

Twelve-Year Analysis of Severe Cases of Drug Reaction With Eosinophilia and Systemic Symptoms

A Cause of Unpredictable Multiorgan Failure

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Background: Factors implicated in the severity of drug reaction with eosinophilia and systemic symptoms (DRESS) have not been identified. We retrospectively describe and analyze severe cases of DRESS defined by history of intensive care unit admission and death due to DRESS.

Observations: Of 15 patients retrospectively recruited in France, 14 were admitted to the intensive care unit and 3 died. The culprit drugs were already known to cause or trigger DRESS: allopurinol, minocycline hydrochloride, anticonvulsants, sulfonamides, and antibiotics. Visceral involvement with severe manifestations responsible for intensive care unit admission or death was variable and often multiple (pneumonitis, hepatitis, renal failure, encephalitis, hemophagocytosis, cardiac failure, and pancytopenia) and resulted in multiorgan failure in 11 patients.

These severe complications sometimes developed late in DRESS. Human herpesvirus 6 infection was demonstrated in 6 of 7 patients. In addition, human herpesvirus 6 infection was demonstrated in involved viscera in 2 patients.

Conclusions: Severe DRESS is rare. Some specificities of visceral involvement were associated with allopurinol and minocycline. However, visceral involvement comprising multiorgan failure seemed to be unpredictable. Better knowledge of DRESS is necessary to propose specific and prompt treatment. Early demonstration of human herpesvirus 6 reactivation could be considered a prognostic factor for identifying patients at higher risk and, hence, needs to be evaluated.

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DRUG REACTION WITH EOSINOPHILIA and systemic symptoms (DRESS) is a severe drug-induced adverse manifestation that occurs in most patients 3 to 6 weeks after drug administration. Clinical and biological manifestations of DRESS are characteristic: high fever, facial edema, erythroderma followed by an exfoliative dermatitis, diffuse lymphadenopathy, eosinophilia, atypical circulating lymphocytes, and abnormal results of liver function tests.^{1,2} Numerous systemic manifestations may occur (pneumonitis, pancreatitis, renal failure, neurologic symptoms, and many others). This adverse drug reaction is known to occasionally be severe and life-threatening, but no prognostic factors are identified.

Many mechanisms have been suggested to explain these visceral manifestations in DRESS, including drug toxicity, immunologic responses, eosinophilia, the hemophagocytic syndrome, and bacterial or viral infection.^{3,4} The role of viral infection in the development of this adverse drug reaction is well recognized.⁵⁻⁸ Human herpes-

virus 6 (HHV-6) reactivation is now one of the criteria proposed by a Japanese consensus group to diagnose drug-induced hypersensitivity syndrome or DRESS.⁹ Bacterial infections also seem to be frequent and may complicate this disorder. Common transient hypogammaglobulinemia also has been observed.^{10,11}

However, the most severe cases have not been specifically studied in the literature. We describe and better characterize the most severe cases of DRESS in France. Better knowledge of these severe cases may have many implications, including finding prognostic criteria for DRESS, identifying at-risk patients or culprit drugs, and proposing a treatment plan and follow-up for these patients.¹²

METHODS

We retrospectively recruited all patients with severe DRESS documented between January 1, 1995, and December 31, 2006. The diagnostic criteria for DRESS were those defined by Begon and Roujeau.² All the patients displayed typical cutaneous manifestations of DRESS (fa-

Table. Clinical Characteristics and Course of DRESS in the 15 Study Patients

Patient No./ Sex/Age, y	Inclusion Criteria ^a	Culprit Drug ^b	Associated Diseases	Interval, d			Systemic Symptoms	HHV-6 Infection (PCR)	Treatment
				From First Drug Intake to ICU Admission/ Death	From ICU Admission to Last Clinical or Biological Manifestation	From ICU Admission to End of Treatment			
1/F/25	1	Phenobarbital sodium	Epilepsy	13	210	630	Hepatitis, hemophagocytosis, infection	+	Glucocorticoid, etoposide
2/F/40	1, 2	Sulfadiazine	HIV, cerebral toxoplasmosis	10/31	NA	NA	Encephalitis, hemophagocytosis, pneumonitis, rhabdomyolysis, pancytopenia, infection	+	Glucocorticoid, intravenous gammaglobulins
3/F/30	1	Sulfasalazine	Ankylosing spondylitis	7	44	NA	Fulminant hepatitis	+	Glucocorticoid, liver transplantation
4/F/71	1	Allopurinol	None	6	ND	ND	Hepatitis, renal failure, pneumonitis	ND	None
5/M/35	1	Methicillin sodium	None	10	360	450	Hepatitis, renal failure, pneumonitis, intestinal perforation	ND	None
6/M/54	1	Telithromycin	None	23	ND	ND	Pneumonitis, infection	ND	None
7/F/65	1	Allopurinol	Alcoholic cirrhosis	25	48	69	Cardiac failure, pneumonitis, renal failure, capillary leak	ND	Glucocorticoid
8/M/71	2	Allopurinol	Hyperuricemia	7	NA	NA	Hepatitis, renal failure	ND	None
9/F/15	1, 2	Minocycline	Sickle cell disease	107/164	NA	NA	Hepatitis, renal failure, pneumonitis, shock, infection	+	Glucocorticoid, gammaglobulins
10/M/44	1	Allopurinol	Hyperuricemia	17	34	50	Hepatitis, renal failure, pneumonitis	ND	Glucocorticoid
11/F/25	1	Lamotrigine	Epilepsia	25	10	60	Pneumonitis, infection, shock	ND	Glucocorticoid
12/F/53	1	Sulfadiazine	Toxoplasmosis	5	30	60	Pneumonitis (HHV-6 infection +)	+	Glucocorticoid
13/M/16	1	Minocycline	None	6	60	150	Pneumonitis, multiorgan failure	ND	None
14/F/21	1	Phenytoin	Epilepsia	5	17	59	Encephalitis, hepatitis, pancytopenia	-	Glucocorticoid, intravenous gammaglobulins
15/F/33	1, 2	Minocycline	Malaria	59/65	NA	NA	Myocarditis, pneumonitis, hepatitis	+	Glucocorticoid

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; ICU, intensive care unit; NA, not applicable; ND, not done; PCR, polymerase chain reaction; +, positive; -, negative.

^aFor inclusion criteria, 1 indicates ICU admission; 2, death due to DRESS.

^bMinocycline administered as minocycline hydrochloride.

cial edema, exanthema, and lymphadenopathy). Severe cases of DRESS were defined by the presence of at least 1 of 2 criteria: (1) admission to the intensive care unit (ICU) and (2) death due to DRESS. The only exclusion criterion was DRESS that developed in the ICU but that was not the cause of admission to the ICU. The cases were retrospectively selected by members of the French Group of Cutaneous Drug Adverse Reactions of the French Society of Dermatology.

Analyzed items included age, ethnic origin (white, North African, black African, Arab, and Asian), associated disorders, culprit drugs, time elapsed between DRESS development and transfer to the ICU or death, systemic involvement, concomitant infection, and treatment. Serologic analysis and polymerase chain reaction (PCR) methods for HHV-6 infection have been described previously.^{5,7,13}

RESULTS

We included 15 patients (10 women and 5 men) with severe DRESS documented during this 12-year study (**Table**). In 3 patients, DRESS was the cause of death. Fourteen patients were hospitalized in the ICU due to

systemic manifestations of DRESS. Two patients were previously described (patients 1 and 2).^{5,14} The mean patient age was 39 years. The ethnic origin was various, including white (6 patients), North African (4 patients), black African (3 patients), Arab (1 patient), and Asian (1 patient).

Most of the culprit drugs that we identified had already been established as trigger factors for DRESS before conducting this study: allopurinol (4 patients), minocycline hydrochloride (3 patients), anticonvulsants (1 patient each: phenobarbital sodium, lamotrigine, and phenytoin), and sulfonamides (1 patient: sulfasalazine; 2 patients: sulfadiazine). In addition, 2 cases were caused by telithromycin and methicillin sodium.

Time between development of the first manifestations of DRESS and admission to the ICU (mean, 18 days; range, 5-95 days) or death (mean, 64 days; range, 7-164 days) was variable. Severe manifestations responsible for admission to the ICU or death were multiple and included pneumonitis (10 patients), hepatitis (7 patients), renal failure (5 patients), encephalitis (2 pa-

tients), hemophagocytic syndrome (2 patients), cardiac failure (1 patient), and pancytopenia (2 patients).

Some specificities of visceral involvement were associated with allopurinol and minocycline treatment: renal failure was observed in all 4 patients with allopurinol-induced DRESS and pneumonitis in all 3 with minocycline-induced DRESS. However, we noticed that different organs failed in different combinations to give several "multiorgan failure" pictures. In 7 patients, bacterial infections (mainly due to *Staphylococcus aureus*) were demonstrated and may have contributed to the severity of the illness.

When looked for, HHV-6 infection was demonstrated by positive PCR results in blood or serum samples in 6 of 7 patients. The HHV-6 infection was demonstrated in 2 different viscera: the liver and the central nervous system in patients with hepatitis and encephalitis, respectively. In addition, HHV-6 infection was confirmed in the liver by means of immunohistochemical and DNA PCR analyses (patient 3). Detection in the cerebrospinal fluid was achieved by means of DNA PCR analysis (patient 2).

Treatment consisted mainly of glucocorticoids (systemic treatment in 10 patients). However, in 3 patients, intravenous gammaglobulins were prescribed in addition. In 1 patient, liver transplantation was necessary. Follow-up and treatment needed to be long-term (50-630 days after admission to the ICU) because of frequent flaring (10-360 days after the date of admission to the ICU) (Table).

Patients 3 and 9 illustrate the unpredictability and severity of this syndrome.

Patient 3 was a 30-year-old woman treated with sulfasalazine for ankylosing spondylitis. Three weeks after beginning treatment, she developed typical DRESS (fever, erythroderma, facial edema, diffuse lymphadenopathy, eosinophilia, and atypical lymphocytes with mononucleosis syndrome). She developed fulminant hepatitis with a fast increase (within 5 days) in aspartate transaminase levels (2-185 times the normal value). A liver transplantation was performed in an emergency setting despite treatment with glucocorticoids. Histologic examination confirmed massive hepatic necrosis with dense inflammatory infiltrates containing lymphocytes and eosinophils. Virologic analysis demonstrated the presence of anti-HHV-6 IgM antibodies and an increase in anti-HHV-6 IgG antibodies (from a titer of 320-2560). Serologic analysis of a serum sample collected several months before the episode was positive for anti-HHV-6 IgG antibodies (a titer of 620). This confirmed that the pretransplantation episode had been an HHV-6 reactivation and not a primary infection. Real-time quantitative DNA PCR analysis of a serum sample performed before transplantation demonstrated a high level of HHV-6 viremia (431 000 copies/mL). The HHV-6 infection was demonstrated in the explanted liver by means of DNA PCR and immunohistochemical analyses. Results of hepatitis B virus, hepatitis C virus, cytomegalovirus, and human immunodeficiency virus analyses were negative.

Patient 9 was a 15-year-old African girl treated with minocycline for acne. She had never had a drug allergy. Twelve days later she developed pharyngitis, which was treated with amoxicillin-clavulanic acid. The pharyngi-

tis was probably the first manifestation of typical DRESS (day 0). The clinical manifestations of DRESS were completed 4 days later (day 4) by a progressive development of fever (temperature, 40°C), diffuse maculopapular exanthema, facial edema, diffuse lymphadenopathy, hepatosplenomegaly, and eosinophilia. Tachycardia and tachypnea were documented. No radiologic abnormality was found. Serial biological tests progressively demonstrated an increase in transaminase levels (20-fold the reference values). Infection with HHV-6 was demonstrated by means of DNA PCR blood analysis.

Glucocorticoid treatment was started on day 21 (intravenous methylprednisolone and then oral prednisolone, 1 mg/kg/d). Liver test results progressively improved, and the dosage of glucocorticoids was decreased. Three weeks after the beginning of glucocorticoid treatment (day 42), a flare up of DRESS occurred, when the oral prednisolone dosage was 0.3 mg/kg/d, with the following manifestations: pruritus, exanthema, eosinophilia, renal insufficiency, and hypertension. The glucocorticoid dosage was increased to 0.8 mg/kg/d immediately. Good clinical and biological responses were observed, and the daily dose of glucocorticoids was progressively decreased by 5 mg each week. One month later (day 73), while receiving a corticosteroid dose of 20 mg/d, a second flare up of DRESS occurred, with reappearance of cutaneous lesions along with facial edema and eosinophilia; therefore, topical corticosteroids were also administered (clobetasol propionate, 20 g/d). One month later (day 107), she was admitted to the ICU due to encephalitis (status epilepticus). She also had erythroderma, with 20% skin detachment. Peripheral thrombocytopenia and eosinophilia were noted.

At this point, HHV-6 infection was not investigated, but other infections (herpes simplex virus, varicella zoster virus, and cytomegalovirus) were ruled out by means of cerebrospinal fluid analysis. The working diagnosis was hypertensive encephalitis. Then, after the patient became normotensive, glucocorticoids were given with intravenous gammaglobulins (for the thrombocytopenia) in addition to an anticonvulsant agent. She also experienced concomitant septicemia (*Staphylococcus aureus* and *Pseudomonas aeruginosa*), which was treated; her condition improved, so she was extubated and discharged. However, 3 weeks later, she suddenly developed multivisceral organ failure, with pneumonitis, adult respiratory distress syndrome, disseminated intravascular coagulation, and shock. The HHV-6 DNA was demonstrated in her blood sample by means of PCR, and cytomegalovirus was demonstrated in the bronchoalveolar lavage fluid. She died 164 days after the beginning of DRESS.

COMMENT

DRESS is known to be a life-threatening adverse drug reaction. Severe DRESS, as defined by the study criteria (DRESS requiring admission to the ICU or resulting in death) is infrequent but not rare. In the 12-year period that we investigated, only 15 patients were retrospectively recruited. This study is probably not exhaustive, but such a dramatic presentation as that of DRESS would

not be easily forgotten by the members of the French Society of Dermatology, the exclusive source of the patients in this study. Furthermore, because these 15 patients are distributed equally across the 12-year period, we have reason to believe that the number of patients is almost representative of the true prevalence. The major critique may be that these reported cases of DRESS were those seen by dermatologists where cutaneous manifestations were significant. It is possible that some rare severe cases of DRESS with visceral manifestations (hepatitis, renal failure, pneumonitis, encephalitis, pancytopenia, and others) but minimal or absent cutaneous symptoms were not recruited in this study. That is why *reaction* was proposed instead of *rash* in the acronym DRESS, making it *drug reaction with eosinophilia and systemic symptoms*.²

It is important to define predictive factors for cases that may warrant more careful and long-term follow-up, in addition to introduction of aggressive treatment. This is not the aim of this study, which is a descriptive study that includes only severe cases of DRESS. However, the detailed analyses of severe cases can help reveal important information that may be helpful in the future.

It is known that several drugs induce DRESS. The present findings suggest that some drugs are more likely to produce a more severe form of the disease. In recently published data by the Network of the French Pharmacovigilance Center, 216 patients with DRESS have been reported to the French pharmacovigilance database during a 15-year period (1985-2000), where only anticonvulsants, allopurinol, minocycline, and abacavir sulfate were considered.¹⁵ When we compared the prevalence of each drug in the present series vs the pharmacovigilance database, allopurinol was involved in 4 of 15 patients with severe DRESS vs 21 of 216 patients ($P=.04$). Therefore, we consider allopurinol to be more likely to induce a severe form of DRESS.¹⁴ Moreover, the only 2 deaths reported from 1985 to 2000 to the French pharmacovigilance database (and not included in the present series [1995-2006]) were due to allopurinol (written communication, H. Peyriere, PhD, 2007). Minocycline was associated with 2 of 3 deaths in the present series and may be considered a higher-risk medication.

No associated disorder was found. Conditions that alter the immune response were observed in 2 patients: human immunodeficiency virus infection and the connective tissue disease ankylosing spondylitis. The severity of DRESS was most frequently determined by the importance of visceral involvement. Contrary to toxic epidermal necrolysis, the general condition of the patient did not seem to be a major risk factor in DRESS. In toxic epidermal necrolysis, age older than 40 years and neoplasia are 2 bad prognostic criteria.¹⁶ In the present series, the mean age of the patients was 39 years, whereas the mean age of patients who died was 40 years. In addition, no association with neoplasia has been found. This demonstrates an important difference between toxic epidermal necrolysis and DRESS.

In DRESS, a genetic predisposition may explain the susceptibility to some drugs. Recently, for example, HLA-B*5801 was described as a genetic marker for allopurinol-induced severe drug reaction in Han Chinese patients.¹⁷

Polymorphism in the promoter region of tumor necrosis factor α was also observed in carbamazepine-hypersensitive patients.¹⁸

A major breakthrough in the understanding of the pathogenesis of DRESS was identification of the significant role of the herpesviruses, in particular, HHV-6. Today, 10 years after the first description of the association of DRESS with HHV-6 infection, the reactivation of HHV-6 has been demonstrated in many patients with DRESS, and it is considered to be a diagnostic criteria by the Japanese consensus group for drug-induced hypersensitivity syndrome.^{5,9} Reactivation of HHV-6, cytomegalovirus, or Epstein-Barr virus and the immune response against viruses (HHVs) in infected tissue are considered to be paramount in the pathogenesis of DRESS.^{4,8,12} In a recent series, Tohyama et al¹⁹ demonstrated HHV-6 reactivation in 62 of 100 patients. In the present retrospective series, only 7 patients were studied by means of PCR for an active HHV-6 infection, and in 6 patients (patients 1, 2, 3, 9, 12, and 15), an active HHV-6 infection was demonstrated. In 2 of these patients, HHV-6 was demonstrated in the viscera: cerebrospinal fluid and liver in patients with encephalitis and fulminant hepatitis, respectively.¹⁴ In the patient with fulminant hepatitis, the virus was demonstrated in the liver and serum. Analysis of a previous serum sample confirmed that HHV-6 infection was a reactivation and not a primary infection. However, the sequence of the events may be debatable. This case report confirms that HHV-6 reactivation occurs early, as we previously observed in another case report,¹³ suggesting concomitant reactivation of the virus with both, the beginning of the clinical manifestations of DRESS and the mononucleosis syndrome. We believe that mononucleosis syndrome can be observed in the same manner at the beginning of DRESS and severe HHV-6 primary infection.²⁰ It is probable that the culprit drug induced a state of immunosuppression that favors HHV-6 reactivation. The transitory hypogammaglobulinemia that has been demonstrated at the very beginning of DRESS may favor HHV-6 reactivation.^{10,11} In addition, culprit drugs may also have a direct effect on HHV-6 replication. Recently, we demonstrated that an anticonvulsant agent, sodium valproate, also induced a direct stimulation of HHV-6 replication in vitro.²¹ All this illustrates the critical role of HHV infection in this syndrome.

Tohyama et al¹⁹ also demonstrated an association of HHV-6 reactivation with the flaring of DRESS. Decreasing the glucocorticoid dose may induce an amplification of the antiviral immune response, with subsequent flaring of the disease. Patient 9 in this study, who had minocycline-induced DRESS with a waxing and waning course, may illustrate the possible interaction among virus reactivation, antiviral immune response, and glucocorticoids.

The visceral involvement has often been a multiorgan failure that may have occurred later in the disease. The explanation for these multiorgan failures is not clear. These cases illustrate that many factors may contribute to multiorgan failure, for example, viral infection, bacterial infection, and hemophagocytosis. The already known multiorgan failure syndrome (different from

DRESS) is characterized by the development of progressive organ dysfunction. During this syndrome, a high level of proinflammatory cytokines is released, such as tumor necrosis factor α . Reactivation of HHV-6 has been reported, independent of DRESS, in association with multiorgan failure syndrome.²² Inversely, multiorgan failure may be observed after disseminated infection with HHV-6 after a primary infection in infancy and childhood or in immunocompromised patients, such as transplant recipients.²³⁻²⁶ It is associated with hepatosplenomegaly, hepatitis, pneumonitis, hemophagocytic syndrome, thrombocytopenic purpura, and aseptic meningitis. The mechanism is not well understood.²³ It is probable that, in the same way as in DRESS, multiorgan failure is not the direct consequence of local virus reactivation but the consequence of a complex immune response with a cytokine storm.

Treatment of severe DRESS is not well defined. Whereas glucocorticoid treatment is often satisfactory, sometimes it may not be effective (patients 2, 3, 9, and 15), and decreasing the dosage may be associated with flaring of the disease. Glucocorticoids are effective against the immune response, but we believe that they may be detrimental when virus infection is not controlled by host immunity. New treatment modalities need to be evaluated (intravenous gammaglobulins and antiviral drugs, such as valganciclovir hydrochloride) in addition to glucocorticoids to target HHV-6 and other herpesviruses.^{4,8,12} In 2 (patients 2 and 9) of 3 patients, intravenous gammaglobulins, when prescribed very late during the course of DRESS, did not prevent a fatal outcome. In the third patient (patient 14), early treatment with intravenous gammaglobulins associated with corticosteroids was effective. Antiviral drugs have toxic effects, so their benefit needs to be evaluated in clinical trials.

The high incidence of bacterial infections may be related to the HHV-6-mediated immunosuppression. It has recently been demonstrated that HHV-6 suppressed the secretion of interleukin 12 and impaired the ability of dendritic cells to stimulate allogeneic T-cell proliferation.²⁷

Severe cases of DRESS are infrequent, and the progression of DRESS is often unpredictable. From this descriptive study, it is difficult to propose prognostic factors for DRESS. No factor specific to the patient (an associated disorder, a medical condition, or race/ethnicity) was demonstrated. No specific visceral involvement seems to be responsible for these severe cases of DRESS. This type of visceral involvement is often multiple. In this series, allopurinol and minocycline seem to be associated with a higher risk of severe DRESS.

Further studies are necessary to identify valuable prognostic factors that may contribute to the severity of DRESS. These factors may include a certain genetic background and the early demonstration of an active HHV-6 infection. It is clear that DRESS has to be diagnosed rapidly to withdraw all putative drugs. DRESS is variable in its course, and no one factor helps identify which patients will progress with a more severe course. Hence, careful and long-term clinical and biological follow-up is needed to diagnose internal involvement.

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REFERENCES

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331(19):1272-1285.
2. Begon E, Roujeau JC. Drug hypersensitivity syndrome: DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) [in French]. *Ann Dermatol Venerol*. 2004;131(3):293-297.
3. Descamps V, Mahe E, Ranger-Rogez S. Systemic reactions to HHV-6 infection. In: Krueger G, Ablashi D, eds. *Human Herpesvirus-6: General Virology, Epidemiology and Clinical Pathology*. Amsterdam, the Netherlands: Elsevier Science BV; 2006:152-156. *Perspectives in Medical Virology*; vol 12.
4. Hashimoto K, Yasukawa M, Tohyama M. Human herpesvirus 6 and drug allergy. *Curr Opin Allergy Clin Immunol*. 2003;3(4):255-260.
5. Descamps V, Bouscarat F, Laglenne S, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. *Br J Dermatol*. 1997;137(4):605-608.
6. Tohyama M, Yahata Y, Yasukawa M, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol*. 1998;134(9):1113-1117.
7. Descamps V, Valance A, Edlinger C, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol*. 2001;137(3):301-304.
8. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int*. 2006;55(1):1-8.
9. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol*. 2007;156(5):1083-1084.
10. Kano Y, Seishima M, Shiohara T. Hypogammaglobulinemia as an early sign of drug-induced hypersensitivity syndrome. *J Am Acad Dermatol*. 2006;55(4):727-728.
11. Boccara O, Valeyrie-Allanore L, Crickx B, Descamps V. Association of hypogammaglobulinemia with DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). *Eur J Dermatol*. 2006;16(6):666-668.
12. Descamps V. The role of viral infections in the development of cutaneous inflammatory reactions: the drug hypersensitivity syndrome. *Rev Fr Allergol*. 2006;46:227-229.
13. Descamps V, Collot S, Mahe E, Houhou N, Crickx B, Ranger-Rogez S. Active human herpesvirus 6 infection in a patient with drug rash with eosinophilia and systemic symptoms. *J Invest Dermatol*. 2003;121(1):215-216.
14. Descamps V, Collot S, Houhou N, Ranger-Rogez S. Human herpesvirus-6 encephalitis associated with hypersensitivity syndrome [letter]. *Ann Neurol*. 2003;53(2):280.
15. Peyrière H, Dereure O, Breton H, et al; Network of the French Pharmacovigilance

- Centers. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2006; 155(2):422-428.
16. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115(2):149-153.
 17. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A*. 2005;102(11):4134-4139.
 18. Pirmohamed M, Lin K, Chadwick D, Park BK. TNF α promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology*. 2001;56(7):890-896.
 19. Tohyama M, Hashimoto K, Yasukawa H, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. *Br J Dermatol*. 2007;157(5):934-940.
 20. Akashi K, Eizuru Y, Sumiyoshi Y, et al. Brief report: severe infectious mononucleosis-like syndrome and primary human herpesvirus 6 infection in an adult. *N Engl J Med*. 1993;329(3):168-171.
 21. Mardivirin L, Lacroix A, Delebassée S, Descamps V, Ranger-Rogez S. Augmentation de la réplication in vitro de l'herpèsvirus humain 6 en présence de valproate de sodium. *Virologie*. 2007;11:51-53.
 22. Desachy A, Ranger-Rogez S, François B, et al. Reactivation of human herpesvirus type 6 in multiple organ failure syndrome. *Clin Infect Dis*. 2001;32(2):197-203.
 23. Sergi C, Daum E, Pedal I, Hauroeder B, Schnitzler P. Fatal circumstances of human herpesvirus 6 infection: transcriptome data analysis suggests caution in implicating HHV-6 in the cause of death. *J Clin Pathol*. 2007;60(10):1173-1177.
 24. Clark DA, Emery VC, Griffiths PD. Cytomegalovirus, human herpesvirus-6, and human herpesvirus-7 in haematological patients. *Semin Hematol*. 2003;40(2):154-162.
 25. Zerr DM, Corey L, Kim HW, Huang ML, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2005;40(7):932-940.
 26. Zerr DM. Human herpesvirus 6 and central nervous system disease in hematopoietic cell transplantation. *J Clin Virol*. 2006;37(suppl 1):S52-S56.
 27. Smith AP, Paolucci C, Di Lullo G, Burastero SE, Santoro F, Lusso P. Viral replication-independent blockade of dendritic cell maturation and interleukin-12 production by human herpesvirus 6. *J Virol*. 2005;79(5):2807-2813.

Archives Web Quiz Winner

Congratulations to the winner of our October quiz, CDR Tamara Scalise, MC, USN, Department of Dermatology, Naval Medical Center San Diego, San Diego, California. The correct answer to our October challenge was *pityriasis rotunda*. For a complete discussion of this case, see the Off-Center Fold section in the November Archives (Finch JJ, Olson CL. Hyperpigmented patches on the trunk of a Nigerian woman. *Arch Dermatol*. 2008;144[11]:1509-1514).

Be sure to visit the *Archives of Dermatology* Web site (<http://www.archdermatol.com>) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the *Archives*. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.