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DRESS syndrome – A dermatological emergency – Sulfasalazine-related acute drug reaction case report

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) or drug-induced hypersensitivity syndrome (DIHS) is a severe skin reaction associated with general symptoms and mortality reaching up to 10% of cases. DRESS/DIHS is one of the few dermatological emergencies which need to be taken into consideration when dealing with a patient with acute exanthema and systemic symptoms like: fever, lymphadenopathy, muscle pain, hepatosplenomegaly, abnormal blood count results and systemic inflammation. The aim of this article is to summarize the literature finding regarding this dermatological emergency and present the case of a 42-year-old male suffering from DRESS syndrome as a consequence of sulfasalazine intake due to an inflammatory bowel disease, who was effectively treated with oral prednisolone and immediate drug withdrawal.

1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) or drug-induced hypersensitivity syndrome (DIHS) is a severe skin reaction with general symptoms: fever, lymphadenopathy, abnormal blood count results, systemic inflammation and HHV-6 reactivation reaction. DRESS/DIHS is sometimes fatal with mortality reaching up to 10% overall and 40% if cardiovascular complications are present. Hereby we present a case of a 42-year-old male suffering from DRESS syndrome as a consequence of sulfasalazine intake due to an inflammatory bowel disease.

2. Case report - DRESS syndrome in patient with inflammatory bowel disease due to sulfasalazine intake

PL, a 42-year-old male patient was hospitalized in our Department of Dermatology because of an acute maculo-papular skin exanthema of the whole body with pruritus, fever up to 40 °C, muscle pain and general malaise (Fig. 1, Fig. 2).

The patient reported to have taken sulfasalazine because of unspecified inflammatory bowel disease. After four weeks of drug intake he observed a rash consisting of erythematous macules predominantly on sun-exposed areas, such as face and forearms. Two days later he ceased the drug's intake. Consequently, the exanthema continued to spread with general inflammation of the whole skin in the consecutive 8 days, when high fever (up to 40 °C) and pharynx pain occurred. The patient contacted his general practitioner, who administered bilastine (80 mg daily) and prednisone (3 mg daily). On the following day the patient arrived at the Hospital

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Emergency Department, where he was referred to our Department due to erythroderma.

The patient had not ever been treated dermatologically. Chronically, the patient suffered from Hashimoto disease (in euthyreosis at the time) and had received a prosthetic implant of the hip due to its dysplasia three years prior. Family history - his mother suffered from psoriasis, and his daughter from atopic dermatitis. He denied suffering from any former allergies to pharmaceuticals.

On admission a confluent erythematous and papular exanthema of the whole body was observed and the patient complained of an itching sensation. Moreover, pustular lesions were present on the skin of the neck and the nose. The exanthema was accompanied by cervical, axillary and inguinal lymphadenopathy, pharyngitis, non-purulent tonsillitis, and subtle periocular edema.

Laboratory tests revealed elevated serum transaminases (ALT - 265 U/l, AST - 97/l), phosphate alkalase (348 U/l) and gamma-glutamyltransferase levels (264 U/l). Peripheral blood count showed leukocytosis (20,55 G/l), eosinophilia (3,28 G/l with relative blood count of 11,7%), lymphocytosis, monocytosis and a left shift response of granulocytes.

Further tests revealed increased C-reactive protein level (9 mg/l), impaired fasting glucose level (124 mg/dl), total (1,3 mg/dl) and direct bilirubin (0,96 mg/dl) and decreased total protein (5,17 g/dl) and albumin (2,88 g/dl) levels.

Viral tests for SARS-CoV-2, HAV, HBV, HCV, CMV, EBV, HIV, HHV6 and HHV7 were negative. Increased serum level of *anti*-Yersinia IgM antibodies was observed (160 U/ml). CEA, AFP, Ca 19.9, PSA were within the normal range. Antinuclear antibodies (titer of $<1/160$) with granular fluorescence were observed. Radiological findings consisted of chest X-ray, abdomen and pelvis MRI and abdominal ultrasonography which revealed only an enlarged spleen (135 mm in longitudinal axis). Due to changes in peripheral blood count the patient was consulted by a hematologist; a bone marrow sample was collected for flow cytometry, which excluded any potential lymphoproliferative disorder. A skin biopsy was also performed.

Based on diagnostic criteria of the RegiSCAR group (Registry of Severe Cutaneous Adverse Reactions) (see below in the discussion section) the patient was diagnosed with DRESS syndrome by having 6 points in total.

The patient was treated using methylprednisolone in pulse therapy - 1000 mg i.v. daily in the first 3 days, later 32 mg p.o. daily for 7 consecutive days. The patient was discharged with a tapering dose. Adjuvantly, the patient was treated with antihistamines (clemastine 4 mg daily i.v.), doxycycline 100 mg twice daily for its antichemotactic properties, as well as low molecular weight heparin for antithrombotic prevention. Due to concomitant oral herpes infection the patient received acyclovir 200 mg 5 times daily. Topical treatment consisted of boric acid creme with 1% hydrocortisone.

The applied treatment resulted in gradual remission of the symptoms with diminution of serum enzyme levels: ALT (153 U/l), AST (48 U/l), ALP (221 U/l), GGTP (220 U/l) and lowered leukocytosis (WBC 12,13 G/l) and CRP (1,9 mg/dl) levels.

After 13 days of treatment the patient was discharged with good clinical response. Four weeks later we saw the patient again in our dermatological outpatient clinic and observed complete remission of skin symptoms (Fig. 3) with no noticeable adverse outcomes by the patient. All the major events and chronological order of the patients symptoms and treatment are summarized in Table 1.

We received the patient's permission to public this case in the medical literature.

3. Discussion

Many pharmaceuticals may be responsible for rapid development of DRESS/DIHS - the most common ones are listed below (Table 2.) [1]. Sulfasalazine is one of the most incriminated drugs in DRESS. Its pathogenesis is related to the existence of drug-specific $CD4^+$ and $CD8^+$ T cells that, after the application of specific drug, activate and produce large, uncontrolled amounts of tumer necrosis factor alpha (TNFα) and interferon gamma (IFNγ). Moreover, some studies suggest that a reactivation of viral infections from the *Herpesviridae* family (most commonly HHV6, but also HHV7, EBV and CMV) are present in up to 75% of cases, as shown by *in vitro* studies, where beforementioned T cells' were enriched by copies of viral DNA [2,3]. The characteristic feature is its long latency period between 3 and 8 weeks since the beginning of the drug admission, which may lead to diagnostic difficulties in patients, as they may not initially associate the symptoms with their proper causative factor [4].

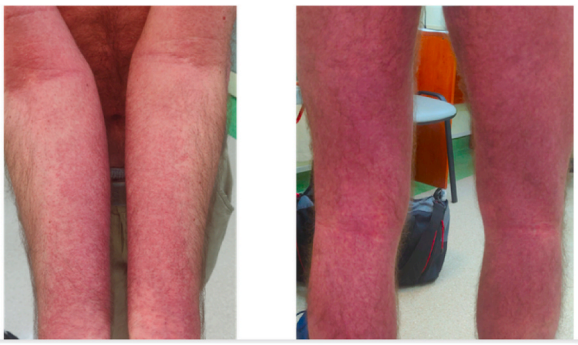

Fig. 1. Confluent erythematous and papular exanthema on patient's forearm and legs.

4. 1. Epidemiology

DRESS/DIHS syndrome is a quite rare clinical entity, with different literature sources providing different epidemiological numbers - between 1 in 1000 to 1 in 100 000 cases of drug exposition. These figures may be in fact higher as it is often misdiagnosed by non-dermatologists. The information regarding sex preponderance is equivocal, with some authors' data showing 0,8 male to female ratio [3] Pathologically, DRESS is often associated with latent viral infection reactivation - mostly with *Herpesviridae.* [5].

5. 2. Clinical presentation

The most characteristic feature of DRESS/DIHS syndrome is its skin lesions, which occur in 73–100% of patients [6].

> Hematological abnormalities consist mostly of eosinophilia (present in 66–95% of patients). Eosinophilic infiltrates in specific organs account for the wide heterogeneity of symptoms and a broad clinical spectrum of the disease. Between 27 and 67% of patients have atypical lymphocytes in peripheral blood smear, and more than half of them have enlarged, palpable lymph nodes [7].

The most common systemic complication of DRESS/DIHS is liver damage (observed in 75–94% of patients), which may occur before the skin lesions and may be associated with atypical blood lymphocytes [8]. The kidneys may also be afflicted, but the symptoms are usually mild and no subsequent damage is usually present. However, in some cases, severe interstitial nephritis, acute tubular necrosis or vasculitis may lead to renal insufficiency and, subsequently, death [9]. The third most common systemic manifestation is a lung disease, which presents as dyspnea, interstitial lung disease, pleuritis or acute respiratory distress syndrome [9,10].

In around 4–27% of patients cardiological complication occurs - mostly with electrocardiographic changes, left ventricular dysfunction and arrhythmias, which are associated with worse outcomes in patients [11,12].

Sometimes, neurological symptoms are also present: headache, seizures, coma or ataxia. These may result from meningitis or meningoencephalitis. The symptoms usually last 15 days [10].

The case of our patient's clinical presentation is, in general, consistent with the general findings in DRESS/DIHS patients with skin, blood and liver involvement. It also underlines the importance of drug eruptions as an important diagnostic consideration in patients presenting with erythroderma and flu-like symptoms.

5.1. Diagnosis

DRESS/DIHS syndrome is difficult to diagnose, as there is no single test for its diagnosis. Many diseases may present similarly, such as: mononucleosis, measles, Kawasaki disease, acute retroviral syndrome or hematological malignancies. Thus the diagnosis should be based on excluding other differentials. Several different criteria were developed to aid the clinicians in the diagnosis (such as Bocquet criteria or Japanese criteria) [12], but the most widely accepted one was developed by the RegiSCAR group (Table 3.).

An important clinical problem is the differential diagnosis between DRESS/DIHS and Stevens-Johnsons Syndrome (SJS) or toxic epidermal necrolysis (TEN). The lymphocyte transformation test (LTT) is a valid *in vitro* test for the differentiation between the former and the latter. In case of DRESS/DIHS, the positive result is possible to be obtained in the convalescence period, whereas in SJS/TEN - only in the acute phase. Thus, a negative LTT test may be exceedingly useful in the diagnosis [13].

Because of *Herpesviridae* infection association, Some authors suggest that IgG antibodies against HHV-6 may be helpful in DRESS/DIHS diagnosis, but due to low availability of this test in clinical practice, it is not widely used [14].

5.2. Treatment

The most important aspect of treatment for DRESS syndrome is the immediate withdrawal of the causative drug [15]. The second treatment option is the administration of systemic corticosteroids - the proposed initial doses of prednisolone is 40–50 mg daily with subsequent dose tapering. Therapy should last for a minimum 2–3 months [16,17]. The reason for this is a possible development of the immune reconstitution inflammatory syndrome (IRIS) [18]. In our patient, the treatment was administered immediately on admission,

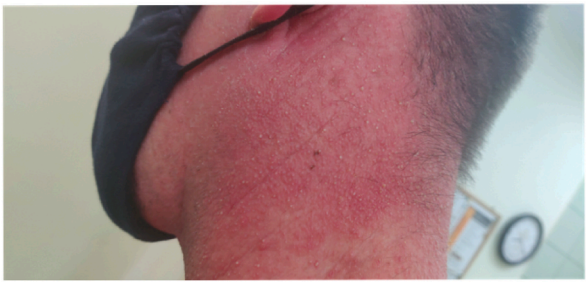

Fig. 2. Papulo-pustular exanthema on patient's neck.

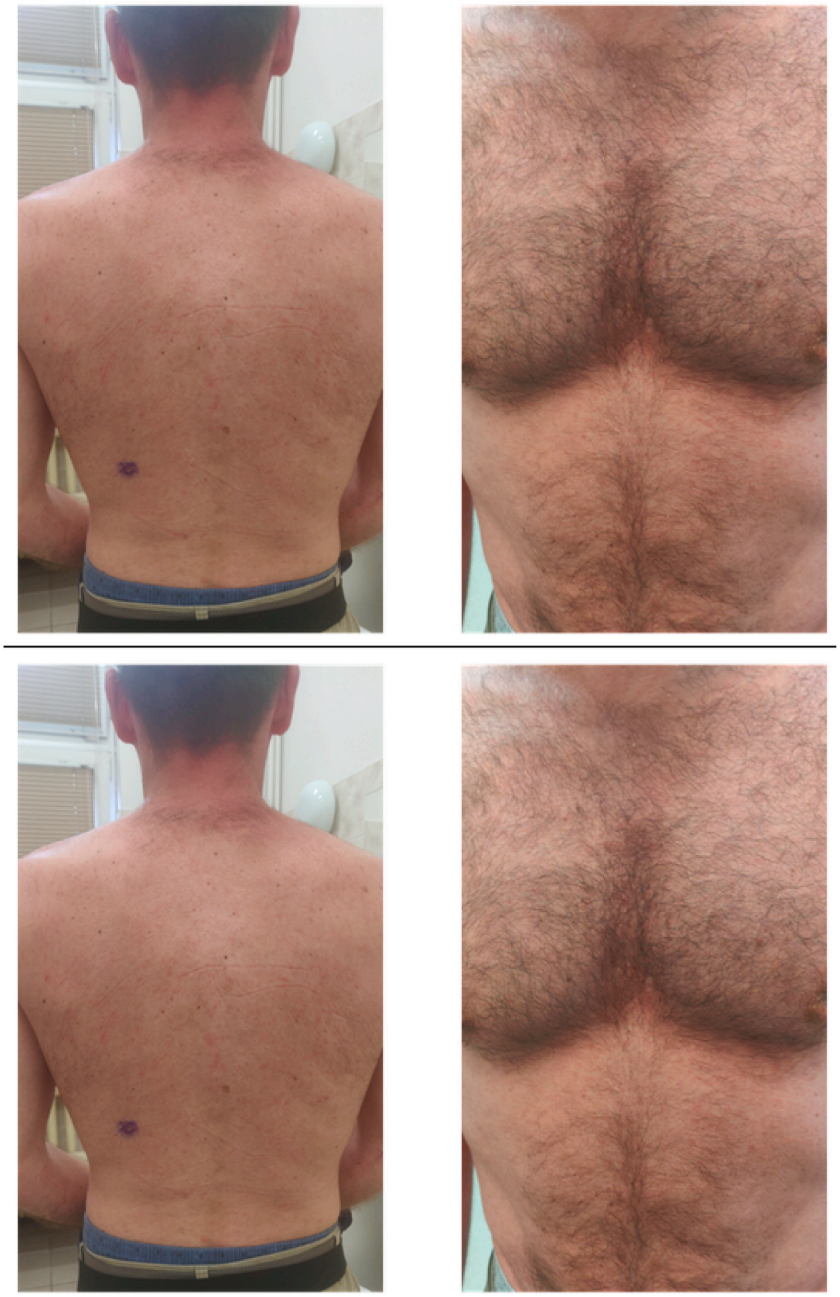

Fig. 3. Complete remission of symptoms after hospitalization.

Table 1
The brief summary of the patient's history.

Day 1	Day 29	Day 31	Day 40	Day 53	Day 81
The beginning of sulfasalazine intake	The beginning of the symptoms	Drug's intake cessation	Exacerbation of the symptoms, hospitalization	Release from the hospital	Outpatient follow-up

Table 2
Drugs that are most often associated with DRESS/DIHS syndrome [4].

Drug group	Drugs
Anticonvulsants	carbamazepine, lamotrigine, phenobarbital, phenytoin, oxcarbazepine, gabapentin
Antibiotics	amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, piperacillin/tazobactam, vancomycin
Antituberculous drugs	ethambutol, isoniazid, pyrazinamide, rifampin, streptomycin
Antiretroviral drugs	abacavir, nevirapine
Drugs used in HCV treatment	boceprevir, telaprevir
NSAIDS and antipyretics	diclofenac, celecoxib, ibuprofen
Sulfonamides	dapsone, sulfamethoxazole-trimethoprim, sulfasalazine
Drugs used in target therapy	sorafenib, vismodegib, vemurafenib, imatinib
Other	allopurinol, herbal drugs used in Chinese medicine, mexiletine, omeprazole

Table 3
Scoring system for the diagnosis of DRESS by RegiSCAR.

Clinical parameters		Score			Comments
		−1	0	1	
Fever ≥101.3 °F (38.5 °C)	N/U	Y			
Lymphadenopathy		N/U	Y	>1 cm, at least 2 sites	
Eosinophilia ≥0.7 × 109 or ≥10% if leucopenia		N/U	Y	Score 2 points if ≥ 1.5 × 109	
Atypical lymphocytes		N/U	Y		
Skin rash					
Rash suggestive of DRESS	N	U	Y	Suggestive features: ≥2 facial edema, purpura, infiltration, desquamation	
Extent ≥50% of BSA		N/U	Y		
Skin biopsy suggestive of DRESS	N	Y/U			
Organ involvement		N	Y	1 point for each organ involvement, maximum score: 2	
Disease duration ≥15 days	N/U	Y			
Exclusion of other causes		N/U	Y	1 point if 3 of the following tests are performed and are negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture	

N - no, Y - yes, U - unknown.
Total score.
<2: Excluded.
2 to 3: Possible.
4 to 5: Probable.
≥6: Definite.
DRESS: drug reaction with eosinophilia and systemic symptoms; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; ANA: antinuclear antibody.

that is on the 9th day since the symptoms' onset.

6. Conclusion

In conclusion, DRESS is a rare, albeit potentially lethal syndrome, which is an important clinical entity to take in consideration whilst assessing a patient with a sudden, erythrodermic skin rash, fever and systemic involvement. Therefore, DRESS syndrome may be considered as a hypersensitivity drug reaction with a significant skin presentation, representing one of the emergency clinical situations in dermatology. Due to the lack of commercially available tests, its diagnosis is based on clinical symptoms and laboratory results. Quick withdrawal of the causative drug is a necessity and the treatment with glucocorticosteroids is the first line of treatment.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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