中文題目: Chlormezanone 引起之伴隨嗜伊紅性白血球增加與全身症狀的藥物反應伴隨急性肝失償及急性胰臟炎

英文題目:Chlormezanone-induced DRESS syndrome presented with liver decompensation and acute pancreatitis

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Abstract

Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a severe adverse drug-induced reaction that usually presents clinically as an extensive skin rash, accompanied by fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve multiple organs [1-2]. Early identification of this syndrome is of particular importance, since the mortality rate can reach 10% and the possible persistence or aggravation of symptoms can occur despite the discontinuation of the culprit drug [3-4]. The drugs most frequently associated with the development of DRESS syndrome are carbamazepine and allopurinol, although up to 50 drugs can induce DRESS [5].

Chlormezanone (CM) are widely prescribed in the treatment of patients with chronic pain [6]. We report a case of an 88-year-old Chinese woman who developed DRESS syndrome with liver decompensation and acute pancreatitis after CM treatment. DRESS should be considered in patients with symptoms including skin rash, liver involvement, fever, and hypereosinophilia. It also stresses the importance of a complete drug history and the awareness of this rare and lethal adverse effect.

Case Report

An 88-year-old woman presented to our hospital with fever, poor appetite and generalized skin rash for 3 days. The skin rashes first appeared on the face, and then spread to the upper extremities, trunk and lower extremities. Thirteen days before presentation, she took etodolac 200mg, cimetidine 400mg and CM 100mg for 3 days.

She had stage II chronic kidney disease, hypertensive cardiovascular disease and left femoral neck fracture post sugery 6 years ago, no prior liver disesae. No prior allergic history to flurbiprofen or other NSAIDs. On physical examination, fever up to 38.5°C, facial oedema, yellow sclera and generalized itchy maculo-papular exanthema all over the body were found. There was no peripheral lymphadenopathy. Laboratory data shown in table 1. Abdominal ultrasonography and a computed tomography scan showed normal liver size and gallbladder stones (1.9 cm in size)

without wall thickening. Transthoracic echocardiography showed normal left ventricular systolic function and ejection fraction was 60%.

She was started on ceftriaxone 2 g intravenous once daily for Escherichia coli urinary tract infection. However, diffuse erythematous confluent macules and patches with scales over the whole body (Fig. 1 & 2) worsened even when treated with intravenous Betamethasone. Her renal and liver function become worse during the follow-up. Thrombocytopenia (platelet, 40000/mm^3) and pancytopenia (Hemoglobin, 7.9 g/dl; WBC, 3470/mm^3; platelet, 13000/mm^3) were noted by the 10^{th} and 17^{th} day after admission. We performed further blood cultures and PCR assays for the detection of HSV, CMV and EBV. Anti-cytomegalovirus IgM antibody and polymerase chain reaction (anti-CMV IgM and PCR) were all positive. A chest X-ray showed bilateral interstitial infiltrates. Hemodialysis and mechanical artificial liver were performed for acute renal failure and liver decompensation. The clinical status of the patient gradually deteriorated. On day 18 of admission, the patient died of multiple organ failure.

Our patient is diagnosed with DRESS syndrome as defined by the two diagnostic criteria, the RegiSCAR criteria and the Japanese consensus group criteria.

Discussion

CM-induced fulminant hepatitis or severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis has been reported before [6-7], but it has not been reported as the culprit drug in DRESS syndrome. Our patient is diagnosed as CM-induced DRESS syndrome because of (1) the close relationship between the initiation of CM and the onset of symptoms, (2) the elimination rate of CM in elderly patients is reduced related to the reduction in renal function and aging [8], (3) the risk of acute nephrotoxicity of NSAIDs increases with age [9], (4) fever, (5) skin rash with facial edema, (6) typical laboratory tests included the presence of eosinophilia and atypical lymphocytes, (7) a positive finding of human herpes virus infection which is associated with the development of DRESS, (8) multiple organ involvement including the liver, kidney, lung and pancreas, (9) persistent and worsening symptoms after withdrawal from the causative drug. Upon consideration of the overall findings and using the RegiSCAR scoring system for grading DRESS cases, we recorded a score of 5 points for this, which is classified as definite DRESS syndrome.

DRESS is a severe adverse drug-induced reaction. Diagnosing DRESS is challenging due to the diversity of cutaneous eruption and the organs involved [1]. Life threatening multiple organ

failure has been documented in DRESS syndrome; it carries a mortality rate of about 10% [10-12]. However, no predictive factors for serious cases have yet to be found.

A delayed onset of symptoms 2-6 weeks after the initiation of the causative drug is a feature of DRESS. The pathogenesis is related to specific drugs, especially aromatic anticonvulsants, altered immune response, sequential reactivation of the herpes virus and association with HLA alleles [2]. An easily ignored sequela of DRESS is end-organ decompensation, especially in middle-aged and elderly patients [13]. Persistent and aggravated symptoms appear to be more apparent in elderly patients with underlying renal or liver function impairment.

In conclusion, DRESS should be highly suspected in patients with symptoms including skin rash, liver involvement, fever, hypereosinophilia and lymphadenopathy. Early withdrawal of the culprit drug is necessary once the diagnosis is established. This report stresses the importance of a complete drug history and the awareness of this rare and lethal adverse effect.

Conflict of interest

There is no conflict of interest to be disclosed.

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TABLE 1

	VALUE	NORMAL RANGE
WBC(10^3/UL)	7.53	4.50 - 11.00
HB(G/DL)	10.5	12.0 - 16.0
PLT(10^3/UL)	162	150 - 400
EOSINOPHIL(%)	14.7	0.0 - 7.0
ALT(U/L)	187	- 31
AST(U/L)	124	- 32
GGT(U/L)	11	5-36
ALP(U/L)	47	35-104
LDH(U/L)	143	135-225
BUN(MG/DL)	36	6 – 20
CREATININE(MG/DL)	2.2	0.5 - 0.9
INR	1.3	-
TOTAL BILIRUBIN(MG/DL)	3.8	- 1.2
DIRECT BILIRUBIN(MG/DL)	3.2	
IMMUNOGLOBULIN E(IU/ML)	89.6	- 165.0
LIPASE(U/L)	454	13 - 60
CRP(MG/DL)	1.80	0.00 - 0.50
HBSAG	Negative	
ANTI-HBC IGM	Negative	
ANTI-HCV	Negative	
ANTI-HBS	positive	
ANA	Negative	
WEIL–FELIX TEST	Negative	

ALT, alanine aminotransferase; AST, aspartate aminotransferase ; ALP,alkaline phosphatase; gGT, gamma glutamyl transpeptidase; ANA,antinuclear antibodies;; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase.

Figure legends

Fig.1 Whole body of the patient showing diffuse erythematous confluent macules and patches with scales.

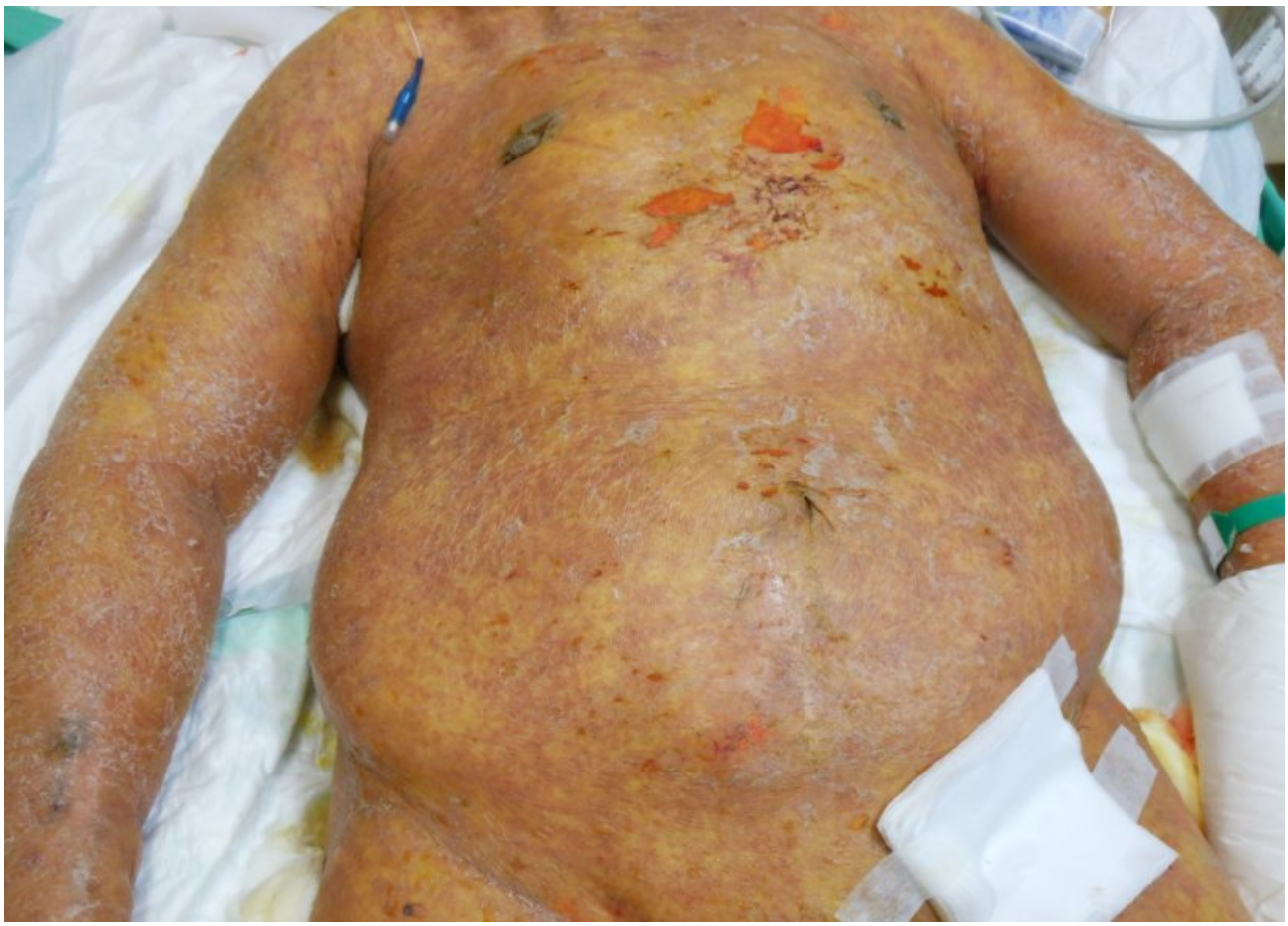

Fig. 2 Right knee of the patient showing erythema and exfoliation.