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Case Report: Adult Haemophagocytic Lymphohistiocytosis, with chronic active EBV infection and ocular immune reconstitution inflammatory syndrome

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Case Report: Adult Haemophagocytic Lymphohistiocytosis, with chronic active EBV infection and ocular immune reconstitution inflammatory syndrome

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À minha avó Palmira *(In memoriam)*,
a luz que ilumina o meu caminho e
que me tornou na pessoa que sou hoje.

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RESUMO

O Síndrome Hemafagocítico (SHF) ou Linfohistiocitose Hemofagocítica associado à infeção crónica ativa por vírus Epstein-Barr (EBV) é raro e tem elevada mortalidade. Apresentamos o caso clínico de um síndrome inflamatório de reconstituição imune (SIRI) ocular, num paciente com SHF associado a infeção por EBV. Homem de 38 anos apresenta-se com de febre, mal-estar geral, hepatoesplenomegalia, adenopatias torácicas e abdominais, pancitopenia e hiperferritinemia. Iniciou tratamento para SHF associado a EBV com corticosteróides, imunoglobulinas e valganciclovir. Após 3 recidivas graves, fez rituximab com supressão eficaz da carga viral de EBV. Três dias depois, desenvolveu SIRI ocular (retinite bilateral, panuveíte necrótica aguda grave) devido à diminuição abrupta da carga viral de EBV, aumento da contagem de linfócitos T, retinite ocular por EBV passada e inflamação exagerada local. Um mês após iniciar ciclosporina, a imunodisfunção grave dos linfócitos B e T, conduziu a pneumocistose com síndrome de dificuldade respiratória aguda fatal. O SHF associado a EBV é uma condição rara e ameaçadora de vida, com apresentação inespecífica. Que tenhamos conhecimento, até à data, este é o primeiro caso reportado de SIRI ocular associada a rituximab.

Palavras Chave: Síndrome Hemafagocítico; Infeção crónica ativa por EBV; Síndrome inflamatório de reconstituição imune; Imunologia

ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) associated with chronic active Epstein-Barr virus (CAEBV) is rare and with high mortality. We report a case of ocular immune reconstitution inflammatory syndrome (IRIS), in a patient with EBV-driven HLH. A 38-year-old male presented with fever, malaise, hepatosplenomegaly, thoracic and abdominal adenomegalies, pancytopenia and hyperferritininemia. EBV-driven HLH was diagnosed and treated with corticosteroids, immunoglobulin and valganciclovir. After 3 severe HLH relapses, rituximab lead to viral load suppression, but soon after ocular IRIS was developed (bilateral retinitis, acute necrotic severe panuveitis) due to abrupt EBV viral load decrease, increase in T lymphocytes count, past ocular EBV retinitis and exaggerated local inflammation. One month after starting cyclosporine, severe B and T lymphocyte suppression grounded severe pneumocystosis with fatal acute respiratory distress syndrome. EBV-driven HLH is a rare life-threatening condition with unspecific presentation. To our knowledge this is the first report of ocular IRIS associated with rituximab.

Key words: Haemophagocytic Lymphohistiocytosis; Chronic Active Epstein Barr Virus; Immune Reconstitution Inflammatory Syndrome; Immunology

LIST OF ABREVIATIONS

HLH – Haemophagocytic Lymphohistiocytosis

EBV - Epstein-Barr Virus

IRIS - Immune Reconstitution Inflammatory Syndrome

HIV - Human Immunodeficiency Virus

CAEBV - chronic active EBV Infection

EBNA – Epstein Barr Nuclear Antigen

VCA – Virus Capsular Antigen

IVIG - Intravenous Immunoglobulin

PFR1 – Perforin 1

UNC13D - Unc-13 Homolog D

STX11 – Syntaxin 11

STXBP2 - Syntaxin Binding Protein 2

RAB27A - Member RAS oncogene family

XIAP - X-linked inhibitor of apoptosis

RE - Right Eye

ARDS – Acute Respiratory Distress Syndrome

LYST gene - lysosomal trafficking regulator

NLRC4 - NLR family CARD domain containing 4

BIRC4 - Baculoviral IAP repeat-containing protein 4

GATA2 - GATA-binding factor 2, transcription factor

CTPS1 - CTP Synthase 1, Protein Coding gene

DDX3X - DEAD-Box Helicase 3 X-Linked, Protein Coding gene

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) associated with chronic active Epstein-Barr virus (CAEBV) is rare and with high mortality. We report a case of ocular immune reconstitution inflammatory syndrome (IRIS), in a patient with EBV-driven HLH. A 38-year-old male presented with fever, malaise, hepatosplenomegaly, thoracic and abdominal adenomegalies, pancytopenia and hyperferritininemia. EBV-driven HLH was diagnosed and treated with corticosteroids, immunoglobulin and valganciclovir. After 3 severe HLH relapses, rituximab lead to viral load suppression, but soon after ocular IRIS was developed (bilateral retinitis, acute necrotic severe panuveitis) due to abrupt EBV viral load decrease, increase in T lymphocytes count, past ocular EBV retinitis and exaggerated local inflammation. One month after starting cyclosporine, severe B and T lymphocyte suppression grounded severe pneumocystosis with fatal acute respiratory distress syndrome. EBV-driven HLH is a rare life-threatening condition with unspecific presentation. To our knowledge this is the first report of ocular IRIS associated with rituximab.

Key words: Haemophagocytic Lymphohistiocytosis; Chronic Active Epstein Barr Virus; Immune Reconstitution Inflammatory Syndrome; Immunology

INTRODUCTION

Haemophagocytic Lymphohistiocytosis (HLH) is a rare cytokine storm syndrome, characterized by an over expression of activated macrophages and cytotoxic T cells [1,2], with unspecific features: fever, cytopenia, liver dysfunction, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, ferritin elevation and bone marrow haemophagocytosis [2–4]. Epstein-Barr virus (EBV) infection is the main trigger of familial and sporadic HLH [5]. HLH patients are immunocompromised not only by the intrinsic immune deregulation but also by commonly used immunosuppressive drugs. When the therapeutic strategy results in rapid lymphocytes recovery it may lead to a paradoxical worsening of occult pre-existing infection – immune reconstitution inflammatory syndrome (IRIS) – as seen in HIV infected patients soon after antiretroviral therapy [6].

We present a 38-year-old male case, with ocular IRIS after rituximab for chronic active EBV (CAEBV) infection manifested as HLH.

CASE DESCRIPTION

A 38 years old male presented, in 2013, with otherwise asymptomatic 4 months of intermittent fever that progressed in the previous month to persistent fever, general malaise, pancytopenia, hyperferritininemia, hypertriglyceridemia, hepatosplenomegaly and thoracoabdominal adenopathies. Additional workup excluded rheumatologic diseases, solid neoplasms and lymphoma and documented chronic EBV infection (high IgG EBNA and VCA serology, negative IgM and high EBV viral load 317,100 copies/mL) and haemophagocytic syndrome (H-score 254 points). An asymptomatic small right retinal hemorrhage was seen in screening fundoscopy. He was treated with methylprednisolone 1g/day for 3 days, followed by prednisolone 60mg/day, intravenous immunoglobulin (IVIG) 0.4g/kg/day for 5 days and valganciclovir. After consistent improvement, (Figure 1), he was discharged, and steroids were slowly tapered to 10mg/day. He was stable for 5 months and, after a common cold, he relapsed (H-score 272 points) and responded to high steroids and IVIG again. Mutation screening were negative for PFR1, UNC13D, STX11, STXBP2, RAB27A, SH2D1A and XIAP. No matched bone marrow donor was ever found.

Three months later, he relapsed (H-score 228 points) with multiorgan dysfunction (coagulopathy, encephalopathy, severe hypoalbuminemia, hyperbilirubinemia) unresponsive to methylprednisolone and IVIG.

Three days after 500mg rituximab, he had no fever or encephalopathy but a new feature of acute progressive bilateral retinitis, with acute severe necrotic right eye (RE) panuveitis refractory to ganciclovir and intravitreal corticosteroids. An ocular IRIS was considered based on: retrospective assumption of previous non-severe self-limiting EBV retinitis (RE haemorrhage on first admission); triplication of T lymphocyte count with B cell depletion; abrupt decrease in blood EBV viral load; exclusion of cytomegalovirus infection; and response to methylprednisolone bolus. RE enucleation was prevented by addition of cyclosporine. He gradually recovered bilateral sight, but unfortunately, one month later, was readmitted due to severe bilateral *Pneumocystis jirovecii* interstitial pneumonia and relapsed EBV viral load (39584copies/mcL), with progression to ARDS and multiorgan dysfunction, unresponsive to intensive care management with aggressive ventilation techniques and died on the 2nd July 2014.

DISCUSSION BASED ON LITERATURE REVIEW

Current thinking on adult HLH is radically different from that in 2014. Even when there is a predisposing condition (rheumatological, blood or solid malignancy) it seems that HLH only occurs when there is a genetic contribution/risk (affecting lymphocyte cytotoxicity and immune regulation), most of them still unknown [2,3,7]. Although none of the available known screened mutation were positive, there are arguments to think our patient had a familial (previous primary) HLH variant: there was no other predisposition condition; it was driven by a persistently active chronic EBV infection; and its relapsing pattern ultimately led to death, without bone marrow transplant. Since 2014, other genes related to EBV-driven HLH have been described, like LYST, BIRC4, NLRC4, GATA2, CTPS1 and DDX3X [2,7–9].

CAEBV is rare since, after primary infection, in otherwise uncompromised immune system, it tends to become latent [10]. There is specific clinical phenotype [11], but viral load should be measured when EBNA and VCA IgG and IgM are both positive, and in every HLH suspicion.

HLH diagnosis criteria are well established in paediatrics, but most of the adult forms only fulfil HLH-2004 criteria in advanced severe stages[12]. Since prognosis is highly dependent on early detection and management [2,4], H-score has been more widely used on adults for diagnosis probability [2,4,8,13]. From presentation, our patient had 6 of 8 HLH-2004 criteria for diagnosis and highly probable diagnosis on H-score.

In the absence of treatment, CAEBV with or without recurrent HLH ultimately lead to death [9]. The only curative treatment is hematopoietic stem cell transplantation both it may not be achieved if no donor is available (as in our case) or if the patient succumbs to opportunistic infection or organ dysfunction due to HLH or EBV-related lymphoproliferative involvement [2,9,14]. Several strategies have been reported to treat adult CAEBV and HLH none of which is completely efficient. Most of the consensus schemes are divided in supportive and aetiology targeting combined measures [12,15]. Although steroids and IVIG are the classical initial supportive approach (as we used), anakinra have been recently purposed to be the safest and more effective drug [12,14], while the driven aetiology is been pursued. Antiviral therapy (ganciclovir and valganciclovir) has no effect in the long term [9,16], although good results were

achieved when combined with lytic lymphocyte inducers, like bortezomib [16]. At the time, we chose to treat him with rituximab after the first report of 42 EBV-HLH patients [17], which is currently one of the most used option [9,15]. The rationale for rituximab relies on clearing the B cell reservoir of EBV in EBV-triggered HLH [9,15,17], which was confirmed in our patient: EBV viral load was suppressed for the first time.

The rapid onset ocular paradoxical IRIS has not been reported before in any of the rituximab exposed patients, possibly due to their concomitant use of other immunosuppression.

Paradoxical IRIS is characterized by clinical deterioration during the course of apparently successful treatment for an infection, historically known after initiation of highly active antiretroviral therapy in HIV infected patients [18]. IRIS also occurs in non-HIV related conditions: recovering neutropenia after chemotherapy; withdrawal of anti-tumor necrosis factor drugs in autoimmune disorders; reduction or cessation of immunosuppressive therapy in organ transplant recipients [18]. We hypothesize that EBV was hidden in an ocular sanctuary (previous retinal haemorrhage), B depletion rapidly decreased the systemic EBV viral load leading to rapid rise in T lymphocytes count, atypical exaggerated reactive inflammation in pre-existent localized infected tissues, fulfilling IRIS criteria [6]. Specific IRIS treatment should cover the underlying pathogen treatment, supportive local measures and additional immunosuppression [18]. Cyclosporine seemed to be the best option: blocks T cell response, has excellent ocular biodistribution, and has proven efficacy on recurrence prevention in EBV-driven HLH [9,15]. Unfortunately, the iatrogenic B and T cell suppression provided the ground for fatal acute respiratory distress syndrome due to severe pneumocystosis.

To our knowledge this is the first report of IRIS associated with rituximab and highlights the need for concomitant immunosuppression and narrow surveillance during treatment. The EBV-driven HLH is still currently challenging both in diagnosis and management, despite recent consensus of many supportive treatments and stem-cell transplant. This rare, challenging, and unfortunate case was the index case that lead us to develop a multidisciplinary cooperative team for early detection and treatment of adult onset HLH.

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Ethical approval

Institutional ethics approval was waived for this case report.

Declaration of Competing Interest

None.

REFERENCES

[1] X. Shao, Y. Xu, X. Xu, Y. Xu, H. Chen, M. Hong, L. Liu, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults: A retrospective analysis of 23 patients in China, Isr. Med. Assoc. J. 20 (2018) 80–85.

[2] P. La Rosée, A.C. Horne, M. Hines, T.V.B. Greenwood, R. Machowicz, N. Berliner, S. Birndt, J. Gil-Herrera, M. Girschikofsky, M.B. Jordan, A. Kumar, J.A.M. Van Laar, G. Lachmann, K.E. Nichols, A. V. Ramanan, Y. Wang, Z. Wang, G. Janka, J.I. Henter, Recommendations for the management of hemophagocytic lymphohistiocytosis in adults, Blood. 133 (2019) 2465–2477. https://doi.org/10.1182/blood.2018894618.

[3] M. Hutchinson, R.S. Tattersall, J.J. Manson, Haemophagocytic lymphohisticytosis — an underrecognized hyperinflammatory syndrome, Rheumatology. 58 (2019) 23–30. https://doi.org/10.1093/rheumatology/kez379.

[4] J. Skinner, B. Yankey, B.K. Shelton, Hemophagocytic Lymphohistiocytosis, AACN Adv Crit Care. 30 (2019) 151–164. https://doi.org/10.4037/aacnacc2019463.

[5] W. Lai, Y. Wang, J. Wang, L. Wu, Z. Jin, Z. Wang, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults and adolescents—a life-threatening disease: analysis of 133 cases from a single center, Hematology. 23 (2018) 810–816. https://doi.org/10.1080/10245332.2018.1491093.

[6] M.A. French, Immune Reconstitution Inflammatory Syndrome: A Reappraisal, Clin. Infect. Dis. 48 (2009) 101–107. https://doi.org/10.1086/595006.

[7] M.B. Jordan, C.E. Allen, J. Greenberg, M. Henry, M.L. Hermiston, A. Kumar, M. Hines, O. Eckstein, S. Ladisch, K.E. Nichols, C. Rodriguez-Galindo, B. Wistinghausen, K.L. McClain, Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO), Pediatr. Blood Cancer. 66 (2019) 1–12. https://doi.org/10.1002/pbc.27929.

[8] R.A. Marsh, Epstein-Barr virus and hemophagocytic lymphohistiocytosis, Front. Immunol. 8 (2018) 1–9. https://doi.org/10.3389/fimmu.2017.01902.

[9] H. Kimura, J.I. Cohen, Chronic active Epstein-Barr virus disease, Front. Immunol. 8 (2017) 1–6. https://doi.org/10.3389/fimmu.2017.01867.

[10] Y.D. Wang, L.L. Wu, L.Y. Ma, X.B. Shang, Z.Y. Li, W. Wang, C. Shen, J.J. Yang, L.X. Sun, C.Y. Zhao, Chronic active EBV infection associated with NK cell lymphoma and hemophagocytic lymphohistiocytosis in a 27-year-old woman: A case report, Medicine (Baltimore). 98 (2019) e14032. https://doi.org/10.1097/MD.0000000000014032.

[11] Z. Wang, Y. Zhang, M. Duan, Y. Zhang, Chronic active Epstein–Barr virus infection with intrapulmonary shunting: A case report, J. Infect. Chemother. 26 (2020) 502–505. https://doi.org/10.1016/j.jiac.2019.12.012.

[12] K. Bauchmuller, J.J. Manson, R. Tattersall, M. Brown, C. McNamara, M. Singer, S.J. Brett, Haemophagocytic lymphohistiocytosis in adult critical care, J. Intensive Care Soc. 0 (2020) 1–13. https://doi.org/10.1177/1751143719893865.

[13] L. Fardet, L. Galicier, O. Lambotte, C. Marzac, C. Aumont, D. Chahwan, P. Coppo, G. Hejblum, Development and validation of the hscore, a score for the diagnosis of reactive hemophagocytic syndrome, Arthritis Rheumatol. 66 (2014) 2613–2620. https://doi.org/10.1002/art.38690.

[14] P. Mehta, R.Q. Cron, J. Hartwell, J.J. Manson, R.S. Tattersall, Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome Puja, Lancet Rheumatol 2020. 2 (2020).

[15] S.J. Carter, R.S. Tattersall, A. V. Ramanan, Macrophage activation syndrome in adults: Recent advances in pathophysiology, diagnosis and treatment, Rheumatol. (United Kingdom). 58 (2019) 5–17. https://doi.org/10.1093/rheumatology/key006.

[16] C.M. Bollard, J.I. Cohen, How I treat T-cell chronic active Epstein-Barr virus disease, Blood. 131 (2018) 2899-2905. https://doi.org/doi:10.1182/blood-2018-03-785931.

[17] D. Chellapandian, R. Das, K. Zelley, S. Wiener, H. Zhao, D.T. Teachey, K.E. Nichols, EBV-HLH Rituximab Study Group, Treatment of Epstein Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo- immunotherapeutic regimens, Br. J. Haematol. 162 (2013) 376–382. https://doi.org/10.1038/jid.2014.371.

[18] M. Fane, S. Mustapha, A. Chakib, M. K, L. Filali, HIV and Immune Reconstitution Inflammatory Syndrome (HIV-IRIS), J. Infect. Dis. Pathog. 1 (2018) 1–8.

APPENDICE

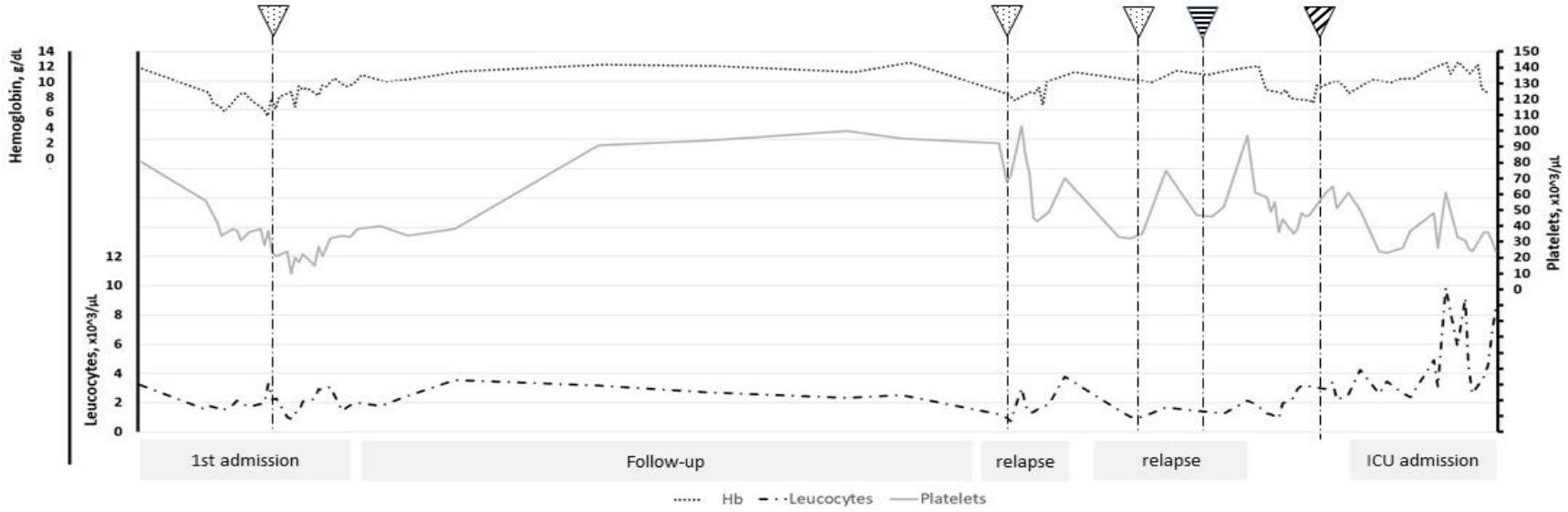

Figure 1 - Cytopenia evolution through time with treatment regimens. Dotted triangles correspond to "methylprednisolone bolus, intravenous immunoglobulin (IVIG) and valganciclovir", horizontal lined triangle correspond to "endovenous rituximab 500mg" and obliquos lined triangle corresponds to "cyclosporine beginning"