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Clinicopathological Conference

Warren Alpert Medical School at Brown University: Clinicopathologic Conference: April 1st, 2022. Case 02-2022: A 66 Year-Old Male with Nausea, Vomiting, Fever and Rash.

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CASE PRESENTATION

A 66 year-old man presented to hospital with nausea and vomiting, associated with fever and rash of 1.5 weeks in duration. He complained of decreased oral intake, increasing malaise, and generalized weakness. He also reported daily fever for which he took oral acetaminophen at home. He described a new skin rash which began on the chest and spread to his back and extremities over the same time period. He denied new environmental exposures and recent sick contacts. In addition, he reported dizziness, chills, epigastric discomfort, and myalgias. He denied night sweats, chest pain, palpitations, dyspnea, cough, diarrhea, dysuria, urinary frequency, arthralgias, joint swelling, headaches, and neck stiffness.

His medical history included hypertension, hyperlipidemia, and migraines. His medications included atenolol, lamotrigine, losartan, omeprazole, sumatriptan as needed, and zolpidem. He lived with his wife and was independent with activities of daily living. He denied alcohol intake or tobacco use. He reported occasional use of medical cannabis prescribed for treatment of migraine. He reported a history of diabetes mellitus and hypertension in his family.

Upon physical examination, temperature was 39.5 ℃, heart rate 132 beats per minute, respiration rate 18 per minute, blood pressure was 128/84 mmHg. The patient had mildly toxic appearance with flushing of the face. He appeared drowsy but was rousable to voice. Thrush was noted in the oral cavity. Cardiac examination was notable for regular tachycardia without murmurs or extra heart sounds. Pulmonary auscultation was unremarkable. The abdomen was notable for mild epigastric tenderness without organomegaly and normal bowel sounds. Bilateral lower extremity edema was noted. On skin examination a diffuse, blanchable maculopapular rash was present on the chest, neck, back, bilateral upper extremities to mid forearm, abdomen, and bilateral lower extremities to mid shin. See Table for relevant laboratory data.

WARREN ALPERT MEDICAL SCHOOL STUDENT PRESENTATIONS

Student (The Miriam Hospital)

Working Diagnosis: Secondary Syphilis

This is a 66-year-old male presenting with 1-2 weeks of nausea, vomiting, fevers found to be tachycardic and febrile with oral thrush, diffuse maculopapular rash and drowsiness on exam. Laboratory workup is significant for eosinophilia, bandemia, transaminitis, elevated serum creatinine with proteinuria, overall most concerning for secondary syphilis. This diagnosis is supported by the presence of a maculopapular rash, eosinophilia, and can present with neurologic symptoms, explaining this patient's drowsiness/confusion. It may also explain the gastrointestinal symptoms, including hepatitis, presenting here as transaminitis and vomiting. The presence of possible oral thrush is concerning for an immunocompro-

Table 1. Laboratory Data

Laboratory Result	Reference Range, Adult	On Admission
WBC	3.5-11.0 x 10^9/L	11x 10^9/L
Hemoglobin	13.5-16.0 g/dL	15.4 g/dL
Hematocrit	37.0-47.0%	44.9%
MCV	80.0-98.0 fL	91.3 fL
Platelets	150-400 x 10^9/L	102 x 10^9/L
Neutrophil %		42%
Lymphocyte %		10%
Monocyte %		1%
Eosinophil %		13%
Band Neutrophil %		34%
Sodium	135-145 mEq/L	128 mEq/L
Potassium	3.6-5.1 mEq/L	4.9 mEq/L
Chloride	98-110 mEq/L	85 mEq/L
Bicarbonate	22-32 mEq/L	22 mEq/L
Anion Gap	3-13	11
BUN	6-24 mg/dL	31 mg/dL
Creatinine	0.64-1.27 mg/dL	1.67 mg/dL
Glucose	67-99 mg/dL	119 mg/dL
Calcium	8.5-10.5 mg/dL	8.5 mg/dL
AST	10-42 IU/L	414 IU/L
ALT	6-45 IU/L	129 IU/L
Alkaline Phosphatase	34-104 IU/L	85 IU/L
Protein, total	6.0-8.0 g/dL	6.4 g/dL
Albumin	3.5-5.0 g/dL	3.2 g/dL
Bilirubin, total	0.2-1.3 mg/dL	0.8 mg/dL
Bilirubin, direct	0.0-0.3 mg/dL	0.2 mg/dL
Urinalysis		
Appearance		Hazy
Color		Yellow
Glucose		Negative
Bilirubin		Negative
Ketones		1+
Specific Gravity		1.017
Protein		30 mg/dl
RBC		2 /HPF
WBC		4 /HPF

mised state as this patient is not prescribed inhaled steroids and increases my suspicion for a concomitant human immunodeficiency virus (HIV) infection (which could also cause the eosinophilia); these are two infections that are commonly diagnosed together, particularly in men who have sex with men. I would order VDRL (Venereal Disease Research Laboratory) and HIV antigen/antibody tests and obtain a more thorough sexual and drug use history.

Student (Rhode Island Hospital)

Working Diagnosis: Murine Typhus

Murine typhus is caused by *Rickettsia typhi* that is carried by fleas, most often infecting humans when exposed to domestic cats, dogs, or rodents. This condition commonly presents with fever, chills, and myalgias alongside non-specific gastrointestinal symptoms. Nausea and vomiting typically occur over the course of about a week and are often mistaken for a gastroenteritis as in our patient. After 5-7 days, a blanchable maculopapular rash erupts, most often starting on the trunk, spreading peripherally to the extremities, and sparing the palms and soles. This characteristic finding was described by the patient, and skin exam notably shows sparing of the distal arms and legs. Murine typhus often causes neurologic, hepatic, cardiac, renal, and/or pulmonary dysfunction. Our patient has renal involvement, evidenced by his azotemia, elevated creatinine, and slight proteinuria. Hepatic involvement may be evidenced by the patient's moderate transaminitis. Further, laboratory findings of thrombocytopenia and mild leukocytosis, hyponatremia, hypochloremia are consistent with murine typhus. Lastly, the patient's cerebrospinal fluid analysis is suggestive of aseptic meningitis with an elevated protein level, matching what is expected of this disease. Rickettsia species cannot be cultured, I would send indirect fluorescent antibodies (IgM and IgG) for *R. typhi* to confirm the diagnosis.

Student (Kent County Hospital)

Working Diagnosis: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

The most likely diagnosis in this patient is drug reaction with eosinophilia and systemic symptoms (DRESS). The patient is experiencing fever, fatigue with weakness, and has new onset of diffuse, blanchable maculopapular rash on the chest, neck, back, bilateral upper/lower extremities, and abdomen. Additionally, the patient is on lamotrigine, which is a high-risk drug associated with DRESS. We were not given the time of initiation of the lamotrigine, as there is typically a latency phase from the initiation of the drug to the onset of reaction. The latency phase is typically 2-8 weeks and prodromal symptoms include fever, malaise, and lymphadenopathy. After two weeks, the skin manifestations begin which typically start as a maculopapular eruption that is symmetrically distributed on the trunk and extremities; facial edema is common but was not seen in this patient.

In addition to the skin findings associated with DRESS, the systemic symptoms include fever, hematologic abnormalities including eosinophilia, as well as symptoms and laboratory abnormalities associated with visceral involvement. This patient has a fever, epigastric

tenderness, and rash. Laboratory findings showed thrombocytopenia, eosinophilia, reduced kidney function, and transaminitis. Typical hematologic abnormalities associated with DRESS include thrombocytopenia, eosinophilia, and atypical lymphocytosis. Liver injury is seen in 53 to 90 percent of cases with abnormalities consistent with hepatocellular or cholestatic injury. Gastrointestinal involvement associated with DRESS includes pancreatitis which could explain the patient's epigastric pain and vomiting.

Student (Veterans Affairs Medical Center, Providence, RI)

Working Diagnosis: Hemophagocytic Lymphohistiocytosis (HLH)

HLH may present nonspecifically with multisystem involvement, as observed in this patient. This may involve high temperature, gastrointestinal symptoms, elevated liver enzymes, renal injury and an associated syndrome of inappropriate anti-diuretic hormone secretion (SIADH)-like syndrome, and rash. HLH may also present with elevated protein in cerebrospinal fluid due to inflammation. HLH is associated with lamotrigine use and may present after 2 to 8 weeks of initiation, with reports of HLH even after this period. Viral reactivation and immunosuppression may also be observed, as suggested by oral thrush. Eosinophilia is not typically observed, and it is common to see at least bi-cytopenia (92%). Splenomegaly is also common (89%). I would perform an H-score for risk of reactive hemophagocytic syndrome which requires known underlying immunosuppression, temperature (most points if over 39.4), hepatomegaly or splenomegaly, at least bi-cytopenia, elevated ferritin, elevated triglycerides, decreased fibrinogen, elevated AST, hemophagocytic features on bone marrow aspirate. Additional work-up for this condition includes coagulation studies (including PT/INR, fibrinogen), serum triglycerides, serum ferritin, abdominal ultrasound for splenomegaly, and bone marrow aspiration.

Dr Hadeel Zainah

This case could be approached from the eosinophilia standpoint. Hypereosinophilia is defined when the absolute eosinophil count exceeds 1500 x 10^9/L. Hypereosinophilic syndrome occurs when there is hypereosinophilia and end organ involvement. This patient has evidence of hypereosinophilic syndrome with skin rash and elevated liver enzymes, while receiving the anticonvulsant drug, lamotrigine. This suggests DRESS syndrome. Syphilis and acute human immunodeficiency virus (HIV) infection should be kept in mind in a patient who presents with febrile illness and a rash. However, eosinophilia is usually seen in advanced HIV rather than early HIV disease. Multisystem inflammatory syndrome in adults (MIS-A) should also be mentioned, which could be associated with eosinophilia in the case of Kawasaki syndrome-like presentation of MIS-A. Other etiologies include viral infections or tick-borne illnesses which could explain some of the symptoms.

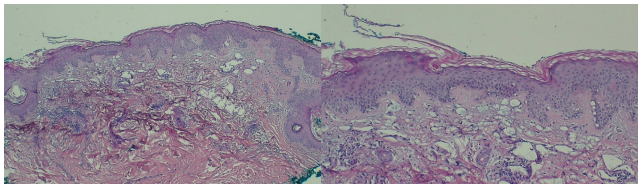

Figure 1. Light microscopy of skin punch biopsy.

HOSPITAL COURSE

Lamotrigine was discontinued. The patient received supportive care and a skin biopsy was performed.

Pathological Discussion

Sections from a skin biopsy demonstrated non-specific inflammatory changes affecting primarily the dermis and the dermal-epidural junction. The inflammatory pattern seen in Figure 1 includes interface dermatitis in the form of basal cell vacuolization. The dermis is superficially edematous and contains focal neutrophilic infiltrate as well as perivascular lymphocytic inflammation (Figure 1). Perivascular lymphocytes in DRESS are thought to be predominantly comprised of CD8-positive and granzyme-positive T-cells,[1] though this was not examined with further staining. No eosinophils were seen in this sample, and they are not required for a diagnosis of DRESS. Previously published DRESS histopathology demonstrated that as few as 20% of cases contain cutaneous eosinophilic involvement.[1] The described histopathologic findings of this sample have been previously observed in DRESS syndrome, but they are ultimately non-specific. Clinical presentation consistent with DRESS syndrome is required for a conclusive diagnosis.

FINAL DIAGNOSIS

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DISCUSSION

Drug reaction with eosinophilia and systemic symptoms is an adverse drug reaction characterized by a rash with fever, eosinophilia, visceral organ involvement, lymphadenopathy, and atypical lymphocytosis.[2,3] Symptoms typically develop 2-8 weeks after initiation of high-risk drugs such as aromatic anticonvulsants, sulfonamides,

and allopurinol.[3,4] The proposed pathogenesis includes delayed T-cell hypersensitivity reaction and reactivation of Herpesviridae viruses.[2,5,6] Cutaneous involvement includes non-specific facial edema and a diffuse rash that can vary in description (i.e., maculopapular, pustular, exfoliative).[3,6] Visceral organ involvement is diverse and can include liver, pulmonary, kidney, cardiac, and central nervous system manifestations. Laboratory abnormalities include eosinophilia and atypical lymphocytosis with other abnormalities dependent on involved visceral organs.[1] Dermal biopsy findings are non-specific and include interface dermatitis, basal vacuolization, spongiosis, perivascular infiltration, and vascular damage.[3,6] Diagnosis is confirmed or excluded based on the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system which assigns points based on the presence of classic clinical manifestations of DRESS.[3] Treatment consists of discontinuation of the offending drug and immunosuppression with corticosteroids or cyclosporine.[7] Most cases of DRESS resolve in weeks to months after discontinuation of the offending drug however mortality rates are estimated at 2-10% and relapses are common.[3,6]

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Conflicts of Interest

The authors declare they have no conflicts of interest.

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