CASE REPORT
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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome and Myocarditis: A Case Report and Literature Review on Fatal Complications of Reactivated Viral Infections

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ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a complex and potentially fatal hypersensitivity condition. We present a unique case report and literature review focusing on DRESS syndrome-associated myocarditis resulting from reactivated viral infections in a 21-year-old female.

3 weeks after 5-day oral co-trimoxazole consumption due to acne, she developed symptoms consistent with DRESS syndrome, including a generalized maculopapular rash. Despite prednisolone treatment, the patient developed fatal fulminant myocarditis linked to HHV-6 and CMV reactivation.

The patient's death highlights the importance of early recognition and careful management of DRESS syndrome, especially considering the potential viral reactivation that can lead to severe complications. Postmortem investigations revealed that viral reactivation caused myocarditis. Careful consideration must be given to corticosteroid usage in DRESS treatment, as inappropriate prescribing may promote viral reactivation and subsequent complications.

While high-dose corticosteroids initiated within the first week effectively suppress HHV-6 reactivation. Conversely, low-dose or late-start high-dose corticosteroids prove ineffective in preventing HHV-6 viremia. Late- onset or low- dose corticosteroids may lead to fatal complications following the primary viral reactivation.

Keywords: Cytomegalovirus; Drug hypersensitivity syndrome; Herpesvirus 6, human; Myocarditis; Sulfamethoxazole drug combination; Trimethoprim; Virus latency

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INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe but uncommon drug-

induced hypersensitivity reaction that can potentially be life-threatening. It manifests through various symptoms, including skin eruptions, hematologic abnormalities like eosinophilia and atypical lymphocytosis, lymphadenopathy, and internal organ involvement, particularly affecting the liver, kidney, heart, and lung.[1,2]

One of the defining features of DRESS is its prolonged latency period, typically ranging from two to eight weeks between drug exposure and the onset of the disease. Despite discontinuing the causative drug, DRESS can have a prolonged course with frequent relapses.[3] Additionally, there is often a notable association with the reactivation of latent Herpesviridae family infections during this condition.[4]

While fatal DRESS-myocarditis is typically associated with severe hypersensitivity reactions, we report a unique case of fatal fulminant myocarditis attributed to reactivated viral infections, highlighting the importance of considering viral reactivations in DRESS-related myocarditis.

CASE PRESENTATION

A 21-year-old female patient with an unremarkable medical history and no previous drug or food allergic reaction record was admitted to the hospital due to fever, nausea, and a generalized maculopapular rash.

One month before admission, the patient had been experiencing acne and had started treatment with oral co-trimoxazole (Trimethoprim / Sulfamethoxazole) and clindamycin topical gel. However, after five days, the patient discontinued this treatment without providing any specific reason. Three weeks after treatment discontinuation, maculopapular lesions manifested in the chin area, which spread to the rest of the face. After an additional 2 days, the lesions extended to the rest of the body. Furthermore, erythema and edema developed on the eyelids and lips (Figure 1).

Just before hospitalization, the patient was prescribed 5 mg of Prednisolone daily by a physician in an outpatient setting. However, the patient's condition did not improve, ultimately leading to her inpatient admission. Upon admission and physical examination, the patient's vital signs revealed a body temperature of 38.7°C, blood pressure of 100/70 mmHg, a pulse rate (PR) of 88, and a respiratory rate (RR) of 15. Her oxygen saturation was 98% in room air.

The Nikolsky sign was negative. Erythematous macules and papules were observed throughout her body without bullous lesions. Bilateral lymphadenopathy, measuring approximately 1.5 cm, was palpable in the neck and submandibular angle. The patient's electrocardiogram showed no significant changes.

prescribed 50 mg of Prednisolone for treatment.

Upon admission, the patient's laboratory test results were as follows, keeping in mind that the patient had been on a daily regimen of 5 mg prednisolone for some days before admission: WBC: 11,500 (LYM: 27%, N: 60%, EOS: 6%, atypical LYM: 2%), Hemoglobin: 12 g/dL, Platelet count: 146,000, Blood Urea Nitrogen: 8.2 mg/dL, Creatinine: 1.04 mg/dL, Aspartate Aminotransferase: 61 IU/L, Alanine Aminotransferase: 126 IU/L, C-reactive Protein: 3+ (elevated), Immunoglobulin E (IgE): 815 IU/mL, Antinuclear Antibody Test: Negative.

The patient's RegiSCAR and SCAR-J diagnostic criteria evaluation is presented in the supplementary materials (Supplementary Table 1 and 2). The patient received a definite diagnosis of DRESS syndrome based on RegiSCAR criteria[5] score of 7, and was Three days later, the patient was discharged from the hospital in good general condition and skin lesions improved noticeably. During a follow-up visit one week later, it was observed that the skin lesions had entirely resolved, and the liver function tests (LFT) had returned to the normal range. Theprednisolone dose was reduced to 25 mg and eventually to 12.5 mg. It's noteworthy that myocarditis occurred when the patient was on 12.5 mg reduced dosage.

A week after the dose reduction, the patient experienced shortness of breath, dyspnea, palpitations, and epigastric pain. However, the patient neglected to take these symptoms seriously and did not seek medical attention. Tragically, her condition deteriorated two days later, resulting in cardiogenic shock. She passed away while being transferred to the hospital by Emergency Medical Services.

After the patient's demise, her body underwent a comprehensive investigation in the forensic medicine department. The postmortem evaluation revealed that the heart was three times heavier than its normal weight. Moreover, an atherosclerotic plaque was identified in the carotid artery. Toxicology tests were conducted to ascertain any potential substance involvement, and the results were negative.

The Endomyocardial Biopsy (EMB) results revealed diffuse and intense infiltration primarily of small lymphocytes, accompanied by extensive foci of

myocardial fiber necrosis and degeneration. Furthermore, scattered macrophage infiltration and a limited number of plasma cells were observed, while, eosinophils were absent. Mild pericardial membrane involvement was also noted (Figure 2).

Viral nucleic acid was extracted from paraffin-embedded tissue using the QIAamp DNA Mini QIAcube Kit in a Qiacube instrument (Qiagen, Hilden, Germany) following the manufacturer's protocol. To assess the quality of the genomic extract, the Nanodrop 2000 system (ThermoFisher Scientific, Wilmington, USA) and internal control of the Real-time PCR kits were used. Subsequently, the sample was evaluated for Enterovirus species, adenovirus, HSV-1/2, VZV, EBV, CMV, HHV-6, and HHV-8 by commercial qualitative Real-time PCR kits (HanagGene, Arak, Iran).

PCR analysis of myocardial tissue confirmed the presence of HHV-6 (Cq=29) and CMV (Cq=31) infections, leading to a definitive diagnosis of viral myocarditis.

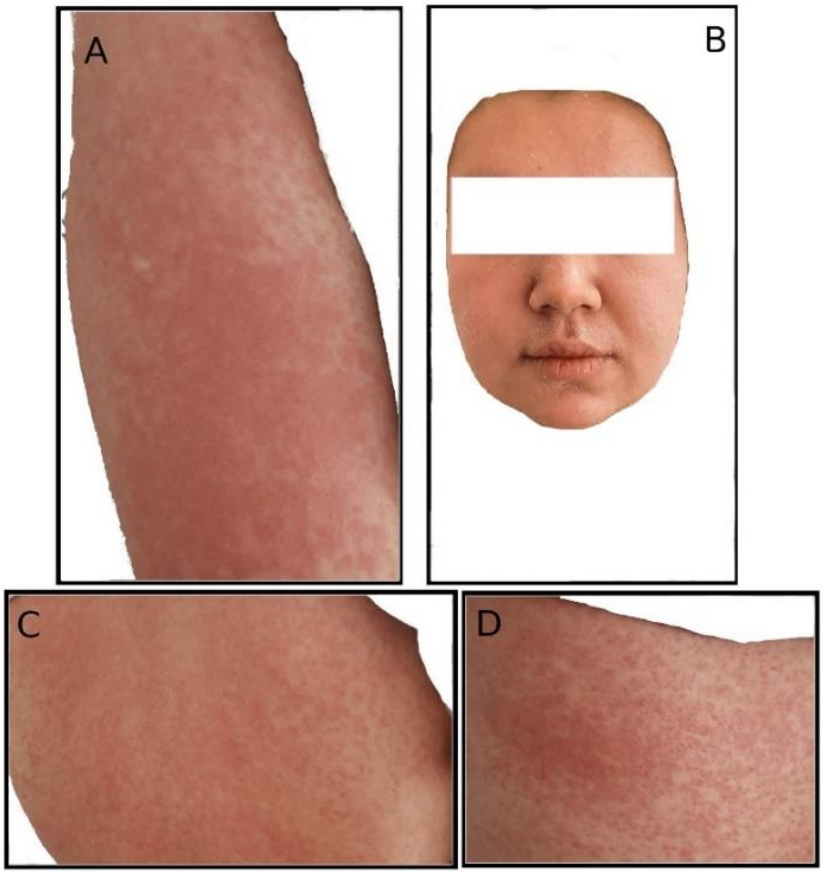

Figure 1. Skin Manifestations. The patient presented with a generalized maculopapular rash at the time of admission, as depicted in the following images: arm (A), face (B), back (C), and thigh (D).

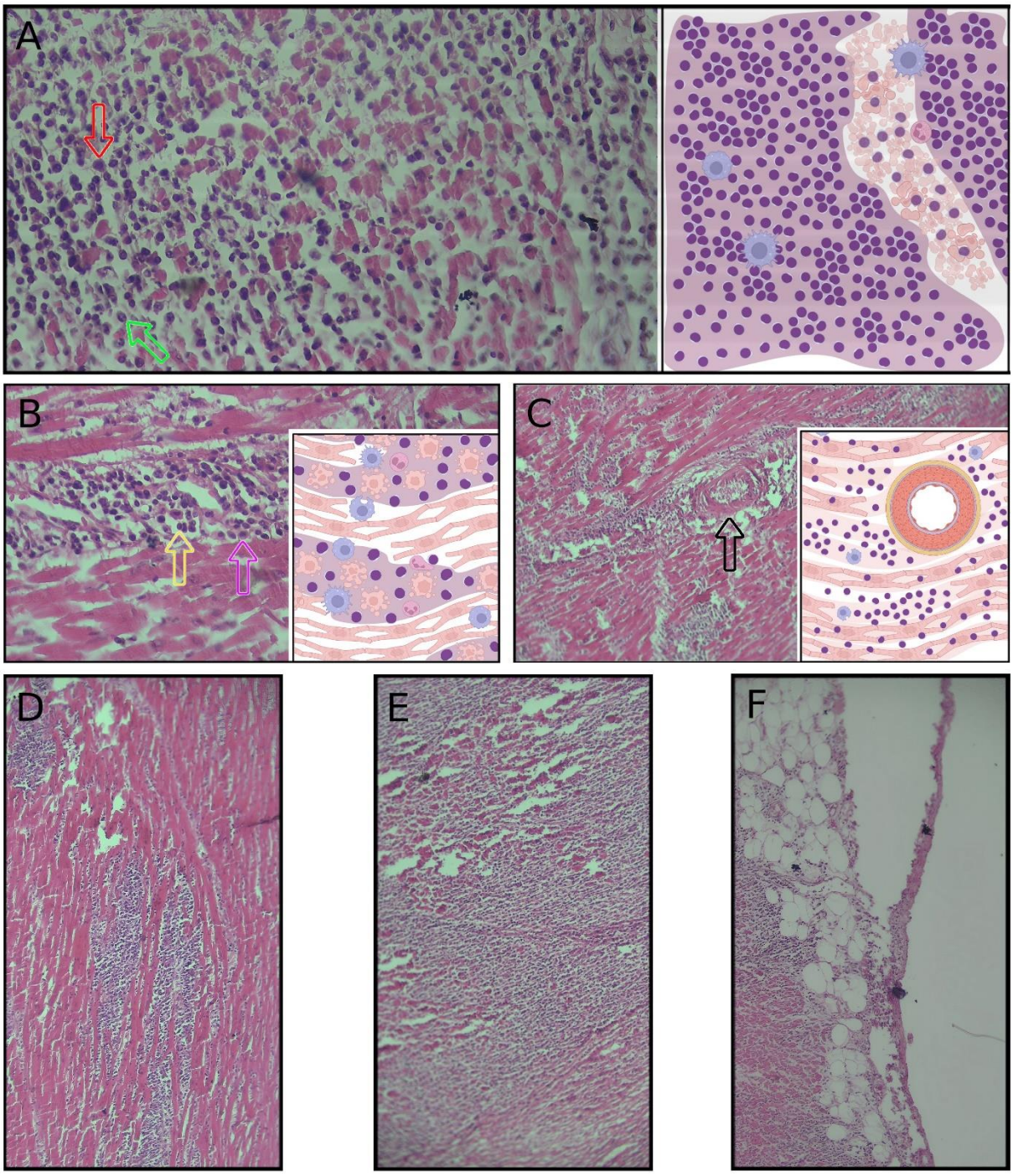

Figure 2. Endomyocardial Biopsy. substantial infiltration of small lymphocytes and scattered macrophages, along with extensive myocardial fiber necrosis and degeneration was observed. A: adjacent to the myocardial tissue, there are necrotic foci, red arrow shows a macrophage, green arrow shows an activated lymphocyte characterized by open chromatins and the absence of nucleus indentation. B: necrotic foci next to myocardial tissue, yellow arrow shows a lymphocyte, purple arrow shows a monocyte. C: black arrow shows a medium-sized vessel with no signs of inflammatory involvement, thus ruling out vasculitis. D: necrotic foci X30. E: complete necrosis X30. F: pericardial involvement.

DISCUSSION

DRESS syndrome, categorized as a form of Severe Cutaneous Adverse Reactions (SCARs), stands out from other forms due to its delayed onset, persistent symptoms, co-sensitization to entirely different drug families, and its link to multiple, though limited in number, causal drugs. The symptoms of DRESS can also resemble those of viral infections, making it a challenging syndrome to diagnose and manage.[6-8]

Delayed-type hypersensitivities (DTHs) pose significant therapeutic challenges in clinical settings. When exposed to a drug, its metabolites and drug-altered peptides circulate in the body, capable of binding to human leukocyte antigen (HLA) and triggering T cell activation, thereby escalating hypersensitivity reactions.[9]

Upon activation, T helper cells release cytokines such as IL-4, IL-5, and IL-13, causing eosinophilia. Simultaneously, increased pro-inflammatory cytokines like IFN-γ, TNF, IL-6, and IL-15 promote systemic inflammation, defining the distinctive features of DRESS.[9]

As shown in Figure 3, drugs or their metabolites can directly trigger HHV6 and CMV replication or cross-react with Herpesviridae, prompting oligoclonal CD4 and CD8 T cell activation and subsequent antiviral responses, leading to inflammation and systemic symptoms.[10,11]

Antiepileptic agents like carbamazepine, lamotrigine, phenytoin, and phenobarbital, as well as allopurinol, are frequently reported as causes of DRESS. Moreover, sulfonamides, especially sulfasalazine, along with dapsone, minocycline, and vancomycin, are also commonly associated with DRESS.[3,12] (see Figure 4).

Symptomatic treatment is sufficient for mild cases with mild liver involvement (liver transaminase levels are less than 3 times the normal upper limit). However, in severe cases with other organ involvement, oral glucocorticoids are recommended. Several retrospective studies have reported that 34-57% of DRESS patients will require systemic corticosteroid therapy to control cutaneous and systemic inflammation and prevent symptom relapse.[4]

It is important to note that corticosteroids, along with the underlying disease, can potentially reactivate HHV-6 from day 10 to day 27 after clinical onset.[10,13]

In Ishida et al, study, corticosteroid treatment for DIHS/DRESS increased HHV-6 and CMV load compared to non-corticosteroid-treated patients.[14] Tohayama et al, research stressed the crucial consideration of dose and timing of systemic corticosteroids for DIHS/DRESS treatment. High-dose corticosteroids initiated within the first week inhibit HHV-6 reactivation by suppressing T cell activation, while low-dose or late-start high-dose corticosteroids did not effectively deter HHV-6 viremia. They further observed that CMV proliferation was promoted by corticosteroids, regardless of start time.[15]

In our case, the initiation of low-dose prednisolone at the onset of rashes may explain the reactivation of HHV6 and CMV viruses. Based on these findings, it is advisable to administer high-dose corticosteroids at the onset of severe symptoms in DIHS/DRESS treatment, while carefully considering the potential effects of HHV-6 and CMV reactivation.

We identified another case of DRESS syndrome induced by cotrimoxazole. This case was associated with latent HHV6 infection approximately 2-3 weeks after symptom onset. This raises the question of whether this viral reactivation can potentially lead to organ damage or not, and further investigation is warranted.[16]

Tohyama et al, in a separate study of 100 DRESS patients, found that individuals with increased HHV6 IgG antibodies had more severe organ involvement and a longer illness duration than those without HHV-6 reactivation. Additionally, all fatalities occurred within the group showing HHV-6 reactivation.[17]

Miyashita et al. documented a case of fatal DRESS induced by cotrimoxazole, where despite successful prednisolone treatment, the patient died due to direct HHV6 reactivation in renal tissue. This case underscores the need to consider potential viral reactivation and closely monitor DRESS patients, especially when using corticosteroids.[18] Another study reported a case of lamotrigine-induced DRESS with severe hepatitis. HHV-6 PCR positivity was observed in liver tissue alongside substantial HHV-6 viremia in this case.[19]

In this study, we present the first reported case of HHV and/or CMV myocarditis as a consequence of DRESS syndrome, occurring three weeks after cutaneous presentation. Cardiac involvement in DRESS syndrome ranges from 4% to 21%. It may occur anywhere from the onset of rash manifestation to four months after skin rashes the improvement.

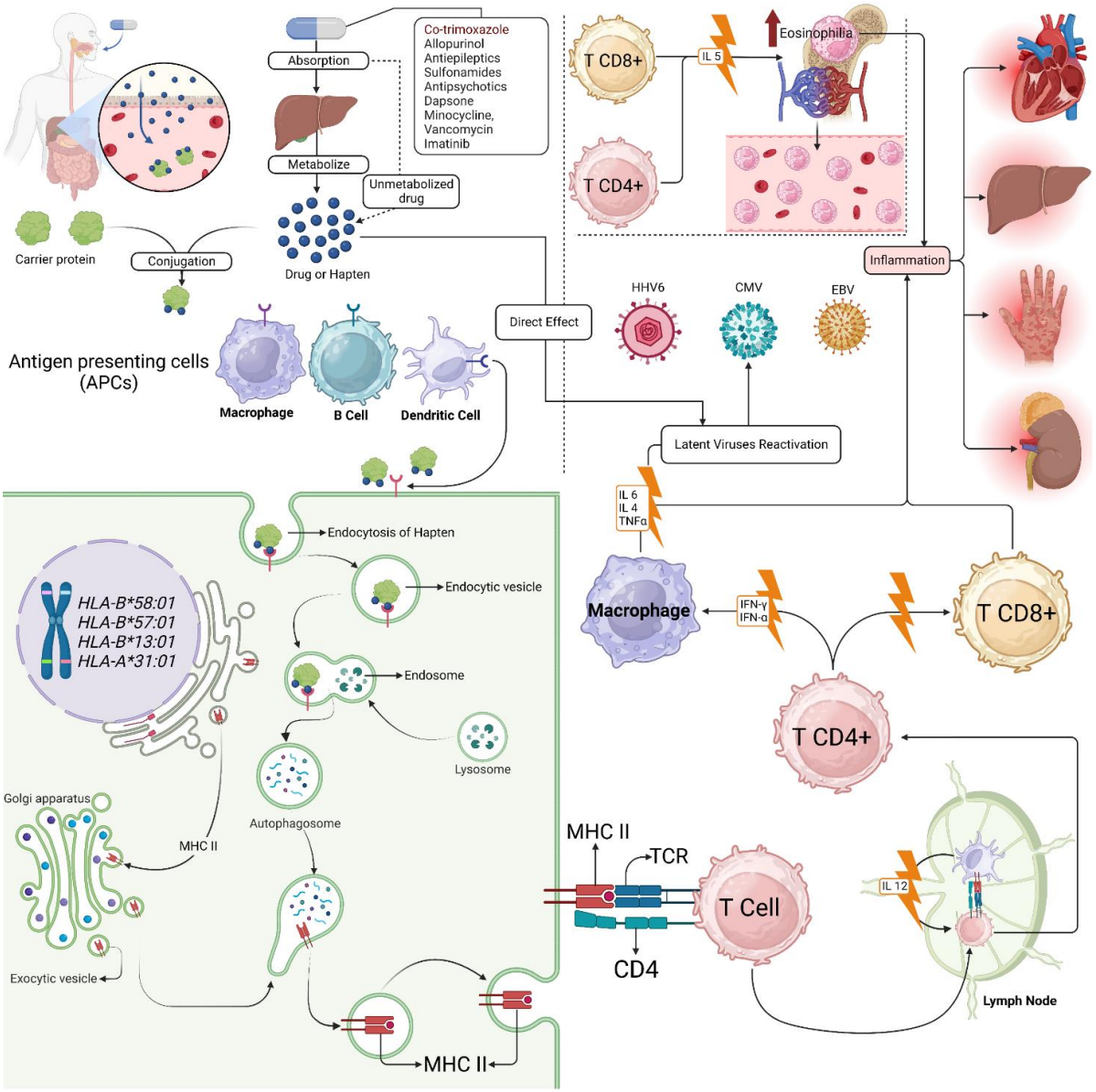

Figure 3. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Pathophysiology. The figure illustrates how a drug, or its metabolites can initiate intricate reactions, potentially resulting in tissue inflammation, eosinophilia, and viral reactivation.

Cardiac involvement in DRESS syndrome is often underdiagnosed but can have fatal consequences if not promptly treated. Therefore, early recognition of cardiac symptoms is crucial and lifesaving. Myocarditis may occur shortly after the rash appears or be delayed for up to 4 months. There is a greater risk of cardiac involvement associated with minocycline, ampicillin, and sulfonamides.[20]

EM and GCM constitute the primary forms of DRESS syndrome myocarditis. EM displays notable eosinophilic infiltration and varied clinical manifestations, ranging from mild symptoms to severe conditions like fulminant cardiomyopathy. Conversely, GCM showcases widespread cardiomyocyte necrosis with an inflammatory mix of cells.[21] However, our patient's histopathological findings didn't align with either EM or GCM, revealing lymphocyte infiltration, extensive necrosis, and macrophage presence, associated with a viral etiology.[22]

HHV-6 infection myocarditis is often initially asymptomatic but can lead to a deteriorating prognosis due to lymphomonocytic infiltration in nerve sheaths.[23] CMV myocarditis can induce acute heart injury, even

without evident symptoms such as chest pain or shortness of breath.[24]

Spotnitz and Lesch delineated three stages of viral myocarditis: (1) acute phase with myocyte damage/necrosis due to active viral infection; (2) subacute/chronic phase with prolonged viral infection and immune response-related damage; and (3) dilated cardiomyopathy (DCM) due to chronic myocarditis with cardiac tissue scarring/fibrosis. Prognostically, outcomes for viral myocarditis approximate one-third full recovery, one-third residual dysfunction, and one-third heart failure leading to death or transplantation.[25]

Quantitative PCR blood tests measure viral load levels and indicate active viremia in acute infections. On the other hand, serological testing for IgM and IgG antibodies can be employed to confirm the presence of HHV-6 infection, typically 2-4 weeks after myocarditis onset. However, it may take up to 2 weeks for detectable IgM responses to develop.[23]

Treatment with acyclovir, ganciclovir, and valacyclovir may be considered for patients with herpes virus infection; however, their efficacy, particularly in HHV6-related myocarditis, remains unproven.

Glucocorticoid therapy has shown positive responses mainly in chronic virus-negative forms, giant cell myocarditis, and active myocarditis defined as autoimmune (e.g., virus-negative and autoantibody-positive). On the other hand, immunosuppression had a neutral effect on patients with myocarditis of unknown etiology.[26]

In cases without biopsy results, myocarditis diagnosis was suggested based on a combination of symptoms, laboratory testing, and decreased cardiac function. Notably, many patients showed improvement in cardiac function after antiviral therapy.[27]

Corticosteroids are often not recommended for mild reactions due to their potential to reactivate latent viral infections. In cases where corticosteroids are prescribed for DRESS syndrome with long-term use in mind, physicians should be aware of the risk of HHV-6 reactivation, which typically occurs 2-3 weeks after symptom onset. Any systemic reactions should be carefully evaluated as potential viral reactivation. Antiviral agents may be considered, even though their benefits have not been officially approved.

STATEMENT OF ETHICS

This study was evaluated by the Research Ethics Committee of Arak University of Medical Sciences and approved on 2023-10-08 (Approval ID: IR.ARAKMU.REC.1402.170). In compliance with ethical guidelines, we affirm that appropriate informed consent was obtained for this case report submission. Before her demise, the patient provided informed consent during her first visit. Subsequently, her parents provided consent for the publication of the case report, including any accompanying anonymized visual elements.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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