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Fluconazole-induced drug rash with eosinophilia and systemic symptoms syndrome: a case report

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Abstract

Background Drug rash with eosinophilia and systemic symptoms syndrome is a severe T-cell-mediated adverse drug reaction characterized by a skin rash, fever, hematologic abnormalities, and internal organ involvement following prolonged exposure to a causative medication. Drugs associated with drug rash with eosinophilia and systemic symptoms syndrome include anticonvulsants, allopurinol, antibiotics, and nonsteroidal anti-inflammatory drugs. Fluconazole is an exceedingly rare cause of drug rash with eosinophilia and systemic symptoms syndrome, with only one previously reported case in abstract form. We present a case of a woman with pulmonary coccidioidomycosis who developed fluconazole-induced drug rash with eosinophilia and systemic symptoms syndrome, presenting with an unusual clinical feature.

Case presentation A 19-year-old Hispanic woman was taking fluconazole for pulmonary coccidioidomycosis. A total of 30 days after starting fluconazole, she developed a generalized skin rash. Despite this, she continued taking the medication. Then 1 week later, she experienced facial swelling and a sensation of "throat closing." She also developed fever, axillary lymphadenopathy, eosinophilia, atypical lymphocytes, and hepatitis. Fluconazole was discontinued, and she was treated with intravenous methylprednisolone, which led to an overall improvement in her condition. During hospitalization, her antifungal therapy was switched to posaconazole. However, within 24 hours, she again experienced the "throat closing" sensation, which was relieved with an epinephrine injection. The patient was discharged on Day 6 with oral methylprednisolone. Again, 9 days after discharge, her symptoms recurred, including facial swelling and new skin rashes. She was readmitted and treated with famotidine, corticosteroids, and diphenhydramine. Her general condition and skin rashes gradually improved, with complete resolution of the rash 3 months after the initial eruption.

Conclusion We present a case of a woman with pulmonary coccidioidomycosis who developed drug rash with eosinophilia and systemic symptoms syndrome induced by fluconazole. Our case meets Bocquet's diagnostic criteria and is categorized as "definite" drug rash with eosinophilia and systemic symptoms by the Registry of Severe Cutaneous Adverse Reactions. Drug rash with eosinophilia and systemic symptoms syndrome is a T-cell-mediated type IV hypersensitivity reaction; however, our patient also exhibited a unique symptom—a sensation of "throat closing"—suggestive of angioedema and a Type I hypersensitivity component. This symptom appeared while she continued fluconazole after the onset of drug rash with eosinophilia and systemic symptoms syndrome and recurred upon the initiation of posaconazole. Although both fluconazole and posaconazole belong to the triazole antifungal

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class, true allergic cross-reactivity medicated by IgE is rare probably due to their structural differences. This suggests cross-reactivity may occur even with structurally unrelated drugs in drug rash with eosinophilia and systemic symptoms syndrome. Clinicians managing suspected cases of drug rash with eosinophilia and systemic symptoms syndrome should promptly discontinue the offending drug and exercise caution when prescribing alternative medications to minimize the risk of further hypersensitivity reactions.

Keywords DRESS syndrome, Fluconazole, Drug-induced hypersensitivity syndrome

Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening adverse drug reaction characterized by a skin rash, fever, hematologic abnormalities, and visceral organ involvement, including the liver, kidneys, lungs, and heart, with a latency period of 2–6 weeks [1–4]. The drugs most commonly associated with DRESS syndrome include anticonvulsants, allopurinol, antibiotics, and nonsteroidal anti-inflammatory drugs [1–4]. Although speculative, its pathogenesis involves a complex interplay between drugs, viruses, genetic factors, and the T-cell-mediated immune system [1–4]. Given the high mortality rate of DRESS (5–10%) [1, 5], prompt diagnosis and treatment are critical.

Three sets of diagnostic criteria have been proposed by various dermatology groups [5–8]: Bocquet (Table 1), the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) (Table 2), and the Japanese Research Committee on Severe Cutaneous Adverse Reactions (J-SCAR) (Table 3).

Discontinuation of the suspected offending drug and initiation of systemic corticosteroids remain the first-line treatment [1, 3, 4]. Fluconazole, a commonly prescribed triazole antifungal agent, rarely causes cutaneous drug hypersensitivity reactions, such as Stevens–Johnson syndrome or fixed-drug eruption [9]. However, reports of fluconazole as a causative agent in DRESS syndrome are extremely rare, with only one previous case described in abstract form, lacking sufficient diagnostic detail to confirm the diagnosis of DRESS [10]. Here, we report a case of fluconazole-induced DRESS syndrome presenting with an unusual symptom, further emphasizing the need for awareness of this potentially life-threatening adverse reaction.

Table 1 Bocquet's criteria for drug reaction with eosinophilia and systemic symptoms syndrome [5]

1. Skin eruption
2. Eosinophilia (> 1.5 × 103/μL) or the presence of atypical lymphocytes
3. Internal organ involvement:
(a) Lymphadenopathies (> 2 cm in diameter); or
(b) Hepatitis (liver transaminases values > twice the upper normal limit); or
(c) Interstitial nephritis; or
(d) Interstitial pneumonia; or
(e) Carditis

Diagnosis of DRESS syndrome requires all 1–3 features

Case presentation

A 19-year-old Hispanic woman was taking fluconazole 400 mg daily for pulmonary coccidioidomycosis. The diagnosis was based on symptoms of cough and fever, positive serology for *Coccidioides* IgM and IgG immunodiffusion, a complement fixation (CF) titer of 1:8, and a cavitary lingular infiltrate observed on chest X-ray.

A total of 30 days after starting fluconazole, she developed a pruritic and painful morbilliform skin rash on the abdomen, which progressed to the face, trunk, and upper and lower extremities. She visited an urgent care center, where she received an intramuscular injection of diphenhydramine and a prescription for acyclovir, which she did not fill. She continued taking fluconazole.

Then, 1 week after the onset of the skin rash, she developed facial swelling and a sensation of "throat closing," prompting a visit to another primary care clinic. There, she received intramuscular epinephrine (0.3 mg), diphenhydramine (50 mg), and prednisolone (50 mg) before being transferred to the emergency room (ER). In the ER, her temperature was 38.5 °C (oral), pulse 125 beats per minute, respiratory rate 18 breaths per minute, and blood pressure 94/63 mmHg. She received an additional intramuscular dose of epinephrine (0.3 mg) and intravenous methylprednisolone (60 mg) and was subsequently admitted. Fluconazole was discontinued.

Initial laboratory test findings

On admission (Day 1), laboratory tests (Table 4) showed an absolute eosinophil count (AEC) of 1.5×10^9/L. The eosinophil counts increased and peaked on Day 6 (AEC: 9.7×10^9/L), then gradually decreased and normalized by Day 25. Atypical lymphocytes also increased to 2% on Day 6. A peripheral blood smear revealed a marked increase in eosinophils and occasional atypical lymphocytes (Fig. 1). The chemistry panel showed normal renal function. Liver function remained normal until Day 4, when alanine transaminase (ALT) and aspartate transaminase (AST) levels began to rise. By Day 6, ALT and AST

Table 2 Registry of Severe Cutaneous Adverse Reactions scoring system [6]

Criterion	Score -1	Score 0	Score +1	Score +2
Fever >38.5°C	No/U	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia			0.7-1.499 x 109/L	>1.5 x 109/L
(Eosinophilia in case of WBC <4 x 109/L)			10-19.9%	≥20%
Atypical lymphocytes		No/U	Yes	
Skin rash				
(Extent >50% BSA)		No/U	Yes	
(Skin rash suggesting DRESS)	No	U	Yes	
(Biopsy suggesting DRESS)	No	Yes/U		
Organ involvement				
(Liver, kidney, heart, pancrease, etc)		No/U	Yes =1 organ	Yes ≥2 organs
Resolutio ≥15 days	No/U	Yes		
Evaluation of other cuases*			If ≥3 are negative	

Total score: −4 to +9

Final score < 2: No case

2–3: Possible case

4–5: Probable case

≥ 6: Definite case

U, unknown; BSA, body surface area; HAV, hepatitis A; HAV, hepatitis B; HCV, hepatitis C

* ANA; blood culture; serology for HAV, HBV and HCV; chlamydia/mycoplasma

Table 3 Diagnostic criteria for drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome by the Japanese Research Committee on Severe Cutaneous Adverse Reactions [8]

1. Maculopapular rash developing > 3 weeks after starting with a limited number of drugs
2. Prolonged clinical symptoms after discontinuation of the causative drug
3. Fever (> 38 °C)
4. Liver abnormalities (ALT > 100 U/L)*
5. Leukocyte abnormalities (at least one present)
   a. Leukocytosis (> 11×10^9/L)
   b. Atypical lymphocytosis (> 5%)
   c. Eosinophilia (> 1.5×10^9/L)
6. Lymphadenopathy
7. HHV6 reactivation

The diagnosis is confirmed by the presence of the seven criteria above (typical drug-induced hypersensitivity syndrome) or of five (1–5) of the seven (atypical drug-induced hypersensitivity syndrome)

* This can be replaced by other organ involvement, such as renal involvement

Table 4 White blood cell count with differentials

	WBC (cell × 10^9/L)	ANC (cell × 10^9/L)	AEC (cell × 10^9/L)	ALC/AMC (cell × 10^9/L)	Atyp Lymph (cell × 10^9/L)
Day 1	13.8	9.1	1.5	1.7/1.5	
Day 2	18.3	11.7	1.6	3.2/0.9	1%
Day 3	22.0	15.4	3.3	3.1/0.2	
Day 4	25.5	15.4	5.1	2.8/0.8	
Day 5	23.2	13.2	9.5	3.5/0.7	
Day 6	29.3	12.3	9.7	6.2/1.2	2%
Day 15	23.7	9.5	9.5	4.3/0.2	
Day 16	17.2	8.3	5.3	2.4/1.0	
Day 25	21.6	3.3	0	1.6/1.8	

WBC, white blood cell; ANC, absolute neutrophil count; AEC, absolute eosinophil count ;

ALC, absolute lymphocyte count; AMC, absolute monocyte count; Atyp Lymph, atypical lymphocytes

peaked at 100 U/L and 48 U/L, respectively, before gradually decreasing and returning to normal by Day 15.

Other laboratory tests showed negative human immunodeficiency virus (HIV)-1 and HIV-2 antigen/antibody results, a negative molecular test for mycoplasma, and non-reactive hepatitis B and C serology. Blood cultures were negative. Antinuclear antibody (ANA) was positive at 1:320 (nuclear speckled pattern), but rheumatoid factor and double-stranded DNA antibody were negative.

Viral serology tests performed on Day 6 showed a cytomegalovirus (CMV) IgM level of < 30.00 AU/mL and an

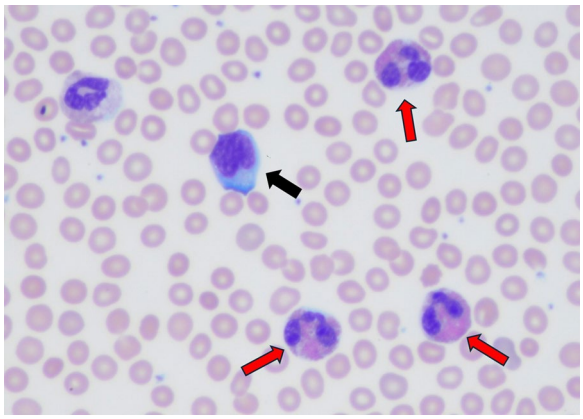

Fig. 1 Increased circulating eosinophils (red arrows) and an atypical lymphocyte (black arrow)

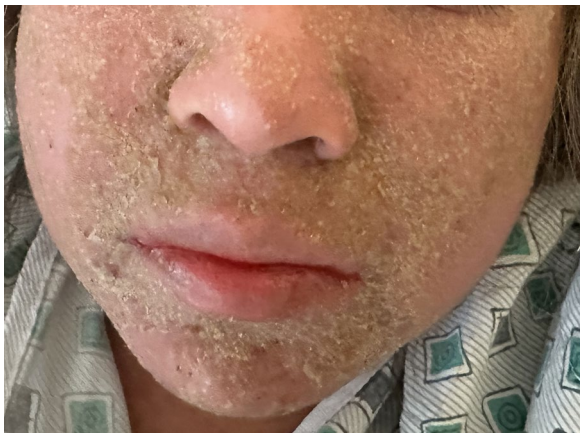

Fig. 2 Exfoliative dermatitis and facial swelling

IgG level of 1.10 AU/mL. Epstein–Barr virus (EBV) viral capsid antigen (VCA) IgM was < 36.00 units/mL, IgG was 47.50 units/mL, and Epstein–Barr nuclear antigen (EBNA) IgG was < 18.00 units/mL. Polymerase chain reaction (PCR) testing for human herpesvirus (HHV)-6 and HHV-7 DNA was negative. However, serial IgM and IgG measurements for HHV-6 were not performed.

Clinical course and recurrence of drug rash with eosinophilia and systemic symptoms

She was administered a single dose of posaconazole 300 mg on Day 4 of hospitalization due to concerns regarding her coccidioidomycosis infection. Initially, she did not experience any adverse reactions. However, on the following day (Day 5), she developed a recurrence of the "throat closing" sensation. She was treated with intravenous epinephrine (0.3 mg), hydrocortisone (195 mg), and diphenhydramine (50 mg), which alleviated her symptoms. Despite this, her skin rashes persisted.

A hematology consultation was requested on Day 5 of hospitalization due to eosinophilia (9.5×10^9/L). On physical examination, she exhibited facial swelling with erythematous, scaling skin rashes consistent with exfoliative dermatitis (Fig. 2). Additional findings included coalesced maculopapular rashes on the extremities (Figs. 3 and 4), trunk, and back, covering approximately 80% of her body surface area, as well as enlarged bilateral axillary lymph nodes (2.0 cm on the right and 1.5 cm on the left). No mucosal blisters were observed in the mouth.

The patient's general condition improved, and the skin rashes began to fade despite persistent eosinophilia. She was discharged from the hospital on Day 6 with a prescription for a methylprednisolone dose pack, topical triamcinolone 0.025%, and hydroxyzine 50 mg. The methylprednisolone dose pack was prescribed as follows:

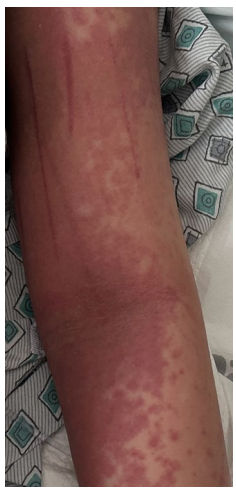

Fig. 3 Coalesced maculopapular sking rashes on the arm with scratch marks indicating severe itching

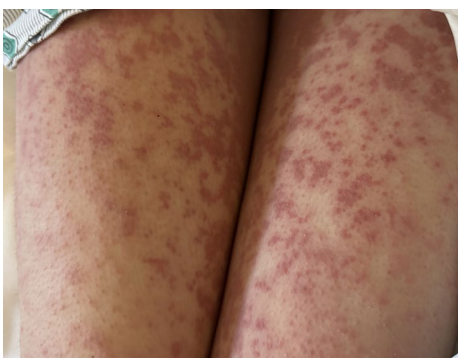

Fig. 4 Maculopapular rashes on the thighs

six tablets (4 mg each) on Day 1, five tablets on Day 2, four tablets on Day 3, three tablets on Day 4, two tablets on Day 5, and one tablet on Day 6. Although her skin rashes persisted, they continued to improve gradually.

However, 9 days after discharge (Day 15 after initial admission), she developed new erythematous maculopapular rashes in addition to the fading lesions, accompanied by left cervical tender lymphadenopathy, facial swelling, and a headache. She was readmitted to the hospital through the ER. During this second hospitalization, she was treated with intravenous methylprednisolone, diphenhydramine, and famotidine. Her condition improved, and she was discharged 2 days later with another oral methylprednisolone dose pack. Her general condition and skin rashes continued to improve gradually, with complete resolution of the skin lesions occurring three months after the initial eruption.

Follow-up and laboratory tests

A total of 3 months after her initial presentation, *Coccidioides* serology showed negative IgM, positive IgG, and a CF antibody titer of < 1:2. The ANA titer was 1:320 with a nuclear speckled pattern. At 6 months, her HHV-6 IgM was < 1:20, and HHV-6 IgG was 1:80. Since initial serology studies for HHV-6 were not performed, HHV-6 reactivation could not be determined. EBV-VCA IgM was < 36.00 U/mL, EBV-VCA IgG was 73.20 U/mL, and EBV-EBNA IgG was < 18.00 U/mL. CMV IgG was 2.90. The ANA titer at 6 months was 1:80 with a nuclear speckled pattern. A total 6 months after her first hospitalization, the patient reported feeling well, with no skin rashes, cough, arthralgia, or signs of autoimmune disease.

Discussion

DRESS syndrome is a life-threatening hypersensitivity reaction characterized by maculopapular or morbilliform exanthema, fever above 38 °C, hematologic abnormalities such as eosinophilia, atypical lymphocytosis, and leukocytosis, as well as visceral organ involvement. Symptoms typically appear 2–6 weeks after the initiation of the offending drug [1–3], though shorter latency periods have been reported with beta-lactams and vancomycin [11]. The drugs most commonly associated with DRESS syndrome include anticonvulsants, allopurinol, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs) [1–4].

DRESS syndrome is a T-cell-mediated type IV hypersensitivity reaction, triggered by a complex interplay of drugs, viruses, genetic factors, and immune activation [1–4]. Japanese researchers have demonstrated the sequential reactivation of herpesviruses during the clinical course of DRESS, including HHV-6, HHV-7, EBV, CMV, and varicella-zoster virus [4, 13]. However, DRESS syndrome associated with coccidioidomycosis infection has not been previously reported. While immunopathogenesis is not fully understood, T-cell activation and cytokine release are believed to play a central role [1].

Visceral involvement

Unlike other severe cutaneous drug reactions, internal organ involvement leading to high mortality is a unique feature of DRESS syndrome. While the liver is the most commonly affected internal organ, virtually every other visceral organ can be involved, potentially resulting in esophagitis, gastritis, enteritis, colitis, pancreatitis, and late autoimmune sequelae due to pancreatic injury, such as type 1 and type 2 diabetes mellitus [12].

With the exception of the liver, gastrointestinal organs are rarely the sole visceral manifestations of DRESS syndrome. Instead, they typically occur as part of multiorgan involvement, which has been associated with a higher mortality rate (15.7%) than previously reported [12].

Diagnostic challenges in DRESS syndrome

The diagnosis of DRESS syndrome is challenging due to its broad spectrum of clinical presentations, prolonged latency, and the absence of a specific diagnostic test [1–4]. Three sets of diagnostic criteria for DRESS syndrome have been proposed by different dermatology groups: Bocquet, the RegiSCAR, and the J-SCAR [5–8]. Each has its own limitations and flaws [14]. Notably, the J-SCAR criteria include HHV-6 reactivation as an essential feature [8]. Clinicians often face difficulties in selecting the appropriate set of diagnostic criteria, which may lead to potential diagnostic inaccuracies.

For example, in a comparative analysis of the RegiSCAR and J-SCAR criteria for atypical drug-induced hypersensitivity syndrome (DiHS)/DRESS, the J-SCAR criteria demonstrated reduced sensitivity in diagnosing definite or probable DRESS [15]. The Spanish guidelines recommend the RegiSCAR criteria due to their broader applicability [16]. Misapplication of these diagnostic flowcharts may result in errors, as seen in the RegiSCAR study [7], where 41% of 201 potential cases were not validated as probable or definite DRESS (27 patients were categorized as "no cases" and 56 as "possible" cases). Similarly, Cacoub *et al.* [17] found that 28% (48 out of 172 cases) of published DRESS reports did not meet the criteria for "probable" or "definite" DRESS when reassessed using the RegiSCAR criteria.

Our patient met Bocquet's diagnostic criteria and was categorized as having "definite" DRESS according to the RegiSCAR criteria, with a score of 8. We did not use the J-SCAR criteria due to the lack of information regarding HHV-6 viral reactivation in this case.

Unique clinical feature

This case is unique due to the patient's "throat closing" sensation, indicative of angioedema. While DRESS syndrome is typically a type IV (delayed) hypersensitivity reaction mediated by T cells [1, 18], angioedema is characteristic of type I hypersensitivity reactions [19]. In this patient, the symptom developed 1 week after the onset of the skin eruption while she was still taking fluconazole and recurred within 24 hours of initiating posaconazole, another triazole antifungal agent. This suggests possible cross-reactivity between these medications.

Patients with DRESS syndrome often exhibit unexplained cross-reactivity to multiple drugs, even those with distinct chemical structures [4]. This phenomenon underscores the importance of immediately discontinuing the suspected offending drug and exercising caution when prescribing alternative medications. Severe type I hypersensitivity reactions, such as anaphylaxis, are potentially more life-threatening than delayed type IV hypersensitivity reactions, emphasizing the critical need for careful management and monitoring.

Management of DRESS syndrome

The primary treatment for DRESS involves the immediate discontinuation of the offending drug and the initiation of systemic corticosteroids [1, 3, 4]. A gradual taper of glucocorticoids over 6–12 weeks is recommended to reduce the risk of relapse [20]. However, retrospective studies suggest that systemic corticosteroid therapy may increase the risk of relapse, viral reactivation, infectious complications, and autoimmune sequelae [3]. Despite these risks, corticosteroids remain the standard of care due to the high morbidity and mortality associated with undertreated DRESS. In patients with severe visceral involvement, corticosteroids are strongly recommended [12].

For mild cases, topical corticosteroids may be sufficient [21, 22]. Intravenous immunoglobulin (IVIG) is not recommended as monotherapy due to potential adverse effects [23], but it may be beneficial as adjunctive therapy to systemic corticosteroids in refractory cases [3]. A thorough investigation for CMV reactivation is crucial in severe or refractory cases, as CMV reactivation is associated with poor prognosis and high mortality. In such cases, immediate anti-CMV therapy is advised [24].

Steroid-sparing agents such as mycophenolate mofetil, cyclosporine, cyclophosphamide, and monoclonal antibodies (including anti-interleukin-5 agents) have also been reported in the management of DRESS; however, evidence remains limited to case reports and series [1, 3].

Flare-up of DRESS

Relapses or flare-ups of DRESS syndrome frequently occur days to weeks after the withdrawal of the original causative drug [4]. This phenomenon may be attributed to the intake of new drugs that cross-react with the offending agent, even if they have different chemical structures [4], viral reactivation [13], or the rapid discontinuation of corticosteroids [20]. In our patient, symptoms and signs of DRESS recurred 15 days after discontinuation of fluconazole, likely due to the rapid tapering and abrupt discontinuation of steroid therapy. A gradual glucocorticoid taper over the course of 6–12 weeks is recommended to reduce the risk of relapses [20].

Fluconazole and DRESS syndrome

Fluconazole is a widely used anti-fungal agent with a well-documented safety profile. While rare cases of Stevens–Johnson syndrome and fixed drug eruption have been attributed to fluconazole [9], no confirmed reports of fluconazole-associated DRESS syndrome have been identified in the published literature, including PubMed/MEDLINE searches, except for one abstract [10]. However, that abstract lacked the comprehensive clinical and laboratory findings necessary to confirm a diagnosis of DRESS.

Cross-reactivity of drugs in DRESS syndrome

Our patient experienced recurrent symptom of "throat closing· after the intake of posaconazole, which was suggestive of angioedema and a Type I hypersensitivity reaction. Although both fluconazole and posaconazole belong to the triazole antifungal class, true allergic cross-reactivity between these two drugs is rare, as no case reports have been found in the literature (PubMed/Medline), likely due to their differing chemical structures [25]. Instead, there are reports demonstrating a lack of cross-reactivity between fluconazole and posaconazole [26] or other triazole antifungals [27–30].

This suggests cross-reactivity may occur even with structurally unrelated drugs in DRESS syndrome. Therefore, clinicians managing suspected cases of DRESS syndrome should promptly discontinue the offending drug and exercise caution when prescribing alternative medications to minimize the risk of further hypersensitivity reactions. Amphotericin B may be a suitable alternative for invasive fungal disease in cases of fluconazole hypersensitivity [31]. Nevertheless, close and vigilant observation is required when introducing alternative treatments to minimize the risk of further hypersensitivity reactions.

Skin tests (patch and prick) and the lymphocyte transformation test (performed 5–8 weeks after the onset of DRESS) may help identify the offending drug. However, their clinical utility is limited, as these tests are not widely

available and are often informative only when the test result is positive [32].

Conclusion

We report the case of a young woman with pulmonary coccidioidomycosis who developed fluconazole-induced DRESS syndrome, an extremely rare occurrence. In addition to the typical symptoms and signs of DRESS, her case was notable for an unusual "throat closing" sensation, indicative of angioedema and a type I hypersensitivity reaction. The overlap of type I and type IV hypersensitivity reactions in this case underscores the complexity of DRESS syndrome and highlights the importance of prompt drug discontinuation and cautious selection of alternative therapies.

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Author contributions
All three authors contributed significantly to prepare this manuscript. Dr. Stanley Kim (hematology faculty), Mr. Kevin Chen (medical student rotating hematology service), and Dr. Willian Stull (staff pathologist) were involved in patient's care and contributed to writing the manuscript as below: Stanley Kim: Conception, design, data collection, analysis, interpretation of the data and results, direct patient care, drafting, and revising. Kevin Chen: Data collection, analysis, interpretation of the data and results, direct patient care, and drafting. William Stull: Data collection, analysis, interpretation of the data and results, direct patient care, drafting, and revising.

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Availability of data and materials
All supporting data can be found and retrieved from the stored electric medical record of the patient at Kern Medical Center.

Declarations

Ethics approval and consent to participate
This case report was approved by the Institutional Review Board (including ethical approval) at Kern Medical Center, Bakersfield, CA, USA.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
There are no competing interests.

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