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DRESS syndrome associated with carbamazepine and phenytoin

Drug Rash with Eosinophilia and Systemic Symptoms (*DRESS*) syndrome reflects a serious hypersensitivity reaction to drugs. Its clinical manifestations include diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathy, fever, multivisceral involvement and it is associated with a high mortality rate. We report a 62-year-old patient suffering from epilepsy presenting erythroderma following carbamazepine intake. Blood tests revealed eosinophilia, leukocytosis, elevated liver enzymes and high levels of Eosinophil Cationic Protein (ECP). We applied systemic steroids and anticonvulsant therapy was switched to phenytoin, which had been taken previously without adverse reactions. The skin eruptions persisted and the patient developed fever. Anticonvulsant medication was discontinued and skin eruptions finally resolved under steroid application. This case report demonstrates that cross reactivity between carbamazepine and phenytoin may not only lead to the development but also to the worsening of *DRESS* syndrome. ECP blood levels may represent a sufficient parameter to monitor the development of *DRESS* syndrome.

Key words: anticonvulsant, *DRESS* syndrome, eosinophil cationic protein

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The term "hypersensitivity reaction" refers to a severe, idiosyncratic cutaneous reaction to drugs, which leads to long-lasting skin eruptions in combination with lymphadenopathy and visceral involvement. Drug Rash, Eosinophilia and Systemic Symptoms, also termed *DRESS* syndrome, was first introduced in 1996 by Bocquet to decrease the equivocality of the term "hypersensitivity syndrome" [1]. So far, numerous drugs such as sulfonamides, nevirapine, phenobarbital, sulfasalazine, carbamazepine and phenytoin have been reported to cause a *DRESS* syndrome [2-6]. Its clinical manifestations include a diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathy, fever, multivisceral involvement, eosinophilia and lymphocytosis. It usually appears acutely in the first two months after initiation of the drug, persists in some cases for months and is potentially life threatening with a mortality rate of 10% [1]. The incidence of a *DRESS* syndrome in response to phenytoin, carbamazepine or phenobarbital treatment is currently about 1/5000 exposures [7]. Currently, an association of drug reactions with Human Herpesvirus 6 infection has been discussed, although the exact pathophysiological pathway is unidentified [8]. In most cases, systemic corticosteroid therapy in combination with the rapid withdrawal of the drug responsible represents the basic therapeutical principles, even though randomized clinical trials for the benefit of systemic corticosteroids are missing [9].

Case report

A 62-year-old patient suffering from epilepsy presented erythroderma following carbamazepine intake. Prior to this, the patient had been taken phenytoin for 1/2 year without adverse reaction. This medication was switched to carbamazepine 12 weeks before the onset of skin eruptions which started one week before admission with a maculopapular rash on both legs spreading within days all over the integument, upper extremities and face (*Fig. 1*). Later, an exfoliative dermatitis started to involve both hands (*Fig. 2*). The patient also reported simultaneous occurrence of back pain. Clinical examination disclosed no further abnormal findings. Hematologic and blood chemical laboratory test results revealed a strong eosinophilia, leukocytosis, elevated liver enzymes, increased level of Eosinophil Cationic Protein and hypogammaglobulinemia (*Table I*). A histological examination of a skin biopsy revealed a lymphocytic infiltrate with edema and only a few eosinophils. On admission the anticonvulsant therapy was switched back from carbamazepine to phenytoin. Later, we applied systemic steroids (0.5 mg/kg bodyweight p.o.) daily. The skin eruptions persisted and the patient started to develop fever accompanied by a further increase of eosinophils (peak 58.8%) and an abrupt rise of serum creatinine (peak 2.6 mg/dl [<1.4 mg/dl]). The levels of leukocytes, CRP and liver enzymes remained elevated. At the same time a massive diarrhoea occurred. Stool specimens were negative for infectious agents and a colonoscopy was performed to rule out eosinophilic enterocolitis. Just as in the skin specimen, the



Figure 1. a) Involvement of the face. Note the facial edema. b) Maculopapular rash of the back with transition into erythroderma on the day of admission. c) Disappearance of skin eruptions after steroid therapy.



Figure 2. a) Exfoliative dermatitis of the left palm. b) Left palm after therapy.

histological examination revealed lymphocytic infiltration with few eosinophils. At this point all anticonvulsant medication was discontinued and the skin eruptions finally resolved under high-dose steroids (1 mg/kg body weight p.o.) application (Figs 1 and 2). The clinical condition stabilized and the elevated hematologic and chemical parameters normalized (Table I). Anticonvulsant therapy was continued with clobazam, which was well tolerated.

Discussion

Patients presenting eosinophilia pose a large number of differential diagnoses to physicians (Table II). Additionally, the diagnostic procedures often comprise different specialities like general physicians, dermatologists and pediatricians. Considering dermatological diseases, a maculopapular rash in combination with eosinophilia may occur

Table I. Hematologic and blood chemical laboratory test results

	On admission	Peak	After treatment	Standard
Leukocytes [G/l]	22.1	25.9	13.8	4.3-10.5
Eosinophils [%]	33.1	54.8	1.7	< 7
Neutrophils [%]	52.9	52.9	67	19-48
C-reactive Protein (CRP) [mg/l]	123	123	0.9	< 3
AST [U/l]	24	30	12	< 19
ALT [U/l]	61	70	21	< 28
Gamma-GT [U/l]	260	270	95	6-28
Creatinine (mg/dl)	1.1	2.6	1.3	0.5-1.4
Lactate Dehydrogenase (LDH) 25C [U/l]	459	459	392	100-240
Eosinophil Cationic Protein [μg/l]	205	205	4.02	< 4.4
Gammaglobulins [g/l]	1.6	1.6	9.9	6-10

Table II. *Eosinophilic disorders*

Atopic diseases	Atopic eczema, atopic rhinitis, atopic asthma
Allergy	Hypersensitivity reaction
Malignancies	Hodgkin's disease, myeloproliferative disorders, acute myeloid leukemia (M4)
Infections	Parasitic infections
Skin disorders	Wells' syndrome, hypereosinophilic syndrome, eosinophilic fasciitis
Pulmonary diseases	Churg-Strauss syndrome, eosinophilic pneumonia
Gastrointestinal disorders	Eosinophilic gastroenteritis

among patients with atopic dermatitis, hypereosinophilic syndrome (HES), malignancies, eosinophilic cellulitis (Wells' syndrome) or hypersensitivity reactions to drugs (Table III).

In view of the significant mortality rate of the DRESS syndrome, which is about 10%, the correct and fast diagnosis of this entity is of great importance. A detailed medical history – and especially the history of systemic medications – plays a central role. The time spread between the initiation of the drug and the onset of skin eruptions may vary between 2 to 6 weeks up to 2 months [1]. Therefore, it is important to recognize the initial signs of a DRESS syndrome, especially to avoid any delay in the withdrawal of the culprit drug. Further hematological findings besides eosinophilia, like leukocytosis and abnormal blood chemical test results, just as elevated liver enzymes and serum creatinine levels, indicate a visceral involvement. The herein reported hypogammaglobulinemia has been described early in adverse reactions to anticonvulsants [10]. This is contrary to HES, in which a hyperglobulinemia can frequently be found [11].

The histological pattern of the skin lesions in DRESS syndrome sometimes imitates pseudolymphoma but often shows a lymphocytic infiltrate with few eosinophils, like in

this case. The same histological pattern was found in the bowel specimen of our patient which was taken to rule out an eosinophilic enterocolitis.

The high ECP levels associated with the massive eosinophilia may lead to the systemic symptoms as eosinophil-derived protein toxicity is involved in the development of systemic symptoms in HES [12, 13]. As reported here for the first time, serum ECP levels may represent a sufficient parameter to monitor patients developing a DRESS syndrome and serve as helpful tool to accelerate the diagnosis. Although the pathological findings of a DRESS syndrome resolve slowly in general, a possible cross-reactivity between aromatic anticonvulsants (such as phenytoin, carbamazepine) could not be excluded in this case and may not only lead to the development, but also to the worsening of a DRESS syndrome, even though these drugs have been well tolerated before. Therefore, all of these drugs should be strictly avoided. Taken together, the diagnostic and therapeutic challenge of a DRESS syndrome necessitates interdisciplinary approaches combining the expertise of dermatologists and other medical disciplines, which are indispensable for the optimal care of the patient. ■

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Table III. *Differential diagnosis in skin disorders associated with eosinophilia*

	Medical history	Laboratory test	Systemic symptoms	Skin lesion	Skin pathology
DRESS syndrome	Drug initiation or change within the past 2 months	Eosinophilia, leukocytosis, elevated liver enzymes, high ECP levels	Liver failure, renal failure, arthralgia, diarrhea	Maculopapular rash, exfoliative dermatitis, edema of the face	Lymphocytic infiltration, sometimes pseudolymphoma
HES	No association with drugs	Eosinophilia > 6 months, in some cases leukocytosis, elevated liver enzymes, high ECP levels	Endocarditis, congestive heart failure, thrombosis, strokes, peripheral neuropathy, encephalopathy, hepatosplenomegaly, diarrhea, arthralgia	Erythroderma, edema, pruritus	Eosinophilic infiltration, cutaneous microthrombembolism
Wells' syndrome	In some cases relation to drugs or insect bite at lesional site	Eosinophilia in > 50% of cases, leukocytosis and thrombocytosis may occur	None	Erythema and edema in initial phase, pruritic papular, annular plaques and urticaria-like eruptions, sometimes vesicles and blisters	Dermal infiltration of eosinophils, initially edema, cell debris between collagen bundles forming "flame figures"

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