## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## REFERENCES

1. Owens DC. Sodium valproate in psychiatric practice: time for a change in perception. Br J Psychiatry. 2019;215:516-8.
2. Angus-Leppan H, Arkell R, Watkins L, Heaney D, Cooper P, Shankar R. New valproate regulations, informed choice and seizure risk. J Neurol. 2024;271:5671-86.
3. Coste J, Blotiere PO, Miranda S, Mikaeloff Y, Peyre H, Ramus F, et al. Risk of early neurodevelopmental disorders associated with in utero exposure to valproate and other antiepileptic drugs: a nationwide cohort study in France. Sci Rep. 2020;10:17362.
4. Tallon E, O'Donovan L, Delanty N. Reversible male infertility with valproate use: a review of the literature. Epilepsy Behav Rep. 2021;16:100446.
5. Medicines and Healthcare Products Regulatory Agency. Valproate: review of safety data and expert advice on management of risks. 2023. [cited 2024 Nov 19]. Available from: https://assets.publishing.service.gov.uk/media/65660310312f400013e5d508/Valproate-report-review-and-expert-advice.pdf.

Margarida ALVES✉[1], Diana DURÃES[1], Cátia SANTOS[1]
1. Department of Psychiatry and Mental Health. Centro Hospitalar de Setúbal. Setúbal. Portugal.
✉ **Autor correspondente:** Margarida Alves. margarida.alves@ulsa.min-saude.pt
**Recebido/*Received*:** 08/09/2024 - **Aceite/*Accepted*:** 21/11/2024 - **Publicado/*Published*:** 02/01/2025

https://doi.org/10.20344/amp.22284

# Infection and Immunosuppression as Causes for Immune Dysfunction Presenting as Hemophagocytic Lymphohistiocytosis and Thrombotic Microangiopathy

# Infeção e Imunossupressão como Causas de Disfunção Imune Manifestada como Linfohistiocitose Hemofagocítica e Trombomicroangiopatia Trombótica

**Keywords:** Lymphohistiocytosis, Hemophagocytic/etiology
**Palavras-chave:** Linfohistiocitose Hemofagocítica/etiologia

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease associated with a hyperinflammatory state, cytokine storm, and macrophage and lymphocyte activation.[1] Because of its rarity and low specificity of clinical symptoms, the diagnosis is difficult, and the prognosis is bad.

We describe the case of a 35-year-old man with Crohn's disease (CD). The disease had recently flared, requiring treatment with vedolizumab (VDZ), prednisolone (40 mg/d) and azathioprine (100 mg/d).

Ongoing complications led to admission due to a recurrent intra-abdominal abscess. Failure of empirical antibiotic therapy led to right hemicolectomy with direct ileo-colonic anastomosis. On preoperative evaluation, a nasopharyngeal swab for SARS-CoV-2 was positive, when it had been negative on admission, and the patient had no symptoms. Five days after the surgery, fever (maximum 38.5ºC), haematochezia, and a cutaneous rash (Fig. 1) appeared, alongside the development of *de novo* multiorgan failure (Table 1), namely acute kidney injury, acute hepatic failure, and thrombotic microangiopathy. An abdominal computed tomography (CT) scan showed hepatomegaly with no surgical complications. *Enterococcus faecium* was isolated in blood cultures, and therapy was adjusted accordingly. Further work-up led to the diagnosis of HLH given the presence of hyperferritinaemia, hypertriglyceridemia, hemophagocytosis on bone marrow and high serum soluble CD25 (fulfilling six out of eight HLH-2004 diagnostic criteria). Additionally, other aetiologies such as cytomegalovirus, human immunodeficiency virus, thrombocytopenic thrombotic purpura, and haemolytic uremic syndrome were excluded. Suppressive therapy with high-dose corticosteroids was added and the patient steadily recovered with resolution of all organ dysfunctions (Table 1). Predisposing mutations in *STXBP2*, *STX11*, *PRF1* and *UNC13D* were searched and turned out negative.

Hemophagocytic lymphohistiocytosis was assumed secondary to sepsis due to *E. faecium* bacteriemia, probably in the context of intestinal translocation after abdominal

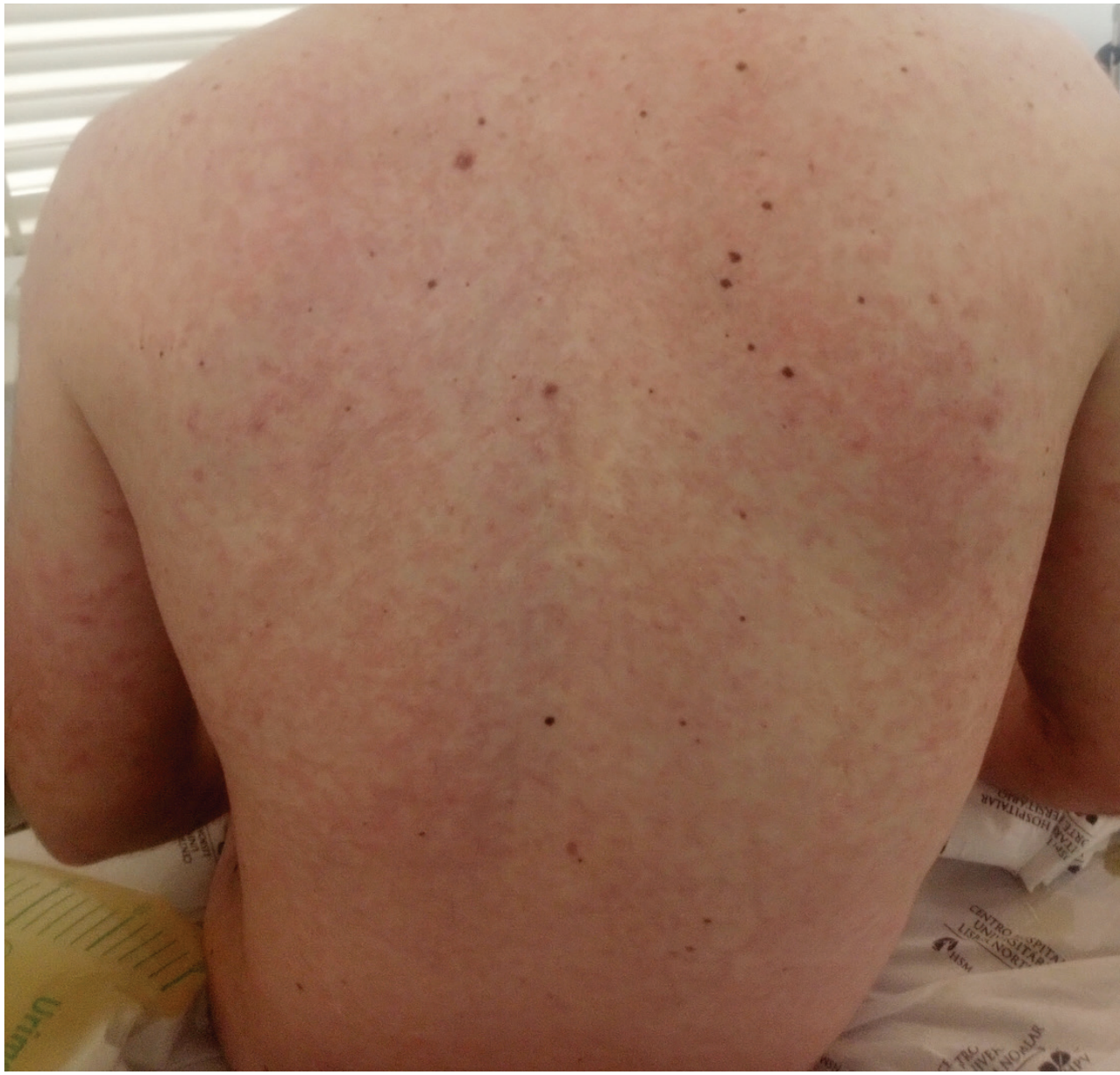

Figure 1 – Cutaneous macular rash in the patient's back

surgery. However, the SARS-CoV-2 co-infection and the patient's baseline immunosuppression cannot be overlooked as contributors. Cases of HLH secondary to SARS-CoV-2 infection have been described, and the virus is known to modulate the immune system by reducing natural-killer T cells and increasing levels of IL-6, TNF-α and IFN-γ.[2-4] Moreover, the rash presented by the patient was biopsied and showed findings suggestive of viral exanthema, hence denoting the pathological viral role in this case. Additionally, the patient was on high-dose maintenance corticosteroids, as well as on azathioprine and VDZ, an α4β7 integrin inhibitor with a prolonged half-life, and with a known infectious risk, with some authors even suggesting a higher risk of post-surgical complications associated with its use.[5] Regardless, both factors may have contributed to the dysregulated immune response to the infectious stimulus and progression to HLH in this patient. One note must be given to the association of HLH and thrombotic microangiopathy, namely the causal relationship between the two pathological processes, a rare combination, and the exclusion of major differential diagnosis.

This case highlights the intricate relationships between infection and immune system modulation, some of which are still unknown, and their life-threatening potential.

## PREVIOUS AWARDS AND PRESENTATIONS

Case report presented as an oral communication on the 27th Portuguese Congress of Internal Medicine.

## AUTHOR CONTRIBUTIONS

HAB, MAQF: Study conception and design, data acquisition and analysis, writing of the manuscript.

Table 1 – Blood work evolution during hospital admission

| Parameters | Reference range and units | D1[a] | D3 (Pre-op)[b] | D4 | D6 | D7[c] | D10[d] | D12[e] | D16 | D38 (discharge) |
|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | 13 - 16 g/dL | **11.4** | **11.9** | **9.4** | **7.8** | **8.1** | **8.7** | **7.1** | **7.9** | **9.6** |
| Leukocyte | 4.0 - 11.0 x $10^9$/L | **22.3** | 5.5 | 6.4 | **16.4** | **17.2** | **26.0** | 10.2 | 11.0 | 9.0 |
| Platelets | 150 - 450 x $10^9$/L | 426 | 445 | 266 | **101** | **75** | **40** | **34** | **105** | 240 |
| INR | 1.0 | 1.2 | 1.1 | **1.8** | 1.1 | 0.98 | 1.04 | - | 1.20 | 1.05 |
| Fibrinogen | 200 - 400 mg/dL | - | - | - | - | **170** | 339 | **175** | 317 | 298 |
| D-dimers | < 0.5 ug/mL | - | - | - | - | **66.52** | **109.30** | **55.57** | **11.57** | **1.64** |
| CRP | < 0.5 mg/dL | **25.3** | **3.1** | **33** | **41.5** | **43.9** | **26.3** | **3.99** | **3.83** | 0.16 |
| Cr | 0.7 - 1.2 mg/dL | 0.77 | 0.88 | **1.82** | **7.62** | **8.74** | **10.38** | **5.21** | 1.15 | 0.55 |
| ALT | < 41 U/L | 17 | 14 | **49** | **60** | **106** | **45** | 17 | 15 | **100** |
| AST | < 40 U/L | 17 | 15 | **463** | **382** | **443** | **68** | 27 | 38 | 35 |
| GGT | < 60 U/L | **75** | 51 | - | **1055** | **757** | **450** | **241** | - | - |
| Alkaline phosphatase | 40 - 130 U/L | 70 | 62 | **372** | **594** | - | **348** | **154** | - | - |
| Total bilirrubin | < 1.2 mg/dL | - | 0.1 | 0.4 | 0.2 | 0.26 | 0.28 | 0.21 | 0.24 | 0.20 |
| Lactate dehidrogenase | 100 - 250 U/L | 194 | - | **4760** | **5951** | **5192** | **2079** | **559** | **468** | 200 |
| Haptoglobin | 30 - 200 mg/dL | - | - | - | - | < 20 | - | - | - | - |
| Ferritin | 30 - 400 ng/mL | - | - | - | - | **65757** | - | - | - | 55.6 |
| Triglycerides | < 150 mg/dL | - | - | - | - | **274** | - | - | - | - |
| Urinary analysis | | | | | | **Proteinuria of 25 mg/dL Hemoglobinuria of 150 cel/uL Rare hyaline casts** | | | | |
| Direct and Indirect Coombs Test | | | | | | | Negative/ Negative | | | |
| Peripheral blood smear | | | | | | Multiple schistocytes, without other findings | | | | |
| Other tests (no particular date) | Complement (C3/ C4) and ADAMTS13 were normal. Shiga toxin was negative. | | | | | | | | | |

**a**: Empiric antibiotic therapy started;
**b**: SARS-CoV-2 RT-PCR positive;
**c**: Starting of fever;
**d**: Beginning of methylprednisolone pulse 1 g/d;
**e**: Ending of methylprednisolone pulse 1 g/d and starting of prednisolone 1 mg/kg/day with a weaning scheme of 10 mg/week.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: serum creatinine; CRP: C-reactive protein; GGT: gama glutamiltransferase; INR: international normalized ratio;

IML, MG, PHM: Data acquisition and analysis, writing of the manuscript.

All authors approved the final version to be published.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October

2024.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## PATIENT CONSENT

Obtained.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## REFERENCES

1. McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. May 2022. UpToDate. [cited 2024 June 15]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis?search=hemophagocytic%20lymphohistiocytosis&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1.
2. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. autoimmunity reviews. Autoimmun Rev. 2020;19:102537.
3. Meazza Prina M, Martini F, Bracchi F, Di Mauro D, Fargnoli A, Motta M, et al. Hemophagocytic syndrome secondary to SARS-Cov-2 infection: a case report. BMC Infect Dis. 2021;21:811.
4. Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. Rheumatol Int. 2021;41:7-18.
5. Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, et al. Comparative efficacy and safety of biologic therapies for moderate-to-severe crohn's disease: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021;6:1002-14.

Henrique ATALAIA-BARBACENA✉[1,2], Maria Ana QUADROS FLORES[3], Inês MATIAS-LOPES[1], Margarida GUIOMAR[1], Patrícia HOWELL-MONTEIRO[1]

1. Internal Medicine Department. Hospital de Santa Maria. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
2. Instituto de Farmacologia e Neurociências Básicas. Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
3. Infectious Diseases Department. Hospital de Santa Maria. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.

✉ **Autor correspondente:** Henrique Atalaia Barbacena. hja.barbacena@gmail.com

**Recebido/*Received*:** 20/06/2024 - **Aceite/*Accepted*:** 21/11/2024 - **Publicado/*Published*:** 02/01/2025



https://doi.org/10.20344/amp.21969