Received: 25 May 2023 | Revised: 26 June 2023 | Accepted: 4 July 2023

DOI: 10.1002/ccr3.7829

Clinical Case Reports Open Access WILEY

CASE REPORT

DRESS syndrome in a patient undergoing stem cell transplantation: Can sirolimus be involved?

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Abstract

We present a case of sirolimus-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a stem cell transplant patient. Sirolimus is an immunosuppressive drug that inhibits the mammalian target of rapamycin (mTOR) pathway. A 24-year-old male with a history of acute lymphoblastic leukemia (ALL) underwent testicular extraction followed by hematopoietic stem cell transplantation (HSCT). He presented with pruritic eczematous lesions, which were initially treated with topical steroids. However, he later developed diffuse xerosis, fever, chills, generalized edema, weight gain, eosinophilia, and leukopenia. Skin biopsy showed spongiotic dermatitis with eosinophils, suggesting a drug or atopic reaction. Investigations ruled out infections, and the RegiSCAR score indicated drug reaction syndrome with eosinophilia and systemic symptoms (DRESS). Sirolimus, an immunosuppressive drug, was suspected as the cause. Sirolimus was discontinued, and oral steroids were initiated. After 3 weeks of therapy, the patient showed improvement with resolution of symptoms. Although no cases of sirolimus-induced DRESS syndrome have been reported, allergic reactions with eosinophilia induced by everolimus have been documented. In our case, the patient's history characterized by stem cell transplantation and multiple immunosuppressive therapies may have contributed to the development of DRESS syndrome after beginning sirolimus therapy. This case may be the first evidence of sirolimus-induced DRESS syndrome in a stem cell transplant patient.

KEYWORDS

DRESS, drug adverse reaction, oncology, transplantation

1 | BACKGROUND

We present the case of a stem cell transplant patient who developed DRESS syndrome[1] (drug reaction with eosinophilia and systemic symptoms) during treatment with sirolimus. DRESS syndrome is a severe adverse drug reaction characterized by fever, skin rash, multiorgan involvement, and eosinophilia. Although no cases of sirolimus-induced DRESS syndrome have been reported, allergic reactions with eosinophilia induced by

everolimus, an mTOR inhibitor like sirolimus, have been documented.[2] Sirolimus, also known as rapamycin, is an immunosuppressive and antiproliferative drug that targets the rapamycin (mTOR) pathway[3] and is commonly used in solid organ transplant patients to prevent acute rejection and improve transplant survival, offering the advantage of reduced nephrotoxicity compared with calcineurin inhibitors.[4] The cutaneous manifestations of DRESS syndrome can range from maculopapular eruptions to severe exfoliative dermatitis, while organ involvement often includes liver, kidney, lung, and hematologic systems. In addition, lymphadenopathy, myocarditis, and interstitial nephritis may appear as systemic symptoms. Early recognition and discontinuation of the causative drug are essential to manage DRESS syndrome and prevent potential complications. Supportive care and close monitoring of organ function are essential, while symptomatic treatment aims to relieve symptoms. Systemic corticosteroids are often administered to suppress the immune response. Although DRESS syndrome is considered a rare condition, it can lead to significant morbidity and mortality. The mortality rate associated with DRESS syndrome varies depending on the severity of organ involvement and the timeliness of diagnosis and initiation of treatment. Mortality rates of 5%–10% have been reported, with liver involvement being a significant predictor of a worse prognosis. Considering this, DRESS syndrome is considered a dermatologic emergency, and potentially fatal complications include severe hepatitis, fulminant liver failure, myocarditis, and multiorgan failure.[2] DRESS syndrome can be triggered by various drugs belonging to different therapeutic classes. Among the most frequently implicated drugs are antiepileptics[5] (such as phenytoin, carbamazepine, and lamotrigine), allopurinol,[6] sulfa drugs[7] (including trimethoprim-sulfamethoxazole), and some antibiotics[8] (such as minocycline and vancomycin). However, the list of potential causative agents is extensive and continues to expand as new cases are reported. For example, a case of DRESS syndrome was recently reported in a patient with COVID 19 and on hydroxychloroquine therapy.[9]

2 | CASE REPORT

A 24-year-old male, who had previously undergone haploidentical testicular extraction (TESE) with hematopoietic stem cell transplantation (HSCT) for acute lymphoblastic leukemia (ALL), presented to the dermatology outpatient clinic with a diffuse eruption of pruritic eczematous lesions. The patient had a positive history of atopic dermatitis, and a suspected exacerbation of the underlying condition led to the recommendation of topical steroid therapy, which was initially beneficial. About 2 months later, the patient returned to the emergency department complaining of diffuse xerosis mixed with pruritic, finely scaling eczematous patches. The patient reported a fever above 38.5°C, chills, and significant generalized edema. He also noted a weight gain of 9 kg in the last month and presented with eosinophilia (>20%) with leukopenia (Figure 1). The patient's medical history revealed a diagnosis of acute lymphoblastic leukemia in 2003 and subsequent treatment according to the AIEOP LLA 2000 protocol (Prednisone, Vincristine, Daunorubicin, L-asparaginase, Methotrexate, 6-Mercaptopurine, Cyclophosphamide, Cytarabine, Dexamethasone). In 2015, the patient relapsed and was treated according to the 2009 AIEOP BFM protocol, which ended in 2017 (Prednisone, Vincristine, Daunorubicin, L-asparaginase, Methotrexate, 6-Mercaptopurine, Cyclophosphamide, Citarabine, Dexamethasone). However, in 2018, the patient had another relapse and subsequently underwent TESE haploidentical stem cell transplantation. Unfortunately, in 2019, the patient developed acute graft-versus-host disease (GVHD), for which he received oral cyclosporine in combination with tacrolimus, with rapid improvement of skin manifestations. Unfortunately, in 2020, he was diagnosed with Evans syndrome

FIGURE 1 Eczematous, itchy, finely scaling patches and significant and consistent oedema.

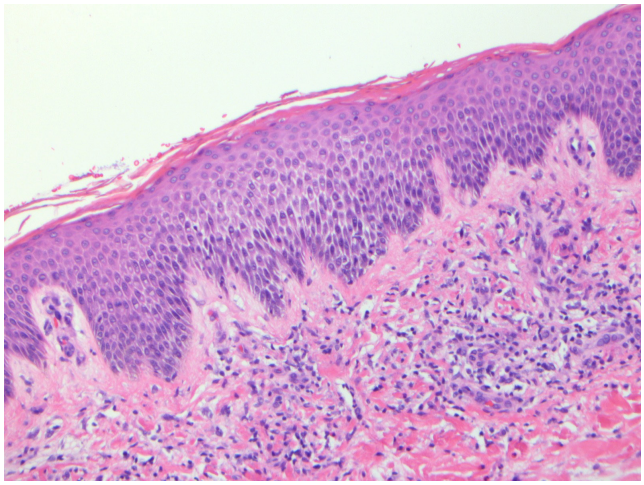

FIGURE 2 Flap of skin with hyperkeratosis, focally confluent spongiosis and irregular acanthosis of the epidermis. Modest infiltrate of lymphocytes, plasma cells, and eosinophils, in the deep dermis.

and was treated with oral steroids. Once the acute phase subsided, the patient started immunosuppressive therapy with sirolimus 2 mg/day. Considering the history and severity of clinical presentation, the patient was admitted to the hospital and a skin biopsy with histological examination was performed. Histological examination revealed hyperkeratosis with focally confluent spongiosis and irregular acanthosis of the epidermis. The superficial dermis showed a modest infiltrate of lymphocytes, plasma cells, and eosinophils, with eosinophils also observed in the deep dermis. Specific histochemical staining did not reveal the presence of mucin or fungi (Alcian Blue and PAS), while immunohistochemical reactions for T and B lymphocytes ruled out the clinical hypothesis of GVHD. Morphologic features showed a spongiotic dermatitis with a significant presence of dermal eosinophils, suggesting the possibility of a drug or atopic reaction (Figure 2). At the same time, investigations were conducted to exclude concomitant viral or bacterial infections, which were negative. Based on the patient's histological examination and clinical presentation, with suspicion of drug reaction syndrome with eosinophilia and systemic symptoms (DRESS), the RegiSCAR score[10–12] was calculated, which further strengthened the suspicion (fever >38.5°C, eosinophilia >20%, lymphopenia, itchy skin rash, generalized edema, other causes ruled out, no ongoing infection, RegiSCAR score: 6). It should be noted that in our patient there was no evidence of visceral or mucosal involvement, although no drugs had been introduced recently and the only noteworthy information was a trip abroad; the patient did not report any recent exogenous substance intake. Considering that sirolimus was the most recent drug introduced into therapy, although it had been

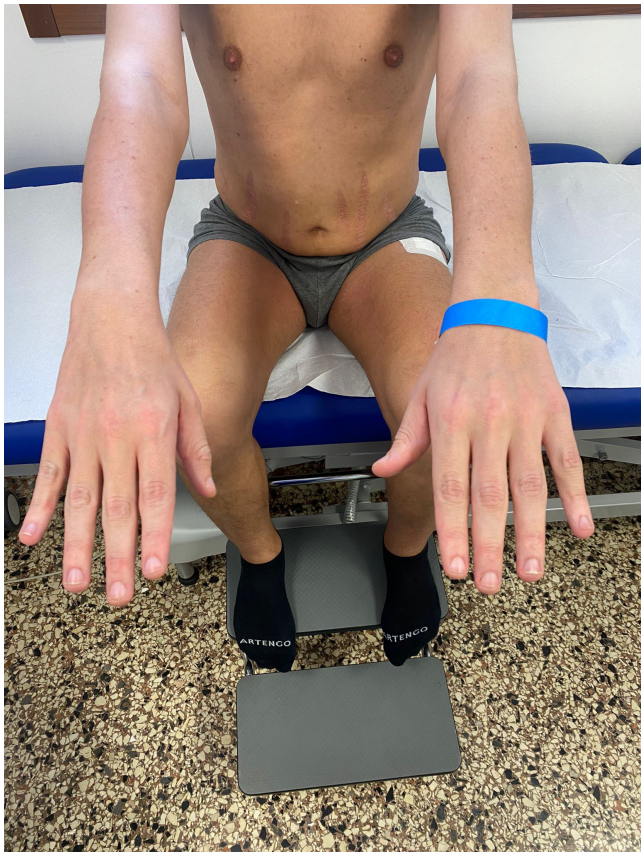

FIGURE 3 One month after withdrawal of sirolimus.

about 2 years since its initiation, we hypothesized that the DRESS syndrome had been caused by sirolimus. The drug was discontinued, and a tapered regimen of oral steroids was started. After 3 weeks of therapy, the patient discontinued oral steroids. At the follow-up visit after 1 month, the edema had resolved, the patient no longer reported any symptoms, and the previously accumulated weight had been lost (Figure 3).

3 | DISCUSSION

The case presented involves a 24-year-old man with a complex medical history, including a previous diagnosis of acute lymphatic leukemia and subsequent relapses that required intensive treatments such as stem cell transplantation and immunosuppressive therapy. The patient had a preexisting condition of atopic dermatitis and presented to the dermatology outpatient clinic with diffuse pruritic eczematous lesions, initially diagnosed as a relapse of atopic dermatitis. Despite topical steroid therapy, the patient's condition worsened, characterized by dry, itchy patches interspersed with xerosis, accompanied by fever, edema, weight gain, and abnormal blood test results. Graft-versus-host disease (GVHD) was ruled out by skin

biopsy. Considering the clinical presentation, histological findings, a suspicion of DRESS syndrome arose. DRESS syndrome, also known as a rare and life-threatening drug reaction, manifests with a broad spectrum of skin symptoms accompanied by mucocutaneous rash, fever, lymphadenopathy, hematologic disorders, and potential involvement of internal organs, with the liver as the most affected organ.[10] Because the patient had not recently introduced any new drugs, it was hypothesized that sirolimus, the most recent drug added to therapy, might be responsible for the reaction. Sirolimus was discontinued and the patient started oral steroid therapy, which was gradually reduced and finally discontinued. After 3 weeks of treatment, the patient's symptoms improved, including resolution of edema, and at the follow-up visit at 1 month the patient appeared asymptomatic and had lost the weight gained during the disease. DRESS syndrome represents a severe form of drug reaction characterized by cutaneous manifestations and systemic involvement. The onset is typically later than other delayed skin reactions, with an average of 6–8 weeks after exposure to the causative drug. Nevertheless, given the patient's complex history, it cannot be ruled out that in our patient's case the onset of the syndrome may have occurred approximately 2 years after the start of therapy due to complex interactions between endogenous and exogenous factors. In fact, DRESS syndrome, IS classified as a severe idiosyncratic T-cell-mediated reaction, which falls under delayed hypersensitivity reactions of type Vb and occasionally IVc. DRESS is believed to result from a complex interaction between drug exposure (such as vaccines or biologic drugs), genetic predisposition, and/or viral reactivation. The development of this serious clinical condition appears to be a cumulative effect of aligned risk factors. Early recognition and discontinuation of the culprit drug are critical to managing DRESS syndrome. Systemic corticosteroids are commonly used to suppress the inflammatory response, while supportive care is administered for any organ involvement. Although cases of sirolimus-induced DRESS syndrome are lacking in the literature, cases of allergic reactions with eosinophilia induced by everolimus, a drug like sirolimus, have been documented.[13] Cases of drug reaction with eosinophilia and systemic symptom syndrome caused by an everolimus-eluting stent have been reported. Sirolimus and everolimus both belong to the class of drugs known as mTOR inhibitors and share several characteristics. These include the mechanism of action, therapeutic indications in immunosuppressive therapy for the prevention of organ rejection in transplant patients, pharmacokinetics (oral administration, rapid absorption, extensive hepatic metabolism), common adverse effects, such as immunosuppression leading to increased risk of infection, delayed wound healing, and altered response to vaccines, as well as potential side effects such as hyperlipidemia, peripheral edema, gastrointestinal disorders, and metabolic abnormalities.[14,15] In addition, both drugs are metabolized by cytochrome P450 enzymes, which may result in drug interactions with other drugs that act on these enzymes. Careful consideration of these interactions is essential when prescribing or administering these drugs. In our case, the patient's history of previous intensive treatment, stem cell transplantation, and immunosuppressive therapies may have contributed to the dysregulation of the immune system and the onset of DRESS syndrome. Although the onset of sirolimus was not recent, discontinuation of the drug along with appropriate therapy facilitated the patient's clinical improvement. Considering everything, although it cannot be stated with certainty, this case potentially represents the first evidence of sirolimus-induced DRESS syndrome.

AUTHOR CONTRIBUTIONS

Fortunato Cassalia: Writing – original draft. **Alice Spiller:** Writing – original draft. **Roberto Salmaso:** Investigation; supervision. **Francesca Caroppo:** Supervision; writing – original draft. **Anna Belloni Fortina:** Supervision; writing – review and editing.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Cassalia F, Spiller A, Salmaso R, Caroppo F, Belloni Fortina A. DRESS syndrome in a patient undergoing stem cell transplantation: Can sirolimus be involved? *Clin Case Rep*. 2023;11:e7829. doi:10.1002/ccr3.7829