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Are Older Women More Susceptible to Dress Syndrome? A Case Series and Literature Review

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Abstract

Background & Aims: We report a case series of women presenting with an Adverse Drug Reaction (ADR), classified according to RegiSCAR criteria as Drug Rash Eosinophilia and Systemic Symptoms Syndrome (DRESS), seen at our Internal Medicine Unit between 2012 and 2019. Our aim was to analyze the clinical pattern of each case/medical report and to highlight the various critical issues arising from a systemic ADR resulting in a severe prognosis and, in some cases, death.

Methods: A systematic search of medical records in the databases of the Unit of Internal Medicine was carried out from 2012 to 2020. For each patient, clinical features, diagnostic tests, and prognostic and therapeutic data were assessed.

Results: All the reported clinical cases were women, with a mean age of 68 years, most of them treated with allopurinol. The time lapse between drug intake and the onset of symptoms was about 3 weeks, and all the women presented with a skin rash. The main organ involved was the liver (53%); half of the patients reported kidney failure, whereas involvement of the lungs and bowel was 42% and 28%, respectively. Five of the six cases examined showed serological hypereosinophilia. Fever was the main symptom in half of the cases. More than 80% of them received corticosteroids, as well as supportive and antibiotic treatment. Two patients recovered; four patients died due to severe complications.

Conclusion: DRESS is a severe systemic ADR and allopurinol is usually the culprit drug. Careful assessment should be recommended before its prescription in elderly women with chronic kidney disease, at cardiovascular risk and/or following poly-pharmacological treatment.

Keywords: DRESS Syndrome; Clinical Outcome; Liver damage; Allopurinol

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Introduction

Adverse Drug Reactions (ADRs) can be defined as "an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product" [1]. Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome (DRESS) is a severe multi-organ hypersensitivity disorder induced by a limited number of drugs in patients with a genetic predisposition. DRESS is one of the delayed drug-induced Severe Cutaneous Adverse Reactions (SCARs) [2], usually occurring within 2 to 6 weeks after starting a new drug therapy and may be associated with specific hematological findings (hypereosinophilia, atypical lymphocytosis), lymphadenopathies and the involvement of internal organs, such as the liver, kidney and heart. Its incidence is unknown, and it is probably under diagnosed, because of a lack of awareness: It has been estimated as occurring in more than one case per 10,000 exposures to anticonvulsants, such as carbamazepine. Although DRESS has been observed both, in older and children, most cases are found in adults regardless of sex [3,4]. This syndrome was first related to aromatic antiepileptic agents, but many other drugs have been associated to DRESS, including allopurinol, febuxostat, olanzapine, sulfonamides, dapsone, minocycline, vancomycin, and kinase inhibitors [5]. Several studies have shown an association between the expression of some Human Leukocyte Antigen (HLA) haplotypes and DRESS susceptibility [6,7]. One of the physio-pathological mechanisms of DRESS is related to the T-cell response elicited by the drug or its metabolites after HLA-presentation by antigen-presenting cells. Another pathophysiological mechanism involves the reactivation of Human Herpesviruses (HHV-6, HHV-7, CMV and EBV), probably related to immune system disorders induced by the drug. This association has been confirmed by several reports, therefore

HHV-6 reactivation is one of the DRESS diagnostic criteria [6,8]. Since DRESS syndrome is a potentially fatal drug reaction with a 10% mortality rate, correct and early diagnosis is essential, especially in internal medicine ward. Diagnosis is challenging, and requires a multidisciplinary approach to exclude other systemic diseases, such as mononucleosis, lupus erythematosus or acute retroviral syndrome. The international Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) suggested as inclusion criteria for suspected DRESS cases the presence of at least three of the following: fever above 38°C, skin rash, enlarged lymph nodes, hematological abnormalities (hypereosinophilia, atypical lymphocytes, lymphocytopenia, thrombocytopenia), internal organ involvement (liver, kidney, lung, pancreas, heart, muscles). However, the Japanese consensus group suggested another panel of criteria, involving HHV-6 reactivation, as diagnostic criteria [9]. Here, we report a small cohort of six women with DRESS syndrome observed at our Internal Medicine ward, aiming to define culprit drug, risk factor and outcomes.

Patients

Healthcare professionals at the "P. Giaccone" University Hospital in Palermo, Sicily, reported 18 notifications of cutaneous suspected adverse reactions to the Italian National Pharmacovigilance Network. Therefore, we report a retrospective series including six women diagnosed as suffering from DRESS syndrome, observed at our Unit of Internal Medicine & Hepatology, between 2012 and 2019. Main demographic and clinical features are presented in Table 1. The RegiSCAR criteria and the Naranjo algorithm were used to assess causality [10]. All patient's waiver informed consent at hospital admission.

Case Series

Case 1

A 77-year-old Caucasian woman presented with a history of treated arterial hypertension, glaucoma, osteoporosis with previous fractures and hypo-mobility with a sacral bed/pressure sore. She underwent implantation of a dual-chamber pacemaker and during hospitalization started therapy with allopurinol for hyperuricemia, together with trimethoprim/sulfamethoxazole for diarrhea. Ten days after discharge, an urticarial rash appeared, which was treated with betamethasone and bilastine, but it was of no benefit. On admittance to our Unit, her vital signs were stable, and she was without fever but presented an extensive urticarial rash spreading over the trunk and limbs. Laboratory tests showed leukocytosis with hypereosinophilia; elevated levels of Alanine-Aspartate-Aminotransferases (ALT/AST), Alkaline Phosphatase (ALP), gamma–Glutamyl Transferase (gamma-GT) and C-Reactive Protein (CRP), as well as altered renal function markers, hyperuricemia and mild hyponatremia, hypocalcemia, and thrombocytopenia. CT scan imaging revealed masses in the base of both lungs, secondary to inflammation and diverticular disease. Echocardiography showed a 60% EF and mild mitral insufficiency. Serological laboratory tests excluded major hepatotropic viruses and other viral infections (CMV; EBV; HSV 1-2; HBV; HCV; HHV-6), *Mycoplasma pneumoniae* and Chlamydia *pneumoniae* infections were also excluded. Non-organ specific antibody pattern was negative, except for Anti-Nuclear Antibodies ANA (positive 1:160). Skin biopsy showed a normal epidermis with fine hyperkeratosis, and a dense lymphocyte infiltrate with a prevalence of T cells and eosinophils, which are typical features of drug-induced dermatitis. An allopurinol-induced DRESS syndrome was diagnosed, which was treated with intravenous methylprednisolone, followed by oral prednisolone, resulting in its clinical resolution. However, because serological testing for cytomegalovirus (CMV-DNA 3154/mL) was positive, treatment was started with ganciclovir, as well as anti-microbials, due to a urinary tract infection, both with success. The patient was discharged following the resolution of clinical symptoms and improvement in laboratory test values. However, after 2 months the patient was again admitted to the hospital and died following a pneumonia.

Case 2

An 81-year-old Caucasian woman, presented with a history of treated hypertension and type 2 diabetes mellitus; for 25 years she had had untreated epilepsy. During the previous three years, she had reported an increasing frequency of seizures and cognitive decline, thus she underwent MRI and CT scans. Almost two months before admittance to our Unit, she had reported erythema/exanthema over her whole body, associated with itching, after assuming phenobarbital. She was treated with antihistamine and oral corticosteroids, with no benefit, and was therefore hospitalized. Following a scrupulous and detailed collection of anamnestic data, the anticonvulsant treatment was interrupted. At admission, the patient presented an erythematous rash with periocular swelling; laboratory tests showed leukocytosis with hypereosinophilia, and slight increases in ALT, ALP<2xN; gamma-GT 5xN, and CRP. The history of a recent administration of phenobarbital, followed by the typical skin rash, systemic involvement, hypereosinophilia and the exclusion of other etiologies, pointed to a diagnosis of DRESS. Therefore, treatment with infusions of methylprednisolone was started. After urine and blood cultures detected *E. coli* and *S. aureus* bacteremia, she was treated with anti-microbials. Unfortunately, CT scan revealed pneumonia, and a subsequent blood culture showed the presence of multi–drug resistant bacteria and fungi. After a long hospitalization, endocarditis occurred, followed by a fast deterioration of her clinical conditions and death.

Case 3

A 78-year-old Caucasian woman presented with treated hypertension, gastroesophageal reflux disease, type 2 diabetes mellitus on diet therapy and glaucoma. About three weeks before admission, her general practitioner had started allopurinol for mild hyperuricemia. After two weeks, she complained of pruritus, so allopurinol was stopped, and symptomatic therapy with cetirizine was commenced. Ten days later, the pruritus reappeared with fever, fatigue, lateral-cervical lymphadenopathy and a progressive erythematous rash on the trunk and face. She was admitted to our Unit presenting fever (>38°C) and an extensive itchy skin rash. At admission, she was in a stable clinical condition, with a generalized erythematous maculopapular-desquamative skin eruption on her face, trunk and upper and lower limbs. Laboratory tests showed leukocytosis with hypereosinophilia, slightly increased levels of AST/ALT and ALP<2xN, Gamma-GT 242 U/L, lactic dehydrogenase 821 U/L, and creatinine 4.9 mg/dL. Other etiologies were excluded by viral and bacterial serological tests (HAV, HBV, HCV, CMV, EBV, *Salmonella*, *Rickettsia*, *Chlamydia* and *Mycoplasma*), Non-organ-specific auto-antibody patterns (ANA, AMA, SMA; ENA, ANCA) were within normal limits. Abdominal and neck ultrasound, echocardiography and total body CT scan with contrast media were negative. Bone marrow aspiration ruled out hematologic diseases. In view of the recent allopurinol administration and the extensive cutaneous manifestations, a DRESS syndrome from allopurinol was diagnosed and the patient was treated with intravenous

methylprednisolone. However, a switch to oral prednisolone caused the re-appearance of both the skin rash and hypereosinophilia. After a further 20 days of IV methylprednisolone at high doses, the steroid therapy was progressively de-escalated. Due to steroid-induced immunosuppression and despite the lymphocyte dysfunction typical of DRESS, viral serology for CMV, EBV and HHV-6 was positive, so IV ganciclovir was started. Later, following an episode of fever (urine and blood cultures positive for Methicillin-Resistant *S. aureus)* she benefitted from linezolid treatment. However, although echocardiography assessment excluded infectious endocarditis, her clinical condition worsened due to septic shock and she died.

Case 4

A 77-year-old Caucasian woman presented with a history of atrial fibrillation, chronic heart disease, metabolic syndrome (type 2 diabetes, hypertension, dyslipidemia). About four days before hospital admission, an erythematous-desquamative rash had appeared, extending over her whole body. The patient had been taking allopurinol for several years, but three days before the appearance of the rash she had also taken acetaminophen. Consequently, corticosteroid therapy was commenced, but without success. Because of the worsening of the skin rash, she was admitted to our Unit. At admission, the patient's vital signs were stable, and she was without fever, but an extensive rash had spread to her whole body. Laboratory tests revealed mild neutrophilic leukocytosis and normal kidney function. Corticosteroid and antihistamine were introduced to treat the skin rash, with benefit.

Case 5

A 60-year-old Caucasian woman presented with a history of treated arterial hypertension, type 2 diabetes and kidney failure, anxiety–depression syndrome, dyslipidemia and hyperuricemia. Ten years earlier, the patient had been hospitalized for hemorrhagic-form bullous erysipelas. In the previous two months, she had reported erythema/exanthema over her whole body, which was treated with antihistamines and ceftriaxone for almost one week, with no benefit. After a visit to a hospital emergency room, the patient was discharged with a diagnosis of ADR due to ceftriaxone. As the exfoliative skin rash and pruritus persisted, she was admitted to our Unit. Scrupulous and detailed anamnesis showed a history of allopurinol treatment, which she had been taking for almost three months, and which was promptly interrupted. At admittance, in addition to the rash, the patient showed edema in lower limbs and periocular swelling; laboratory tests revealed leukocytosis with hypereosinophilia, mild elevated ALP and CRP, alterations in renal function markers and hyperuricemia. The recent administration of allopurinol, followed by the typical skin rash, systemic involvement and hypereosinophilia suggested a diagnosis of DRESS syndrome. Therefore, treatment with infusions of methylprednisolone was started, which was subsequently switched to oral prednisolone for about 1 month and led to a complete recovery. Moreover, CT scan imaging revealed masses with a "tree-in-bud" pattern in the bases of both lungs, secondary to inflammation. During a subsequent fever, blood cultures detected *S. aureus* bacteremia, so treatment was started with ciprofloxacin and linezolid. After about a month of hospitalization, the patient was discharged, but she was readmitted two weeks later, with a diagnosis of endocarditis and sepsis, which led to the patient's death.

Case 6

A 53-year-old Caucasian woman with morbid obesity (BMI 52 kg/m^2), pulmonary heart disease and treated hypertension. Following the sudden onset of progressive chest pain, the patient came to our emergency room, where CT scan excluded pulmonary embolism and showed non-specific pulmonary nodules. The patient was thus admitted to our Unit. At admittance, physical examination showed no abnormalities, and laboratory tests revealed mild neutrophilic leukocytosis and a urinary tract infection, treated successfully with ciprofloxacin. Since mild hyperuricemia was detected during hospitalization, treatment with allopurinol was started, but promptly interrupted on the third day after the appearance of an itchy and exfoliative skin rash, which extended to her face and trunk, associated to mild hypereosinophilia. The patient's condition benefitted from corticosteroids.

Discussion

Assessment of the incidence of DRESS syndrome is limited by the small number of reported cases, the lack of a cohort study including patients with DRESS, and by the variable time delay between drug intake and clinical onset. In the current literature, aromatic anticonvulsant drugs, anti-microbials, anti-tubercular drugs, anti-pyretic/analgesics and allopurinol are the most frequent drugs causing DRESS syndrome in patients with a genetic susceptibility. In addition, many new drugs have recently been reported, such as direct antiviral agents for HCV, direct-acting anticoagulants and targeted therapy agents, such as sorafenib [2,11,12]. In our study, including elder women, we found that although the phenotypes and clinical presentations of DRESS syndrome were similar, they were induced by different agents, and that outcomes varied from full recovery to fatal consequences. Recovery from DRESS was reported for all our six patients and the median time of hospitalization was 33 days; all

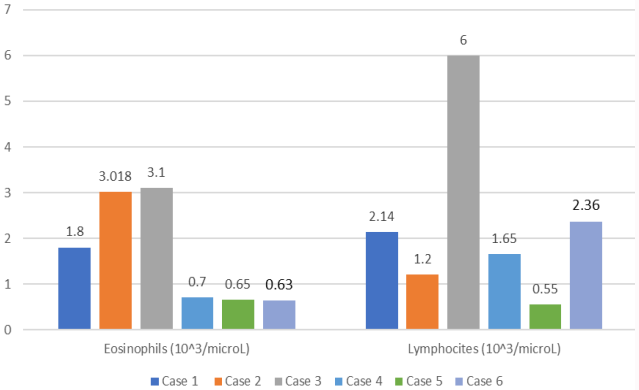

Figure 1: Hematological features of the patients included in our case series.

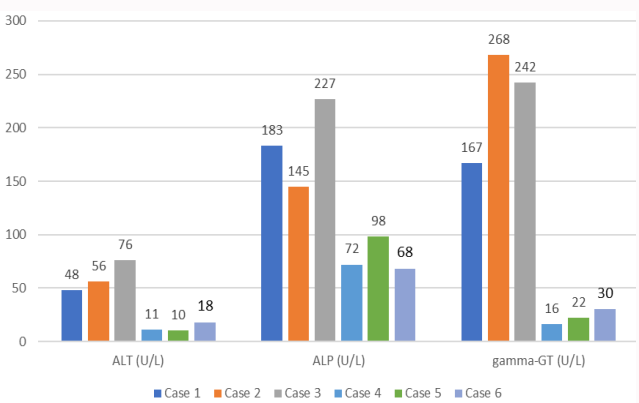

Figure 2: LFT abnormalities of the patients included in our case series.

Table 1: Clinical description of our clinical cases according RegiSCAR criteria.

	Case 1 2019	Case 2 2017	Case 3 2012	Case 4 2018	Case 5 2019	Case 6 2019
Age	77	81	79	77	60	53
Sex	Female	Female	Female	Female	Female	Female
Suspected Drug	Allopurinol	Phenobarbital	Allopurinol	Allopurinol Acetaminophen	Allopurinol	Allopurinol
Lenght of Tx	30 days	65 days	21 days	3 days	90 days	5 days
Latency	20 days	60 days	14 days	7 days	27 days	3 days
Skin rash	Erythematous, maculopapular exfoliative	Erythematous, maculapapular, desquamative	Erythematous, maculopapular,desquamative	Erythemato-Desquamative	Erithema; exanthema; exfoliative	Exfoliative-desquamative
Organ involvement	Liver; Kidney; Lungs	MOF	Liver; Kidney	none	MOF	
Liver injury	Cholestatic	Cholestatic	Cholestatic	-	Cholestatic	
Fever	+	+	+	-	+	
Enlarged lymphonodes	+	+	+	-	+	
Hypereosinophilia	+	+	+	-	+	+
RegiSCAR criteria	6/7	6/7	5/7	1/7	6/7	2/7
Naranjo Score	6	6	6	3	2	4
Lenght of hospital stay	40 days	62 days	64 days	21 days	28 days	10 days
Viral reactivation	CMV	None	CMV, EBV, HSV-6	None	None	None
Corticosteroid use	+	+	+	+	+	+
Outcome	Dress recovery, pneumonia and death	Dress recovery sepsis endocarditis death	DRESS recovery, arrhythmia death	Recovery	Dress recovery, sepsis endocarditis, death	Recovery

patients underwent steroid therapy. However, despite DRESS recovery, four elder patients developed septic complications, leading to a fatal outcome. The classic manifestation of DRESS syndrome is a skin rash, which was present in the majority of our reported cases. It commonly starts as a non-specific measles-like eruption but can progress to infiltrative and confluent papules and plaques changing to purpura and even to generalized forms or erythroderma. When the rash resolves, fine desquamation is common. Facial edema is an important diagnostic feature. There are also hematological abnormalities and internal organ involvement. Among the hematological changes, atypical lymphocytes and hypereosinophilia, found both in blood and tissues, are the most common. In our cases, hypereosinophilia was present in almost all the patients at clinical onset, and a full hematologic recovery was observed after steroid treatment. No significant abnormalities were detected in lymphocyte count (Figure 1). However, some studies have revealed decreased numbers of lymphocytes with hypogammaglobulinaemia in the early phase of the disease [2,9,13]. Atypical lymphocytosis was not present in our cases. Several internal organs may be damaged, mainly the liver and kidneys. Drug-Induced Liver Injury (DILI) is a rare adverse reaction with various clinical manifestations, from jaundice to liver failure, and may even be fatal. The currently available data of DILI associated with SCARs come from retrospective cohort studies [3,14-23] (Table 2). Usually, DILI occurs without manifestations of hypersensitivity, but it may also present during a more generalized immunoallergic syndrome, in which cutaneous manifestations are the most prominent clinical features [24,25]. Several studies have reported that icteric forms of liver injury seen in DRESS syndrome are associated with a worse prognosis than other SCARs (anicteric forms). Among our reported cases, four patients had liver involvement, which was mostly cholestatic (Figure 2). According to the current literature, patients with DILI have a longer period of hospitalization than those without, the occurrence of liver injury is higher in patients over 65 and a cholestatic pattern is the most frequent [16,26], although hepatocellular and mixed patterns have also been observed, particularly in patients with a pre-existing liver disease [18,27,28]. None of our patients had known liver diseases. The role of pre-existing liver disease in DILI is controversial. Two retrospective cohort studies performed in Australia and Taiwan seem to rule out a previous viral Hepatitis B (HBV) or Hepatitis C (HCV) infection as a possible risk factor for DILI, whereas patients with HIV/AIDS seem to have an increased risk, presenting Stevens-Johnson Syndrome/Toxic Epidermolysis Necrosis (SJS/TEN) [14,27,29]. In addition, recurrent elevation of liver enzymes, even without a skin rash or fever, is often related to atypical lymphocytosis and to Herpes Virus (HHV) reactivation [27]. Renal involvement occurs in some patients and usually presents with increased serum creatinine and proteinuria levels [2]. Drug-induced kidney damage has been reported mostly in older patients, or in subjects with chronic renal failure, or when allopurinol is the culprit drug. In fact, underlying renal impairment increases the clearance of oxypurinol, an allopurinol metabolite: raised serum levels have been found to correlate with a higher risk of developing the toxicity syndrome [30,31]. Renal involvement is usually mild and resolves without sequela, but, in some cases, interstitial nephritis or tubular necrosis may develop, leading to renal failure and death. Four of our patients showed kidney involvement, and increased creatinine serum values (>2 mg/dL) were detected during hospitalization, worsening the patients 'outcome. Other visceral organs can be involved in DRESS syndrome. Pulmonary involvement could present as interstitial pneumonitis, pleuritis, Acute Respiratory Distress Syndrome (ARDS). The presence of comorbidities and previous lung diseases may be a risk for lung damage. In our series, three patients developed involvement of the lungs, reported as pulmonary masses at CT scan,

Table 2: Retrospective studies addressing DRESS syndrome and DILI in a literatures review.

Ref	Years	Sex	Age	Drug	Underlying condition	PLD	Indication for therapy	Latency (days)	Pattern	TX	Outcome
Our cases	2012-2019	F	77	Allopurinol	Arterial hypertension, glaucoma, osteoporosis, hypomobility syndrome	No	Hyperuricemia	20	Cholestatic	Methyl-prednisolone	DRESS recovery, died of pneumonia
		F	81	Phenobarbital	Arterial hypertension, diabetes, epilepsy	No	epilepsy	60	Cholestatic	Methyl-prednisolone	DRESS recovery, died of sepsis
		F	78	Allopurinol	Arterial hypertension, GERD, hiatal hernia, diabetes, glaucoma	No	Hyperuricemia	14	Cholestatic	Methyl-prednisolone	DRESS recovery, onset of arrhythmia
		F	77	Allopurinol and acetaminophen	Erythematous-desquamative dermatosis, atrial fibrillation, chronic heart disease,metabolic syndrome (Type II diabetes, Arterial hypertension	No	Hyperuricemia	7	NR	corticosteroid and antihistamine	Recovery
		F	60	Allopurinol	arterial hypertension, type 2 Diabetes Mellitus, renal failure, dyslipidemia and hyperuricemia	No	Hyperuricemia	27	Cholestatic	Methyl-prednisolone	DRESS recovery, died of sepsis
		F	53	Allopurinol	severe obesity, cor pulmonale, arterial hypertension	No	Hyperuricemia	3	NR	Steroids	Recovery
Oberlin et al. [15]	2013-2018	M6 (60%) F4 (40%)	11.5	Lamotrigine (3) Trimethoprim-sulfamethoxazole (3) Ceftriaxone (1) Cefdnir, azithromycin (1) Carbamazepine (1) Piperacillin-tazobactam, cefepime, vancomycin (1)	Bipolar disorder, anxiety, ADHD (3) Acne vulgaris, hyperhidrosis (2) Brain abscess, sinusitis (1) Hypoplastic left heart syndrome (1) Mood disorder (1) Crohn's disease (1) Femur fracture (1)	No	Bipolar disorder (3) Acne vulgaris (2) Brain abscess (1) Hypoplastic left heart syndrome (1) Mood disorder (1) Crohn's disease (1) Femur fracture (1)	26.3-29.8	NR	Steroids	Recovery Hashimoto's disease (1) Undifferentiated connective tissue disorder (1)
Sanader et al. **[16]**		M (1) F (2)	66.3	Clozapine (3)	Chronic paranoid schizophrenia (2), Schizoaffective disorder, arterial hypertension, diabetes (1)	No	Acute exacerbation of a chronic paranoid schizophrenia (2) Schizoaffective disorder (1)	26	Cholestatic (1)	Prednisolone (2) Supportive therapy (1)	Recovery (2)
Han XD et al. [20]	2006-2016	M(6) 60% F(4) 40%	11.2 (4-17)	Trimethoprim-Sulfamethoxazole (3) Carbamazepine (2) Phenobarbitone (2) Sulfasalazine (1) Amoxicillin-clavulanic acid (1) Levetiracetam (1)	NR	NR	NR	19.6 (5-42)	NR	Steroids	Recovery
Fang et al. [27]	2004-2014	(pz with DILI=33) 57.7% M	55 (45-66)	Cephalosporins (8), Vancomycin (7), Penicillins (6), Nevirapine (3), Trimethoprim/ Sulfamethoxazole (3), Lamotrigine (2), Phenytoin (2)	NR	HCV (4), HIV (3), alcohol (3), CLD (2)	NR	ND	23 (69.7%) mixed/ cholestatic, 10 (30.3%) hepatocellular	NR	Recovery (64%) ALF (2) Death (1)
Chua GT et al. [17]	2006-2018	M (1) 25% F(3) 75%	12.2	Doxepin and famotidine, Amoxicillin-clavulanate (1) Carbamazepine (1) Co-trimoxazole (2)	Chronic urticaria and asthma (1) Complex congenital heart disease status-post surgical repair complicated by subsequent left-sided stroke and focal seizures (1) juvenile idiopathic arthritis and IgG2 deficiency (1)	No	Urticarial (1) Focal seizures (1) Salmonella paratyphi A septicaemia (1) Tonsillitis (1)	NR	Cholestatic (3)	Methyl-prednisolone (4) Intravenous immunoglobulin (IVIG) (3)	Recovery (3) Death (1)
Kirchhof M G et al. [18]	2013-2014	F(1) 50% M(1) 50%	35.5	Carbamazepine (1) Minocycline (1)	Paraplegia, chronic renal dysfunction, and seizure disorder (1)	No	Seizure disorder (1) Folliculitis(1)	10	Hepatocellular (1)	Cyclosporine (2)	Recovery (100%)
Hiransuthikul et al. [21]	2004-2014	F 37 (71%) M 15 (29%)	33 (2-86	Phenytoin (12) Nevirapine (9) Allopurinol (8) Cotrimoxazole (7)	HIV (15) Convulsion disorder (12) Hypertension (13) Dyslipidemia (9) Diabetes mellitus (8) Hyperuricemia (8) Chronic kidney disease (4) Others (13)	NR	NR	16 (9-27)	ND	Steroid, iv or oral prednisolone, was administered to 30 patients (57.7%). Forty-nine patients (94.2%) received antihistamine	Recovery (96.1%) ALF/death (1) Death (2)
Lin et al. [26]	2000-2013	F 34 (47.2%), M 38 (52.8%)	49 (6-88)	Allopurinol (15) Phenytoin (10) Sulfonamides/ sulfones (13) Dapsone (8) Carbamazepine (7)	NR	HBV infection (3), HCV infection (3)	NR	ND	Cholestatic type 23 (37.1%), mixed type 17 (27.4%), hepatocellular type 12 (19.4%)	Steroids	Recovery
Skowron et al. [22]	2005-2013	F25 (55%) M 20 (45%)	64 (3-87)	Antibiotics (23) Antiepileptics (5) Allopurinol (5)	NR	NR	NR	ND	NR	NR	Recovery (93%) Death (6%)

Su et al. [23]	2007-2011	F 21 (50%) M(50%)	51.8 (11-94)	Antibiotics (21) Allopurinol (6) Anti-epileptic drugs (5) NSAID (4) Others (7)	Cardiovascular disease (21) Diabetes Mellitus (8) Chronic kidney disease (7) Stroke disease (3) Psychiatric disorders (4) Malignancies/hematological disorders (6) Chronic infections (3)	HBV infection (1)	NR	22.5 (15-30)	NR	Sistemic steroids (85.7%) IVIG (19%)	Recovery (100%)
Lee et al. [29]	2008-2011	F28 (46%), M 33 (54%)	53	Beta-lactam (7) Allopurinol (3) Sulfonamide (2) Anticonvulsants (2)	NR	NR	NR	22.5	NR	NR	Recovery (88%) Death 7
Ang et al. [19]	2003-2008	M 12 (44%) F 15 (66%)	50.6	Allopurinol (6) Phenytoin (5) Carbamazepine (4) Pyrimethamine and dapsone (4) Trimethoprim-sulfamethoxazole (4) Sulfasalazine (1) Ciprofloxacine-metronidazole (1) Metformin (2) Tolterodine tartrate, nifedipine and atenolol (1)	NR	NR	NR	26.7 (3-84)	NR	92.6% systemic (IV or oral) 7,4% topical steroids only	Recovery (100%). Three patients residual renal impairment. One patient myocarditis with impaired myocardial function and thyroiditis requiring propylthiouracil

and it was associated with a worse clinical outcome. In their literature review, Cacoub found that lung involvement was rare, reporting it in only 5% of cases [3]. Cardiac complications may include myocarditis or atrioventricular block. In our case series, no cardiac damage was reported. Although cardiac involvement in DRESS syndrome is rarely reported, it is associated with a high mortality rate. Intarasupht described a 19.5% prevalence of cardiac complication, but they also suggested a more precise cardiac evaluation should be made in patients with a higher probability of having DRESS syndrome, according to RegiSCAR [32]. Neurological symptoms include headache, seizures, coma and motor function impairment [2,9]. None of our patients developed central nervous system involvement. This finding is consistent with the current literature; Cacoub found that neurological involvement was rare, present in 2% of cases [3]. In our case series of elder women, the clinical onset of symptoms occurred between 3 and 27 days after intake of the culprit drug. These data are supported by the current literature [15,16,18-20,23,29]. Most of our patients received the culprit drugs for a period between 1 day and 1 month, and this time lapse can be considered suggestive, when assessing the causality of delayed hypersensitivity reactions. De-challenge was positive in most cases, while re-challenge was not performed. The hypersensitivity reactions were predominant in female patients, as described [10]. The potential mechanism of drug-associated damage is still unknown, but it seems to be related to a strong, drug-specific immune response. Evidence shows that DRESS syndrome occurs in genetically predisposed people when they take the culprit drug. In our reported cases, all patients were female, as observed in recent studies [17,19,21,22]. Female sex has been demonstrated to be a higher risk factor of developing ADR than male sex, probably because of differences in pharmacokinetics and pharmacodynamics. Furthermore, females have a greater percentage of body fat, which can affect the distribution of some drugs. Activity levels of hepatic enzymes, such as Cytochrome P450 (CYP) and Uridine Diphosphate Glucuronosyltransferase (UGT), or transporters are lower in females. Moreover, autoimmune diseases and drug-induced rashes appear to be more frequent in females, probably because sex hormones, particularly estrogens, can influence the course of autoimmune diseases [33]. Drugs or their metabolites accumulate due to the altered activity of metabolizing enzymes, because of cross-reactivity or neo-sensitization phenomena. Furthermore, many studies have shown the involvement of drug-specific T lymphocytes in subjects with genetic background [2]. Positive patch test reactions and *in vitro* lymphocyte proliferation assays support an expansion of activated T lymphocyte (both CD8 and CD4 cells) in the blood during the acute phase of disease [33,34]. Indeed, it has been demonstrated that patients with DRESS present immune system disorders, probably induced by the drug, which reactivate some herpetic viruses such as HHV-6, HHV-7, CMV, EBV [6,8]. The mechanism underlying HHV-6 reactivation is still unknown but accomplishes two different mechanistic approaches, the direct effect of drugs and the role of a cytokine storm leading to a massive anti-viral response, which contributes to DRESS development [2]. Even though HHV reactivation is a "non-essential DRESS manifestation", it could be an aggravating factor in its course [34]. In our case series, two patients presented CMV reactivation, and they had poor outcomes, leading to major complications. The high frequency of allopurinol-related reactions, as reported in our cases, reflects the prescription of this drug in the general population, but it may also be related to the prevalence of some predisposing HLA-haplotypes in susceptible patients. HLA-B*58:01 is strongly associated with allopurinol-induced DRESS syndrome in Chinese and Portuguese populations [6], while HLA-A*31:01 has been associated with carbamazepine-induced DRESS syndrome in European populations [7,28]. A limitation of our study is the lack of HLA typing of our patients, as usually happens in a retrospective cohort study. Allopurinol is the most common cause of SJS/TEN in Europe and Israel and the second most common cause of DRESS in Europe, Israel, and Taiwan, according to EuroSCAR and Taiwan National Health Insurance Research Database registry data. Recent data support a treat-to-target serum urate strategy with a gradual dose escalation of allopurinol, under appropriate monitoring, in individuals established on allopurinol who do not experience adverse effects, including those with chronic kidney disease [27].

Conclusion

DRESS syndrome is an unusual adverse drug reaction mainly due to allopurinol, and internists which commonly prescribing this drug, should be aware of its potential risk especially in elder women. All suspected cases should be reported to the National Pharmacovigilance Service to upgrade epidemiology and clinical knowledge. Caution

would be recommended when using allopurinol as a treatment for asymptomatic hyperuricemia. Careful evaluation should also be advised to avoid an unfavorable and poor outcome in elder women with chronic kidney disease and at cardiovascular risk, as well as in those on poly-pharmacotherapy.

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