DRESS syndrom – nepříjemné překvapení nejen na JIP

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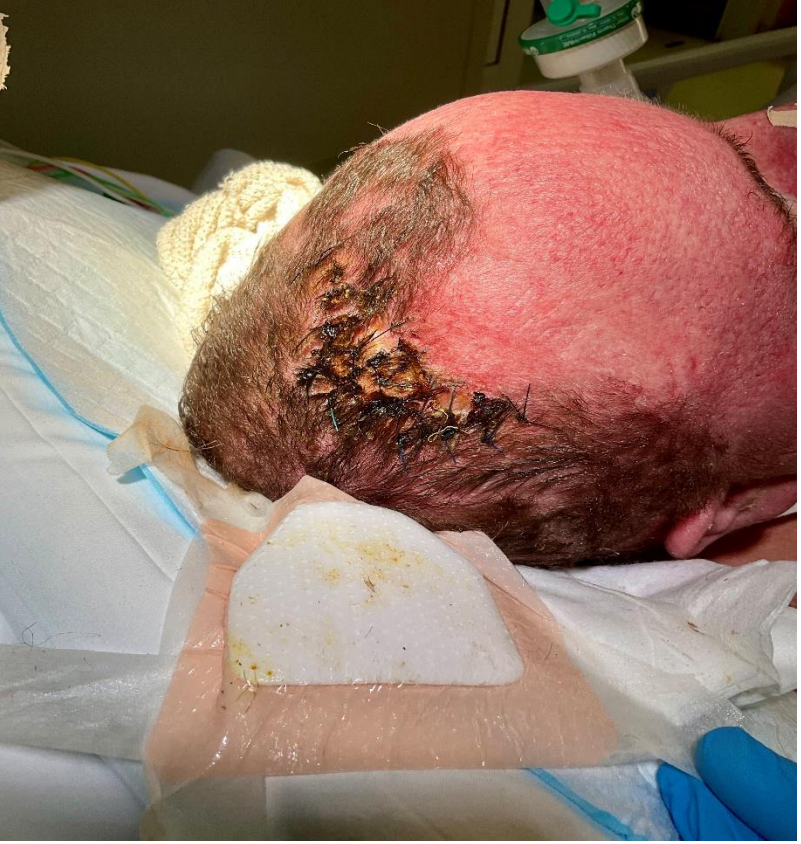
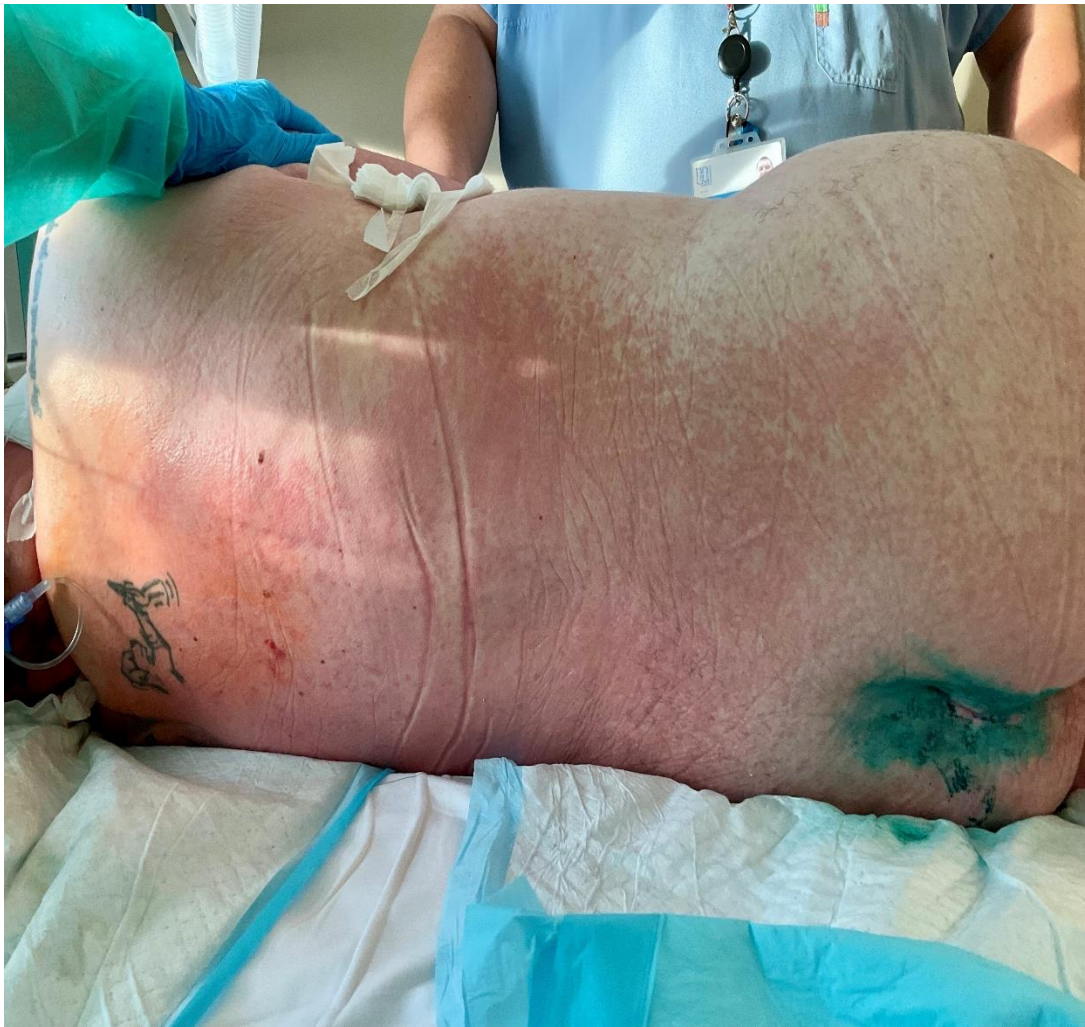
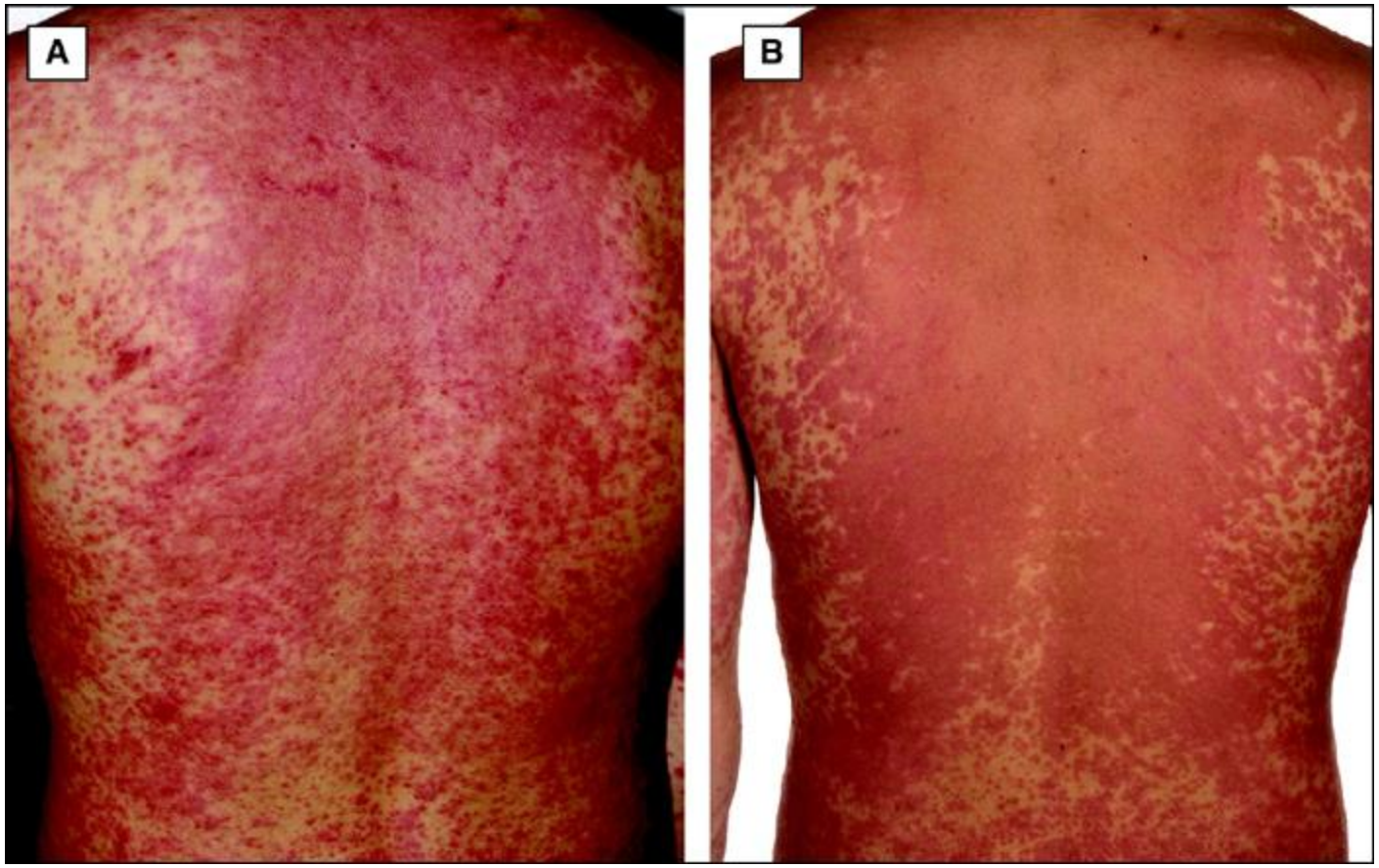
DRESS syndrome

- 29 letá žena přijatá na NCH s diagnózou idiopatické intrakraniální hypertenze
- Dlouhodobá hospitalizace s opakovaným zaváděním shuntů, mikrobiální infekcí a vývojem ATB resistence
- Opakované septické stavy
- Listopad 24 – rozvoj DRESS sy, s hepatopatií, postupným rozvojem MOF, klinické manifestace kožní
- Na základě klinického obrazu a laboratoře stanovena diagnóza DRESS sy a nasazena terapie 3x 1 g Medrolu a následně infuze IVIG – s výrazným zlepšením stavu






A
B

DRESS syndrome

- **Drug Reaction with Eosinophilia and Systemic Symptoms**
- The diagnostic criteria proposed by the international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR)
- A skin biopsy may also be helpful in the diagnostic process. Patch testing is the test of choice to search for the culprit in cases of DRESS. Regarding prognosis, the estimated mortality due to DRESS is 3.8%. The main causes of mortality include fulminant hepatitis and liver necrosis. Several indicators of **poor prognosis have been identified and these include an eosinophil count above 6000 × 10^3/μL, thrombocytopenia, pancytopenia, leukocytosis and coagulopathy.**

Diagnostika

- The diagnosis of DRESS is sometimes made late and can be challenging, due to its variety of clinical presentations. The original diagnostic criteria were proposed by Bocquet et al[1] and included a rash due to drugs, hematological alterations (eosinophils greater than 1500×10^9/L and the presence of atypical lymphocytes) and systemic manifestations (lymphadenopathy, liver, kidney, lung, and cardiac involvement). These were replaced by the **criteria proposed by the RegiSCAR group.**
- These criteria are based on clinical and laboratory findings; by means of a scoring system, they allow the establishment of the diagnosis as "**a negative case", "a possible case", "a probable case", and "a definitive case" of DRESS**

DRESS Syndrome - patophysiology

- **3 klíčové faktory**
- genetické predispozice (HLA-B ∗ 5701 - abacavir-induced DRESS. HLA-B ∗ 5801 - Han ethnic group of China is a risk factor for Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and DRESS způsobený allopurinolem-HLA-DR3, HLA-DQ2 and HLA-A ∗ 31: 01 have been associated with DRESS induced by carbamazepine
- the second factor is related to an alteration in the metabolic pathways of drugs, mainly aromatic anticonvulsants- phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and lamotrigine, are metabolized by **hepatic cytochrome P450 (CYP) enzymes**; therefore, a defect in the **detoxification function mediated by epoxide hydroxylase or glutathione transferase can lead to the production of reactive oxygen metabolites, these accumulate and cause cellular toxicity, generating alarm signals that can stimulate T lymphocytes and induce an immune response.**

DRESS Syndrome - patophysiology

- **3 faktory**
- **reactivation of HHV 6**, which leads to an inflammatory response mediated by T lymphocytes resulting in tissue damage.
- The long latency period between drug administration and the onset of DRESS syndrome manifestations would be the consequence of the period necessary to reactivate and amplify viral replication. It is possible that some of the drugs involved act directly in the transcription of viral DNA, as with valproic acid, which inhibits histone deacetylases, favoring the reactivation of latent viruses. **Most drugs associated with DRESS have immunomodulatory properties and their prolonged administration could have an immunosuppressive action favoring viral reactivation. In the specific case of anticonvulsants, these can lead to transient hypogammaglobulinemia**

HHV -6

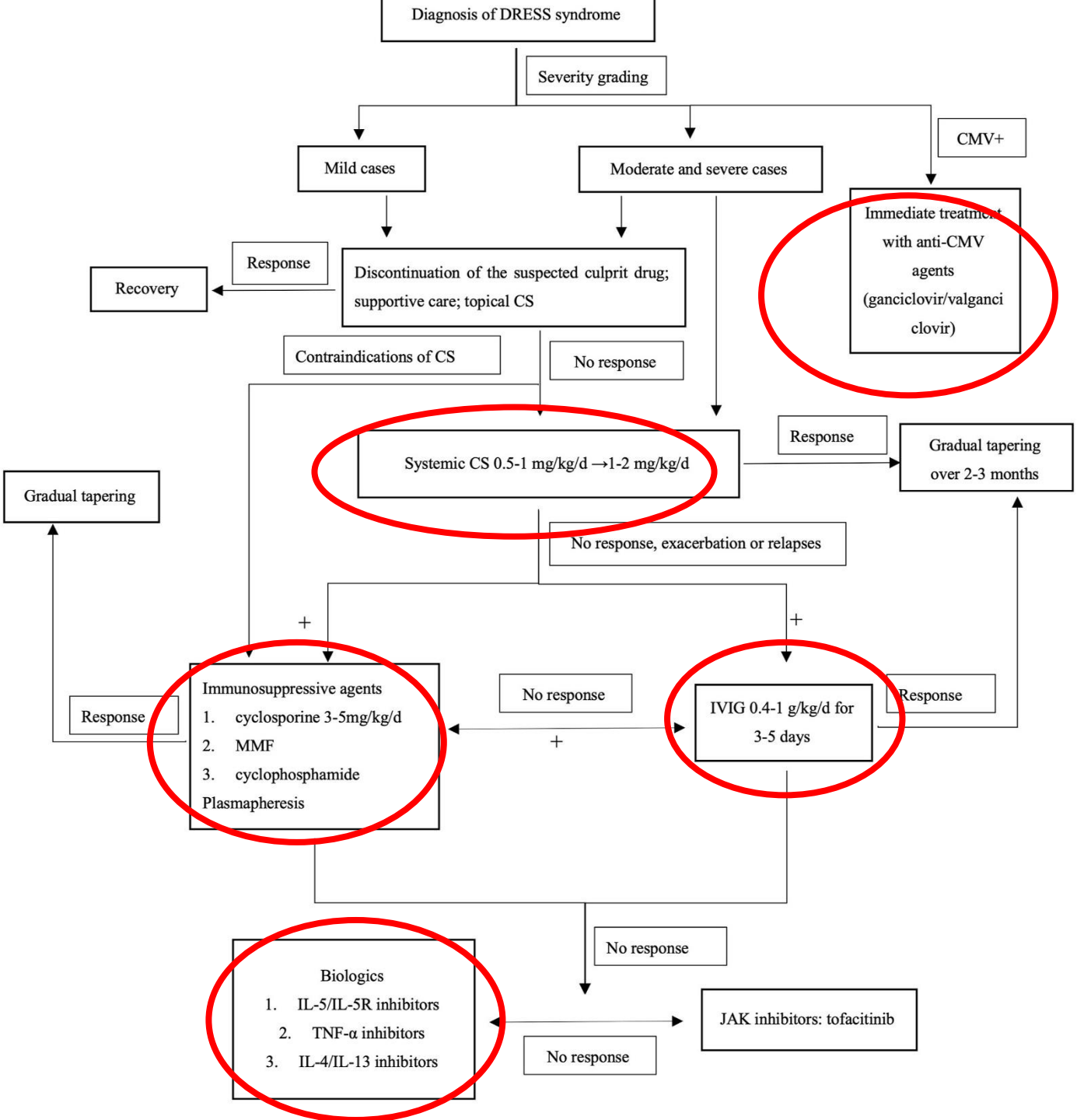
- Lidský herpesvirus 6 (HHV-6) je společný souhrnný název pro lidský herpesvirus 6A (HHV-6A) a lidský herpesvirus 6B (HHV-6B)
- HHV-6A byla popsána jako více neurovirulentní, a jako takový je častější u pacientů s neurozánětlivými onemocněními, jako je roztroušená skleróza. HHV-6B je příčinou běžného dětského onemocnění exanthema subitum (také známé jako roseola infantum nebo šestá nemoc)
- HHV-6 vyvolává jeden typický projev tohoto onemocnění − nezávažný febrilní stav u kojenců a malých dětí buď s vyrážkou – exanthema subitum, nebo bez kožních projevů
- Léčba je zaměřena pouze na zmírnění příznaků nemoci. Virus po nákaze dál přetrvává v organismu.

Klinická manifestace

- DRESS Syndrome usually begins with prodromal symptoms such as general malaise, pruritus and fever (between 38 and 40 °C), the latter is generally preceded by **skin manifestations** for several days and may persist for weeks. **Lymphadenopathies** are present in up to 75% of patients.
- In most patients the reaction occurs **2 to 6 weeks after starting the drug**, this latency period is longer than in most drug eruptions. However, in patients re-exposed to the causative drug, as well as in those with hematological and liver function alterations, the symptoms may appear quicker and with greater severity.
- skin involvement usually begins as a pruriginous **morbilliform rash**, which rapidly progresses, becoming diffuse and infiltrating. Initially it may involve the face, the upper part of the trunk, the upper extremities, and finally the lower extremities. A rash suggestive of DRESS is considered when more than 50% of the total body surface area is involved.

Klinické manifestace

- The hematological manifestations in DRESS include leukocytosis (preceded by leukopenia and lymphopenia), the presence of atypical (reactive) lymphocytes, thrombocytopenia, and anemia. Eosinophilia occurs in 60–70%
- Renal alterations may occur in up to 30% of case
- Pulmonary disease occurs in up to 25% of DRESS cases
- Cardiac involvement, such as eosinophilic myocarditis or pericarditis, can occur months after stopping the drug and be potentially fatal.
- The main cause of mortality in DRESS is due to hepatic necrosis, which can be extensive and cause severe liver failure with coagulopathy, encephalopathy, and ALT greater than 10 times the upper limit


Diagnosis of DRESS syndrome
Severity grading
Mild cases
Moderate and severe cases
CMV+
Immediate treatment with anti-CMV agents (ganciclovir/valganciclovir)
Response
Recovery
Discontinuation of the suspected culprit drug; supportive care; topical CS
Contraindications of CS
No response
Systemic CS 0.5-1 mg/kg/d →1-2 mg/kg/d
Response
Gradual tapering over 2-3 months
Gradual tapering
No response, exacerbation or relapses
+
+
Immunosuppressive agents
1. cyclosporine 3-5mg/kg/d
2. MMF
3. cyclophosphamide
Plasmapheresis
Response
No response
+
IVIG 0.4-1 g/kg/d for 3-5 days
Response
No response
Biologics
1. IL-5/IL-5R inhibitors
2. TNF-α inhibitors
3. IL-4/IL-13 inhibitors
JAK inhibitors: tofacitinib
No response

Terapie

- **Systémové KS**
- **IVIG**
- **Jiná imunosupresiva – cyklophosphamid, MMF, cyklosporin**
- **Biologická léčba – inhibitory TNF, IL-4, IL-4R, IL 5/IL13**