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A CASE OF DRESS SYNDROME DUE TO VANCOMYCIN

Danielle Zimmerman, M4, William Steinmann, MD
University of Missouri – Columbia

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe systemic reaction that usually begins 2-6 weeks after the introduction of the inciting agent. It is most commonly characterized by fever, rash, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, HHV-6 reactivation and internal organ involvement. At least 10% of the cases are fatal. Treatment includes withdrawal of the offending medication and administration of corticosteroids, though the efficacy of the latter has not been fully evaluated.

CASE REPORT

A 64 year-old white male with past medical history of type 2 diabetes mellitus, hypertension, hyperlipidemia, COPD, coronary artery disease, gout, and a fifteen pack-year smoking history presented with complaints of fever, rash and abdominal discomfort. Patient developed a new pruritic, nontender rash on back, chest, arms associated with bilateral arm swelling and shortness of breath. Eight months prior to the admission, he had an open reduction for fracture of the left distal femur after a motor vehicle accident. He had two admissions related to this. One month previously, he was admitted with left septic knee, which was treated by arthrocentesis, screw removal, irrigation and drainage. Intravenous vancomycin was given and vancomyin beads were placed in the knee joint space. Eight days prior to the arrival, the patient was readmitted with complaints of fever, chills, left knee pain and the X-ray of the left knee was suggestive of septic arthritis, which was subsequently managed with irrigation and drainage. Vancomycin was continued and the patient was discharged two days prior to the current admission. The patient hadn't had any recent medication changes and denied any exposure to exotic pets, molds, dusts, chemicals, and drugs.

On physical exam, his temperature was 37.8 °C with a blood pressure of 98/64mmHg. The exam

was remarkable for bilateral upper extremity edema and limited range of motion in the left knee secondary to mild swelling, without erythema or tenderness to palpation or movement. The skin exam revealed a very subtle, erythematous, papular, non-tender and non-confluent pruritic rash on chest and abdomen, more prominent on back and arms. Nikolsky sign was negative.

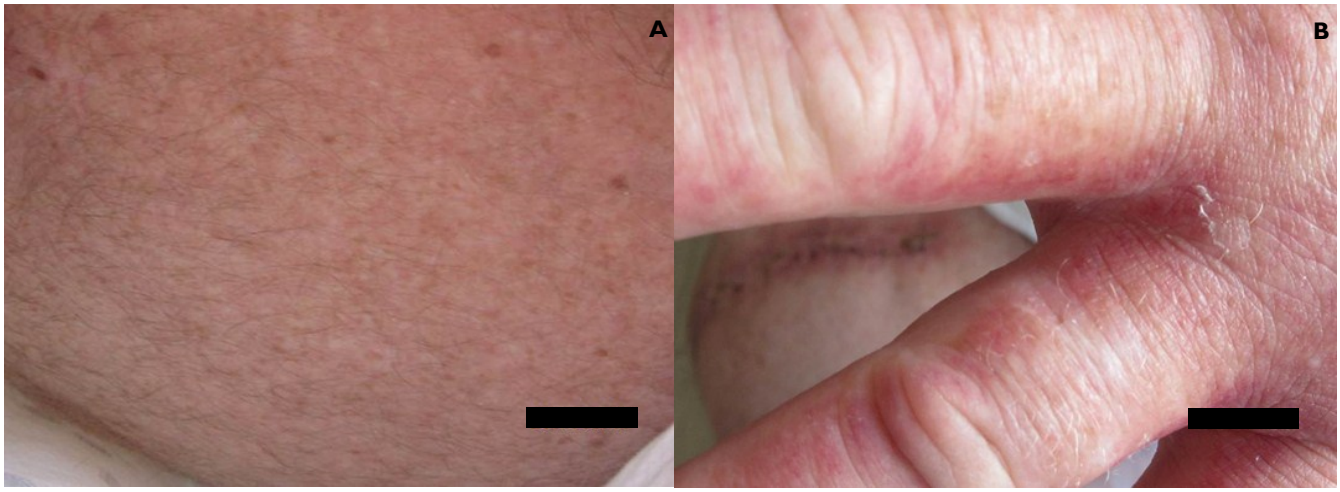

Figure A: Back showing rash with hyperemia and blanching; hospital day 6
Figure B: Edematous fingers and rash, left knee s/p ORIF in background; hospital day 6

Laboratory results on admission revealed white blood cell count of 10,300/μL, with 16.5% eosinophil's (normal 0-10%), and platelet count of 390,000 /μL. Other labs included alkaline phosphatase of 332 U/L, AST of 225 U/L, and ALT of 413 U/L compared to previous normal LFT's. Urinalysis was unremarkable and opacities, likely due to atelectasis. Peripheral smear from later hospital course showed large atypical eosinophil's and no toxic granulations in neutrophils. Blood culture remained negative during the hospital stay. Chest x-ray and abdominal ultrasound were unremarkable.

Given the cutaneous changes, eosinophilia and other systemic signs, a presumptive diagnosis of DRESS syndrome was made. Vancomycin was discontinued and patient was switchd to Daptomycin. Prednisone 60 mg daily was initiated for treatment of DRESS syndrome. The white counts increased to 18,800/μL on day 2, so steroids were held with concern regarding its immunosuppressive effects. Allopurinol was discontinued on hospital day 3, given its reported association with DRESS syndrome. However, as shown in the table over the next several days the white blood cell count escalated dramatically with accompanying eosinophilia. Without further signs of infection in the left knee, prednisone 60 mg was restarted on hospital day 7 to treat presumptive DRESS syndrome.

The prednisone was tapered from 60mg to 30mg daily on hospital day 9. (The patient's white cell count peaked at 44,000/μL on hospital day 10, and then decreased substantially by the day of discharge). Improvement of the patient's rash and edema was noted starting on hospital day 3 and continued until discharge, when the rash was no longer visible. However, bilateral axillary lymphadenopathy persisted. (HHV-6 titer drawn on hospital day 2 were negative; however, a repeat HHV-6 titer drawn on hospital day 8 came back positive). Due to absence of left shift and

Progression of WBC Count				
Date	**Hospital Day**	**WBC X 10^3/ µL**	**% Eosinophils**	**Treatment Notes**
8/13	2	10.3	16	Daptomycin begun One dose prednisone given
8/14	3	18.8	5	Daptomycin increased Allopurinol discontinued
8/15	4	19.9	26	
8/16	5	22.7	20	
8/17	6	29.1	21	
8/18	7	29.9	18	Prednisone restarted 60 mg
8/19	8	29.9	22	Prednisone 60 mg
8/20	9	36.5	22	Prednisone 30 mg
8/21	10	44.0	10	Prednisone 30 mg
8/22	11	38.7	32	Prednisone 30 mg
8/23	12	33.3	41	Prednisone 30 mg
8/24	13	22.1	39	Prednisone 30 mg
8/25	14	15.6	31	Prednisone 30 mg

toxic granulations in the neutrophils the infection and steroid response were less likely. Clonal hypereosinophilic disorder was also deemed unlikely because the eosinophils had been normal within the month. Because the patient continued to have complaints of left knee pain and given the leukocytosis, daptomycin was continued during this hospitalization. Patient was discharged on Prednisone 30mg for total of ten days, and then tapered down to 10 mg every 10 days.

DISCUSSION

DRESS syndrome was originally identified as a hypersensitivity reaction to certain anticonvulsants, including carbamazepine, lamotrigine, and phenobarbital, but a number of other medications with aromatic groups have been reported to cause the syndrome (1, 2, 3, and 5), including about 18 cases reported with allopurinol and four with vancomycin (2). Our patient had been on allopurinol for several years and he had started vancomycin about four weeks prior to the onset of symptoms, which makes vancomycin the most likely causative agent. More support for this conclusion includes the score of 4 which is a "possible adverse drug reaction" according to Naranjo Adverse drug Reaction Scale (1) and a "definite" case of DRESS syndrome per the criteria described by Kardaun et. al (6). Our patient also met all criteria for DRESS syndrome using the diagnostic criteria established by a Japanese consensus group (7).

This case illustrates the challenge in making a definitive diagnosis of DRESS syndrome. As most of the clinical features of DRESS syndrome are non-specific, it may be difficult to exclude other conditions. In this case, our patient's history of recent surgery and infection, leukocytosis, and leg pain made it difficult to rule out re-infection of the knee. Though infection of the knee remained a concern, DRESS syndrome was considered as highly probable because of the patient's multiple negative blood cultures and absence of other signs of infection other than knee pain. The most common manifestations of DRESS syndrome include fever, rash, and systemic symptoms, including lymphadenopathy, leukocytosis, and organ damage. Our patient had elevated liver enzymes, axillary adenopathy and bilateral arm edema.

RegiSCAR Diagnostic Criteria (6)	Naranjo Adverse Drug Reaction Scale
Hospitalization Reaction suspected to be drug-related Acute rash Fever > 38 °C* Enlarged lymph nodes at a minimum of two sites* Involvement of at least one internal organ* Blood count abnormalities* Lymphocytes above or below normal limits Eosinophils above the laboratory limits Platelets below the laboratory limits *3/4 of these are required to make the diagnosis	1. Are there previous conclusive reports on this reaction? *Yes (+1) No (0) Do not know or not done (0)* 2. Did the adverse event appear after the suspected drug was given? *Yes (+2) No (-1) Do not know or not done (0)* 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? *Yes (+1) No (0) Do not know or not done (0)* 4. Did the adverse reaction appear when the drug was readministered? *Yes (+2) No (-1) Do not know or not done (0)* 5. Are there alternative causes that could have caused the reaction? *Yes (-1) No (+2) Do not know or not done (0)* 6. Did the reaction reappear when a placebo was given? *Yes (-1) No (+1) Do not know or not done (0)* 7. Was the drug detected in any body fluid in toxic concentrations? *Yes (+1) No (0) Do not know or not done (0)* 8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? *Yes (+1) No (0) Do not know or not done (0)* 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? *Yes (+1) No (0) Do not know or not done (0)* 10. Was the adverse event confirmed by any objective evidence? *Yes (+1) No (0) Do not know or not done (0)* **Scoring** > 9 = definite ADR 5-8 = probable ADR 1-4 = possible ADR 0 = doubtful ADR

The pathogenesis of DRESS syndrome is complex and has yet to be completely elucidated. Both drug metabolism and genetic susceptibility have been implicated. Hapten-carrier adduct formation, by either the drugs themselves or their metabolites, and nonconvalent drug presentation (8) may lead to T cell activation with an overrepresentation of $CD8^+$ cells. It has been hypothesized that the increased risk for DRESS syndrome and other drug reactions among patients with certain HLA variants is due to the affinity of certain drugs, their metabolites, or hapten-carrier adducts for specific HLA binding sites.

These activated T cells produce the cytokines TNF α, IFN γ, and IL-2 that mediate the "cytokine storm," which may be responsible for the wide constellation of symptoms seen in DRESS syndrome (8, 9). The expansion and activation of $CD8^+$ cells may cause the reactivation of latent human herpes viruses seen at the onset of DRESS syndrome, typically HHV-6, but also HHV-7, CMV, EBV, and VZV (9). The broad inflammatory response in DRESS syndrome encourages expansion of regulatory T cells, which are susceptible to infection by viruses such as HHV-6. The infection and compromise of regulatory T cells may mediate the abnormal immunological function observed in this condition. While it has been proposed that polymorphisms in genes for detoxification enzymes may also contribute to DRESS syndrome by increasing the concentration of immunologically active or toxic metabolites, no such polymorphisms have yet been found (8).

Detection of HHV-6 DNA and anti-HHV-6 IgG by PCR analysis is considered sensitive and specific for the diagnosis of DRESS syndrome outside of the United States (10). Thymus and activation-regulated Chemokine (TARC/CCL17), a chemokine, has recently been proposed as an early marker for DRESS syndrome in a study of 29 patients, due to its role in T_H2 type immunity (11).

Current therapy is limited to withdrawal of the offending agent and initiation of corticosteroids to temper the immune response. Our patient received oral prednisone, and the extreme leukocytosis began to subside four days after continuous therapy. Furthermore, his rash and edema had dissipated by the time of discharge. However, it should be noted that there have been no controlled trials validating steroid therapy for this condition (1, 2, and 4). There are several case reports of DRESS syndrome which showed improvement with IVIG, but given the expense and lack of evidence, it is used on an experimental basis only (12, 13). While there are not yet any definitive indicators of mortality, a recent publication showed that an erythema multiforme-like rash, as opposed to the other cutaneous phenotypes possible with DRESS syndrome, may be prognostic for worse hepatic function during the course of illness (14). Sequelae may include end-organ dysfunction (13) and autoimmune disease (15, 16). The latter may be due to viral reactivation and deregulated immune response (16).

Physicians should maintain a low threshold of suspicion for DRESS syndrome when their patients present with a fever, rash, leukocytosis and eosinophilia and a history of new medication use. Further study of documented cases of DRESS syndrome would be helpful in gaining a better understanding of the pathophysiology and optimal therapy for this potentially life threatening disorder.

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ASK A PATHOLOGIST

Emily Coberly, MD, Krystal Tray, MT, and William Miller, MD
University of Missouri– Columbia

QUESTION: A 53 years old female receives transfusion of 2 units of PRBCs. One hour later, she develops acute dyspnea with decreased O_2 saturations. Chest x-ray demonstrates new bilateral pulmonary infiltrates. Could this patient have TRALI?

ANSWER: Yes, Transfusion Related Acute Lung Injury (TRALI) is an uncommon but extremely serious complication of blood product transfusion. It can occur with transfusion of any blood products that contains plasma, including RBCs, FFP, whole blood, platelets, and cryoprecipitate. The risk of TRALI is estimated to be between1:2000 and 1:5000 units of blood products; and TRALI is the leading cause of transfusion-related mortality.

TRALI is most commonly caused by donor plasma containing anti-leukocyte antibodies, which react with neutrophils in the pulmonary micro-vasculature of the recipient, leading to increased vascular permeability and a pulmonary capillary leak syndrome resembling ARDS.

By definition, TRALI occurs during or within 6 hours of transfusion of a plasma-containing blood product. Symptoms include sudden onset of respiratory distress with clinical and x-ray evidence of acute bilateral pulmonary edema. Hypotension and fever are often present. TRALI is a diagnosis of exclusion and must be distinguished from the more common Transfusion Associated Circulatory Overload (TACO). BNP and NT-pro-BNP levels can be elevated in both conditions and do not reliably distinguish between the two diagnoses. As opposed to TACO, TRALI does not respond to diuretics. Treatment of TRALI is supportive; symptoms typically resolve within 72 hours. Mortality is 5-10%.

If you suspect a patient may have TRALI, it is extremely important to contact your pathologist or blood bank immediately. Since TRALI is often caused by antibodies in donor plasma, the blood donor center must be contacted to quarantine any remaining products from the suspect donors. Suspect donors are tested for anti-leukocyte antibodies, and donors implicated in an episode of TRALI are evaluated for continued eligibility to donate blood products.

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