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Abnormal erythrocyte morphology in drug reaction with eosinophilia and systemic symptoms

To the Editor: Drug rash with eosinophilia and systemic symptoms (DRESS) is a potentially fatal adverse drug reaction that is difficult to diagnose because of its wide range of clinical findings. Diagnosis is commonly made by using the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring criteria, which include rash, fever, lymphadenopathy, eosinophilia, leukocyte abnormalities, thrombocytopenia, transaminitis, and other organ involvement.[1] Incidental abnormal erythrocyte morphology (AEM) is not in the existing diagnostic criteria, and to our knowledge, it has not been associated with DRESS in the literature. This study aimed to assess whether AEM is associated with DRESS.

A retrospective review of the charts of adult patients whose disease was diagnosed by the inpatient dermatology service at Wake Forest Baptist Medical Center and who experienced a drug eruption between January 2012 and July 2018 was performed. Demographics, RegiSCAR criteria, and presence or absence of AEM were noted. Patients with RegiSCAR scores of 2 or higher, indicating possible, probable, or definite cases of DRESS, were included in the DRESS cohort.[2] Patients in the control cohort were inpatients with a diagnosis of morbilliform drug eruption, Stevens Johnson syndrome, or toxic epidermal necrolysis. Only patients who had a complete blood count with differential performed at Wake Forest Baptist Medical Center were included. A Fisher exact test was performed to compare the prevalence of AEM between patients with DRESS and those with other drug eruptions.

Table I. Frequencies of erythrocyte abnormalities in the DRESS cohort

Erythrocyte abnormality	Patients with DRESS and AEM, n (%) (n = 21)
Poikilocytosis	10 (48)
Polychromasia	10 (48)
Burr cells	7 (33)
Ovalocytes	7 (33)
Schistocytes	5 (24)
Target cells	4 (19)
Acanthocytes	2 (10)
Tear drop cells	2 (10)
Nucleated erythrocytes	1 (5)

AEM, Abnormal erythrocyte morphology; *DRESS*, drug rash with eosinophilia and systemic symptoms.

Table II. Frequency of other clinical findings in the DRESS cohort

Clinical finding	Patients with a RegiSCAR score of ≥2, n (%) (n = 38)
Fever (temperature of ≥100.4°F)	27 (71)
LAD	6 (16)
Eosinophilia	29 (76)
Thrombocytopenia	10 (26)
Thrombocytosis	3 (8)
Hepatic abnormalities	23 (60)
Kidney abnormalities	14 (37)
Other systemic abnormalities noted	5 (13)
Biopsy performed	9 (24)
Abnormal erythrocyte morphology	21 (55)

DRESS, Drug rash with eosinophilia and systemic symptoms; *LAD*, lymphadenopathy; *RegiSCAR*, Registry of Severe Cutaneous Adverse Reactions.

The DRESS cohort included 38 patients. Their average age at diagnosis was 55 years. Fourteen patients were male. More than half (55%) of these patients had AEM (Table I). The rates of other clinical findings associated with DRESS are displayed in Table II. Of the patients with DRESS who had AEM, 86% had eosinophilia and 67% had hepatic abnormalities. Of the patients with DRESS without AEM, 65% had eosinophilia and 41% had hepatic abnormalities. The cohort of patients with other drug eruptions included 246 patients; however, 31 were excluded because a complete blood count with differential was not performed during their hospitalization. Of the 215 patients included, 52 (24%) had AEM. AEM was more prevalent with DRESS than the other drug eruptions ($P = .0003$).

The prevalence of each RegiSCAR category in this study is similar to that in other publications on DRESS.[3-5] This study differs as it recorded AEM. The results show that AEM appeared in DRESS as often as the established RegiSCAR criteria, including hepatic abnormalities and acute kidney injury. AEM was significantly more prevalent in patients with DRESS than in patients with other drug eruptions. The cause of AEM in DRESS is not known. This phenomenon may be due to disease involvement of the hematologic organ systems. Toxic eosinophilic granule proteins released during DRESS are thought to mediate organ damage and may affect the bone marrow, liver, and/or spleen and account for abnormalities seen in multiple blood cell lines.[1] Our study supports this theory by showing that patients with DRESS and AEM were more likely to have eosinophilia and hepatic involvement than were patients without AEM. Limitations of this study include small sample size at a single medical center. Larger multicenter studies are needed to determine whether this finding can be replicated elsewhere. The presence of AEM may aid in the diagnosis of DRESS and could be evaluated as a component of the diagnostic scoring system.

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Initiation of methotrexate with or without a test dose: A retrospective toxicity study

To the Editor: Many dermatologists initiate methotrexate with a small test dose (TD), followed by laboratory evaluation before the second dose. Intended to minimize the risk for early adverse events, this practice has been noted in guidelines,[1,2] though some have questioned its necessity.[3] Clinical trials utilizing methotrexate without a TD have reported a low incidence of serious adverse events.[4] We performed a retrospective study to compare the frequency of adverse events in patients initiating methotrexate with and without a TD.

Our electronic medical records were searched for patients with a new prescription for methotrexate from dermatology or rheumatology during 2010-2015. Patients were included if use of a TD, the initial dose, dose changes, date and reason of discontinuation, and baseline and follow-up laboratory values for a 4-month period after initiation of methotrexate were documented. TD was defined as an initial methotrexate dose of ≤10 mg and laboratory monitoring before the second weekly methotrexate dose. Laboratory values were graded according to standard terminology.[5]

The initial search identified 812 patients; 174 met inclusion criteria. Most dermatology patients received a TD, and most rheumatology patients did not (Table I). As expected, the initial methotrexate dose was lower in the TD group, but both groups had a mean initial dose <10 mg, with a range of 5-15 mg in the no-TD group (Table I). Patients receiving a TD had significantly more laboratory draws than those without a TD during the first 4 months of therapy (Table I). Initial doses were lower in dermatology patients (mean 5.9 mg) than rheumatology patients (mean 8.4 mg, $P < .001$).

There were no deaths or hospitalizations attributed to methotrexate toxicity. Laboratory values obtained 1 week after a TD showed no new grade 3 or 4 abnormalities and prompted only 1 management change, which was discontinuation of methotrexate in 1 patient with mild (grade 1) alanine