

DRESS syndrome as a complication of treatment of hepatitis C virus-associated post-inflammatory liver cirrhosis with peginterferon α 2a and ribavirin

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Abstract

Various skin and systemic symptoms may develop as a complication of treatment with different medications and medicinal substances. One of them is a relatively rare drug reaction with eosinophilia and systemic symptoms, referred to as DRESS syndrome. The morphology of skin lesions and the patient's general health can differ; the management involves withdrawal of drugs suspected of triggering DRESS syndrome, and administration of local and systemic glucocorticosteroids. In this paper we present a case of a patient with HCV associated chronic hepatitis, treated with peginterferon α 2a (PEG-IFN- α 2a) and ribavirin, who developed skin lesions and systemic symptoms typical of DRESS syndrome.

Key words: DRESS syndrome, hepatitis C, interferon α , ribavirin.

Introduction

The treatment standard in hepatitis C virus (HCV) associated chronic hepatitis includes administration of peginterferon α -2a (PEG-IFN- α -2a) and ribavirin (RBV). The treatment is long term, lasting between 24 and 72 weeks (depending on e.g. HCV genotype and early treatment response) and is usually associated with a poor response rate (sustained virologic response of 45% in HCV G1 and G4 patients, 75% in HCV G2 patients, and 65% in genotype 3 patients) as well as poor treatment tolerance. Although the efficacy of newly approved anti HCV therapies (combined PEG-IFN α plus RBV plus HCV protease inhibitor: boceprevir or telaprevir) is better, they are associated with an even higher rate of adverse effects, including various skin lesions. They are referred to in the Summary of Product Characteristics (for PEG-IFN- α , which is the key constituent in the said therapeutic schemata) as skin lesions, rash, pruritus, exacerbation or induction of psoriatic lesions. Clinical practice and observation of patients treated according to the standard of care (SOC – that is peginterferon and RBV) shows a wide range of skin and mucous lesions, of variable morphol-

ogy and pathomechanisms. Severe skin lesions develop in approx. 0.4% of patients treated with a standard two-drug combination therapy and in approx. 5% of patients treated with a three-drug combination therapy (including HCV protease inhibitor) [1].

DRESS syndrome – *drug reaction (or rash) with eosinophilia and systemic symptoms* (also referred to as DIHS – *drug-induced hypersensitivity syndrome*) is a special type of the severe drug-induced allergic reaction. It is characterized by the onset between 1 and 8 weeks following treatment commencement, generalized rash, fever, lymphadenopathy, haematological abnormalities (presenting as eosinophilia and/or atypical lymphocytosis), and damage to internal organs. It is associated with a high mortality rate up to 10%, mainly due to liver disease [2, 3].

The pathogenesis of DRESS syndrome has not been fully understood yet; it is probably multifactorial. Reactivation of infections with HHV-6 (human herpes virus 6) and HHV-7, Epstein-Barr virus (EBV), cytomegalovirus (CMV), parasitic infestation [4], or disturbed free acetylation-associated drug detoxification pathways are

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considered to trigger the syndrome [5]. The estimated prevalence ranges between 1 : 1000 and 1 : 10,000 drug exposure cases [6].

The drugs most commonly associated with DRESS syndrome are:

- anticonvulsants: phenobarbital, carbamazepine, phenytoin, lamotrigine,
- antidepressants: fluoxetine, amitriptyline,
- sulphonamides: dapsona, sulphasalazine, trimethoprim-sulfamethoxazole,
- β -blockers: atenolol,
- antiviral medications and antibiotics: doxycycline, metronidazole, ceftriaxone, abacavir, telaprevir, boceprevir,
- non-steroidal anti-inflammatory drugs (NSAIDs): naproxen, diclofenac, ibuprofen,
- other medications: allopurinol, diltiazem, dobutamine, thalidomide, propylthiouracil [7].

DRESS syndrome diagnostic criteria according to the RegiScar Project [8] (≥ 4 must be present): 1) hospitalization; 2) sudden onset of rash concomitant with fever over 38°C ; 3) peripheral lymph node enlargement in at least 2 sites; 4) at least one internal organ involvement (lungs, liver, kidneys, pancreas, muscles, heart); 5) eosinophilia $> 10\%$ or $700/\text{ql}$; atypical lymphocytes; lymphopenia < 4000 or lymphocytosis; thrombocytopenia.

Japanese diagnostic criteria of DRESS syndrome (7 of 9 or first 5 criteria must be present) [9]: 1) maculopapular rash, which develops after 3 weeks of treatment; 2) symptoms persisting over 2 weeks following drug withdrawal; 3) fever over 38°C ; 4) liver disease (ALT > 100 IU/l) or other organ involvement; 5) increased white blood count; 6) atypical leukocytes; 7) eosinophilia; 8) lymphadenopathy; 9) reactivation of HHV-6 infection.

In doubtful cases, skin biopsy is useful as a diagnostic tool, although histopathological lesions are not specific. Lymphocyte infiltrations have been described which can also contain eosinophils.

Treatment of severe drug-induced allergic reaction requires hospitalization, withdrawal of drug(s) triggering the symptoms, administration of local and systemic glucocorticosteroids, as well as antipyretic medications. Secondary prevention is also crucial, which involves future avoiding generic drugs and the ones of chemical structure similar to the known allergen [10].

Below we present a case of DRESS syndrome.

Case report

A male Caucasian 52-year-old patient with the active, HCV associated cirrhosis (positive HCV RNA, genotype 1b) diagnosed in February 2011, and the history of HBV (negative HBsAg, positive anti-HBc, positive HBV DNA) was admitted to hospital.

The disease was diagnosed during the first episode of hepatic decompensation manifested as ascites. Cirrhosis was confirmed based on the clinical manifestation: in

clinical examination, spider veins were shown on the patient's trunk, concomitant with hepatic palmar erythema and hepatosplenomegaly; laboratory tests revealed mild thrombopenia (PLT $146 \times 10^3/\text{ql}$; reference range: $150\text{--}420 \times 10^3/\text{ql}$), α -fetoprotein level = 14.82 ng/ml (reference range: < 10 ng/ml), decreased total cholesterol level = 116 mg/dl (reference range: $150\text{--}200$ mg/dl), decreased albumin level = 3.2 g/dl (reference range: $3.5\text{--}5.2$ g/dl), decreased prothrombin time = 63% (reference range: $80\text{--}120\%$). Esophagogastroduodenoscopy revealed the presence of grade I/II esophageal varices, suggestive of portal hypertension; the abdominal ultrasound revealed cirrhotic liver without focal lesions.

After ascites resolved; since the liver function was retained, no symptoms of liver failure persisted (Child Pugh score of 6/A) and no significant contraindications were found, combined treatment with peginterferon $\alpha 2a$ (180 μg s.c., once a week) and RBV (1200 mg p.o./24 h) was started in October 2011. The three-drug combined therapy based on PEG-IFN- α + RBV + IP HCV was not reimbursed in Poland at that time. The patient was also treated with propranolol (primary prevention of esophageal varicose bleedings), cyclonamine (thrombocytopenia), pantoprazole (gastropathy and gastric mucosal lesions due to gastritis), amiloride and hydrochlorothiazide (blood hypertension).

After the treatment was started, typical flu-like symptoms developed with slightly increased body temperature, but they resolved spontaneously. In the 12th week of treatment (mid-January 2012), the general health of the patient deteriorated, he reported generalized weakness and tiredness. Skin lesions, manifested as severe desquamating maculopapular eruption against the erythematous background, and local oedema concomitant with inguinal lymph node enlargement. Rapidly progressing skin lesions involved almost the entire skin of the upper extremities, buttocks and lower legs (approx. 36% of body surface), although their severity differed between the individual locations (Figures 1, 2). The described lesions were associated with severe generalized pruritus and skin burning sensation, and chronically increased temperature up to 38.5°C .

The patient was hospitalized in First Department of Infections Disease, J. Gromkowski Specialist Regional Hospital in Wrocław, where the antiviral treatment was discontinued. Laboratory tests showed eosinophilia of $2.9 \times 10^3/\text{ql}$ (reference range: $0.04\text{--}0.4 \times 10^3/\text{ql}$) (31.9% of all white blood counts, reference range of 1.0–6.0%), thrombopenia of $115 \times 10^3/\text{ql}$ (reference range: $150\text{--}500 \times 10^3/\text{ql}$), whereas C-reactive protein level was normal. Taking into consideration the type of skin lesions, additional symptoms such as pruritus, fever, lymphadenopathy and eosinophilia, symptoms of active liver disease, DRESS syndrome was suspected, based on the criteria discussed above. Hepatic decompensation or damage to other parenchymal organs were not observed.



Figure 1. Papular desquamating lesions on the elbow skin



Figure 2. Skin lesions on lower legs during treatment

Initially, for the first 3 days the treatment involved intravenous infusion of Solu-Medrol (40 mg); subsequently it was replaced with prednisone p.o. The dose was tapered and the treatment was discontinued after 20 days. Moreover, corticosteroid (Hydrocortisone 1%) and moisturizing ointments were applied. The treatment led to gradual resolution of skin lesions, pruritus, lymphadenopathy and eosinophilia (Figure 3).

Discussion

During the anti-HCV therapy, skin lesions may appear in over 30% of patients treated with PEG-IFN and RBV, at different stages of treatment [11]. They typically present as erythematous rash, local skin desquamation and irritation or local erythema at the injection site, which spontaneously resolve during subsequent treatment or after the treatment is completed. The management of such lesions should include local treatment and, in some cases, reduction of the RBV dose.

DRESS syndrome has been described in patients treated for chronic hepatitis C, as a complication of the three-drug combined treatment, i.e. the one including telaprevir, which is a new protease inhibitor administered for the first 12 weeks of PEG-IFN and RBV-based combined treatment [12]; or the two-drug combined treatment (fewer cases – only 3 patients in our own unpublished material).

In the case of our patient, the onset of systemic symptoms, such as fever, lymphadenopathy and severe



Figure 3. The effect of treatment

pruritus was an indication to immediate treatment discontinuation. However, it cannot be determined unequivocally, which drug triggered the described skin reaction.

A good rapport with the patient and treatment discontinuation caused complete resolution of this rapidly progressing life-threatening complication.

Unfortunately, HCV eradication was not achieved, which is sometimes observed despite a relatively short treatment duration.

Therefore, the advanced progressing post-inflammatory cirrhosis and an active HCV infection still need to be treated in this particular patient. The patient awaits for

the new anti-HCV medications, from a group of direct acting antivirals that is the interferon-free HCV treatment algorithm, based on combined new HCV protease and polymerase inhibitors with/without RBV, to be reimbursed by the Polish National Health Fund (NFZ). The first such treatment algorithm for 2 and 3 genotype based on sofosbuvir and RBV has been approved by the Food Drug Administration this year [13].

Conclusions

Antiviral treatment in HCV-infected patients requires extensive experience on the part of the therapeutic interdisciplinary team (infectious medicine specialists, dermatologists, haematologists), a good rapport with the patient, his/her understanding of therapeutic recommendations and easy access to proper specialist care, once adverse effects of treatment occur.

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