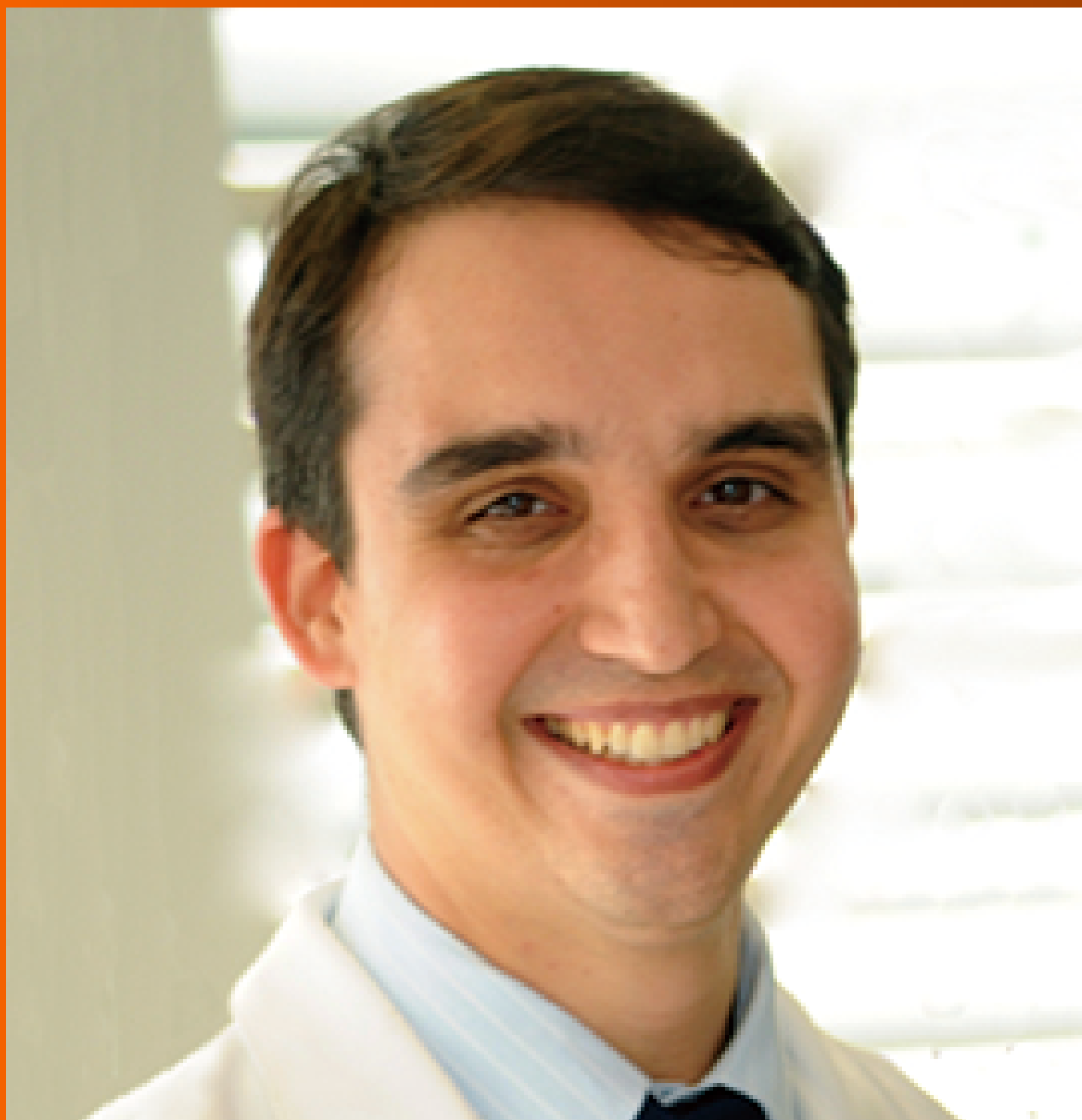


World Journal of *Clinical Cases*

World J Clin Cases 2019 March 26; 7(6): 691-808





REVIEW

- 691 Effects of apoptosis on liver aging
Hu SJ, Jiang SS, Zhang J, Luo D, Yu B, Yang LY, Zhong HH, Yang MW, Liu LY, Hong FF, Yang SL

MINIREVIEWS

- 705 Liver involvement in the drug reaction, eosinophilia, and systemic symptoms syndrome
Martinez-Cabriaes SA, Shear NH, Gonzalez-Moreno EI

ORIGINAL ARTICLE

Retrospective Cohort Study

- 717 Surgical method choice and coincidence rate of pathological diagnoses in transduodenal ampullectomy: A retrospective case series study and review of the literature
Liu F, Cheng JL, Cui J, Xu ZZ, Fu Z, Liu J, Tian H

Retrospective Study

- 727 Individualized minimally invasive treatment for adult testicular hydrocele: A pilot study
Lin L, Hong HS, Gao YL, Yang JR, Li T, Zhu QG, Ye LF, Wei YB

Observational Study

- 734 Successful totally transthoracic echocardiography guided transcatheter device closure of atrial septal defect in pregnant women
Chen Q, Cao H, Zhang GC, Chen LW, Xu F

CASE REPORT

- 742 Cardiac amyloidosis: A case report and review of literature
Taiwo AA, Alapati L, Movahed A
- 753 Successful treatment with hysteroscopy for infertility due to isthmocele and hydrometra secondary to cesarean section: A case report
López Rivero LP, Jaimes M, Camargo F, López-Bayghen E
- 759 *Aeromonas veronii* biovar *veronii* and sepsis-infrequent complication of biliary drainage placement: A case report
Monti M, Torri A, Amadori E, Rossi A, Bartolini G, Casadei C, Frassinetti GL

- 765** Induction chemotherapy with docetaxel, cisplatin and fluorouracil followed by concurrent chemoradiotherapy for unresectable sinonasal undifferentiated carcinoma: Two cases of report
Watanabe S, Honma Y, Murakami N, Igaki H, Mori T, Hirano H, Okita N, Shoji H, Iwasa S, Takashima A, Kato K, Kobayashi K, Matsumoto F, Yoshimoto S, Itami J, Boku N
- 773** Lump type crossed fused renal ectopia with bilateral vesicoureteral reflux: A case report
Choi T, Yoo KH, Song R, Lee DG
- 778** Multiple gastric angiolipomas: A case report
Lou XH, Chen WG, Ning LG, Chen HT, Xu GQ
- 785** Primary hepatic follicular dendritic cell sarcoma: A case report
Chen HM, Shen YL, Liu M
- 792** Effective chemotherapy for submandibular gland carcinoma ex pleomorphic adenoma with lung metastasis after radiotherapy: A case report
Chen ZY, Zhang Y, Tu Y, Zhao W, Li M
- 798** Photodynamic therapy as salvage therapy for residual microscopic cancer after ultra-low anterior resection: A case report
Zhang SQ, Liu KJ, Yao HL, Lei SL, Lei ZD, Yi WJ, Xiong L, Zhao H
- 805** Unexplained abdominal pain due to a fish bone penetrating the gastric antrum and migrating into the neck of the pancreas: A case report
Xie R, Tuo BG, Wu HC

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Liver involvement in the drug reaction, eosinophilia, and systemic symptoms syndrome

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Abstract

First described in 1996, the drug reaction, eosinophilia, and systemic symptoms syndrome (DReSS) is considered, along with Stevens-Johnson syndrome and toxic epidermal necrolysis, a severe cutaneous drug reaction. It is characterized by the presence of a maculopapular erythematous skin eruption, fever, lymphadenopathy, influenza-like symptoms, eosinophilia, and visceral involvement such as hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis. The prognosis of patients with DReSS is related to the severity of visceral involvement. The mortality ranges from approximately 5% to 10%, and death is mainly due to liver failure, which is also the organ most commonly involved in this syndrome. Although it was previously hypothesized in 1994, DReSS syndrome can lead to reactivation of one or more human herpesvirus family members. Now being included as diagnostic criteria in a proposed diagnostic score system, this reactivation can be detected up to 2-3 wk after DReSS syndrome onset. Other causes of mortality in DReSS syndrome include myocardial or pulmonary lesions and hemophagocytosis. We reviewed the literature of previously reported case-series of DReSS and liver involvement, highlighting the pattern of liver damage, the treatment used, and the outcome.

Key words: Drug reaction, eosinophilia, and systemic symptoms syndrome; Severe

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Core tip: Drug reaction, eosinophilia, and systemic symptoms syndrome (DReSS) is considered a severe cutaneous drug reaction. It can present with a broad spectrum of clinical manifestations making its diagnosis challenging. Factors associated with a poor prognosis include delayed diagnosis, viral reactivation, the presence of systemic inflammatory response syndrome, and severe organ involvement. Liver injury, presented in more than half of DReSS patients, ranges from mild transaminasemia to acute liver failure and is one of the most common causes of death in these patients. Prompt withdrawal of the culprit agent and a multidisciplinary approach in patients with internal organ affection are of utmost importance.

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INTRODUCTION

Adverse drug reactions commonly involve the liver, the main organ in which drug metabolism occurs. It has been estimated that more than 600 medications have been related to significant liver injury^[1]. Furthermore, herbal, complementary, and alternative medications, as well as illicit drugs such as anabolic steroids and amphetamines, have also been related to this problem^[2,3]. Drug-induced liver injury (DILI) is one type of adverse drug reaction, which was ranked as one of the major causes of acute liver failure^[4-6]. It is classified into two main types: intrinsic or idiosyncratic^[7]. The former is all the predictable adverse drug reactions that are dose-dependent and manifested shortly after the drug was ingested^[8]. In this case, the culprit is direct-chemical damage to the drug or its metabolite^[9]. The idiosyncratic drug reaction, which is unpredictable, is characterized by a delayed onset of symptoms once the drug was taken^[10]. It is subdivided into two categories: non-allergic and allergic reaction. In the non-allergic, the liver frequently is the only organ involved; however, in the allergic reaction, multisystemic organ involvement may be observed^[11,12].

Drug reaction, eosinophilia, and systemic symptoms syndrome (DReSS), also widely known as drug-induced hypersensitivity syndrome (DiHS), corresponds to a hypersensitivity drug reaction^[13]. This syndrome was recognized in 1981 when Spielberg and Shear identified drug hepatotoxicity along with fever and a rash, which they called anticonvulsant hypersensitivity syndrome^[14]. Several diagnostic criteria have been proposed for DReSS/DiHS, which is characterized by the presence of a maculopapular erythematous skin eruption, fever, lymphadenopathy, eosinophilia, and visceral involvement such as hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis, and the liver is the most common organ involved^[15]. Importantly, DReSS/DiHS might present with acute liver failure, which increases its mortality^[16]. In this context, liver failure is usually classified in the group of drug-induced liver injuries^[17]. This review focuses on the liver involvement present in DReSS/DiHS reported in the literature in case series.

LITERATURE REVIEW

We reviewed the literature and summarized all reported case-series of DReSS-associated with liver involvement obtained from MEDLINE and EMBASE between January 1990 and July 2018 using the following terms: "DReSS syndrome," "drug reaction with eosinophilia and systemic symptoms," "drug rash with eosinophilia and systemic symptoms," "drug hypersensitivity and eosinophilia," "drug-induced hypersensitivity syndrome". The search was limited to the English language. After

gathering all articles, we described the number of patients included, those with liver involvement, type of presentation, blood work, drug involved, other associations, treatment received, mortality, and follow-up.

DEFINITIONS

In this review, we will use the acronym DReSS/DiHS instead of DRESS as a recent review highlighted the importance of clarifying that eosinophilia is not mandatory to confirm this syndrome^[18]. In 1996, Bocquet *et al*^[19] established three criteria needed for diagnosis of DReSS/DiHS syndrome: skin eruption, eosinophilia ($\geq 1.5 \times 10^9/\mu\text{L}$), and visceral involvement (transaminase elevation ≥ 2 times upper normal limit, lymphadenopathy > 2 cm in diameter, nephritis, interstitial pneumonia, or carditis). In 2006, Shiohara *et al*^[20] proposed to include as diagnostic criteria the presence of human herpes virus 6 (HHV-6) reactivation, as they documented HHV-6 IgG titers and DNA 2-3 wk after the onset of the rash. The group suggested this virus to be a cause of this hypersensitivity syndrome. Finally, in 2007 the RegiSCAR group developed a new scoring system. Hospital admission as a result of the suspected drug-related reaction and at least three of the following findings: acute skin rash, fever, lymphadenopathy of at least two sites, the involvement of at least one internal organ, lymphocytosis/lymphocytopenia, peripheral eosinophilia, and thrombocytopenia. According to this scoring system, patients were classified into definite, probable, possible, or no diagnosis of DReSS/DiHS (Table 1)^[21].

With regard to DILI, a previous definition set the following threshold for defining its diagnosis: elevation of AST and/or ALT or bilirubin or alkaline phosphatase > 2 upper limit of normal (ULN)^[22,23]. Subsequently, given the adaptation or tolerance that may occur in up to 20% of drugs, the levels of transaminases elevations were modified to > 5 ULN without symptoms, or rise in alkaline phosphatase > 2 ULN, or rise in bilirubin > 2 ULN with any transaminases increasing. Alternatively, AST or ALT < 5 ULN with symptoms also defines DILI^[24].

Patients with acute hepatitis and elevated prothrombin time or international normalized ratio levels without mental status changes are frequently labeled as having a severe acute liver injury^[25].

EPIDEMIOLOGY

Although liver involvement is the most common visceral manifestation of patients with DReSS/DiHS, it presents mainly as hepatocellular injury, sometimes cholestasis, or both and rarely fulminant hepatitis and death^[26]. Asymptomatic transaminasemia may occur in up to 20% of patients on drugs^[27]. An estimation of a severe cutaneous drug reaction is about 1 of every 1000 hospitalized patients^[28]. The DReSS/DiHS belongs to this category with an estimated incidence of one in 1000 to one in 10000 drug exposures^[29,30] and mortality of approximately 5% to 10%^[31]. Liver injury is the most common organ damage seen in cases of DReSS/DiHS with rates ranging from 51% to 87%^[15,31-34]. Kardaun *et al*^[35] reported that liver injury was the most common internal organ involvement seen in 75% (81/114) of DReSS/DiHS cases, in which 91% of the cases had visceral organ involvement. Shiohara^[20] reported liver complications in up to 70% of drug-induced hypersensitivity syndrome patients. Cacoub *et al*^[13] reported liver injury in 94% of DReSS/DiHS patients. One study reported β -lactams antibiotics, allopurinol, non-steroidal anti-inflammatory drugs, and sulfonamide as the most commonly associated drugs with DReSS/DiHS accompanied by liver dysfunction in 23 cases^[36]. Another study reported sulfonamides (13/14; 92.9%), followed by antiepileptic drugs (19/22; 86.3%), and allopurinol (15/19; 78%) to have the highest risk of inducing liver injury in DReSS/DiHS^[37]. To put DILI in context, Russo *et al*^[38] reported that drug hepatotoxicity was the cause in 15% of liver transplantation as a result of acute liver failure from 2291 transplants in the United States between 1990 and 2002. Even though acetaminophen either as a single treatment or combined with another drug, was the principal drug related in 133/270 (49%) cases, idiosyncratic liver injury leading to 42% of liver transplants, was associated with four drugs: isoniazid, propylthiouracil, phenytoin, and valproate^[38].

PATHOGENESIS

The pathogenesis of DReSS/DiHS is multifactorial including genetic polymorphisms and environmental factors. One hypothesis is based on the combination of a drug

Table 1 RegiSCAR scoring system for classifying drug reaction, eosinophilia, and systemic symptoms syndrome/drug-induced hypersensitivity syndrome

Clinical manifestations	SCORE				Range	
	-1	0	1	2	Min	Max
Fever	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia						
Eosinophils		No/U	700-1499/ μ L	$\geq 1500/\mu$ L	0	2
Eosinophils, if leukocytes < 4000		No/U	(10%-19.9%)	($\geq 20\%$)	0	2
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement						
Skin rash extent, % BSA		No/U	> 50%		-2	2
Skin rash suggesting DReSS	No	U	Yes			
Biopsy suggesting DReSS	No	Yes/U				
Organ involvement ¹						
Liver		No/U	Yes		0	2
Kidney		No/U	Yes		0	2
Lung		No/U	Yes		0	2
Muscle/heart		No/U	Yes		0	2
Pancreas		No/U	Yes		0	2
Other organ(s)		No/U	Yes		0	2
Resolution ≥ 15 d	No/U	Yes			-1	0
Evaluation other potential causes: ANA; blood culture; serology for HVA/HVB/HVC/Chlamydia-/Mycoplasma pneumonia; other serology/PCR.						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					-4	9
Final score meaning: < 2: no case; 2-3 possible case; 4-5: probable case; and > 5: definite case						

¹After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs. Adapted from Kardaun *et al* [21]. U: Unknown/unclassifiable; DReSS: Drug reaction, eosinophilia, and systemic symptoms syndrome; ANA: Antinuclear antibody; PCR: Polymerase chain reaction.

covalently joined to a protein acting as a hapten, accompanied by a co-stimulatory trigger-virus infection or reactivation, bacterial infection, or inflammatory disorder in a genetically susceptible individual leading to T-cell responses to the antigen, which could be expressed on the hepatocytes surface [39]. Studies have shown the presence of drug-specific cytotoxic T cells in the serum and liver of DILI patients and the skin of DReSS/DiHS patients [40,41]. These cells, which release perforin, granzyme B, and Fas/Fas L-dependent cell death, are believed to induce cell death in both organs [40,42].

Another proposed mechanism involves the immune response to reactivation of latent viruses of the herpesvirus family [43,44], which is seen in DReSS/DiHS complicated cases. It is hypothesized that DReSS/DiHS triggers reactivation of latent viral infection, which may produce a viral exanthema of fevers and rash that may overlap with, or be difficult to distinguish from DReSS/DiHS. Tohyama *et al* [43] compared 100 patients with or without an increase of anti-HHV-6 IgG titers and reported that the flare-up of symptoms such as fever and hepatitis was closely related to HHV-6 reactivation. In Eshki *et al* [45] retrospective study, only seven patients were

examined for an active HHV-6 infection. An active HHV-6 infection was found in six patients, including a patient with fulminant liver failure. Further tests confirmed that HHV-6 infection was a reactivation and not a primary infection. Furthermore, HHV-6 may also cause hepatitis, including fulminant liver failure that is rapidly reversed when antiviral treatment is promptly initiated^[46].

Liver damage in patients with DReSS/DiHS could be caused by eosinophilic infiltration driven by interleukin IL-5^[47-49]. Hypereosinophilia, if persistent, can be toxic to endothelial cells and contribute to organ damage such as interstitial nephritis, pneumonitis, myositis, eosinophilic carditis, pancreatitis, thyroiditis or encephalitis, and possibly hepatitis^[21].

CLINICAL PRESENTATION

The liver may be the first organ involved in a hypersensitivity drug reaction^[37]. It could range from a mild increase of liver enzymes to acute fulminant hepatic failure with the cholestatic type as the most common. The cholestatic pattern is characterized by increased serum transaminases and alkaline phosphatase with prolonged jaundice after drug withdrawal. The hepatocellular pattern presents with increased serum transaminases, minimal serum alkaline phosphatase elevation, and variable jaundice. A mixed pattern has combined features of hepatocellular and cholestatic injury (Figure 1). Peyrière *et al*^[15] reported liver involvement in more than 60% of 216 DReSS/DiHS cases with a hepatocellular necrosis more common than the cholestasis. Lin *et al*^[37] reported that atypical lymphocytosis was seen more frequently on DReSS/DiHS cases with liver injury than cases without liver involvement (74.2% *vs* 30.0%, $P = 0.010$). One study reported that younger patients most commonly presented with a hepatocellular-type, and that the cholestatic-type was seen more often in older patients ($P = 0.044$).

Compared to other severe drug hypersensitivity reactions such as Stevens-Johnson syndrome, a study found a more severe hepatocellular pattern and a moderate to severe cholestatic-type liver injury along with longer liver recovery in DReSS/DiHS cases. They emphasized that the long duration of the liver involvement could last months after the rash resolved^[36]. Wang *et al*^[50] reported a hyperbilirubinemia in 12 (31.58%) patients, aspartate aminotransferase (AST) elevation (> 100 IU/L) in 19 (50.50%) patients, and 9 (23.68%) patients developed hepatic failure. Several case reports have reported liver injury before skin eruption. Lin *et al*^[37] noticed this clinical presentation in 9.7% of cases. Lee *et al*^[17] reported that renal dysfunction was more common in patients with liver dysfunction (39% *vs* 1%, $P = 0.001$), and patients with liver dysfunction were more likely to have renal dysfunction (96% *vs* 34%, $P = 0.001$). Lymphadenopathy was also commonly seen in patients with liver involvement (23% *vs* 6%, $P = 0.005$). Mortality was significantly higher in patients with liver dysfunction (11% *vs* 1%, $P = 0.018$). Ichai *et al*^[16] described the histological features on the liver from DReSS/DiHS cases. They reported acute hepatitis with cytotoxic phenotype. Eosinophils were found in five of seven cases. Kupffer cell hyperplasia with erythrophagocytosis was observed in six of seven cases. They also reported a diminished factor V level at admission (less than 40%), or a reduction at day 2 was predictive of death or liver transplant (Table 2).

SKIN BIOPSY

Lin *et al*^[37] did not find any difference in the eosinophils in the dermis between patients with or without liver injury (64.5% *vs* 60%, $P = 1$). On the other hand, they reported that eosinophils in the dermis were present more frequently in patients with non-severe hypersensitivity hepatitis (88.9% *vs* 30.8%, $P = 0.002$), concluding that the extreme group cases might be more related to the immunoallergic attack to the hepatocytes^[37]. Walsh *et al*^[51] reported that patients with clinical presentation of erythema multiforme-like were associated with higher elevations of AST ($P = 0.01$), concluding these patients have worse liver involvement^[51].

TREATMENT

Although further studies are needed to evaluate the role of systemic corticosteroids in drug-induced systemic hypersensitivity and liver injury, it seems this therapy has a role in the treatment with DReSS/DiHS and liver involvement. A favorable outcome has been reported when fulminant hepatitis associated with DReSS/DiHS was treated

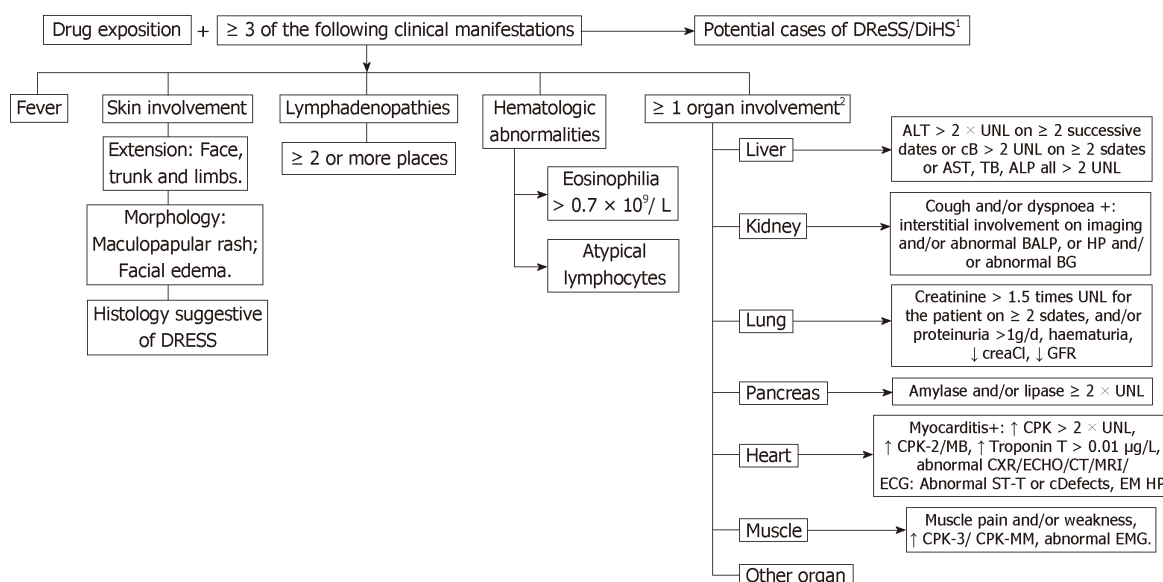


Figure 1 Diagnostic algorithm of drug reaction, eosinophilia, and systemic symptoms syndrome / drug-induced hypersensitivity syndrome case series.

ALT: Alanine aminotransaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; BALP: Broncho-alveolar lavage fluid; BG: Blood gasses; cB: Conjugated bilirubin; cdefects: Conduction defects; CPK: Creatine phosphokinase; CPK-2/MB: Creatine phosphokinase for heart muscle involvement; CPK-3/CPK-MM: Creatine phosphokinase for skeletal muscle involvement; creaCl: Creatinine clearance; CT: Computed tomography; CXR: Chest-x-ray; ECG: Electrocardiogram; ECHO: Echocardiogram; EMG: Electromyography; EM: Endomyocardial; HP: Histopathology; MRI: Total bilirubin; UNL: Upper normal limit. ¹The RegiSCAR criteria should be done to potential cases of DReSS for more accurate diagnosis and classification (see [Table 1](#)). ²Organ involvement after exclusion of other explanations.

with intensive corticosteroid therapy (methylprednisolone 1 g/d) for 3 d (3750 mg prednisone within 30 d)^[52]. On the other hand, the study by Lee *et al*^[36] demonstrated that in patients with DReSS/DiHS associated with liver injury, the use of systemic corticosteroids did not confer additional benefits regarding disease duration and recovery of liver function.

MORTALITY

Concerning DReSS/DiHS, acute-stage mortality ranges from 5% to 10% and is mainly attributed to specific liver injury, myocardial or pulmonary lesions, and hemophagocytosis^[19,26]. Fifteen percent of liver transplantation cases in the United States are caused by DILI^[38]. The mortality of 10% in those patients with a combination of hepatocellular injury and jaundice, first described by Zimmerman, has been confirmed in several studies^[53-55]. In their case-series Ichai *et al*^[16] reported that 43.7% of patients (7/16) with DReSS/DiHS related acute liver injury/acute liver failure underwent transplantation ($n = 5$) or died ($n = 2$).

CONCLUSION

Although rare, DReSS/DiHS is considered a severe cutaneous drug reaction, which could potentially lead to death, especially in patients with delayed diagnosis, viral reactivation, the presence of systemic inflammatory response syndrome, and severe organ involvement. A better understanding of its pathophysiology is required to elucidate risk factors for severe visceral involvement, as it is demonstrated to be the main cause of mortality. Patients with ongoing deterioration of liver function must be tested for reactivation of latent viruses of the herpesvirus family. Furthermore, a multidisciplinary approach in patients with severe internal organ affection is of utmost importance.

Table 2 Liver involvement reported in drug reaction, eosinophilia, and systemic symptoms syndrome/drug-induced hypersensitivity syndrome case series

Ref.	N	Liver, n (%)	Presentation, n (%)	Blood work, n (%)	Drug, n (%)	Associations	Treatment	Mortality, n (%)	Follow-up, n (%)
Chiou <i>et al</i> ^[32]	30 (M: 15 F: 15)	26 (86.6)	Jaundice 5 (16.6); Mild LI to FH; Toxic liver 6 (20)	Eos (> 1500/ μ L) 14 (48); Serology HHV-6: 7/11 (63); CMV, EBV, HSV IgM: all negative; HIV 3	Allopurinol 11 (37); CBZ 6 (20)	RI 16 (53.3); ATL 13 (45)	HC/PDN: 22 (76); TS + Anti-H: 7 (23)	3 (10) (acute RF, sepsis, and GA bleeding)	DM type 1: 2 patients
Mansur <i>et al</i> ^[56]	31 (M: 15; F: 16)	22 (71)	² LI: > 2 fold of UNP to 20 -fold of increase; Hepatitis 16 (51); Hepatomegaly 7 (22.6)	ALT: 2-5 fold increase 3 (10.0); \geq 5 fold increase 4 (13.3); AST: 2-5 fold increase 1 (3.3); \geq 5 fold increase 4 (13.3); GGT: 2-5 fold increase 6 (20.7); \geq 5 fold increase 9 (31); Eos (> 350) 18/28 (64.3)	CBZ 11 (48); Phenytoin 11 (35.4); Lamotrigine 3 (9.6)	RI 2 (6.45)	MTP: 27; TS + anti-H: 3	One TEN patient died of sepsis	6 (19.4) developed a blister dermatitis; 3 SJS and 3 TEN. All the hepatitis recovered well
Ben m'rad <i>et al</i> ^[34]	24 (M: 12; F: 12)	22 (91.6)	Cholangitis or non-lithiasis cholecystitis	ALT increased in 22 patients; \geq 5N 13 (54); Eos (> 500 μ /L) 12 (50); Serology/PCR for HHV6, HHV8, CMV, and EBV were negative	Allopurinol 4; SSE 3; SMX-TMP 3	RI 4 (17); Heart 5 (21); ATL 14	PDN: 11 (45)	0	No relapses occurred; Sequelae: myocarditis 1; Steroid dependent: 1
Eshki <i>et al</i> ^[45]	15 (M: 5; F: 10)	9 (60)	HP of FH: massive hepatic necrosis + eosinophilic and lymphocytic inflammatory infiltrates	DNA PCR HHV-6: serum 6/7 patients; liver 1/7; CNS: 1/7; HHV-6 IgM and IgG1 patient with FH (reactivation); HIV+ 1 patient	Allopurinol 4; Minocycline 3; Antiepileptics 3	FH + HHV-6: 1; Hypertensive encephalitis (HHV-6 DNA CSF): 1 RI: 6	Non-AT: 5; SS: 10; + IVIG: 3; LT: 1	3 (20); MOF + DIC: 1	14 were admitted to the ICU where 3 died; 1 Flared twice when tapering of SS
Picard <i>et al</i> ^[57]	40 (M: 19 F: 21)	39 (99)		Eos 32 (80); EBV react 16 (42); HHV-6 react 17 (45); HHV-7 react 12 (32)	Anticonvulsants 12 (30); Antibiotics 11 (27)	RF 10 (25); FH 2 (5)	LT: 1	3 (7.5); Endocarditis (1) septicemia (1) stroke (1, unrelated to DReSS)	17 (42) symptoms were still present at 180 d
Chen <i>et al</i> ^[31]	60 (M: 26, F: 34)	48 (80)	LI > 2 UNL	Eos (> 700/ μ L) 31 (52) EBV and CMV IgG + 9 patients; HHV-6-IgG + 1 patient, but negative PCR (only patient tested)	Allopurinol (32); Phenytoin (18); Dapsone (17)	RI 24 (40); RF 5 (8); HF 4; ATL (63)	SS: 45 (75); + IVIG: 2; Non-AT: 6	6 (10) (1 MOF; 3 septic shock; 1 cardiogenic shock; 1 shock)	Hyperthyroidism

Ang <i>et al</i> ^[58]	27 (M: 12 F: 15)	26 (96.3)		Liver enzymes > 10 UNL: 13 (48); Eos 22 (%); Serology was not done	Phenytoin 5; CBZ 4	RI 4 (15); RF 2	SS: 25 (93); TS: 2 (7); LT: 0	0	8 (32) flared while SS tapering; 17 completed SS treatment (7 to 160 d, mean of 50); Sequelae: RI 3; AT 1, and myocarditis 1
Um <i>et al</i> ^[47]	38 (M: 18, F: 20)	38 (100)		ALT (mean 383.39 IU/L, range 26-3633); AST (mean 382.73 IU/L, range 28-2360); Eos (> 500/ μ L) 35 (91); Serology negative to CMV, EBV, or HSV	Anticonvulsants 18 (47); Antibiotics 7 (18); NSAIDs 5 (13)	RI 6 (16); ATL 18 (47)	TS + anti-H: 22 (58); SS: 16 (42)	1 (3) LF + opportunistic infection	36 (95) recovered completely; 1 (2.6) LI was lost at FU
Wongkitisophon <i>et al</i> ^[59]	27 (M: 14; F: 13)	26 (96.3)	LI > 2 UNL; Hepatomegaly (7.4)	ALT mean 188 IU/L (<i>r</i> 132-1708); AST 132 IU/L (<i>r</i> 89-857); TB 9 (33.3) mean 32.7 μ mol/L (<i>r</i> 18.9-244.2 μ mol/L); Eos (> 700/ μ L) 19 (70)	Phenytoin 9 (33); Allopurinol 4 (15); Nevirapine 4 (15)	RI 2 (7); ATL (19)	Non-AT: 4; SS (DMT/PDNL): 23 (85.2)	1 (4) died from MOF	5 (19) relapse of DReSS during tapering of SS; 21 (77.8) recovered well; Sequelae: 5 (19) that recovered within 6 mo
Kardaun <i>et al</i> ^[35]	117 (M: 52; F: 65)	86/114 (75)	Transiently disturbed; liver function tests; Hepatomegaly and coagulopathy	Eos (\geq 1500 μ L ⁻¹) 92 (81); (700-1499 μ L ⁻¹) 16 (14); HIV 1; HHV-6 react 21/58 (36)	Anticonvulsants 41 (35); Allopurinol 21 (18); Sulfonamide 14 (12)	RI 40/108 (37); ATL 68/102 (67); SJS, TEN or AGEF features were seen in 8 patients	NA	2 (2)	1 overlap with SJS/TEN; and 1 overlap with AGEF
Walsh <i>et al</i> ^[51]	27 (M: 10; F: 17)	27 (100); TRC of HPB	LI before rash 4 (14.8); Significant LI: 20; Mild LI: 7; Cholestatic pattern was associated with interface dermatitis (<i>P</i> = 0.036)	AST mean 970 IU/L, median 250 (31-5183); GGT mean 522 IU/L, median 379 (9-1903); ALP mean 295 IU/L, median 266 (57-819); Eos (> 0.4 \times 10 ⁹ /L) 25 (93)	Anticonvulsants 12; Antimicrobials 10; Anti-rheumatics 5	RI 2 (7); Pericarditis (1 patient); GA (1 patient) MOD 3 patients	LT: 2	3 (11) All had severe liver injured. Two after failed LT	18 patients completed FU and normalized liver function
Lee <i>et al</i> ^[36]	23 (M: 12; F: 11)	23 (100)	Significant LI 23 (100)	ALT 186 IU/L (114.0-458.0); AST 207 IU/L (90.0-766.0); ALP 147 IU/L (116.0-338.0); TB 1.1 (0.8-13.3); Eos 17 (74)	Beta-lactams 7 (54); Allopurinol 3 (13); Sulfonamide 2 (15)	RI 13 (56); If LI higher risk of RI (<i>P</i> < 0.001); and of LN (<i>P</i> = 0.005)	LT: (2 patients; 1 died); IVIG: 1 (4); PDNL	4 (17.39)	Duration of the disease in survivors on steroids: 25.3 \pm 14.8 d
Uhara <i>et al</i> ^[60]	12 (M: 4; F: 8)	11 (92)	Peak of LI appeared 7 d after the rash (range 3-22); ALT mean 176 (range 91-311)	Eos (>1.5 \times 10 ⁹ /L) 4; HHV-6-IgG 12 (100)	CBZ 6; Salazosulfapyridine 4	ATL 8 (66)	Non-AT on the first weeks of examination Hydration: 7; TS: 5 PDNL: 1 patient had RA; DMT (single dose): 1	0	All patients recovered; 7 to 37 d (median, 18) after withdrawal of the drug

Sultan <i>et al</i> ^[61]	17 (M: 8 F: 9)	17 (100)	LI defined as ALT > 100 IU/L; Hyperbilirubinemia 11 (64.7); Hepatomegaly 5 (29.4)	ALT (> 100 IU/L) 17 (100); AST (> 100 IU/L) 7 (41); HF 1 (5.9); Eos (> 1.5 × 10 ⁹ cells/) 15 (88.2)	Anti-convulsivants (65); Phenytoin 6 (35.3); Phenobarbitone 2 (12)	RI 11 (64.7); RF 1 (5.9) requiring dialysis; ATL 2 (11.7)	SS (DMT switched to PDNL): 17 (100)	1 (6) died of HF	13 (76.5) recovered without complication 1 (5.9) DReSS recurrence after withdrawal of steroids
Avancini <i>et al</i> ^[62]	27 (M: 17; F: 10)	23 (85.1)	LI defined as liver enzyme level > 3 UNL	ALT 569 ± 911.5 U/L (mean ± SD; 46–4347 U/L); AST 474 ± 743 U/L (mean ± SD; 38–2662 U/L); Eos 26 (96); HCV + 1 patient	Phenytoin 12 (44); CBZ 8 (30)	ATL 17 (62.9); Associated to and higher ALT ($r = 0.62$; $P < 0.001$)	PDN: 27 (100); LT: 1 (patient)	1 (4) due to HF	1 AT
Funck-Brentano <i>et al</i> ^[63]	38 (M: 19; F: 19)	29 (76)	Cytolysis 27 (71). Duration of 47 d (12–120); Cholestasis 26 (68); No HF was observed	Eos (> 7–1.5 × 10 ⁹ /L) 26 (68); PCR HHV-6 11/28 (39); EBV 3/28 (11); CMV 2/29 (7)	Allopurinol 13 (34); CBZ 4 (11); Sulfonamide 4 (11)	RI 21 (55); ORF 16 (42); FRF 8 (21); ATL 21 (55)	SS (MTP/PDN): 13 (34); TS: 25 (66)	1 (3); Hypovolemic shock few weeks post-discharged	Treatment duration 40 d (15–360); Relapses 15 (39)
Lin <i>et al</i> ^[37]	72 (M: 34; F: 38)	62 (86.1)	LI before rash 6 (9.7); Pattern: Cholestasis 23 (37.1); Mixed 17 (27.) Hepatocellular 12 (19.4); Unknown 10 (16.1)	Eos (> 700/ml) 49 (58.3); ALT values as high as 3806 U/L or ALP values of up to 2616 U/L	Anticonvulsants (30.6); Phenytoin 13 (18); Allopurinol; 19 (26.4) ³ ; Sulfonamides 14 (19.4)	ATL (79.2); related to LI ($P = 0.010$) and with fever ($P = 0.026$).	PDNL + IVIG: 1; NAC: 0	0	22 (35.5) recovered in 30 d; 40 (64.5) recovered after
Lee <i>et al</i> ^[63]	25 (M: 11; F: 14)	20 (80)	LI if liver enzymes > 2 UNL	BT increased 6 (24); Eos (> 0.7 × 10 ⁹ /L, 20 (80), 7 of them had (> 1.5 × 10 ⁹ /L). PCR HHV-6 tested in 1 patient: negative	CBZ (28); Allopurinol (16); Anti-tuberculosis drugs (12)	RI 7 (28); ATL 12 (48); Pulmonary involvement 5 (20)	SS (MTP or PDN): 13 (52); + IVIG: 2 (8); TS + anti-H: 12 (48)	3 (12); 1 Septic shock + LI; 1 septic shock + LI + RF; 1 septic shock + LI + RI + Pneumonia	The remaining patients had fully recovered. No significant cutaneous sequelae
Wang <i>et al</i> ^[64]	104 (M: 38; F: 66)	94 (90.4)	Jaundice 5 patients	Eos 72 (69.2): (0.7 × 10 ⁹ /L–1.499 × 10 ⁹ /L) 37 (35.6); (≥ 1.5 × 10 ⁹ /L) 35 (33.7); HIV 1 (1); Serology for HVA/HBV/HCV 18 (17.3)	Antibiotics 37 (35.6); CBZ 7 (6.7); TCMs 14 (13.5)	RI 9 (8.7) ATL 26 (25); MOD 19 patients	PDN: 58 (58) + IVIG: 1 patient; + Cy: 1 patient; Anti-H: 45 (43); IVIG: 1 patient	1 (< 1) had progression of his previously renal disease + <i>Acinetobacter baumannii</i>	103 were successfully discharged
Ichai <i>et al</i> ^[16]	16 (M: 5 F: 11)	(100) TTC	ENC: 7 (43.75) Admission 3 (Grade I: 1; III: 2); After admission 4 Liver necrosis (10%–90% of parenchymal surface) 7; panlobular 1; central; 3; periportal 1; spotty 2. Kupffer cell hyperplasia: 6; and Erythrophagocytosis	ALT 1693 IU/L (1252–2256); PCR HHV6 5/6 (83); HIV+ 4 (25)	Allopurinol 2; CBZ 2 Anti-tuberculosis drugs 3	RI 5 (31.2)	NAC: 16 (100); PDNL: 9 (56); LT: 5 (31.2)	4 (25): 2 MOF; 1 LR 4 yr after LT; 1 systemic fungal infection + HF 4 d after LT	LT survival: 60%; DReSS recurrence 75 ± 91 d after LT in 3/5 patients. LR was rule out. DReSS recurrence in 1 patient 2 months after spontaneous recovery

Wu <i>et al</i> ^[65]	52 (M: 34; F: 18)	43 (83)	LI if ALT >2 UNL	Eos (> 700/ μ L) 42 (81); DNA HHV-6 17 (33); DNA EBV 10 (19)	Allopurinol 18 (35); SSP 11 (21); CBZ 5 (10)	RI 2 (4)	MTP: 52 (100); + IVIG: 32 (62)	3 (6) MOF + sepsis within 3 months post-discharge.	3 (6) AT
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¹Case series with Anticonvulsant hypersensitivity syndrome.

²Authors reported that DReSS induced by phenytoin appeared sooner after the drug intake compared to carbamazepine ($P = 0.01$).

³Allopurinol was related to cholestatic pattern. Hepatocellular-type pattern was seen in younger people while the cholestatic-type was seen in elderly ($P = 0.044$). Patients treated with SS had more ATL and Eos than those treated with TS ($P < 0.05$), but no differences in liver involvement. AGEP: Acute generalized exanthematous pustulosis; Anti-H: Antihistamines; AHA: Autoimmune hemolytic anemia; AT: Autoimmune thyroid; ATL: Atypical lymphocytosis; BT: Bilirubin total; CBZ: Carbamazepine; CMV: Cytomegalovirus; CNS: Central nervous system; CSF: Cerebrospinal fluid; Cy: Cyclosporine; DIC: Disseminated intravascular coagulation; GA: Gastrointestinal; ICU: Intensive care unit; DMT: Dexamethasone; EBV: Epstein Barr virus; Eos: Eosinophilia; ENC: Encephalopathy; FH: Fulminant hepatitis; FU: Follow-up; HC: Hydrocortisone; HSV: Herpes simplex virus; HHV-6: Herpes virus type 6; HPB: Hepatobiliary disease; LN: Lymphadenopathies; LT: Liver transplant; LR: Liver rejection; MOD: Multi-organ damage; MOF: Multi-organ failure; MTP: Methylprednisolone; NA: Not-available; NAC: N-acetylcysteine; Non-AT: Non-active treatment; NSAIDs: Non-steroidal anti-inflammatory drugs; PCR: Polymerase chain reaction; PDN: Prednisone; PDNL: Prednisolone; RI: Renal injury; RF: Renal failure (ORF: Organic RF; FRF: Functional RF); SJS: Stevens-Johnson syndrome; SMX-TMP: Sulfamethoxazole-trimethoprim; SS: Systemic steroids; SSE: Sulfasalazine; SSP: Salazosulphapyridine; TEN: Toxic epidermal necrolysis; TMCs: Traditional Chinese Medicines; TRC: Tertiary Referral Center; TS: Topical steroids; TTC: Tertiary Transplant Center.

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