Pseudomembranous colitis in a patient with lamotrigine-induced drug rash with eosinophilia and systemic symptoms syndrome

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a hypersensitivity reaction with rash, fever and multiorgan dysfunction potentially lethal in up to 10% of cases. It often affects liver function, but it can also affect kidney, lungs, and heart. Severe gastrointestinal involvement is rare. We present a case of a 31-year-old hispanic woman with pseudomembranous colitis associated with lamotrigine-induced DRESS syndrome. To the best of our knowledge, this is the fourth reported case of severe involvement of the gastrointestinal tract and the first to report pseudomembranous colitis in the setting of DRESS syndrome.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as DIHS (drug induced hypersensitivity syndrome), is a potentially lethal and many times under diagnosed idiosyncratic reaction associated with several drugs, specially antiepileptic medication.[1]

Patients with DRESS syndrome typically present with skin rash (a generalized maculopapular rash with follicular accentuation and sometimes facial edema with periorbital predominance), eosinophilia, fever and systemic manifestations such as a liver, renal, cardiac and pulmonary involvement. However, gastrointestinal involvement has been rarely described in literature.[2]

Although DRESS syndrome pathophysiology is still unknown, eosinophilic infiltrates are probably the mechanism of multi organic damage.[3,4] Other possible mechanisms are abnormalities in drug detoxification enzymes with subsequent accumulation of metabolites and sequential activation of herpes virus such as cytomegalovirus, Epstein-Barr, and human

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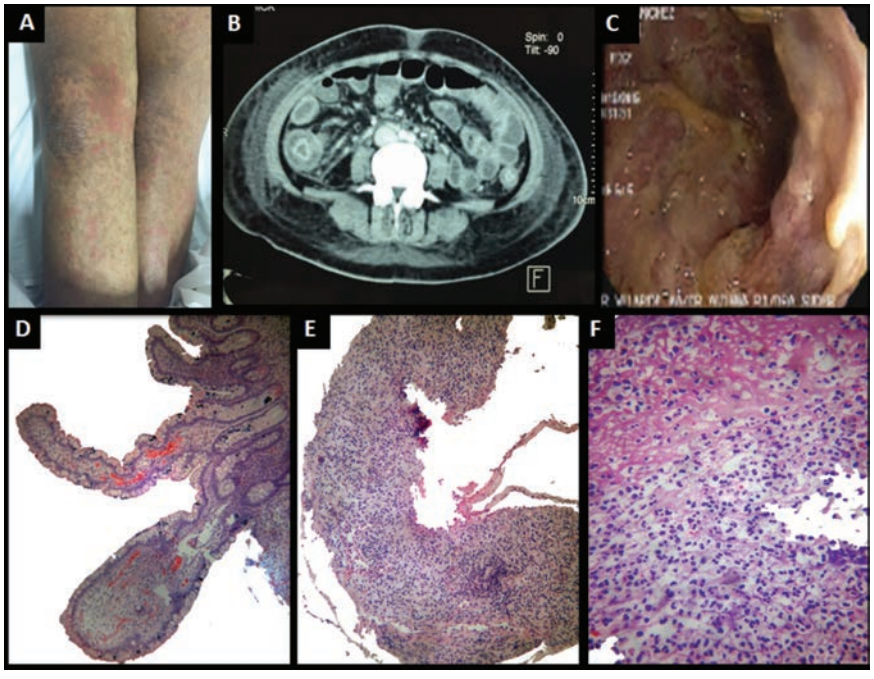

Figure 1. A) Patient showing a maculopapular rash on limbs with follicular accentuation; B) abdominal contrast-enhanced computed tomography scan showing generalized colonic wall edema; C) endoscopy revealing presence of pseudomembranes in sigmoid and rectum; D) photomicrographs HE-Section (10×) showing fragment of ileal mucosa with focal erosion, edema in the lamina propria and subtle increased number of inflammatory cells with predominance of mononuclear cells within terminal ileum (E), (4×) fragment of ulcerated colonic mucosa with extensive loss of crypts and presence of mixed inflammatory infiltrate. F) At a higher magnification (10×), fibrinoid-necrotic material, cellular debris and dense inflammatory infiltrate of lymphocytes, macrophages and numerous polymorphonuclear leukocytes essentially neutrophils are seen.

herpes virus 6 and 7.[5] Likewise it has been found predisposition mediated by leukocyte antigen alleles such as HLA-B*58:01 for allopurinol[6] and HLA-A*31:01 for carbamazepine.[7] On the other hand, vitamin D deficiency has been implicated as a possible contribution to the pathogenesis DRESS syndrome for its protective effects against inflammatory and autoimmune conditions.[5]

Pseudomembranous colitis is a manifestation of severe colonic disease. It can be associated with different etiologies. The list of associated etiologies is vast, although *Clostridium difficile* infection (CDI) remains the most common cause.[8,9]

The following case report demonstrates the wide spectrum of multiorgan involvement associated with DRESS syndrome, including gastrointestinal involvement in the form of pseudomembranous colitis.

Case Report

A 31-year-old Hispanic woman presented to our clinic with a one-month history of fever and maculopapular rash, and diarrhea of one-week duration; she had a diagnosis of epilepsy and had been prescribed lamotrigine two weeks before initiation of these symptoms. On admission, her vital signs were as follows: temperature of 39.5°C, heart rate of 120/min, respiratory rate of 18/min, systemic blood pressure of 110/60, and oxygen saturation of 96%. At physical examination she had a left retroauricular adenopathy, a maculopapular confluent rash over the trunk and limbs with follicular accentuation (Figure 1A), diminished breath sounds at both lung bases and bilateral lower limb edema. The rest of examination was unremarkable.

Initial laboratory findings revealed hemoglobin of 8.35 g/dL (N=12.20-18.10), platelets of 84,000/mm^3 (N=142,000-450,000), white blood cells of 10,500/mm^3 (N=4600-10200), with hypereosinophilia 1800/mm^3 (N=0-500/mm^3), aspartate aminotransferase (AST) of 144.70 U/L (N=10-50 u/L), and alanine aminotransferase (ALT) of 120.31 U/L (N=0-41), creatinine of 2.47 mg/dL (baseline of 0.78 mg/dL), and urea of 76.4 (N=15-39) were obtained. Stool examination was positive for 50 polymorphonuclear cells per field and no evidence of parasites or ova. Serum electrolytes and urinalysis were normal. During hospitalization she developed bloody diarrhea and further investigations were obtained. Other laboratory findings are shown on Table 1. The electrocardiogram and echocardiogram were unremarkable. Bone marrow aspirate showed moderate eosinophilia and hemophagocytosis. Skin biopsy reported interface dermatitis. Chest computed tomography (CT) scan revealed bilateral pleural effusions and passive atelectasis. Abdominal contrast-enhanced CT scan showed generalized intestinal and colonic wall edema suggestive of colitis (Figure 1B); colonoscopy was performed revealing pancolitis, ulcerative ileitis and presence of pseudomembranes in sigmoid and rectum (Figure 1C). Histopathological analysis of colonic biopsies reported ulcerated mucosa with fibrinoid material and inflammatory infiltrates with polymorphonuclear leukocytes compatible with sub-acute colitis, without characteristics consistent with inflammatory bowel disease, and no evidence of granulomas, pathogenic organisms or viral inclusions (Figure 1D-F). Because of the high prevalence in our hospital for CDI, and the fact that she had been treated with several antibiotics for presumed brucellosis previous to admission, polymerase chain reaction (PCR) for *Clostridium difficile* in stool was performed and was reported negative. After exclusion of infectious, autoimmune/inflammatory and neoplastic diseases, she was diagnosed with pseudomembranous colitis associated with lamotrigine-induced DRESS syndrome and treatment was started

Table 1. Laboratory findings.

Test	Result (reference)
Hemoglobin	8.35 g/dL (N=12.20-18.10)
White cells	10,500/µL (N=4600-10,200)
Lymphocytes	1800/µL
Neutrophils	5200/µL
Eosinophils	1890/µL
Platelets	285,000/µL (N=142,000-450,000)
Glucose	90 mg/dL (N=60-125)
Urea	76.4 (N=15-39)
Creatinine	2.47 (N=0.4-1.1)
Aspartate aminotransferase	144 IU/L (N=10-42)
Alanine aminotransferase	120.31 IU/L (N=10-40)
Alkaline phosphatase	618 IU/L (N=32-92)
Lactic dehydrogenase	124 IU/L (N=91-180)
Total protein	6.76 g/dL (N=6.3-8.2)
Albumin	3.81 g/dL (N=3.5-5)
Uric acid	4.8 mg/dL (N=2-6.5)
Cholesterol	120 mg/dL (N=150-200)
Triglycerides	129 mg/dL (N=35-160)
Serum iron	45 ng/dL (N=40-160)
Ferritin	452 ng/dL (N=4.5-260)
C-reactive protein	8.14 mg/dL (N<10)
Erythrocyte sedimentation rate	22 mm/hr (N<10)
Procalcitonin	0.44 ng/dL (N<0.50)
HIV serology	Negative
Hepatitis B virus serology	Negative
Hepatitis C virus serology	Negative
Cytomegalovirus serology	Negative
Epstein Barr virus serology	Negative
Rose Bengal test	Negative
2-mercaptoethanol	Negative
Blood cultures	Negative
Urine culture	Negative
Polymerase chain reaction for *C.difficile*	Negative
C3	103 mg/dL (N=90-180)
C4	11.9 mg/dL (N=10-40)
Direct Coombs test	Negative
Rheumatoid factor	10.4 UI/mL (N=0-15.0)
Antinuclear antibodies	Negative

Table 2. Summary of published reports of cases that showed sever involvement of digestive tract in association with drug reaction with eosinophilia and systemic symptoms.

Authors	Year	Patient	Regi SCAR score	Drug implicated	Systemic symptoms	GI symptoms	Endoscopy	Histology	Treatment	Outcome
Do-Pham *et al.*[12]	2011	70 F	6	Leflunomide	Hematologic, renal, liver affection	Diarrhea	Circumferential erosive esophagitis and ulcerative colitis	Diffuse inflammatory lymphocytic infiltrate without granuloma, eosinophils or viral inclusions	Ganciclovir and antibiotic therapy	Patient died from a massive digestive hemorrhage 5 weeks after
Do-Pham *et al.*[12]	2011	28 F	7	Lamotrigine	Hematologic, renal, pulmonary affection	Bloody diarrhea	Diffuse ulcerating colitis	Inflammatory infiltrate mostly including lymphocytes without either eosinophils or cytomegalovirus inclusions within the colon	Systemic corticosteroids, which were replaced by local corticosteroids	Symptoms resolved
Swanson *et al.*[8]	2014	21 F	6	Phenytoin, lamotrigine	Hematologic, liver affection	Nausea, vomiting, diarrhea	Duodenopathy with ulceration and submucosal hemorrhage. Erythematous, granular, and friable mucosa with multiple rectal and sigmoid ulcers	Severe chronic colitis and mucosal damage with prominent crypt destruction and loss. Mixed inflammation composed of lymphocytes, plasma cells, histiocytes, and neutrophils.	Oral steroid taper	Patient died from HLH
Present report	2016	31 F	8	Lamotrigine	Hematologic, liver, renal, pulmonary affection	Bloody diarrhea	Pancolitis, ulcerative ileitis and presence of pseudomembranes in sigmoid and rectum	Ulcerated mucosa with inflammatory infiltrates with polymorphonuclear leukocytes compatible with sub-acute colitis	Systemic corticosteroids	Symptoms resolved

GI, gastrointestinal; M, male; F, female; HLH, hemophagocytic lymphohistiocytosis.

with systemic corticosteroids with prednisone 1 mg/kg/day with subsequent complete clinical resolution. Patient was discharged after 15 days of hospitalization; within 2 months, systemic corticosteroids were progressively tapered down and anticonvulsant therapy was replaced with levetiracetam 1000 mg q8 hr.

Discussion

DRESS syndrome is a type IV hypersensitivity reaction. However, the hallmark of DRESS syndrome is the presence of systemic manifestations.[10] Although diagnostic criteria have not been adopted officially, a Japanese work group established a series of guidelines for the diagnosis of DRESS syndrome in 2007, and alternatively Kardaun and colleagues in association with the Severe Cutaneous Adverse Reactions study group (RegiSCAR) published a scoring system in 2007.[11] The patient described here met previous criteria for a *definitive case* for DRESS syndrome.

Gastrointestinal involvement in the setting of anticonvulsant hypersensitivity syndrome is rare, with less than a dozen of cases reported in the literature.[8] Gastrointestinal involvement in DRESS syndrome has only been reported in three previous cases (Table 2).[8,12] Most cases of anticonvulsant-induced drug reactions with gastrointestinal involvement reported eosinophils as the predominant inflammatory infiltrate in the biopsies; mucosal erosion and ulceration have been reported as well. Nonetheless, a detailed description of pathological findings in gastrointestinal injury in DRESS syndrome has not been described to date.[8] In our case, colonoscopy showed pancolitis and ulcerative ileitis with presence of pseudomembranes. Histological features were not consistent with inflammatory bowel disease or infectious colitis. In addition, other important causes of pseudomembranous colitis were ruled out, mainly CDI (negative PCR in stool). Pseudomembranous colitis has been reported secondary to other medications and drugs, such as alosetron, cisplatin, cocaine, cyclosporine A, dextroamphetamine and paraquat;[9] to our knowledge, pseudomembranous colitis associated with lamotrigine-induced DRESS syndrome, has never been reported before. The diagnosis of drug-related gastrointestinal injury was made based on the pattern of clinical presentation and the temporal association between the addition of the offending drug and the onset of symptoms and gastrointestinal involvement.

In the clinical context of hypersensitivity reactions an extensive work up to stablish systemic involvement should be performed. The main lessons learned from the field out of this case are to rise up clinical awareness, stablish the importance of an exhaustive patient inter-

rogation and physical examination, and exclude other infectious and inflammatory autoimmune process. Antinuclear antibodies and complementary work up for autoimmune process; polymerase chain reaction for *Clostridium Difficile* and discard of other infective causes of pseudomembranous colitis and generalized rash, in addition to computed tomography, colonoscopy and biopsy are example of valuable tools in this case report and should not be delayed and be considered in the right clinical practice scenario.

Prompt recognition of the adverse drug reaction and discontinuation of offending medication are imperative steps in limiting the progression of DRESS syndrome. The French Society of Dermatology published a report in 2010 outlining a consensus on therapeutic management of DRESS syndrome, recommending the use of systemic corticosteroids and/or IVIG for patients with life-threatening disease.[13]

Conclusions

In summary, DRESS syndrome is a relatively rare entity; however, given the frequent use of antiepileptic drugs, it is paramount that clinicians be aware of the possibility of enterocolitis associated with antiepileptic drugs and DRESS syndrome in the appropriate clinical context. Furthermore, DRESS syndrome should be regarded as an etiology of pseudomembranous colitis. Early recognition and the immediate cessation of the offending medications are essential steps to achieve the best outcome.

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