Review

DRESS syndrome

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A B S T R A C T

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, initially recognized as a serious form of cutaneous drug adverse reaction, is now viewed as a drug-related syndrome that can cause life-threatening organ dysfunctions. Characteristic features include a long time interval from first drug exposure to symptom onset and a prolonged course, often with flares, even after discontinuation of the causal drug. The pathophysiology of DRESS syndrome remains incompletely understood but involves reactivation of herpes viruses (HHV-6, HHV-7, EBV, and CMV), against which the body mounts a strong immune response. The culprit drugs may not only affect epigenetic control mechanisms, thereby promoting viral reactivation, but also induce an antiviral T-cell response by interacting with the major histocompatibility complex receptor in individuals with genetic susceptibility factors. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a potentially life-threatening form of cutaneous drug adverse reaction. The severity of this syndrome is related to the systemic manifestations, which can result in multiorgan failure. DRESS syndrome is characterized by highly specific features, most notably regarding the timing of the manifestations. New insights into the underlying pathophysiological mechanisms indicate a role for immunogenetic susceptibility factors and for reactivation of human herpes viruses (HHVs), chiefly HHV-6. We report a typical case of DRESS syndrome and discuss recent data about this condition.

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1. Case report

This 62-year-old man from Laos was admitted for a febrile morbilliform skin rash that progressed rapidly to erythroderma (Fig. 1). One week earlier, he had seen a physician for odynophagia and received a prescription for amoxicillin but stopped this drug after only three days because of the onset of the rash. He was then referred to us for suspected cutaneous adverse reaction due to amoxicillin.

The physical findings consisted of erythroderma, facial edema, purpura over the extremities, lymph node enlargement at multiple sites, odynophagia, and a fever of 39 °C. Standard laboratory tests showed a mononucleosis-like appearance of the blood smear, cytolytic hepatitis (transaminase levels, 6 N), and eosinophilia (900/mm³).

DRESS syndrome was diagnosed based on the presence of a febrile skin rash, facial edema, multiple enlarged lymph nodes, increased peripheral mononuclear cells, eosinophilia, and involvement of the liver. The causality assessment established that the patient had started allopurinol therapy three weeks earlier. The odynophagia that led to the prescription of amoxicillin was interpreted to be the first manifestation of DRESS syndrome. The most likely diagnosis was allopurinol-induced DRESS syndrome, with a Begaud causality score of C3S3I4.

Four days after admission, he developed hemophagocytic syndrome with pancytopenia (68,000/mm³ platelets, 83/mm³ neutrophils, and anemia) and increased serum levels of ferritin, lactic dehydrogenase (LDH), and triglycerides. Examination of a bone marrow biopsy confirmed the diagnosis (Fig. 2). Concomitantly, the liver transaminase level increased further, to 20xN. The patient was transferred to the intensive care unit and given specific treatment (intravenous immunoglobulins and systemic glucocorticoids).

The PCR test for HHV-6 was strongly positive on bone marrow (5,411,000 copies/10⁶ cells) and peripheral blood (20,000 copies/10⁶ cells) at the time of the hemophagocytic syndrome. This test had already been found strongly positive at admission (68,000 copies/10⁶ cells); it was also positive when performed retrospectively on an early serum sample obtained to evaluate the odynophagia (983 copies/mL). PCR tests were positive for HHV-7 and negative for the Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

After complete resolution of all clinical manifestations and normalization of the laboratory tests, tapering of the systemic
glucocorticoid dose was started. This process was slow, as the eosinophilia and pruritus recurred when the dose was lowered. Finally, glucocorticoid therapy was stopped 9 months after symptom onset.

Ten months after the diagnosis of DRESS syndrome, he presented with a goiter and tachycardia. Laboratory tests showed very low ultra-sensitive TSH levels and high levels of free thyroxine and triiodothyronine, confirming the diagnosis of hyperthyroidism. Tests were positive for antibodies to thyroperoxidase, thyroglobulin, and TSH receptor. The diagnosis was autoimmune Graves’ thyroiditis complicating DRESS syndrome.

2. Well-defined clinical and laboratory abnormalities

Diagnostic criteria for DRESS syndrome have been defined (Table 1) [1,2]. Established DRESS syndrome is characterized by an erythematous rash, often with pruritus and facial edema, enlarged lymph nodes at multiple sites, and high-grade fever. The rash progresses rapidly to erythroderma. Pustular skin lesions may develop. Involvement of the mucous membranes with inaugural pharyngitis and oral ulcers is common.

Eosinophilia is often lacking initially in DRESS syndrome. Earlier changes consist of lymphopenia or lymphocytosis with atypical hyperbasophilic lymphocytes that should be looked for on a blood smear and produce a mononucleosis-like appearance. The other clinical and laboratory findings are related to the organ involvements.

3. The severity of DRESS syndrome is related to the organ involvements

The liver is the organ most often involved in DRESS syndrome. However, renal failure, interstitial lung disease, myocarditis, pancreatitis, meningoencephalitis, or hemophagocytic syndrome may occur. Hemophagocytic syndromes are common and may manifest as isolated laboratory abnormalities (high levels of serum ferritin, LDH, and triglycerides) before the development of the bone marrow abnormalities. Hypocalcemia with serum procalcitonin elevation is common. The concomitant involvement of several organs may progress to multiorgan deficiency. In a retrospective study of severe DRESS syndrome (with intensive care unit admission or death), 11 of 15 patients had multiorgan failure [3].

Rather than a form of cutaneous drug adverse reaction, DRESS syndrome is a systemic condition in which the skin lesions may be overshadowed by the organ involvements. Consequently, in the acronym DRESS, the “R” previously used to indicate “rash” now indicates “reaction” [4].

4. Characteristic timing of the manifestations

The most typical features of DRESS syndrome are related to the timing of the manifestations. There is a long interval of two weeks to 2 months from initial drug exposure to symptom onset. Furthermore, the symptoms persist for more than two weeks [4]. Time to onset is shorter after re-challenge with the same drug. The outcome is usually favorable after discontinuation of the causal drug, although full symptom resolution requires at least two weeks and flares may occur.

5. A long list of differential diagnoses

DRESS syndrome can mimic a variety of conditions such as viral and bacterial infections, connective tissue diseases, Still’s disease, and hematological diseases. Patients with DRESS syndrome should be carefully interviewed about drug exposures to allow the early discontinuation of the causal agent. The RegiSCAR group has developed criteria for the retrospective diagnosis of DRESS syndrome [1].

6. A limited number of causal drugs

Few drugs are known to cause DRESS syndrome. Published cases were reviewed recently [5]. The main drugs are allopurinol, anticonvulsants (phenobarbital, carbamazepine, phenytoin, lamotrigine, and sodium valproate), minocycline, sulfasalazine, disulone, fluindione, proton pump inhibitors, and strontium ranelate (Table 2). Amoxicillin can cause DRESS syndrome but more often acts as an aggravating factor, as was probably the case in our patient. This aggravating effect is reminiscent of amoxicillin-induced rash in patients with infectious mononucleosis. We have reported seven cases of DRESS syndrome worsened by the use of amoxicillin [6]. Thus, in patients with DRESS syndrome shortly after the initiation of amoxicillin therapy (in the absence of previous hypersensitivity to this antibiotic), patients should be interviewed carefully about the possible introduction of another drug within the last few weeks.

7. A specific immunogenetic background

DRESS syndrome is rare (1/5000 to 10,000 prescriptions of each of the causal drugs). The genetic susceptibility factor or factors have not yet been identified. DRESS syndrome has been associated with specific HLA groups in some ethnic groups and for some causal
Table 1
Diagnostic criteria for DRESS syndrome.

Criteria developed by a Japanese consensus group for DRESS (known in Japan as drug-induced hypersensitivity syndrome or DIHS) (from reference 4)
1. Maculopapular rash developing more than 3 weeks after drug initiation
2. Clinical symptoms persisting more than 2 weeks after stopping the drug
3. Fever >38 °C
4. Transaminase elevation (ALT >100 IU/L)
5. One of the following
   - Leukocytosis (>11x10^9/L)
   - Atypical lymphocytes (>5%)
   - Eosinophilia (>1.5x10^9/L)
6. Lymphadenopathy at multiple sites
7. HHV-6 reactivation

The presence of five criteria indicates atypical DIHS and the presence of seven criteria typical DIHS

Criteria developed by the RegiSCAR study group for classifying DRESS cases as definitive, probable, possible, or no case (from reference 3)

<table>
<thead>
<tr>
<th>Score</th>
<th>–1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 38.5 °C</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td>–1</td>
<td>0</td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>No/U</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.7–1.499 × 10^9 L^-1</td>
<td>≥ 1.5 × 10^9 L^-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils, if leukocytes &lt;4.0 × 10^9 L^-1</td>
<td>10–19.9%</td>
<td>≥ 20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–2</td>
<td>2</td>
</tr>
<tr>
<td>Skin rash extent (% body surface area)</td>
<td>No/U</td>
<td>&gt;50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash suggesting DRESS</td>
<td>No</td>
<td>U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin biopsy suggesting DRESS</td>
<td>No</td>
<td>Yes/U</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ involvement*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle/heart</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other organ</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution ≥ 15 days</td>
<td>No/U</td>
<td>Yes</td>
<td></td>
<td></td>
<td>–1</td>
<td>0</td>
</tr>
</tbody>
</table>

Evaluation of other possible causes
- Antinuclear antibody
- Blood cultures
- Serology for HAV/HBV/HCV
- Chlamydia/mycoplasma
- If none positive and ≥3 of above negative

score total | –4 | 9 |

U: unknown; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus.
* After exclusion of other explanations: 1, one organ; 2, two or more organs: final score <2, no case; final score 2–3, possible case; final score 4–5, probable case; and final score >5, definite case

8. Two original pathophysiological possibilities

The first pathophysiological mechanism links the causal drug to the major histocompatibility complex (HLA). The pathophysiology of drug-induced hypersensitivity classically involves a T-cell response induced by the drug or its metabolites after HLA presentation by antigen-presenting cells. Depending on their chemical reactivity, drugs are classified as haptons if they can bind directly to a protein without undergoing previous modifications or as pro-haptons if they become reactive only when metabolized. Most drugs are pro-haptons. Many studies have evaluated the link between genetic polymorphisms of drug detoxification pathways and “drug hypersensitivity”. To explain the various situations, four presentation modalities have been suggested:

- presentation of the hapten bound covalently to the peptide presented by the HLA molecules;
- non-covalent binding of the hapten, independently from the peptides located in the HLA binding groove;
- pharmacological interaction (P-I concept), with direct binding of the hapten to the T-cell receptor;
- modification by the hapten anchored in the HLA binding groove of the peptide presented by the HLA molecules [11,12].

Drugs [7]. Thus, HLA-B*5801 is associated with allopurinol-induced DRESS syndrome in the Han Chinese but not in Japanese individuals [8,9]. Similarly, HLA-B*5701 is associated with abacavir-induced DRESS syndrome, and testing for HLA-B*5701 as part of the pre-treatment workup has therefore been suggested to avoid using abacavir in these high-risk individuals. DRESS syndrome seems more common in Asia than in other parts of the world. Finally, the risk of minocycline-induced DRESS syndrome seems increased in Caribbean blacks [10].
Table 2
DRESS syndrome. Causal drugs identified in 62 patients with DRESS syndrome seen at the Bichat hospital, Paris, France.

<table>
<thead>
<tr>
<th>Causal drug</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>15</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>11</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>3</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6</td>
</tr>
<tr>
<td>Minocycline</td>
<td>4</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>4</td>
</tr>
<tr>
<td>Pyrimethamine-sulfadiazine</td>
<td>3</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>3</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>2</td>
</tr>
<tr>
<td>Myambutol or antituberculous agents</td>
<td>2</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>1</td>
</tr>
<tr>
<td>Fluindione</td>
<td>1</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>1</td>
</tr>
</tbody>
</table>

Recent data support the fourth presentation modality.

The most interesting data come from studies of abacavir-induced DRESS syndrome associated with HLA B*5701. Direct binding of abacavir to HLA B*5701 has been demonstrated. Molecular and crystallographic studies have shown non-covalent binding of abacavir to the binding groove of HLA B*5701. The result is increased intensity of the CD8+ T-cell response to antigens containing the VTTDIQKV peptide [13]. Thus, the presence of abacavir modifies the peptide repertoire to include self-peptides, by altering tolerance mechanisms. Self-peptides become capable of inducing a cytotoxic T-cell response that results in manifestations of autoimmunity. HLA B*5701 is also associated with an increased risk of fluoxacillin-induced hypersensitivity hepatitis [14]. However, some HLA B*5701-positive patients do not develop abacavir-induced DRESS syndrome or fluoxacillin-induced hepatitis, indicating that other factors are also in play.

The second pathophysiological mechanism involves viral reactivation. Studies done in the past few years have established that the systemic manifestations of DRESS syndrome are related to herpes virus reactivation and to the host immune response against the virus (Fig. 3). We reported the first case of DRESS syndrome with documented HHV-6 reactivation. The patient was a woman, also from Laos, and the reaction was induced by phenobarbital [15]. Many subsequent reports confirmed this association [16–19]. HHV-6 reactivation is among the criteria developed by Japanese experts for the diagnosis of DRESS syndrome (known in Japan as drug-induced hypersensitivity syndrome or DIHS) [2]. Furthermore, studies established that reactivation of other herpes viruses, namely, the EBV, CMV, and HHV-7, is involved in the systemic manifestations and flares of DRESS syndrome [19–21]. Two scenarios have been suggested: an immune response against the drug with secondary viral reactivation related to a cytokine storm, and early viral reactivation responsible for most of the manifestations of DRESS syndrome [22]. A prospective immunological and virological study in 40 patients with DRESS syndrome was conducted in France to investigate links between drug exposures, viral reactivation, and the immune response [23]. The results showed early herpes virus reactivation in the course of DRESS followed by sequential reactivation of additional viruses. The Th1 response was chiefly directed against the viral antigens, as shown by immunoscopy sequencing of the T-cell receptor VB chain and by studies of tetramers loaded with viral peptides. CD8+ T cells producing large amounts of TNFα, IFNγ, and IL-2 and directed against EBV peptides were identified in the peripheral blood and involved tissues (liver, skin, and lungs). In addition, the T-cell receptor VB chain sequence shared strong homology with the sequences identified during T-cell responses to EBV infection. The EBV was used instead of the HHV-6 because at the time of the study the viral epitopes, repertoire, and VB chain sequence in HHV-6 infection were unknown. The results explain why the clinical picture in DRESS syndrome resembles the massive viral reactivations seen in patients with immunodepression (organ transplant recipients, intensive care unit patients, and HIV-infected patients), which may be mistaken for DRESS syndrome [24].

9. Recent data on the HHV-6

HHV-6 is a typical example of a latent virus that can undergo reactivation, particularly when immunodepression occurs [26]. Two types have been identified, HHV-6A and HHV-6B, which share 90% of sequence homology [26]. Over 95% of individuals in the general population carry HHV-6 and produce antibodies against this virus [27,28]. HHV-6 infection is acquired via saliva droplets between 6 and 15 months of age. HHV-6 infection is usually asymptomatic but causes 20% of the febrile episodes seen between 6 and 12 months of age [27,28]. HHV-6 is the cause of roseola infantum (exanthema subitum), which has an incubation period of 1 to 2 weeks and can induce gastrointestinal, nasopharyngeal, and/or respiratory symptoms, as well as seizures [27,28]. Severe manifestations such as hepatitis, meningoencephalitis, and pneumonia are rare and usually caused by the HHV-6B variant. HHV-6A preferably infects the nervous system. Severe HHV-6 infections occur predominantly in patients with immunodepression. A role for HHV-6 has been suggested in graft-versus-host disease, epilepsy, chronic fatigue syndrome, multiple sclerosis, and Hodgkin’s disease. The HHV-6 receptor (CD46) is expressed by a broad range of cell types, and the virus is consequently found in many organs (skin,
liver, brain, bowel, lungs...). However, the latent virus resides chiefly in the T cells and monocytes, where the viral genome persists in episomes [26]. A recent study demonstrated that the HHV-6 can integrate into the host cell genome [29]. Thus, in 1% to 3% of the population the HHV-6 genome is integrated into the chromosomes of all cells in the body and can be transmitted from generation to generation. This phenomenon is probably secondary to integration within the genomic DNA of the germ cells during evolution. Although viral transcription does not occur, PCR tests for HHV-6 DNA in whole blood may suggest a high viral load, with more than 1 million copies/mL. The diagnosis of chromosomal integration can be confirmed by identification of the viral genome in the hair follicles. The consequences of chromosomal integration and the factors that promote reactivation are under evaluation. Chromosomal HHV-6 integration has been reported in patients with DRESS syndrome. However, a study involving routine hair follicle examination in 10 patients with a history of DRESS syndrome failed to indicate chromosomal integration of the virus [30]. Thus, chromosomal integration is present in only a minority of patients.

10. The link between drugs and viruses

The factors responsible for the reactivation of herpes viruses, and more specifically of HHV-6, remain controversial. We hypothesized that some drugs may directly affect viral reactivation and replication. In an in vitro study, we found that drugs associated with DRESS syndrome (sodium valproate, carbamazepine, amoxicillin) can potentiate HHV-6 replication [6,31]. After incubation of an HHV-6-infected T-cell line, viral replication was increased in the presence of drug concentrations within the therapeutic ranges. This original effect was confirmed in another model involving EBV transformation of lymphocytes from patients with a history of DRESS syndrome [24]. Exposure to drugs known to cause DRESS syndrome resulted in increased EBV production.

DRESS syndrome can therefore be viewed as a model for investigating potential links between specific drugs and viral reactivation. Amoxicillin-induced rash in patients with infectious mononucleosis was described many years ago. We reported an in vitro study showing that amoxicillin increased the replication of HHV-6 and EBV. In addition, in a patient with EBV infection, ampicillin therapy caused a skin rash that subsequently resolved then recurred upon each ampicillin re-challenge, concomitantly with an increase in the EBV load [32].

The mechanism underlying the direct drug-virus interaction remains unknown. Several of the drugs associated with DRESS syndrome (sulfasalazine, minocycline, allopurinol...) are known to exert immunomodulating effects. Prolonged use of these drugs may promote viral reactivation by inducing immunosuppression. In addition, independently from DRESS syndrome, anticonvulsant drugs can induce hypogammaglobulinemia. Interestingly, studies showed a higher prevalence of hypogammaglobulinemia among patients with DRESS syndrome than among patients admitted for erythoderma [33,34]. These drugs may also act directly on the viral or host-cell DNA to affect silencing mechanisms, most notably of viral promoters. Two main mechanisms of epigenetic control have been identified to date: methylation and histone acetylation [35]. Sodium valproate inhibits the histone deacetylases, an effect that may promote the reactivation of latent viruses [36]. Under this hypothesis, chromosomal integration of HHV-6 may constitute a risk factor for viral reactivation. Studies are investigating this possibility.

11. A pathophysiological model for DRESS

DRESS results from two characteristics: an ability to develop viral reactivation and an ability to mount a strong antiviral immune response. Both are determined by genetic factors and partly induced by the causal drug. The long time interval between initial drug exposure and DRESS syndrome onset may reflect the time needed to reactivate the virus and to enhance its replication. Conceivably, the causal drug or drugs may directly affect viral DNA transcription via epigenetic factors and via immunological modulation (expansion of regulatory T cells) [37]. The ability to generate an antiviral response may be induced by drugs that interfere with the major histocompatibility complex binding groove. This mechanism has been demonstrated for abacavir. It promotes an immune response against viral peptides or self-peptides, as well as against the causal drug.

Several genetic susceptibility factors have been suggested:

- susceptibility of the virus to reactivation related to chromosomal HHV-6 integration or to HHV-6 integration in a large number of T cells;
- HLA groups associated with a given drug and capable of effectively presenting viral antigens;
- and an inappropriate immune response related to genetic polymorphisms for cytokines, receptors, or antagonists (as demonstrated for the TNFα receptor).

Interestingly, patients with immunodepression (transplant recipients and HIV-infected patients) can exhibit clinical pictures that closely resemble DRESS syndrome, in the absence of exposure to a drug associated with this syndrome. These clinical pictures, which are far more common than DRESS syndrome, could be designated “virus reactivation with eosinophilia and systemic symptoms” (VRESS syndrome). In this situation, the immunodepression is the cause of the viral reactivation. However, systematic studies show that only a minority of transplant recipients with marked viral reactivation develop systemic manifestations. These systemic manifestations are related to a strong immune response against the reactivated virus. Thus, as with DRESS syndrome, they develop only in patients with both marked viral reactivation and an ability to mount a strong antiviral immune response.

12. The management depends on the severity of the manifestations

No prospective randomized trials are available on which to base the management of DRESS syndrome [4]. The following steps must be taken concomitantly:

- a causality assessment to enable early discontinuation of the causal drug;
- an evaluation of disease severity based on findings from a standardized workup (Table 3) [4]; Quantitative PCR on whole blood is used to detect viral reactivations, as viral serologic tests are unhelpful;
- and therapeutic management appropriate for the severity of the manifestations.

The treatment goals are to control the antiviral immune response and to block viral replication. In most cases, the immune response is effective in controlling the viral replication and, consequently, discontinuing the causal drug is sufficient. This fact explains why tests for viral reactivation may be negative. In moderately severe forms, local high-dose glucocorticoid therapy ensures disease control. Patients with severe DRESS syndrome should be given systemic glucocorticoid therapy (1 mg/kg/d) until complete disease control is achieved. The dose is then tapered slowly, often over several months [4]. Finally, life-threatening forms require intravenous immunoglobulin therapy in addition to
systemic glucocorticoid therapy. A recent study established that intravenous immunoglobulin therapy alone was not adequate in DRESS syndrome [38]. Antiviral agents (ganciclovir, cidovir) may be given in addition to intravenous immunoglobulins and systemic glucocorticoids as soon as viral reactivation is detected. However, toxicities limit the use of these agents. The introduction of drugs that are safer and more effective, particularly against HHV-6, will probably expand the indications for antiviral therapy.

DRESS syndrome must be reported to the drug surveillance center and the patient must be informed of the lifetime contraindication to use of the causal drug. At a distance from the DRESS syndrome episode, skin tests can assist in the causality assessment [39]. In the future, ELISPOT-type in vitro tests will probably be developed.

13. Prolonged follow-up

Careful follow-up is crucial. Organ involvement may be delayed, and flares may occur, particularly when the glucocorticoid dose is tapered too fast or other drugs are introduced. In addition, patients with DRESS syndrome frequently develop manifestations of autoimmune (thyroiditis, adenyl insufficiency, diabetes insipidus, connective tissue disease, or a reaction resembling graft-versus-host disease) [40].

14. Conclusion

DRESS syndrome can be viewed as a model for investigating the manifestations associated with viral reactivation in patients with immunodepression or exposure to severe stress (intensive care unit admission). The original nature of DRESS syndrome resides in the link connecting the causal drugs, viral reactivation, and the antiviral immune response. The identification of one or more immunogenetic susceptibility factors will constitute a crucial step toward preventing the occurrence of DRESS in response to certain drugs.

Disclosure of interest

V.D. is a consultant for Servier.

References