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DRESS SYNDROME MINING ETIOPATHOGENESIS AND PHARMACOLOGICAL PROBLEMS

Annotation: DRESS-syndrome is a severe generalized drug-induced reaction accompanied by eosinophilia and multiple organ lesions. Symptoms include skin rash, fever, lymphadenopathy, hepatitis, eosinophilic pneumonia, myocarditis, nephritis, pancreatitis, encephalopathy, etc. The condition is diagnosed by hemogram, blood biochemistry, skin tests, instrumental studies (ultrasound, CT, ECG). Treatment begins with the withdrawal of drugs that caused hypersensitivity, requires the appointment of glucocorticoids, immunoglobulins, immunosuppressants, plasmapheresis.

Key words: DRESS-syndrome, drug, blood, anticonvulsant hypersensitivity syndrome.

The term "DRESS-syndrome "(drug-induced reaction with eosinophilia and systemic symptoms) appeared in therapeutic practice relatively recently – in 1996. However, anticonvulsant hypersensitivity syndrome, including exfoliative dermatitis, fever and eosinophilia, has been known since 1938. The abbreviation DIHS (drug-induced hypersensitivity)is also found in the literature. Currently, the prevalence of DRESS syndrome is estimated in the range of 1:3000-1: 10000 people, cases of the disease are noted in persons from 3 to 84 years old. Mortality in DRESS syndrome is 10-20%, which is due to both late diagnosis and severe multi-organ lesions.

Three mechanisms are involved in the etiopathogenesis of DRESS syndrome: genetic predisposition, viral infections, and drug sensitivity. The first mechanism is associated with a specific HLA genotype-the carrier of the B1502, B1508, B5701, and B5801 alleles.

The second factor of DRESS syndrome is infectious antigens. Recent studies have shown that the triggers that trigger the manifestation of the disease can be some viruses, in particular herpesgroup viruses (6 and 7 types), Epstein-Barr, cytomegalovirus.

Also, in the induction of DRESS syndrome in individuals with a genetic predisposition and latent infection, it is important to take the following groups of medications::

- Anthoconvulsants: phenytoin, phenobarbital, lamotrigine, carbamazepine;
- antibiotics: sulfonamides, cephalosporins, penicillins, azalides, fluoroquinolones;
- anti-TB drugs: isoniazid, streptomycin, ethambutol, rifampicin;
- antirheumatic drugs: gold preparations, hydroxychloroquine, sulfasalazine;
- anti-gout: allopurinol;
- antiarrhythmic drugs: amiodarone, mexiletine;
- anti-retroviral drugs: abacavir, tenofovir, neviparin;
- anticoagulants: enoxaparin sodium, acenocoumarol;
- NSAIDs: ibuprofen, diclofenac, naproxen, etc.

The list of medications associated with DRESS syndrome is constantly expanding.

Pathogenesis

The mechanism of pathology occurrence is considered from the point of view of three theories. Proponents of the" viral " hypothesis regard DRESS-syndrome as a consequence of hyperactivation of antiviral immunity. According to this point of view, medication is accompanied by

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immunosuppression, which contributes to the activation of T-lymphocytes and reactivation of dormant infection. Viral replication stimulates cellular immunity, which leads to a massive release of cytokines (cytokine storm) and damage to various organs. This theory explains why clinical manifestations progress even after drug withdrawal.

Autoimmune theory is based on the phenomenon of molecular mimicry. Reactivation of a viral infection causes an increase in the number of T-lymphocytes. At the same time, activated T-cytotoxic lymphocytes cross-react not only with viral antigens, but also with the body's own tissues that are similar in structure, causing their damage.

The synthetic theory of DRESS syndrome pathogenesis is based on a combination of two mechanisms: activation of the antiviral response and drug-induced autoimmune response. Since the disease develops in a limited number of people when prescribing certain drugs, it seems that genetic factors are important.

Symptoms

Clinical manifestations of DRESS syndrome usually occur 3-8 weeks after the initial appointment of drug therapy (or 2 weeks after repeated drug administration). In some cases, it takes from a few days to six months from the start of taking medication. Often, the onset of an acute systemic reaction is preceded by acute respiratory viral infection.

The first symptom is febrile fever with temperature fluctuations from 38° to 40°C. On the background of febrile syndrome, there are bark-like maculopapular rashes on the skin. There may be swelling of the eyelids and face. Elements of the rash are initially localized on the face and upper body, then spread to the lower extremities. With continued use of drugs, the skin syndrome often takes the form of erythema multiforme, erythroderma, and exfoliative dermatitis.

Also, pathognomonic signs of DRESS syndrome include lymphadenopathy of different groups of lymph nodes (70%), bilateral enlargement of the parotid salivary glands. Concomitant symptoms include dry mouth, conjunctivitis, myositis, and arthralgia.

For DRESS-syndrome, involvement of internal organs in the pathological process is typical. Severe hepatitis with or without jaundice (50-60%), splenomegaly, interstitial nephritis, and eosinophilic pneumonia often develop. Possible disorders of the central nervous system include meningitis, encephalitis, convulsions, from the CVS – eosinophilic myocarditis, pericarditis, granulomatous-necrotizing angiitis. It is characterized by the persistence and even progression of symptoms after the withdrawal of a causally significant pharmaceutical product.

Complications

In patients who have had DRESS-syndrome, an increased frequency of autoimmune pathologies was later noted. Cases of type 1 diabetes mellitus and systemic scleroderma are described. Complicated forms of DRESS syndrome are associated with the development of severe multiple organ dysfunction. An unfavorable prognosis is associated with acute renal failure, liver failure, respiratory distress syndrome, and brain edema. The mortality rate from multiple organ lesions reaches 20%.

Diagnostics

Difficulties in recognizing DRESS syndrome are related to its similarity to infectious diseases. This fact forces the primary care physician to resort to prescribing antibacterial drugs, which further aggravates drug hypersensitivity and aggravates the patient's condition. In the diagnosis of the disease, along with the therapist, the participation of an immunologist is necessary.

To confirm the DRESS syndrome, the RegiSCAR scale is proposed, according to which the absence of each criterion is estimated at 0 points, and the presence – at 1 point. These criteria include: fever, maculopapular rash, lymphadenopathy, eosinophilia, leukocytosis, facial swelling, and systemic lesions (liver, kidneys, lungs, brain, and heart). If the total score is >5, the DRESS syndrome is confirmed, and <2 is excluded.

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Laboratory and instrumental methods are used to objectify clinical data:

- A hemogram. Changes recorded in the general blood count are represented by leukocytosis (>11x10 ^ 9/l), the presence of atypical mononuclears (>5%), eosinophilia (>1.5 x 10^9/L, characteristic of 95% of patients. Leukemoid reactions may occur.
- Blood biochemistry. It is performed to identify markers of internal organ damage. The level of ALT, alkaline phosphatase, bilirubin, creatinine, urea, and CRP is measured, and the blood gas composition is evaluated.
- Virological research. Determine antibodies to HIV, viral hepatitis B and C. Reactivation of herpes virus infection is confirmed by PCR test or detection of serum immunoglobulins G.
- Application test Skin samples. It is used to identify the drug that caused a delayed hypersensitivity reaction. The patch test is performed on the skin of the back. Results are recorded after 48, 72, and 96 hours.
- Skin biopsy. Skin sampling is more often used as part of differential diagnosis. Histological changes in DRESS syndrome are non-specific, usually represented by lymphocytic and eosinophilic infiltration of the upper layers of the dermis, the presence of atypical lymphocytes.
- Instrumental diagnostics. Additional studies are used for signs of internal organ dysfunction. In this case, ultrasound of the liver and kidneys, X-ray and CT of the lungs, ECG, etc. can be performed.

Differential diagnosis

In the early phase of DRESS-syndrome, diseases that occur with fever and skin lesions are excluded, in the advanced stage – pathologies characterized by eosinophilia and multiple organ disorders. The range of diseases with which difdiagnosis is performed is quite wide:

- infectious pathologies: measles, mononucleosis, rubella, enterovirus, adenovirus, herpetic infection of type 6 and 7, cytomegalovirus and parvovirus infection, HIV, etc.;
- skin syndromes: erythema multiforme, drug-induced erythroderma, exanthematous pustulosis, Stevens-Johnson syndrome;
- systemic immune responses: serum sickness, graft - versus-host response;
- Eosinophilia: idiopathic hypereosinophilic syndrome, Charg-Strauss syndrome;
- hemoblastosis: lymphoma.

Treatment of DRESS syndrome

The first step in the treatment of drug hypersensitivity is to cancel the drug that provoked its debut. The next algorithm involves the following steps::

- Systemic corticosteroids Administration of glucocorticosteroids. they are the main line of treatment. In the case of DRESS syndrome, they can achieve rapid clinical improvement, normalize laboratory parameters, prevent organ damage, and reduce the risk of autoimmune reactions.
- Applying reserve methods. If corticosteroids are not effective enough, intravenous infusions of human normal immunoglobulin, immunosuppressants, and plasmapheresis are added to the treatment. If there are signs of activation of a viral infection, antiviral therapy is indicated.

Prognosis and prevention

The prognosis for DRESS syndrome varies from complete recovery to death. Even if the trigger drug is discontinued, the disease can progress and recur. With repeated administration of this drug, severe life-threatening complications may develop. The most severe course and higher mortality risks are observed in the elderly. Prevention of DRESS-syndrome is the appointment of drugs for strict indications, if necessary - conducting preliminary skin allergological testing.

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