

Intracellular agents *Coxiella burnetii* and parvovirus B19 as triggers for DRESS syndrome in a peritoneal dialysis patient

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NefroPlus 2020;12(1):77-81

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ABSTRACT

DRESS syndrome is a rare but severe cutaneous type IV hypersensitivity drug reaction with eosinophilia and systemic symptoms. Its pathophysiology is not well known but associated with viral reactivation of herpes virus and T-cells priming. It occurs 2 to 8 weeks after exposure to the accountable drug. There are less than 30 reported cases caused by vancomycin. In our case, there is an acute parvovirus B19 and *Coxiella burnetii* infection, intracellular microorganisms that are not traditionally associated with this syndrome. A 31-year-old woman with chronic kidney disease undergoing peritoneal dialysis developed a peritonitis treated with intra-peritoneal vancomycin. In three weeks, she initiated fever and diffuse maculopapular pruriginous rash. She had positive IgG/IgM phase-II antibodies for *Coxiella burnetii*, increased hepatic enzymes (cholestatic pattern), eosinophilia, increased IgE and cryoglobulins. She underwent a skin biopsy and started doxycycline, meropenem and steroids with good clinical evolution. In 2 weeks, the fever and rash relapsed and another skin biopsy was performed, with positive parvovirus B19 DNA. Vancomycin is a rare cause of DRESS, especially intra-peritoneal. Viral reactivation has been described, increasing the duration, severity and relapse probability of the syndrome. A young woman survived a DRESS syndrome vancomycin-associated with uncommon microorganisms as triggers.

Keywords: Peritoneal dialysis. DRESS syndrome. Vancomycin. Cryoglobulins. *Coxiella burnetii*. Parvovirus B19.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but severe hypersensitivity drug reaction involving the skin and multiple organs. The diagnosis can be challenging and is largely clinical, with skin rash¹, fever, eosinophilia, atypical lymphocytosis and multiple organ failures, including liver, kidneys and lungs². The hallmark of DRESS is the prolonged latency, with symptoms appearing after 2 to 8 weeks after the initial

drug exposure³. Pathogenesis is not fully understood but is thought to be related to immunosuppression upon drug hypersensitivity reaction and underlying viral infection, such as human herpesvirus 6 (HHV-6). This immunosuppression may lead to more severe systemic drug reactions². Current understanding of pathogenesis, triggers and predisposing factors is incomplete. Antibiotics, anticonvulsants, antidepressants and antiretrovirals have been implicated⁴. Studies have emphasized drug responses *per se* but also on the associated virus reactivation or anti-viral immunity. Registry of severe cutaneous adverse reaction (RegiSCAR) criteria appear to be the most widely used for diagnosis and includes at least 3 of the following characteristics: skin eruption; fever (>38.5 °C); lymphadenopathy in at least 2 sites; involvement of at least one internal organ; lymphocytosis (>4 × 10³/UL) or lymphocytopenia (<1.5 × 10³/UL); blood eosinophilia (>10% or 700/UL); and thrombocytopenia (<120 × 10³/UL)⁵. Cutaneous involvement is the most common clinical feature (70-100% of cases), with a diffuse maculopapular inflam-

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Revisión por expertos bajo la responsabilidad de la Sociedad Española de Nefrología.

matory reaction, erythroderma or pruritic eruptions. Visceral organ involvement is the major cause of morbidity and mortality, and most commonly liver, kidneys, lungs, heart and pancreas are affected. Immediate administration of high dose corticosteroids followed by a gradual tapering over 10 weeks is the treatment of choice. Systemic corticosteroids pose a dilemma during the management of infection.

CASE REPORT

A 31-year-old woman with chronic kidney disease of unknown cause, undergoing Automatic Peritoneal Dialysis (PD) for 3 years, with no known allergies, farm worker with daily contact with several animals, had an episode of a *Bacillus* spp. peritonitis prior to the present setting, for which she underwent intraperitoneal vancomycin. Three weeks later, she presented fever, malaise and a diffuse rash, with clear peritoneal fluid and no abdominal pain. Five days later her rash became confluent and maculopapular, affecting her palms, plants and face.

Diagnostic procedures

Hepatomegaly and palpable adenomegalies appeared (inguinal, submaxillary and occipital), which prompted her hospital admission. We highlight an hemoglobin of 10.7 g/dL, an aspartate transaminase of 74 U/L, an alanine transaminase of 127 U/L, an alkaline phosphatase of 177 U/L, a gamma-glutamyl amino-transferase of 105 U/L and a C-reactive protein of 10 mg/dL. Her imaging studies were normal. Blood and urine cultures were negative. Cryoglobulins were positive (with a cryocyte with no monoclonal component). Regarding the serologies, we found a positive Parvovirus B19 DNA and positive phase-II IgG antibodies for *Coxiella burnetii*. The remaining infectious and immune study was negative. She performed a positron-emission tomography scan that showed hypermetabolic supra and infra-diaphragmatic adenopathies, with a tracer uptake by the spleen and appendicular skeleton, probably relating to medullary reactivity.

Development

She was evaluated by Infectious Diseases for rash aggravation, with pruritus and sustained fever. She was evaluated by Dermatology who posed the diagnose of a viral exanthema, toxidermia and STILL syndrome. She performed a skin biopsy which showed phase-I negative and phase-II positive antibodies for *Coxiella burnetii*, with a negative PCR and negative cultures, therefore being non-specific although compatible with an infectious or drug-induced rash. In a nutshell, we concluded this syndrome was caused by both parvovirus B19 and *Coxiella burnetii*, with transient cryoglobulinemia.

Treatment

She underwent oral doxycycline, intra-venous (IV) meropenem and IV corticosteroids, maintaining a manual PD program and her everyday medication. On the 13th day, fever reappeared, prompting a re-evaluation by Infectious Diseases, who recom-

mended continuing doxycycline for another 3 weeks. Although there was no known cardiac valve lesion, she was a high-risk patient for development of chronic Q fever. She had a period of severe hypotension with need of aminergic support and was ultimately discharged on day 20, stable, with a normal CT scan and scheduled follow-up for Infectious Diseases, Dermatology and PD. She added prednisolone 10 mg, hydroxychloroquine 600 mg and topical betamethasone 1 mg/g (for the skin lesions) to her medication, meanwhile maintaining Continuous Ambulatory PD (CAPD). Two weeks later, she was readmitted for recurrent fever and rash and repeated the skin biopsy (fig. 1), revealing positive parvovirus B19 DNA in the skin tissue and positive serology, maintaining positive *Coxiella burnetii* phase II antibodies. Another 3 weeks later, she was readmitted for fever and abdominal pain, with a cloudy peritoneal effluent, diagnosed with a *Staphylococcus aureus* peritonitis. Due to the recent events, she was treated with intra-peritoneal (IP) daptomycin, ceftazidime and meropenem, which were altered to cefazolin and gentamicin after the antibiotic sensitivity pattern results, to which she had a good response. The sequence of events is outlined in figure 2.

DISCUSSION AND CONCLUSIONS

DRESS syndrome is a dermatological emergency with 10% mortality⁶. Its pathogenesis is not well understood—it is hypothesized to be an immunological reaction with viral involvement, associated with decreasing circulating B-cells and serum immunoglobulin level. This immunosuppression leads to viral reactivations which cause more severe systemic immune reaction. Inflammatory cytokines such as interleukin-5 peak several days before eosinophilia⁷, contributing to organ injury and promoting eosinophilia. Vancomycin is an uncommon cause of DRESS, with 23 cases reported until 2017⁸.

Reactivation of viruses is described with Epstein-Bar, HHV-6 and 7, and cytomegalovirus. It may increase the duration and severity of the disease and the likelihood of relapse. We believe the triggers in this case were the described intracellular agents. IP vancomycin is frequently used as empiric treatment of PD peritonitis for 2 to 4 weeks in methicillin-resistant staphylococcal infections. Due to the slow clearance of vancomycin in advanced renal failure, intermittent dosing of vancomycin is used, and doses are typically administered every 3 to 5 days.

The mainstay of treatment for DRESS is the withdrawal of the offending medication and corticosteroids, starting with 1 mg/kg/day of prednisone, with gradual taper over 3 to 6 months. Significant improvement is expected within a few days³. Rechallenge with the culprit drug is contraindicated. Studies about management of DRESS syndrome during active infection are scarce. One report demonstrated successful management of DRESS syndrome associated with infectious endocarditis involving intravenous immunoglobulins, N-acetylcysteine, montelukast, and gentamicin⁹. Previous cases have been successful in discontinuing antibiotics and starting high-dose corticosteroid following negative cultures¹⁰. A stepwise algorithm was pro-

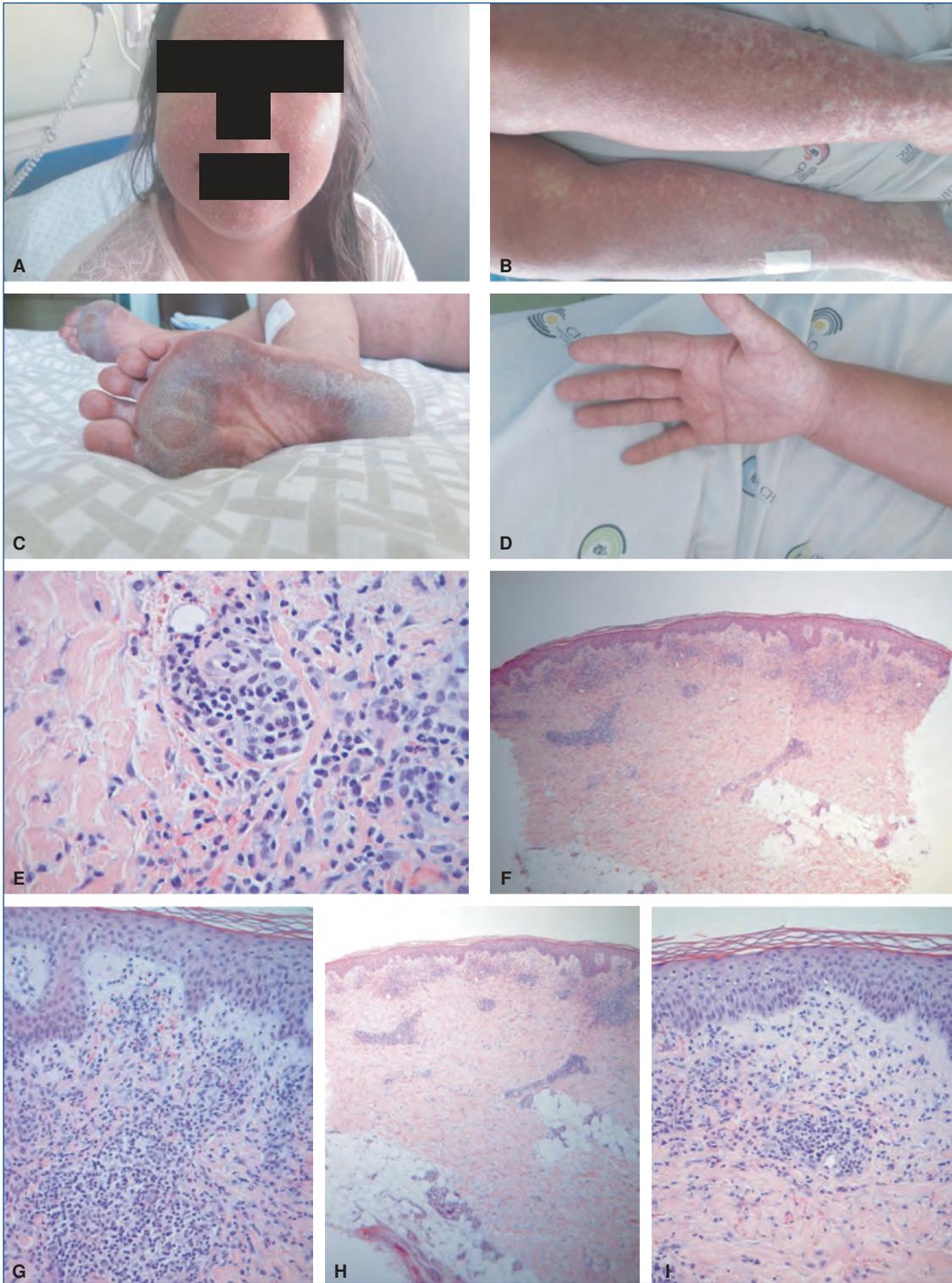


Figure 1. Aggravated cutaneous rash on the 5th day of evolution –maculopapular, confluent. A) Face. B) Lower limbs. C) Plantar surface of the foot. D) Palmar surface of the hands. E-I) Skin biopsy shows diffuse inflammation infiltrate, with mononuclear cells, which is compatible with a drug reaction and also with an infectious cause.

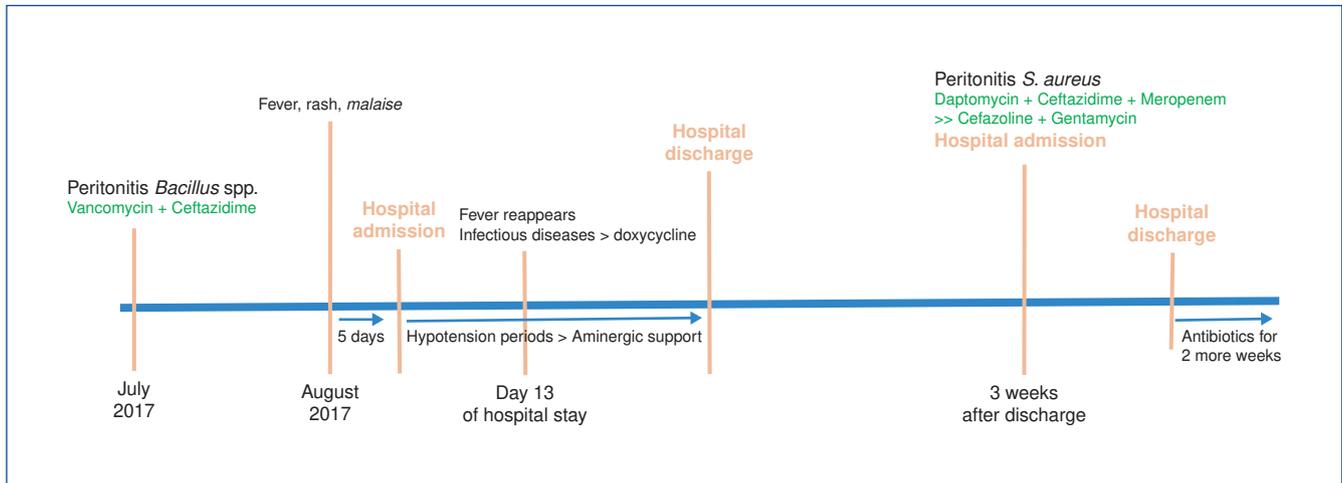


Figure 2. Timeline of clinical events.

posed to treat DRESS syndrome with parenteral corticosteroid until resolution of fever and rash followed by oral corticosteroid for 4 to 6 weeks, immediate withdrawal of the drug and symptomatic treatment such as antipyretics and topical emollients¹¹. Rapid taper of corticosteroid can result in reoccurrence of symptoms and prolonged hospital stay¹². We achieved recovery with 1,25 mg/kg daily of methylprednisolone for 3 days, though use of higher doses is reported¹³. Long-term sequelae of DRESS syndrome include infections, thyroiditis, type-I diabetes and acute interstitial nephritis¹⁴. There are very few reports of severe adverse effects from IP vancomycin and the antibiotic's increasing popularity is concerning because of the role its injudicious use plays in resistance, further emphasizing a conservative use. Susceptible patients have a genetic deficiency in the enzymes needed to metabolize certain drugs and certain human leukocyte antigens may predispose patients to hypersensitivity reactions¹⁵. Vancomycin-induced DRESS syndrome has spiked in the last years due to its increased use, higher trough targets and higher total dosage¹⁶.

Cryoglobulins are immunoglobulins which precipitate when the serum temperature is lower than the body's, usually found as part of 3 immunochemical patterns —types I, II and III¹⁷. Cryoglobulins associated with infections are usually type II (mixed polyclonal with a monoclonal component) or type III (mixed polyclonal). All kinds of microorganisms have been associated with cryoglobulins. Most type-II mixed cryoglobulinemia are associated with chronic hepatitis C infection and benefit from antiviral therapy, but a significant proportion remains

essential. We report a patient with type-II mixed cryoglobulinemia detected in the acute phase of the disease due to infection with parvovirus B19 who was successfully treated with corticosteroids. Parvovirus B19 implication in type-II mixed cryoglobulinemia has been controversial. Serologic evidence was not found in 2 series of patients with mixed cryoglobulinemia^{18,19}, with a case report showing a temporal association with B19 infection and a clear parallel between the kinetics of B19 infection and cryoglobulinemia, demonstrating a significant enrichment of the viral genome in the cryoprecipitate, thus supporting a causal relationship¹⁹.

DRESS syndrome associated with vancomycin is rare, even more if the route is intra-peritoneal, and it is easily missed. Familiarity with clinical features and pathogenesis is important to ensure a correct diagnosis and provide prompt treatment. In our case, a young patient with CKD undergoing PD survived a severe DRESS syndrome associated with vancomycin, presenting as trigger infections by uncommon intracellular agents. This association supports vancomycin judicious use and helps clinicians to make an earlier diagnose before devastating consequences ensue. Lack of awareness of this condition and its possible link to IP vancomycin may delay the diagnose and result in inappropriate empiric therapy.

Disclosure statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

- Cardoso CS, Vieira AM, Oliveira AP. DRESS syndrome: a case report and literature review. *BMJ case reports*. 2011;2011:bcr0220113898.
- Chen YC, Cho YT, Chang CY, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a drug-induced hypersensitivity syndrome with variable clinical features. *Dermatol Sin*. 2013;31:196-204.
- Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part I. Clinical perspectives. *J Am Acad Dermatol*. 2013;68:693.
- Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: A literature review. *Am J Med*. 2011;24:588-97.

5. Kim DH, Koh YI. Comparison of diagnostic criteria and determination of prognostic factors for drug reaction with eosinophilia and systemic symptoms syndrome. *Allergy Asthma Immunol Res.* 2014;6:216-21.
6. Hirahara K, Kano Y, Mitsuyama Y, Takahashi R, Kimishima M, Shiohara T. Differences in immunological alterations and underlying viral infections in two well-defined severe drug eruptions. *Clin Exp Dermatol.* 2010;35:863-8.
7. Choquet-Kastylevsky G, Intrator L, Chenal C, Bocquet H, Revuz J, Roujeau J. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. *Br J Dermatol.* 1998;139:1026-32.
8. Wilcox O, Hassanein M, Armstrong J, Kassis N. Case report: atypical presentation of vancomycin induced DRESS syndrome: a case report and review of the literature. *BMC Pulm Med.* 2017;17:217.
9. Della-Torre E, Yacoub MR, Pignatti P, Della-Torre F, Sabbadini M-G, Colombo G, et al. Optimal management of DRESS syndrome in course of infectious endocarditis. *Ann Allergy Asthma Immunol.* 2013;110:303-5.
10. Sultan SJ, Sameem F, Ashraf M. Drug reaction with eosinophilia and systemic symptoms: manifestations, treatment, and outcome in 17 patients. *Int J Dermatol.* 2015;54:537-42.
11. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology.* 2003;206:353-6.
12. Chiche L, Grados A, Harlé J-R, Cacoub P. Mixed cryoglobulinemia: a role for parvovirus B19 infection. *Clin Infect Dis.* 2010;50:1074-5.
13. Díaz-Mancebo R, Costero-Fernández O, Vega-Cabrera C, Olea-Tejero T, Yébenes L, Picazo ML, et al. Dress syndrome and acute tubulointerstitial nephritis after treatment with vancomycin and beta-lactams - case report and literature review. *Nefrología.* 2012;32:685-7.
14. Tamagawa-Mineoka R, Katoh N, Nara T, Nishimura Y, Yamamoto S, Kishimoto S. DRESS syndrome caused by teicoplanin and vancomycin, associated with reactivation of human herpesvirus-6. *Int J Dermatol.* 2007;46:654-5.
15. Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E. Fever, rash, and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. *J Allergy Clin Immunol Pract.* 2014;2:2.
16. Young S, Ojaimi S, Dunckley H, Douglas MW, Kok J, Fulcher DA, et al. Vancomycin-associated drug reaction with eosinophilia and systemic symptoms syndrome. *Intern Med J.* 2014;44:694-6.
17. Magill SS, Edwards JR, Beldavs ZG, Dumyati G, Janelle SJ, Kainer MA. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. *JAMA.* 2014;312:1438-46.
18. Martín Mola E, Gómez Busto F. Crioglobulinas: aspectos prácticos para su detección en el laboratorio. *Med Clin (Barc).* 1984;82:502-6.
19. Cacoub P, Boukli N, Hausfater P, Garbarg-Chenon A, Ghillani P, Thibault V, et al. Parvovirus B19 infection, hepatitis C virus infection and mixed cryoglobulinemia. *Ann Rheum Dis.* 1998;57:422-4.