DRESS Syndrome: A Review Based on a Clinical Report

Síndrome de DRESS: Uma Revisão Baseada num Caso Clínico

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Abstract:

DRESS syndrome is a rare but potentially life-threatening disease that may present with multiorgan involvement and cutaneous eruptions.

We report the case of a 28-year-old puerperal woman who developed a cutaneous exanthema 2 months after cesarean delivery, along with muscle pain, odynophagia, cough, and fever. The cutaneous eruption started on the lower limbs and progressed throughout the entire body. The patient had received ceftriaxone intravenously during delivery and had a history of oral intake of diclofenac and methyldopa. Scored 6 on RegiSCAR, confirming the diagnosis of DRESS syndrome. The patient also developed toxic hepatitis, which was managed with intravenous corticotherapy. After 2 weeks of treatment and the removal of probable drugs, the patient was discharged with clinical and laboratory improvement.

This case highlights the importance of prompt diagnosis and treatment of late pharmacological reactions, particularly DRESS Syndrome, which can be challenging to diagnose due to its delayed presentation.

Keywords: Drug Hypersensitivity Syndrome; Exanthema; Postpartum Period.

Resumo:

A síndrome DRESS é uma doença rara, mas potencialmente fatal, que pode cursar com erupções cutâneas e envolvimento multiorgânico.

Relatamos o caso de uma puérpera de 28 anos que desenvolveu exantema cutâneo 2 meses após o parto por cesariana, com dores musculares, odinofagia, tosse e febre. A erupção cutânea começou nos membros inferiores e progrediu por todo o corpo. Foi medicada com ceftriaxone durante o parto, tendo também histórico de uso de diclofenac e metildopa. Pontuou 6 no *score* RegiSCAR, confirmando o diagnóstico de síndrome DRESS. A paciente também desenvolveu hepatite tóxica, motivando tratamento com corticoterapia intravenosa. Após 2 semanas de tratamento e evicção dos fármacos responsáveis, teve alta com melhora clínica e laboratorial.

Este caso destaca a importância do diagnóstico e tratamento imediatos das reações farmacológicas tardias, especialmente da síndrome DRESS, cujo diagnóstico pode ser desafiador devido à sua apresentação tardia.

Palavras-chave: Exantema; Período Pós-Parto; Síndrome de Hipersensibilidade a Medicamentos.

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Introduction

DRESS syndrome is a severe pharmacological reaction with systemic symptoms and potential life-threatening risks, with a mortality rate as high as 10%.[1] It is a rare syndrome, with an estimated incidence of 1 in 1000 to 1 in 10 000[1] individuals.

It differs from typical pharmacological reactions by its long latency period until symptom presentation (around 2 to 6 weeks after exposure[2]). The syndrome is characterized by the appearance of skin rashes, usually accompanied by lymphadenopathy, hematological changes (eosinophilia, atypical lymphocytes), and multiorgan involvement.[3] The severity of systemic symptoms and multiorgan involvement is directly related to the mortality of the disease.[4]

This syndrome should be suspected in patients presenting a combination of clinical features, a history of exposure to drugs known to be potential causatives in the previous two to eight weeks, and corresponding laboratory and imaging findings.[1] The final diagnosis is confirmed using a diagnostic score developed in the RegiSCAR study (Table 1), classifying the case as excluded, possible, probable, or confirmed.[5]

The objectives of this report are to present a clinical case and raise awareness among clinicians for the diagnosis and treatment of this syndrome.

Case Report

The case reports a 28-year-old puerperal woman with a history of hypertension during pregnancy who was medicated with methyldopa, folic acid, and oral iron. The patient had a cesarean delivery 2 months before presenting to the emergency department (ED) and has been breastfeeding since then. During cesarean delivery, she was treated with ceftriaxone for surgical prophylaxis, and she also took diclofenac 2 to 3 weeks after the surgery.

One month after delivery, she started to experience symptoms of odynophagia, cough, and myalgia, which motivated medical evaluation and prescription of paracetamol with improvement of symptoms. Three days after the symptoms

disappeared, a maculopapular rash appeared on her lower limbs, which progressed to her whole body, including palms and soles (Fig. 1). She also developed asthenia and fever with progressively higher and more frequent peaks that did not respond to paracetamol. The condition lasted for 10 days, during which she reported diarrhea in the last three days, when she finally went to the urgency department for observation.

At admission, she was normotensive, normocardic and afebrile. Presented a maculopapular rash dispersed throughout her body (including palms and soles) that disappeared with digital pressure, without presenting blisters. Nikolsky's sign was negative, and there were no oropharyngeal changes. Palpation identified painful cervical and axillar lymphadenopathies.

Blood analysis showed no leucocytosis or eosinophilia, normal serum creatinine and urea, a cytocholestatic profile with gamma-glutamyl transferase (GGT): 412 UI/L, alkaline phosphatase (ALP): 283 U/L, lactate dehydrogenase (LDH): 888 UI/L, aspartate aminotransferase (AST): 268 UI/L, alanine aminotransferase (ALT): 303 U/L, C-reactive protein (CRP): 10.64 mg/dL, sedimentation rate (ESR): 3mm. Urine analysis showed inactive sediment with a total protein/urinary creatinine ratio of 650 mg/mg.

Further investigations included negative anti-double-stranded DNA (ds-DNA), antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA). Serology for hepatitis A (VHA), surface antigen of hepatitis B virus (AgHBs), and hepatitis C virus (VHC) were all negative.

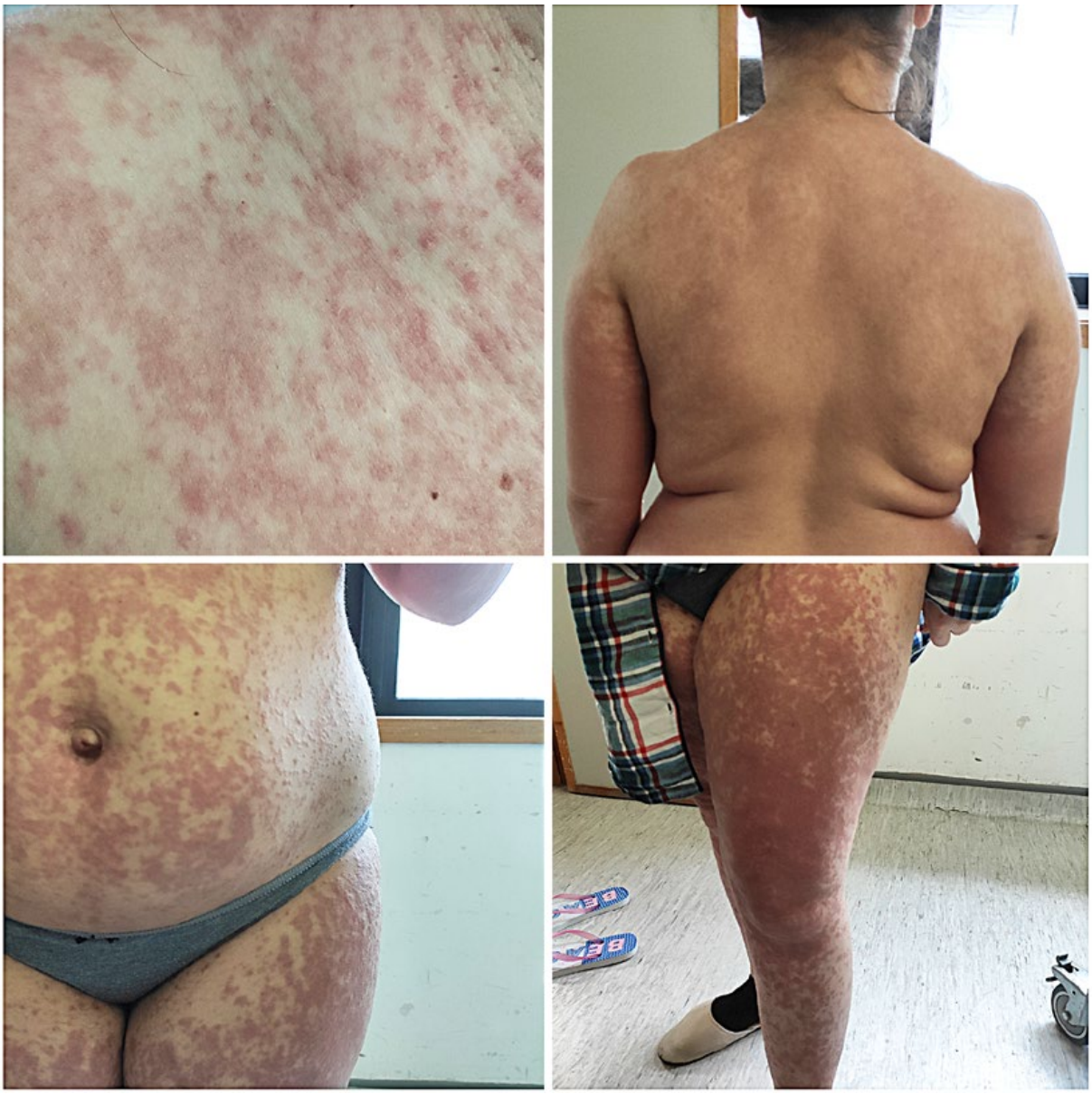

Figure 1: Maculopapular skin lesions observed upon admission.

Table 1: RegiSCAR score[3,10]

Criteria	Score			
	-1	0	1	2
Fever (Temperature ≥ 38.5ºC)	No/U	Yes		
Adenomegaly (>1 cm, at least 2 sites)		No/U	Yes	
Eosinophilia (If leukocytes < 4.0x10^9/L			≥0.77 x10^9/L ≥10%	≥1.5 x10^9/L
Atypical lymphocytes		No/U	Yes	
Skin involvement Skin involvement Suggestive rash (≥2 features)[a] Suggestive skin biopsy	 No No	 No/U U Yes/U	 >50% Yes	
Other organ envolvement[b] Liver Kidneys Lung Muscle/Heart Pancreas Other		 No/U No/U No/U No/U No/U No/U	 Yes Yes Yes Yes Yes Yes	
Resolution in ≥ 15 days	No/U	Yes		
Assessment of other possible causes ANA Blood cultures Serology HAV, HBV, HCV Chlamydia/Mycoplasma If none positive and ≥ 3 negative			 Yes	

[a]Suggestive features: facial edemas, purpura, infiltration, desquamation
[b]If other causes are excluded, score 1 if 1 organ is involved or 2 if ≥ 2 organs are involved
Final score: < 2 excluded case; 2-3 possible case; 4-5 probable case; ≥ 6 confirmed case

Serology for herpes simplex virus 1 and 2 was negative, herpes 6 was positive with <500 copies/mL, herpes 7 was negative, and Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were negative as well.

Abdominopelvic computed tomography showed hepatomegaly with globularity, signs of colitis with slight parietal thickening, and accentuation of haustras in the transverse colon. Increased inguinal, mesenteric, and lumbar-aortic lymph nodes were also reported, as well as a small pelvic peritoneal effusion.

The patient was admitted to the internal medicine ward for further evaluation with a probable diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, affecting three visceral organs: liver, kidney, and colon. She was treated with topical betamethasone and hydroxyzine for pruritus.

Due to the involvement of 3 visceral organs, the decision was made to start treatment with methylprednisolone 1 mg/kg. After 7 days of treatment, there was progressive improvement in liver function and resolution of proteinuria on the 6th day of hospitalization. The patient was discharged after 14 days of treatment with improvement in skin lesions (Fig. 2) and multiorgan dysfunction, with instructions to follow a corticosteroid tapering regimen. There were no implications in breastfeeding, and the patient could resume it immediately after discharge.

Discussion

As mentioned, DRESS syndrome is a rare diagnosis, but it should be considered in patients with symptoms that have a potential temporal relationship with suspected drugs. In this case, the use of drugs during pregnancy and the clinical presentation of maculopapular skin reactions motivated a higher suspicion of a delayed drug reaction. Note that skin reactions are described as present in approximately 70% to 100% of cases, and they can appear in various forms. Diffuse maculopapular reactions are the most observed, typically affecting more than 50% of the body surface area.[6,7] This is consistent with the findings described in the patient, in which there was an estimated affection of 70% of the body surface area.

Retrospectively analyzing the patient's initial symptoms (fever, myalgia, and skin rash), although nonspecific, are reported in the literature as the most described initial symptoms.[3]

According to the scientific literature, the most frequently affected visceral organ is the liver, affected in 45% to 86.1% of cases, and is also the main cause of mortality.[8]

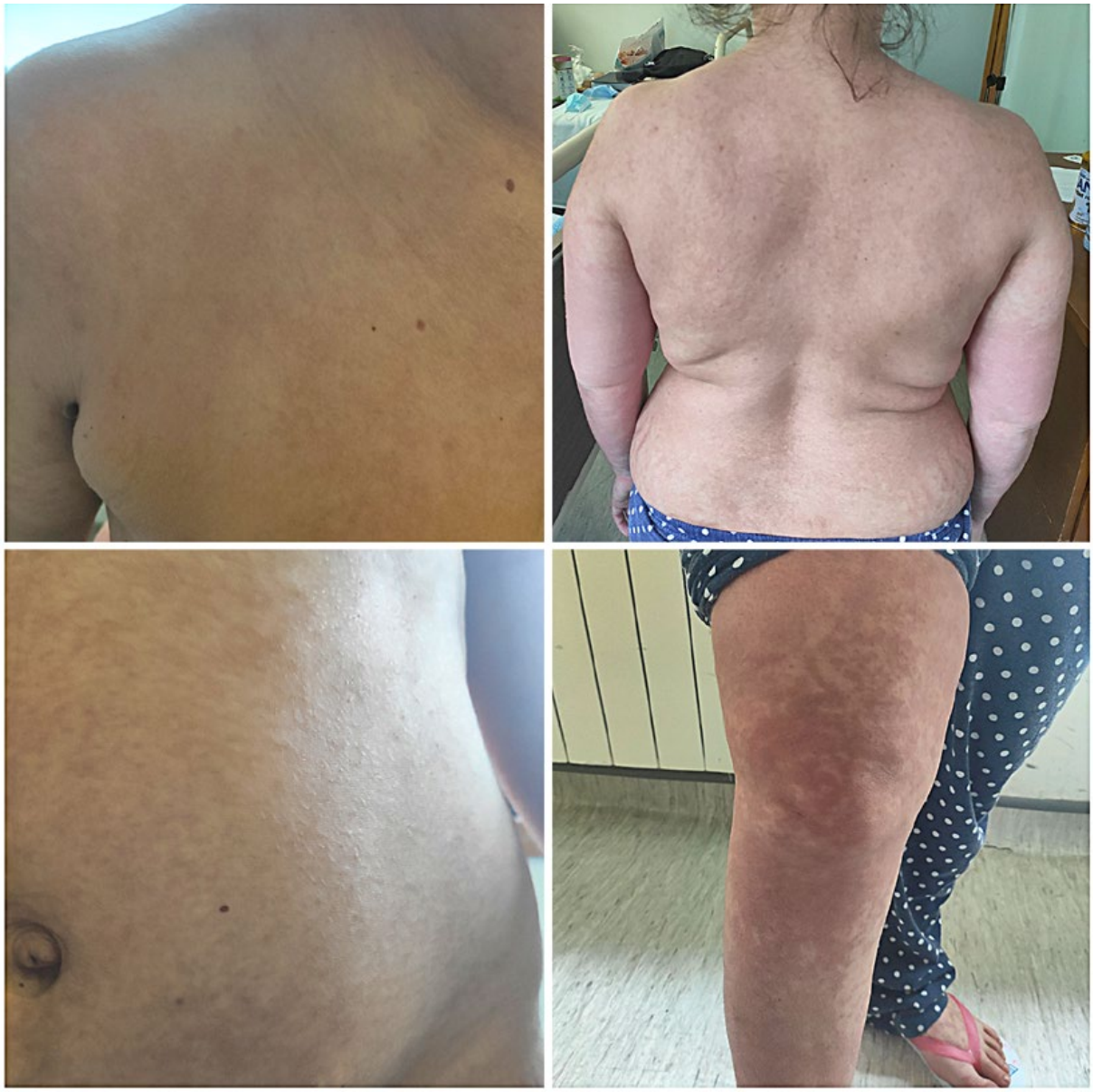

Figure 2: Maculopapular skin lesions observed at the time of hospital discharge.

In the presented case, there was a cytocholestatic profile with GGT levels disproportionately higher than ALP levels, which is a typical finding of a cholestatic pattern secondary to a drug reaction.[9] The cytolysis was also considerable, with maximum AST and ALT values of 268 IU/L and 303 U/L, respectively. There was a worsening from the third day of hospitalization despite maintenance of treatment with intravenous corticosteroids. Globally, the patient presented a favorable evolution, with AST and ALT values of 19 IU/L and 64 U/L, respectively, at the time of discharge (Fig. 3).

In addition to the delayed drug reaction, researchers have been proposing other important factors in the pathophysiology of the disease, particularly the involvement of reactivation of the human herpes virus 6 (HHV-6). This phenomenon was initially described in 1997[11] and then in 1998[12,13] in Japan, being described in patients with DRESS syndrome, due to an immunosuppressive state induced by the drug reaction. Reactivation of this and other viruses in the same family, such as human herpes virus 7 (HHV-7), cytomegalovirus (CMV), and Epstein-Barr virus (EBV), was described as contributing to the severity of systemic symptoms.[4,6] In this sense, a team of Japanese experts developed a diagnostic score for DRESS syndrome, using reactivation of the HHV-6 virus as a diagnostic criterion for the disease (Table 2).[10]

The study of these viruses allows the application of the diagnostic score developed by the Japanese Consensus Group for DRESS, known in Japan as DiHS (drug-induced hypersensitivity syndrome), and it was found that this case scored 7 out of 7 points.

Table 2: Japanese Consensus Group for the diagnosis of DiHS (drug-induced hypersensitivity syndrome)[10,14]

	Drug-induced hypersensitivity syndrome (DiHS) diagnosis Criteria
1	Maculopapular rash, with onset 3 weeks after taking the drug
2	Symptoms present 2 weeks after discontinuation of the drug
3	Fever (>38ºC)
4	Liver abnormalities (ALT>100 U/L)*
5	Abnormalities in leukocytes (≥1 protect): a Leukocytosis (>11x10^9/L) b Atypical lymphocytes (>5%) c Eosinophilia (>1.5 x10^9/L)
6	Lymphadenopathy
7	Reactivation of HHV-6

5 criteria: atypical.. 7 criteria: typical DiHS
*This can be replaced by other organ Involvement, such as renal involvement
DiHS: drug-induced hypersensitivity syndrome; HHV-6: human herpesvirus 6

In this case, the patient's history of undergoing a cesarean delivery might have contributed to an immunosuppressive state, potentially enhancing the reactivation of HHV-6 and the onset of DRESS syndrome. However, it is important to note that this assumption lacks robust studies to firmly establish a direct link between cesarean delivery and this particular drug reaction.

Many drugs are described as potentially causing this type of syndrome, and there are multiple systematic reviews focusing on this topic. The most frequently reported drugs include allopurinol, anticonvulsants such as carbamazepine and phenytoin, sulfasalazine, and some non-steroidal anti-inflammatory drugs (NSAIDs), among others.[3,7,15] In the presented case, pinpointing a definitive causative drug proved challenging due to the presence of multiple potential agents.

Considering diclofenac's frequent association and its prolonged use of more than two weeks, it was considered the most likely causative agent, while ceftriaxone was considered less likely possibility.

Conclusion

DRESS syndrome is a rare syndrome for which clinicians should be aware of the importance of a rapid and timely diagnosis. It should be noted that it is a potentially fatal disease, but when identified and treated early, it has a benign course and good prognosis. ■

Contributorship Statement

PFM - Clinical follow-up, manuscript writing, literature research and final approval
IAM, JCC - Literature search and critical review
ALS - Clinical follow-up, bibliographical research and critical review
PMN - Clinical follow-up, literature search, critical review and final approval
All authors approved the final version to be published.

Declaração de Contribuição

PFM – Acompanhamento clínico, redação de manuscrito, pesquisa bibliográfica e aprovação final
IAM, JCC – Pesquisa bibliográfica e revisão crítica
ALS – Acompanhamento clínico, pesquisa bibliográfica e revisão crítica
PMN – Acompanhamento clínico, pesquisa bibliográfica, revisão crítica e aprovação final.
Todos os autores aprovaram a versão final a ser publicada.

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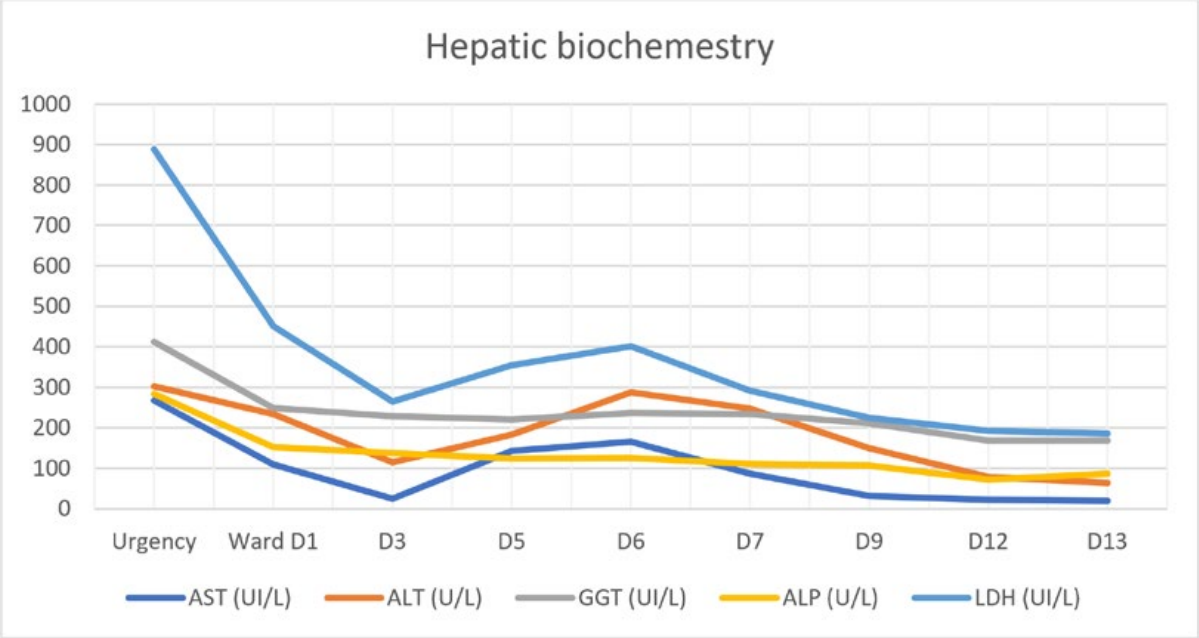

Figure 3: The evolution of hepatic biochemistry during the patient's hospitalization.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase, IU/L: international units per litre.
To assert the diagnosis, RegiSCAR score[3,10] (Table 1) was applied, where the patient scored 6 points: adenopathies: +1, rash involving > 50% body surface area: +1, involvement of two or more organs: +2, atypical lymphocytes: +1, exclusion of other possible causes: +1.

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