A YOUNG LADY WITH A RASH, FACIAL EDEMA AND SIGNS OF A CAPILLARY LEAK

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An online CME quiz on this case can be found at: http://www.eaaci.net...
CASE HISTORY

An 18 year-old female patient was admitted with high fever (>39.5°C) for 3 days, dyspnoea, rash with edema of the face, both hands and feet (Fig. 1A and B). She showed diffuse lymphadenopathy and an enlarged liver.

At the age of 5 years, the patient was diagnosed with celiac disease. Since that time she adhered to a strict gluten-free diet. At age 12 the patient developed an insulin dependent diabetes mellitus (IDDM). Despite intensified insulin therapy, control of hyperglycemia had been difficult during adolescence. Four weeks prior to the actual admission, focal diabetic neuropathy developed with severe pain in the left leg. Treatment with carbamazepin at a dose of 3 X 400 mg for seven days was started. Because of persistence of severe pain attacks gabapentin was added in increasing doses up to 3 X 400 mg. Under this treatment a rash developed after 14 days.

COMMENTS

- Differential diagnosis is very wide: from a generalized viral infection (e.g. in an immune-compromised patient), over an acute autoimmune disease (SLE?), a macrophage activation syndrome, an immunodeficiency syndrome (complement deficiency?), lymphoma or a severe drug hypersensitivity like drug rash with eosinophilia and systemic symptoms (DRESS).

- If you suspect drug hypersensitivity, differential blood count and liver parameters are obligatory. Other laboratory tests depend on the clinical situation.
Strong Eosinophilia (>1.5G/L) is a good hint for an T cell driven hypersensitivity reaction and mirrors a massive immune stimulation.

Lymphocytosis with the presence of atypical lymphocytes illustrates – together with the clinical lymphadenopathy - a massive stimulation of the immune system. This finding is typical in generalized viral infections like mononucleosis or acute HIV, but can also occur in the frame of DRESS or an acute exacerbation of an autoimmune disease (SLE).

The finding of extremely high ferritin levels (> 10.000μg/l) would point to a macrophage activation syndrome (1).

High cytokine levels in the circulation (interleukin-2 (IL-2), IL-5, IFN-γ, etc) would be compatible with a capillary leak syndrome, as it is well described in the frame of IL-2 therapy (2). Negative ANA makes SLE very unlikely.

LABORATORY ANALYSIS
Differential blood count: leucocytosis (25.000/μl) with lymphocytosis (3125/μl) and 3% atypical lymphocytes (normal <0,5%); eosinophilic granulocytes increased (1020G/ml, normal <400G/ml). The CRP was only 8mg/L (normal <5 mg/L), ferritin was 300ng/ml (normal <100ng/ml); ALAT was 44 U/L (N<37), while ASAT was in the normal range. ANA and virus screen (EBV, CMV, HHV-6) were all negative).

DIAGNOSIS
DRESS syndrome was diagnosed, and all drugs were stopped.
This young patient demonstrated the typical combination for DRESS: 1) therapy with a drug known to cause DRESS 2) strong eosinophilia and 3) presence of activated lymphocytes in the circulation, 4) clinical picture of edema in the face and a rash. 5) involvement of systemic organs (liver, lymphadenopathy). The edema with hyponatriaemia (128mmol/l, norm 132-142mmol/l) could reflect a capillary leak syndrome, as it seen in association high cytokine levels in the frame of massive immune stimulations or IL-2 therapy; The patients had indeed
elevated IL-5 (19.2 pg/ml, norm<0.1 pg/ml) and IFN-γ levels (11.6E/ml, norm <0,1E/ml). IL-2 was not measured.

**FURTHER DIFFERENTIAL DIAGNOSIS**

Eosinophilia makes an acute viral infection unlikely, negative ANA makes an acute SLE very unlikely, the macrophage system was not involved, as CRP and ferritin were only slightly elevated, which excludes an macrophage activation syndrome. The blood smear was not compatible with an acute leukaemia, a lymphoma was unlikely and excluded by the clinical course.

**FOLLOW UP**

After an initial improvement of the rash and edema the patient developed in the third week persistent high-grade fever for five days, showed a deterioration of liver function parameters (ALAT and ASAT levels were each >400 U/L, norm 40U/l) and in the blood an substantial increase of atypical lymphocytes to 7% (norm <0,5%). An extensive screening for reactivation of herpes viruses showed now an increase of HHV-6 antibodies (IgG).

Due to the elevation of transaminases treatment with prednisolone was started (50mg/day for three days followed by 25mg/day for further three days). The patient responded well, as the liver values normalized and she could be discharged after 4 weeks.

**ALLERGY TESTS**

Two months later epicutaneous testing (Fig. 2A) unexpectedly revealed hypersensitivity reaction to gabapentin, but not to carbamazepine. Lymphocyte transformation test (LTT; 3) demonstrated marked lymphocytic proliferation in response to gapapentin, but not with carbamazepine (Fig. 2B). The LTT has a high sensitivity in this syndrome (3).
Epicutaneous testing was performed with gabapentin (20% solution) and skin reaction was observed 2 days later.

Lymphocyte transformation assay (3): The patient’s lymphocytes were cultivated for 6 days with carbamazepine or gabapentin. $^3$H thymidin incorporation into DNA was determined and expressed relative to the incorporation in cultures with the respective serum without antigen (stimulation index). A stimulation index above 2.0 is regarded positive (3).

**COMMENT**

The DRESS syndrome, formerly known as drug hypersensitivity reaction, is a rare but potentially fatal drug reaction (4). The patient showed the typical biphasic course, which could be traced back to the common reactivation of HHV-6 in the third week.

Our patient with celiac sprue and IDDM may have a genetic predisposition to autoimmunity and drug hypersensitivity. Although this syndrome is not so rare (treatment with antiepileptics 1:3000), the diagnosis is often delayed, as it is hard to imagine that a drug hypersensitivity could cause such a severe disease. Time lapses by in the search for viral infections or an undefined autoimmune disease. However, this can be dangerous, as the most decisive step is stopping the drug!

This is the first report of a DRESS syndrome that can be clearly attributed to gabapentin. In addition, the co-medication with carbamazepine may have induced the hypersensitivity reaction, similar as in a patient with hypersensitivity against phenytoin after co-medication with carbamazepine (5). An hypersensitivity syndrome after medication with gabapentin has been reported in a 72 years old
patient with similar clinical findings apart from eosinophilia (6). Moreover several cases of hypersensitivity reactions in patients receiving gabapentin have been brought to the attention of both the manufacturer and the UK Committee on Safety of Medicines. The findings in our patient clearly demonstrate, that gabapentin should be added to the list of drugs that can elicit DRESS. Prednisone treatment seemed to have been helpful in this patient with hepatitis after stopping treatment.

References


Summary

One of the most severe forms of drug hypersensitivity reactions is the drug hypersensitivity syndrome, formerly also called the anticonvulsant hypersensitivity syndrome. A new name – DRESS – pinpoints the hallmarks of this syndrome – namely drug rash (reaction) with eosinophilia and systemic symptoms (like hepatitis, nephritis, pneumonitis, pancreatitis, or colitis). It can be caused by antiepileptics, allopurinol, sulfasalazine and some other drugs. Ten to 30% of the patients may die and some require liver transplantation. The most important step is stop of drug treatment. In spite of this, the course of this disease may be prolonged, as often a reactivation of herpes viruses can be observed in the third/fourth week. Typical is also a hypersensitivity to other drugs with flare up reactions (exanthema, hepatitis) for months. Therefore, patients should avoid any unnecessary contact with xenobiotics, in particular antibiotics, until the massive immune stimulation has weaned.