Sirolimus-induced DRESS syndrome in a stem cell transplant patient.

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Title: Sirolimus-induced DRESS syndrome in a stem cell transplant patient.**Authors**: Fortunato CASSALIA[1], Alice SPILLER[1], Roberto SALMASO[1], Francesca CAROPPO[1,2], Anna BELLONI FORTINA[1,2]**Affiliations**:

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Corresponding Author: Francesca Caroppo, MD Unit of Dermatology, Department of Medicine University of Padova, Italy Via Vincenzo Gallucci 4, 35121, Padova, Italy e-mail: francesca.caroppo@outlook.it**Keywords**:**Word count**: 1329**Tables**: None**Figure**: 3**References**: 9**Conflicts of interest**: None**Acknowledgements**: None**Author Contributions**: All authors contributed to designing and conducting the work, drafting, and revising the manuscript and approved the final version for submission.**ABSTRACTBACKGROUND:** We present a case of sirolimus-induced DRESS syndrome in a stem cell transplant patient. Sirolimus is an immunosuppressive drug that inhibits the mTOR pathway. It is commonly used in organ transplants to prevent rejection. While no sirolimus-induced DRESS cases have been reported, allergic reactions with everolimus, a similar drug, have been documented. DRESS syndrome is a severe drug reaction characterized by fever, rash, and organ involvement. Diagnosis is based on clinical findings and laboratory tests. Early recognition, discontinuation of the drug, and supportive care are crucial in managing DRESS syndrome, often involving systemic corticosteroids.**CASE REPORT** A 24-year-old man who had undergone haplo-TESE transplantation for acute lymphatic leukaemia presented with diffuse itchy eczematous lesions. Initially diagnosed as atopic dermatitis, he received topical steroid therapy and NB-UVB phototherapy, but his condition worsened. Two months later, he returned to the emergency department with eczematous patches, xerosis, fever, chills, and generalized edema. His medical history included relapses of leukaemia, acute cutaneous graft-versus-host disease (GVHD), and Evans syndrome. He had been on sirolimus immunosuppressive therapy before the onset of symptoms. A skin biopsy revealed spongiotic dermatitis with dermal eosinophils, suggestive of drug reaction or atopic reaction. Based on the severity of the symptoms and histological findings, the patient was diagnosed with sirolimus-induced DRESS syndrome. Sirolimus was discontinued, and oral steroid therapy was initiated, leading to significant improvement. At the one-month follow-up, the patient was symptom-free and had lost the gained weight.**CONCLUSION** Although no cases of sirolimus-induced DRESS syndrome have been reported, allergic reactions with eosinophilia induced by everolimus have been documented. And since sirolimus and everolimus, both mTOR inhibitors, share a common mechanism of action, therapeutic indications, pharmacokinetics, adverse effects and drug interactions, it cannot be ruled out that sirolimus may trigger DRESS syndrome in patients with risk factors. 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 and highlights how early diagnosis, discontinuation of the culprit drug and appropriate management are crucial for a favourable outcome.**BACKGROUND** We present a case of sirolimus-induced DRESS syndrome[1]in a stem cell transplant patient. Sirolimus, also known as rapamycin, is an immunosuppressive and antiproliferative drug that inhibits the mammalian target of rapamycin (mTOR) pathway[2]. It has a wide range of clinical applications and has been extensively studied in various fields of medicine. Sirolimus is commonly used in solid organ transplants to prevent acute rejection and improve transplant survival with the advantage of reducing the nephrotoxicity associated with calcineurin inhibitors[3]. Although no cases of sirolimus-induced DRESS syndrome have been reported, allergic reactions with eosinophilia induced by everolimus, a similar drug of the mTOR inhibitor family, have been documented. In particular, cases of drug reaction with eosinophilia and systemic symptoms (DRESS) caused by an everolimus-eluting stent have been reported[4]. DRESS syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is a severe adverse drug reaction characterized by fever, skin rash, multi-organ involvement and eosinophilia. The pathogenesis of the DRESS syndrome remains unclear, involving a complex interaction between drug metabolism, immune dysregulation and genetic factors. Skin manifestations vary from maculopapular eruptions to severe exfoliative dermatitis, while organ involvement often involves the liver, kidneys, lungs and haematological system. Other systemic symptoms may include lymphadenopathy, myocarditis and interstitial nephritis. The diagnosis of DRESS syndrome is based on the recently validated RegiSCAR score[5] which considers clinical findings, temporal relationship with drug exposure and blood tests. Early recognition and discontinuation of the involved drug are crucial for the management of DRESS syndrome. Supportive care and careful monitoring of organ function are essential, while symptomatic treatment aims to improve symptoms. Systemic corticosteroids are often administered to suppress the immune response[6].**CASE REPORT**A 24-year-old boy, who had previously undergone haplo-TESE transplantation (transplantation of haploidentical haematopoietic stem cells for acute lymphatic leukaemia, presented to the dermatology outpatient clinic for the onset of a diffuse eruption with itchy eczematous lesions. The initial clinical presentation was diagnosed as atopic dermatitis and topical steroid therapy was recommended. In the following days, due to the lack of clinical response and the worsening of the skin eruption, about two months later the patient returned to the emergency department complaining of diffuse xerosis mixed with eczematous, itchy, finely scaling patches. In addition, the patient complained of fever and chills and significant and consistent oedema all over his body. He also reported a weight gain of 9 kg in the last month and eosinophilia >20% with leukopenia (Figure 1). The medical history revealed that the patient was diagnosed with acute lymphatic leukaemia in 2003 and underwent treatment according to the AIEOP LLA 2000 protocol (Prednisone, Vincristine, Daunorubicin, L-asparaginase, methotrexate, 6-Mercaptopurine, Cyclophosphamide, Cytarabine, Dexamethasone). In 2015, the patient developed a relapse for which he was treated according to the AIEOP protocol BFM 2009 concluded in 2017 (Prednisone, Vincristine, Daunorubicin, L-asparaginase, methotrexate, 6-Mercaptopurine, Cyclophosphamide, Cytarabine, Dexamethasone). However, in 2018, the patient developed a new relapse and therefore underwent haplo-TESE stem cell transplantation. Unfortunately, in 2019, the patient suffered an acute cutaneous GVHD for which he underwent treatment with oral cyclosporine in combination with tacrolimus that led to a rapid improvement of the skin manifestations. Unfortunately, in 2020 he was diagnosed with Evans syndrome and was treated with oral steroids; once the acute phase was over, the patient started immunosuppressive therapy with sirolimus 2 mg/die. Given the history and the severity of the clinical picture, the patient was hospitalized and a skin biopsy with histological examination was performed. The result of the histological examination revealed a hyperkeratosis with focally confluent spongiosis and irregular acanthosis of the epidermide. The underlying superficial dermis shows a modest infiltrate of lymphocytes, plasma cells and eosinophils, the latter also observed in the deep dermis. Specific histochemical stains did not reveal the presence of mucins and fungi (Alcial Blue and PAS) while immunohistochemical reactions for T and B lymphocytes excluded the clinical hypothesis of GVHD. The morphological picture depicts a spongiotic dermatitis with a discrete presence of dermal eosinophils suggesting the possibility of drug reaction vs. atopic reaction (Figure 2).

Considering the clinical picture and the histological examination, the diagnosis of DRESS syndrome induced by sirolimus was made[7]. The drug was withdrawn and scaled-up oral steroid therapy was instituted, after 3 weeks of therapy the patient ceased taking the oral steroid. At the follow-up visit after one month the oedema was in remission, the patient no longer complained of any symptoms and had lost the previously accumulated kg (Figure 3).**DISCUSSION** The case described presents a 24-year-old boy with a complex medical history, including a previous diagnosis of acute lymphatic leukaemia and subsequent relapses, which required intensive treatments such as stem cell transplantation and immunosuppressive therapy. The patient presented to the dermatology outpatient clinic with diffuse itchy eczematous lesions, initially diagnosed as atopic dermatitis. Despite topical steroid therapy, the patient's condition worsened with dry, itchy patches mixed with xerosis concomitant with fever, swelling, weight gain and abnormal blood results. Skin biopsy ruled out the diagnosis of graft-versus-host disease (GVHD). Based on the clinical presentation, histological findings and history of sirolimus therapy, the diagnosis of sirolimus-induced DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome was made. Sirolimus was discontinued and the patient started oral steroid therapy, which was gradually reduced and finally discontinued. After three weeks of treatment, the patient's symptoms improved, including remission of oedema, and at the one-month follow-up visit the patient was asymptomatic and had lost the weight gained during the illness. DRESS syndrome is a severe form of drug reaction in which skin manifestations and systemic involvement are associated. The onset time is usually longer than in other delayed skin reactions, on average 6-8 weeks after the introduction of the responsible drug. It is a severe idiosyncratic T-cell mediated reaction, classified as a type Vb and sometimes IVc delayed hypersensitivity reaction. DRESS is presumed to result from a complex interaction between drug exposure (such as vaccines or biological drugs), genetic predisposition and/or viral reactivation, and the development of this serious clinical condition would appear to be the result of the cumulative effect of aligned risks[1]. Early recognition and discontinuation of the culprit drug are crucial for the management of DRESS syndrome. Systemic corticosteroids are often used to suppress the inflammatory response and supportive care is provided for any organ involvement[6]. Although no cases of sirolimus-induced DRESS syndrome are reported in the literature, allergic reactions with eosinophilia induced by everolimus have been described. In particular, cases of drug reaction with eosinophilia and systemic symptom syndrome caused by an everolimus-eluting stent have been reported[4]. Sirolimus and everolimus both belong to the class of drugs called mTOR inhibitors and share several features[8], including: (1) Mechanism of action: Sirolimus and everolimus act by inhibiting the mammalian target of rapamycin (mTOR); (2) therapeutic indications: both are used in immunosuppressive therapy to prevent organ rejection in transplant patients. (3) Pharmacokinetics: both are administered orally and are rapidly absorbed. They have a large volume of distribution and are extensively metabolised in the liver. (4) Adverse effects: They have common adverse effects including immunosuppression, which may increase the risk of infection, delay wound healing and altered response to vaccines. Other potential side effects include hyperlipidaemia (elevated blood lipid levels), peripheral oedema, gastrointestinal disorders, and metabolic abnormalities; (5) drug interactions: both drugs are metabolised by cytochrome P450 enzymes, which may lead to potential drug interactions with other drugs that act on these enzymes[9]. It is important to consider these interactions when prescribing or administering these drugs. In our case, the patient's history of previous intensive treatments, stem cell transplantation and immunosuppressive therapies may have contributed to immune system dysregulation and the onset of DRESS syndrome following the initiation of sirolimus therapy. Timely diagnosis, discontinuation of the drug and appropriate management led to the resolution of symptoms and general improvement of the patient's condition. The case emphasizes the importance of careful monitoring and consideration of potential adverse drug reactions in patients undergoing complex treatment regimes. This case could be the first evidence of DRESS syndrome induced by sirolimus in a stem cell transplant patient.**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 epider-mide. Modest infiltrate of lymphocytes, plasma cells and eosinophils, in the deep dermis.**FIGURE 3** One month after withdrawal of Sirolimus**REFERENCES**

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