5]. Eosinophilia (≥1500/mL) is an obligatory laboratory finding in DRESS syndrome[6]. Leukocytosis and lymphocytosis are also common[5].

Such reactions to drugs are known for a long time. For instance, the anticonvulsant hypersensitivity syndrome (AHS) was first described in 1950 by Chaiken *et al.*[7]. In 1996, Bocquel *et al.* proposed the acronym DRESS for drug reaction with eosinophilia and systemic symptoms, a syndrome that unites numerous syndromes, also drug reactions with common characteristics: AHS, dapsone syndrome, etc.[5,8]. Therefore, DRESS syndrome is nowadays a frequently used term.

The incidence of DRESS syndrome remains unclear. Because of the variable presentation along with various clinical and laboratory findings, proper recognition of the syndrome is very difficult and routine term utilization is not possible without uniformly accepted criteria.

As in SJS-TEN, in DRESS syndrome cutaneous lesions and systemic disorders occur due to the drug taken. DRESS is most often associated with anticonvulsants, sulfonamides, dapsone, allopurinol, minocycline and gold salts[1,9,10]. Some publications describe rare occurrence of this syndrome as a response to NSAIDs, quinolones, and antiresorptive drugs (strontium ranelate)[11-13].

The pathophysiology of DRESS and SJS-TEN is similar. It is a drug-induced immune reaction, an allergic hypersensitivity reaction type IV. Some authors consider the possibility of enzyme defects (slow acetylators) in the metabolism[14]. Full complexity of the immunopathogenesis in DRESS syndrome is best illustrated through a two-way relationship with autoimmune diseases. Autoimmunity increases the risk of DRESS syndrome, while DRESS can lead to the occurrence of autoimmune reaction[15,16]. A common factor for this bilateral connection could be viral coinfection (especially herpesvirus reactivation, HHV6, EBV)[17-19].

Inflammatory response in patients with DRESS usually begins with high or low fever. The patient develops maculopapular skin rash, lymphadenitis and pharyngitis in the next day or two[19,20]. Then there are organosystemic manifestations, most commonly hepatitis, eosinophilia, blood dyscrasias and nephritis. The presence of three of these criteria is sufficient to diagnose DRESS syndrome. Other possible findings in DRESS patients include pneumonitis, hepatosplenomegaly, oral ulcers, exudative tonsillitis, strawberry tongue, periorbital or facial edema, myopathy, flu-like symptoms, disseminated intravascular coagulopathy, colitis, and hypothyroidism[5].

Although the diagnosis can be set by lymphocyte transformation test and patch test, DRESS is mainly diagnosed by the time of onset (the time elapsed from taking the medication to the occurrence of disease), clinical examination, laboratory tests, and recovery after the culprit drug discontinuation[5]. Sometimes additional diagnostic tests may be required.

When DRESS is timely and appropriately treated, organ damage can usually be reversed and the function of affected organs fully restored. For example, acute interstitial nephritis will spontaneously regress within weeks, if the precipitating agent is removed[21].

Early diagnosis, etiology determination and immediate discontinuation of suspect drug are most important in therapeutic process. Development of this type of allergic reactions to drugs should be suspected at the first glance to skin or mucosa changes, mostly associated with the use of anticonvulsants, sulfonamides, allopurinol, or (in rheumatology) NSAIDs and very rarely antiresorptive therapy. In therapeutic terms, it is crucial to stop the responsible medication. In general, treatment of these allergic reactions

to drugs is symptomatic. In severe cases, treatment is carried out in intensive care units, according to the principles of skin burn management: warm environment, electrolyte disbalance correction, parenteral hyperalimentation and prevention of sepsis[1]. It is difficult to assess the efficacy of drugs described in some case reports: intravenous immunoglobulin (IVIG), cyclosporine, cyclophosphamide, pentoxifylline, and thalidomide. Questionable is the use of corticosteroids in severe forms of TEN. In DRESS syndrome, corticosteroids may be useful to manage damage to internal organs (hepatitis, nephritis, pneumonitis)[1]. The use of the mentioned treatment measures is associated with mortality reduction and faster re-epithelialization of skin lesions.

In the future, the patient should completely avoid usage of the incriminating drug, even in allergic testing.

Case Report

A female patient aged 57 presented to internal emergency clinic for the left lumbar pain. Clinically, she had fever, chills, shivering and dysuria. Laboratory findings and abdominal ultrasonography verified the clinical diagnosis of acute left-side pyelonephritis with ipsilateral nephrolithiasis. Urine microbiology showed *Enterococcus faecalis*. The patient was discharged with recommendation for ciprofloxacin therapy for 10 days, abundant rehydration, diclofenac and paracetamol as needed.

After 10 days of the introduction of ciprofloxacin, the patient presented for follow up with worsening of general symptoms despite regression of dysuric problems. New signs appeared including feeling of weight in the muscles, itching, and mild exanthema mainly on the trunk skin and upper extremities, without mucosal ulceration. The patient was still subfebrile. Laboratory findings showed an increase in leukocyte count (L 28x10^9/L), primarily on the account of eosinophilia (Eo 17.80x10^9/L, 63.5%) (Fig. 1), and in liver enzymes (AST 71.5 IU/L, ALT 104.4 IU/L, AP 321 IU/L, GGT 119 IU/L) (Fig. 2); protein immunoelectrophoresis yielded elevated levels of IgE (368 IU/mL). Leukocyturia and erithrocyturia persisted, with 60% of dysmorphic and 40% of smooth red blood cells. *Escherichia coli* was isolated from urine.

These findings brought into question the efficacy of current therapy. Changes were indicative of possible medication side effects, i.e. ciprofloxacin as a newly introduced drug still used. Therefore, ciprofloxacin was removed from therapy. Amoxicillin with clavulanic acid and mebendazole were introduced instead of ciprofloxacin. There was a decrease in eosinophil count (Eo 12.70x10^9/L, 57.6%) two days after ciprofloxacin discontinuation. Shortly after, the itch and skin rash spontaneously regressed, and the patient's general condition improved. In the next two months, eosinophil count and liver enzyme levels gradually decreased until final follow up values of Eo 1.11x10^9/L (14.9%) (Fig. 1), AST 17 IU/L, ALT 25.8 IU/L, AP 107 IU/L, and GGT 37 IU/L (Fig. 2). There were 100% of dysmorphic erythrocytes in the urine. Repeat abdominal ultrasonography showed a wider prominent pyramid in the left kidney, meaning that the inflammation led to permanent damage.

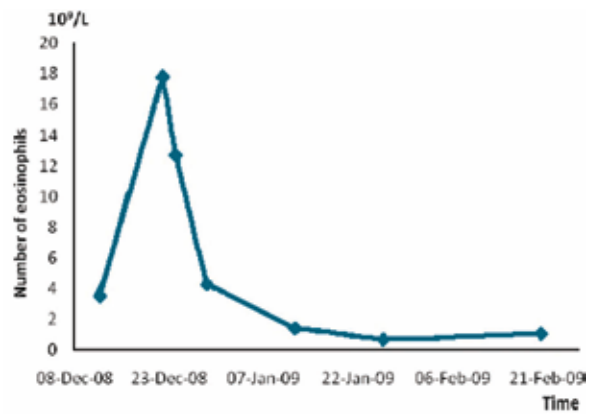

Fig. 1. Trends in the number of eosinophils in circulating blood.

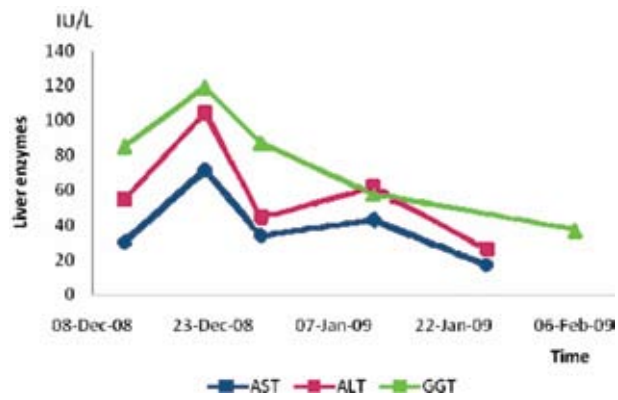

Fig. 2. Changes in the levels of liver enzymes.

Additional serology did not confirm the presence of viral or parasitic infection agents. Analysis of peripheral blood smear yielded normal findings, except for the still present mild eosinophilia, which was on a decline. According to MSCT of the abdomen and values of tumor markers that were within the normal limits, tumor etiology of eosinophilia was ruled out. Additional studies for autoimmune etiology have been planned.

The clinical symptoms in our patient regressed short after discontinuation of the culprit drug, so she did not require differential treatment. Laboratory findings normalized short after drug discontinuation, only kidney function recovered gradually, over several weeks. The patient has been referred for regular follow up of liver and kidney function, with additional diagnostic workup that will rule out the possible disease of other target organs. She was advised to avoid using ciprofloxacin for either diagnostic or therapeutic purpose in the future. A year after the occurrence of DRESS syndrome, the patient was free from recurrence.

Discussion

Regarding the severe systemic drug reactions with skin manifestations, one should always bear in mind the possibility of reaction to the medication the patient has been taken; therefore, adequate information on it should be taken from the patient. Sometimes it is difficult to distinguish types of drug reactions, especially when there is an overlap of symptoms. In DRESS, the most important laboratory finding is eosinophilia, which distinguishes it from other severe systemic drug reactions with skin manifestations[22]. Besides DRESS, another possible manifestation of drug reaction is SJS/TEN, characterized by the presence of blisters (SJS <10% and TEN >30% of total body surface area). In most of these patients, the lining of the mouth, conjunctiva, and genitals is affected. TEN also affects areas on the inner epithelium surfaces (lung, gastrointestinal tract), and multiple organ failure may occur, as in DRESS. TEN and DRESS may occasionally have similar clinical presentation. Our patient had a mild skin reaction, differentially presented in many diseases and syndromes. Although the clinical picture of her skin changes seemed insignificant, after collecting additional history data on the occurrence and diagnostic analysis, DRESS was suspected and subsequently confirmed. Timely elimination of ciprofloxacin prevented progression of the disease. The lesions regressed spontaneously, confirming the diagnosis. Such mild forms of DRESS syndrome have already been reported in the literature[20]. However, the mild form of skin reactions should not mislead us. Involvement of the kidneys and liver, together with significant eosinophilia, were crucial in establishing the correct diagnosis in our patient. Considerable difficulties encountered on setting up the diagnosis impose the question of the actual prevalence of the disease.

In terms of pathophysiology, this reaction with maculopapular exanthema and eosinophilia in DRESS is hypersensitivity reaction type IV, i.e. the mechanism of cellular immunity[22]. Thereby, development of DRESS includes Th2-lymphocytes and CD8+ cells[20]. It is likely that Th2 cells induce type IVb hypersensitivity response affecting the skin, while CD8+ T cells cause damage to internal organs[23].

Study results have shown the mortality of DRESS syndrome to be 10%[22]. It should be noted that liver involvement is a poor prognostic sign, and together with icteric pruritus predicts the possible fatal outcome in 20% of patients[20]. Early elimination of the causal drug results in better patient prognosis. Unfortunately, the factors that determine the severity of organ failure or the number of affected organs remain unknown, although the potential role of genetic factors is considered. Therefore, according to some authors, close patient relatives should avoid the same drug too[22].

Some authors believe that systemic corticosteroid therapy is required in DRESS syndrome[1]. The recommended dose is prednisolone 40-60 mg/day for at least 6-8 weeks to avoid symptom relapse. In our patient, we did not use systemic steroids, but only supportive therapy, rehydration, given that changes gradually regressed spontaneously. However, no randomized placebo-controlled study supports or rejects this opinion[20,22]. Several cases have been described of patients with DRESS and extensive internal organ involvement, such as fulminant hepatitis, responding favorably to systemic corticosteroids[24]. Taking into account the respective therapy side effects (particularly infection and sepsis), we believe that systemic corticosteroids are justified in severe forms of DRESS.

Literature reports on the management of DRESS patients indicate successful treatment with intravenous pulsed dose of methylprednisolone (30 mg/kg for 3 days), IVIG, plasmapheresis, or combinations of these therapies[20]. It is considered that the use of IVIG is indicated in fulminant forms of DRESS syndrome.

According to the possible viral etiopathogenesis of DRESS, future studies should perhaps take into account the antiviral agents like ganciclovir as the possible prevention or treatment agent[19].

Mild forms of DRESS, as in our patient, in general recover spontaneously within weeks without the use of systemic corticosteroids. However, such cases require regular follow up of liver and kidney function, along with additional tests to exclude damage to other target organs, e.g., lungs, heart and thyroid gland. Due attention should be paid to the thyroid gland function because hypothyroidism may occur several months after recovery from the acute illness[20].

Conclusion

The occurrence of itch and rashes in patients taking drug therapy should not be simply considered as transient and benign changes. A more comprehensive analysis is proposed including liver and kidney function studies because the underlying disorder may be a systemic, severe cutaneous reaction to a drug, such as DRESS. Early diagnosis, identification of the etiology and therapy, starting with early discontinuation of the suspected drug, are most important in therapeutic process. For now, only elimination of the drug has a definitely proven therapeutic effect, therefore, early diagnosis is the key factor. This report may hopefully upgrade the awareness of this rare syndrome.

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Sažetak

SINDROM DRESS S BLAGIM MANIFESTACIJAMA KAO DIJAGNOSTIČKI I TERAPIJSKI PROBLEM: PRIKAZ SLUČAJA

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Teške oblike kožnih reakcija na lijekove povezanih sa sistemskim simptomima čini nekoliko sindroma: toksična epidermalna nekroliza, Stevens-Johnsonov sindrom, akutna generalizirana egzantematozna pustuloza te reakcija na lijekove s eozinofilijom i sistemskom reakcijom (DRESS). Kod takvih reakcija se nekoliko dana do 6 tjedana od uvođenja lijeka pojave promjene na koži, a često su zahvaćeni i unutarnji organi (jetra, bubrezi, pluća i dr.). Zbog toga je u ovakvim oblicima preosjetljivosti na lijekove velika smrtnost. Opisuje se slučaj bolesnice kojoj je ambulantno dijagnosticiran pijelonefritis, te je bila otpuštena kući uz preporuku terapije ciprofloksacinom. Deset dana kasnije bolesnica se vratila u ambulantu s pogoršanjem kliničke slike, lošeg općeg stanja, uz pojavu kožnih eflorescencija, oštećenje jetrene i bubrežne funkcije te s eozinofilijom. Na temelju kliničkih nalaza i ostale obrade postavljena je dijagnoza sindroma DRESS. Dijagnoza i terapija teških oblika reakcija na lijekove i u današnje vrijeme predstavljaju medicinski izazov.

Ključne riječi: *Preosjetljivost na lijekove – prevencija i kontrola; Erupcije uzrokovane lijekovima – etiologija; Erupcije uzrokovane lijekovima – dijagnostika; Erupcije uzrokovane lijekovima - terapija*