MEGA JOURNAL OF CASE REPORTS

Case Report of Dress Syndrome Induced by Ribociclib

Carneiro F[1], Bove M[2], Beau-Salinas F[3], Cailleux P[4], San T[5] and Combe P[5*]

[1]Department of Medical Oncology, University Hospital, Tours, France

[2]Department of Medical Oncology, Hospital Center, Blois, France

[3]Department of Pharmacosurveillance, Pharmacovigilance, University Hospital, Tours, France

[4]Department of Dermatology, Pole Santé Leonard de Vinci, Chambray les Tours, France

[5]Centre d'Oncologie et Radiothérapie 37 (CORT37), Chambray les Tours, France

[*]**Corresponding author**: Pierre COMBE, Oncologue medical, RPPS 10100247024, Centre d'oncologie et radiothérapie 37, Recherche Oncologique Clinique 37, Pôle Santé Léonard de Vinci, 11 Avenue Minkowski 37170 Chambray-lès-tours, 0247602060, France

Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but known and potentially severe side effect of antineoplastic drugs. The recent development of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors such as ribociclib has considerably improved the management of hormone receptor positive (HR+) and HER2 negative (HER2-) advanced breast cancer. Here we present the case of a DRESS syndrome induced by ribociclib, presenting with fever, eosinophilia, rash and hepatic cytolysis. The symptomatology evolved favourably with topic and systemic corticosteroids, without any sequel. Another CDK4/6 inhibitor, palbociclib, was introduced later without any cross-toxicity and with an excellent therapeutic response for more than 3 years.

Keywords: DRESS; Ribociclib; CDK4/6 inhibitor; Eosinophilia

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome (DRESS) is a severe delayed T-cell mediated drug reaction. It is characterized by acute maculopapular morbilliform rash, fever, lymphadenopathy, leukocytosis with eosinophilia and atypical lymphocytes, and liver abnormalities **[1,2].** This syndrome is potentially life-threatening, with a mortality of 10% if not properly treated **[3].** DRESS syndrome can occur from 2 to 8 weeks after introduction of the causative drug **[3].** It is also known to be associated with the reactivation of herpes viruses, such as Human Herpesvirus 6 (HHV-6), Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) **[4].** DRESS syndrome remains a rare side effect, with a variable incidence among different ethnicities **[2].** It is usually associated with a limited number of drugs. The most common drugs responsible for DRESS syndrome are antiepileptics in which the risk of DRESS syndrome is 2.3–4.5 in 10,000 patients **[5].** Although, the list of potential causative agents for DRESS has considerably lengthened over the years. The recent development of Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors such as ribociclib has

improved the management of Hormone Receptor positive (HR+) and HER2 negative (HER2-) advanced breast cancer. The main side effects of this treatment are digestive and hematological toxicity **[6].** To our knowledge, no case of DRESS syndrome with ribociclib has been published to date.

Case Presentation

We present the case of an 83-year-old female patient diagnosed with ulcerated HR+ HER2-bilateral breast cancer with synchronous lymph node involvement and bone metastasis. Our patient had an history of hypertension and dyslipidemia treated by candesartan, bisoprolol and atorvastatin as long-term treatments. First-line treatment with letrozole 2,5 mg a day was initiated in mid-July 2019 by gynecologist. In September 2019 the treatment was enhanced adding ribociclib and denosumab. An injection of denosumab at a dose of 120 mg was performed on 5th September 2019 associated with calcium and vitamin D supplementation. Ribociclib was started on the same day at a dose of 600 mg daily but was prematurely stopped on 19th September 2019 due to digestive toxicity, with grade 2 diarrhea and vomiting. Letrozole was then continued alone. During this period, serum creatinine level increased from 0.94 mg/dL baseline to 1.38mg/dL and 1.34 mg/dL on 9th and 19th September 2019, respectively. An urinary tract ultrasonography was performed, showing no evidence of obstructive uropathy nor bowel or renal structural alteration, and urine culture was sterile. Our patient was hospitalized on 4th October 2019 in a context of fever at 39°C, grade 2 asthenia, nausea, and anorexia. Biology at admission showed hepatic cytolysis with elevation of ALTand AST at 574IU/L and 312IU/L, respectively. GGT and ALP were elevated too, at 210IU/L and 313IU/L, respectively. There was no elevation of bilirubin. An eosinophilia was present, at 1460 cells/µL and was associated with presence of atypical hyperbasophilic lymphocytes. As previously mentioned, there was an acute renal failure with creatinine level at 1,48 mg/dL. In the first 24 hours following her admission, she developed a pruriginous maculopapular rash of upper trunk which extended to the arms in 24-48 hours. There was no facial oedema nor recently appeared lymphadenopathy. Axillary tumoral lymphadenopathy were present but already known. A hepatic ultrasonography was performed, showing no evidence of hepatic or biliary tract structural alteration.

Viral serologies for Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Hepatitis B Virus (HBV), Hepatitis C Virus (HVC), Hepatitis A Virus (HAV) and Hepatitis E Virus (HEV) were negative. Serology of treponematoses, brucella, coxiella, bartonella and rickettsia were negative. Aspergillosis serology and dosage of mannan and galactomannan antigens were negative. Epstein Barr Virus (EBV), measles, mumps, rubella, and toxoplasmosis serologies showed long-standing immunization. Human Herpesvirus 6 (HHV6) and EBV PCRs were not performed. Hemocultures were sterile. Immunologic explorations were negative, including dosages for Antinuclear Antibodies (ANAs), Anti-Cardiolipin Antibodies (ACAs), Anti-Neutrophil Cytoplasmic Antibodies (ANCAs), Anti-Smooth Muscles Antibodies (SMAs), Anti-Mitochondrial Antibodies (AMAs), Anti-Liver-Kidney Microsomal (LKM) antibodies, Liver Cytosol antibodies type 1 (anti-LC1). General and topical corticosteroids were started followed by rapid clinical improvement. Fever and rash disappeared within three days. Hepatic cytolysis was already at its maximum at admission and normalized within 6 weeks. Total bilirubin remained subnormal, up to 23 µmol/L at its maximum 15 days after the date of hospitalization. Prothrombin Ratio (PR) decreased with a minimal value of 62% 7 days after admission. Activated Partial Thromboplastin Time (APTT) was not elevated. Eosinophilia increased up to 3030 cells/µL at its maximum ten days after hospitalization and then normalized within ten more days. Creatinine level quickly normalized in few days after

admission after intravenous hydration. Evolution of biological parameters are showed in **Figure 1**. RegiSCAR score was 4, in favor of a probable DRESS syndrome (1 point for fever ≥ 38,5°C, atypical lymphocytes, eosinophilia ≥ 1500 cells/µL, hepatic involvement, and alternative diagnoses excluded by ≥ 3 biological investigations; -1 point for nor edema, infiltration, purpura or scaling). Our patient discharged from the hospital on 15th October 2019, after 11 days of hospitalization, continuing systemic oral corticosteroid with progressively decreasing dose. Ribociclib was already discontinued since 19th September 2019 and was never reintroduced afterwards. She initially continued letrozole alone, and another CDK4/6 inhibitor, palbociclib, was added on 16th December 2019 without toxicity and is still ongoing at this day more than 3 years later with almost complete metabolic response. Denosumab was also reintroduced afterwards without any recurrence of toxicity at this day.

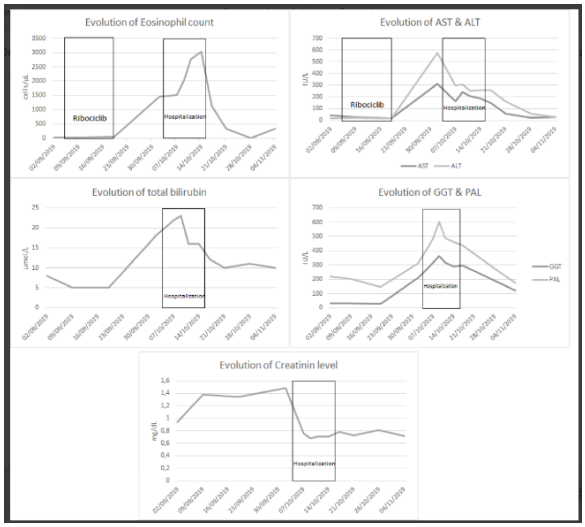

Figure 1: evolution of eosinophil count, liver function tests and creatinine level over time.

Discussion

In this situation, the clinical and biological presentation support the diagnosis of DRESS syndrome. It is noteworthy that the symptomatology of DRESS was preceded by digestive disorders such as nausea, vomiting and diarrhea, which led to discontinuation of the ribociclib even before the appearance of symptoms suggestive of DRESS. These digestive disorders were probably unrelated to DRESS because of their early onset and the usual absence of such manifestations in DRESS syndrome. Moreover, digestive toxicity is very common with ribociclib treatment [6]. Renal acute injury was also present, but the context of clinical dehydration linked to digestive disorders, added to its immediate and complete resolution after intravenous rehydration is in favor of functional renal insufficiency rather than visceral damage due to DRESS. Consequently, renal impairment was not included in the calculation of the REGISCAR score. The temporal relationship between the introduction of ribociclib, the onset of symptoms, and the clinical and biological improvement favors the causality of this molecule, even if ribociclib (which has a long elimination half-life averaging 32 hours) had been stopped 13 days before the discovery of the first manifestations of DRESS. Denosumab had been started concomitantly with ribociclib but the absence of recurrence of toxicity after his reintroduction is not in favor of its imputability. To our knowledge, no DRESS syndrome was revealed during clinical trials of ribociclib, and no case has been published since its marketing. However, 4 other cases than ours, of DRESS syndrome during ribociclib

treatment are recorded in the world health organization (WHO) global pharmacovigilance database, including one case that recurred after read ministration. Moreover, cases of other severe cutaneous adverse reactions during ribociclib treatment have been published, such as Stevens Johnson syndrome and toxic epidermal necrolysis [7-10] and one case of erythema multiforme during ribociclib treatment, reappearing after switch with palbociclib [11]. Recently, the prescribing information of Kisqali in the Food and Drug Administration (FDA) has been updated, adding DRESS syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis to adverse events during post marketing experience, and warning about the risk of severe cutaneous adverse reactions during ribociclib treatment. No case of DRESS syndrome has been published with other CDK 4/6 inhibitor, palbociclib and abemaciclib, and there are respectively two cases with palbociclib and one case with abemaciclib in the WHO global pharmacovigilance database. Cases of bullous skin rashes, Stevens-Johnson syndrome and toxic epidermal necrolysis have been published with palbociclib [12,13] but not to our knowledge with abemaciclib. We presented the first published case of DRESS syndrome associated with ribociclib. It is interesting that treatment with another CDK4/6 inhibitor, palbociclib, could be started after complete resolution of hepatic cytolysis, 2 months after the episode of DRESS syndrome. This treatment was not responsible for cross-toxicity, was very well tolerated clinically and showed remarkable efficacy, with the persistence of an almost complete response 3 years after initiation of the treatment.

Conclusion

We presented a case of probable DRESS syndrome with cutaneous and hepatic involvement caused by ribociclib that favourably responded to systemic and topic corticosteroids. There was no cross reaction with palbociclib which is still ongoing with very good response. It is important to be vigilant in monitoring people treated with ribociclib because of a risk of severe cutaneous adverse reactions emerging since the marketing of the drug.

References

1. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071-80.
2. Behera SK, Das S, Xavier AS, Selvarajan S. DRESS syndrome: a detailed insight. Hosp Pract (1995). 2018;46(3):152-62.
3. Hama N, Abe R, Gibson A, Phillips EJ. Drug-Induced Hypersensitivity Syndrome (DIHS)/Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS): Clinical Features and Pathogenesis. J Allergy Clin Immunol Pract. 2022;10(5):1155-1167.e5.
4. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int. 2019;68(3):301-8.
5. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology. 1997;49(2):542-6.
6. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738-48.

7. López-Gómez V, Yarza R, Muñoz-González H, Revilla E, Enrech S, González-Valle O, et al. Ribociclib-Related Stevens-Johnson Syndrome: Oncologic Awareness, Case Report, and Literature Review. J Breast Cancer. 2019;22(4):661-6.
8. Widmer S, Grossman M. Chemotherapy patient with Stevens-Johnson Syndrome presents to the Emergency Department: A case report. Am J Emerg Med. 2018;36(7):1325.e3-1325.e4.
9. Bozkaya Y, Ay B. Toxic epidermal necrolysis associated with ribociclib in a patient with metastatic breast cancer. Breast J. 2020;26(4):773-4.
10. Kowalczyk A, Radecka B. Stevens-Johnson syndrome in breast cancer patient treated with ribociclib. Oncol Clin Pract. 2023;19(1):59-62.
11. Vrana E, Mylona S, Bobos M, Kontovinis L, Papazisis K. Ribociclib and palbociclib-induced erythema multiforme: a case report. Oxf Med Case Reports. 2022;2022(11):omac116.
12. Karagounis T, Vallurupalli M, Nathan N, Nazarian R, Vedak P, Spring L, et al. Stevens-Johnson syndrome-like eruption from palbociclib in a patient with metastatic breast cancer. JAAD Case Rep. 2018;4(5):452-4.
13. Silvestri M, Cristaudo A, Morrone A, Messina C, Bennardo L, Nisticò SP, et al. Emerging Skin Toxicities in Patients with Breast Cancer Treated with New Cyclin-Dependent Kinase 4/6 Inhibitors: A Systematic Review. Drug Saf. 2021;44(7):725-32.

Citation of this Article

Carneiro F, Bove M, Beau-Salinas F, Cailleux P, San T and Combe P. Case Report of Dress Syndrome Induced by Ribociclib. Mega J Case Rep. 2023; 6: 2001-2005.