Recurrent macrophage activation syndrome in patients with refractory systemic lupus erythematosus treated with emapalumab: a case report

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Hong Kong Med J 2025;31:387–90
https://doi.org/10.12809/hkmj2512876

Case presentation

A 30-year-old woman was diagnosed with systemic lupus erythematosus (SLE) in 2010 based on alopecia, facial rash, skin, biopsy-confirmed lupus nephritis, positive antinuclear antibodies and anti–double stranded DNA antibodies, and low complement levels. Over the past decade, her maximum exposure to prednisone was 40 mg/day with a minimum maintenance dose of 15 mg/day. She had been treated with multiple immunosuppressants including hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, leflunomide, methotrexate, and azathioprine, due to persistent disease activity. Between 2020 and 2024, she was hospitalised multiple times for high fever, alopecia, facial rash, oral ulcers, vasculitis-like rash on the hands and scalp (online supplementary Fig 1a), and foamy urine (biopsy-confirmed lupus nephritis [class V and IV]) [online supplementary Fig 1b]. During each episode, macrophage activation syndrome (MAS) was identified using the HLH-2004 criteria based on elevated inflammatory indicators [C-reactive protein, interleukin 6 (IL-6), ferritin, C-X-C motif chemokine ligand 10 (CXCL10), chemokine (C-C motif) ligand 5 (CCL5), and interleukin-2 receptor], interferon genes (*IFI44*, *MX1*, and *IRF1*), and immune cell fluctuations (CD64 on neutrophils, $CD4^+$ T cells, and $CD8^+$ T cells). Dexamethasone and etoposide were administered during acute phases, and sequentially adjusted to cyclosporin A, mycophenolate mofetil, tacrolimus, tofacitinib, baricitinib, ruxolitinib, and telitacicept due to recurrent alopecia, rash, and joint pain. Despite these interventions, MAS relapsed, and prednisone could not be reduced below 30 mg/day.

In September 2023, 1 month after the last MAS episode, the patient again presented with MAS symptoms, including high fever (39°C), alopecia, vasculitis-like scalp rash, and oral ulcers (online supplementary Fig 1a). Laboratory tests revealed leukopenia (white blood cell count=1.25×10^9/L), thrombocytopenia (platelet count=54×10^9/L), anaemia (haemoglobin level=108 g/L), elevated C-reactive protein level (73.88 mg/L), erythrocyte sedimentation rate (78 mm/h), lactate dehydrogenase level (592 U/L), ferritin level (4508 ng/mL), splenomegaly, and no schistocytes. Extensive infectious workups, including blood cultures, next-generation sequencing, galactomannan, beta-D-glucan, T-SPOT, echocardiography, bone marrow biopsy, and high-resolution computed tomography, were negative, confirming a diagnosis of SLE-MAS. Given the recurrent nature of her condition, whole-exome sequencing was performed, identifying variants in *GATA2* and *MEFV* of unclear significance (online supplementary Fig 2).

Multidimensional immune endotyping to evaluate disease conditions revealed: (1) abundant autoantibodies (online supplementary Fig 1c), high double-stranded DNA levels (>100 IU/mL detected by the Farr method) and low C3/C4 levels, indicating active SLE; (2) marked hyperinflammation with elevated levels of IL-6 (86.86 pg/mL), interferon gamma (IFN-γ) [42.18 pg/mL], C-reactive protein (99.99 mg/L), serum ferritin (6769 ng/mL), interleukin-2 receptor (1602 U/mL), CXCL10 (233.12 pg/mL) and CCL5 (27996.33 pg/mL); (3) upregulated interferon-stimulated genes (IFI44 176.59, MX1 328.63, and IRF1 84.32); and (4) immune dysregulation with increased neutrophil CD64 index, elevated $CD8^+$ T cells, and decreased $CD4^+$ T cells (Fig 1). Initial high-dose dexamethasone (10 mg every 12 hours) and cyclosporin A failed to control MAS with recurrence of fever and symptoms after 3 days. Given prior etoposide treatment and the risk of pancytopenia and infection, the treatment regimen was adjusted to include increased dexamethasone, tacrolimus, and intravenous immunoglobulin. Persistent inflammation led to the initiation of emapalumab (50 mg) on day 16 of hospital stay. Within 24 hours, fever subsided, and levels of C-reactive protein, IL-6, IFN-γ, CD64 on neutrophils, and interferon gene expression improved. Emapalumab was administered biweekly for four doses, significantly reducing steroid dependence and shortening the duration of hospitalisation. Three weeks later,

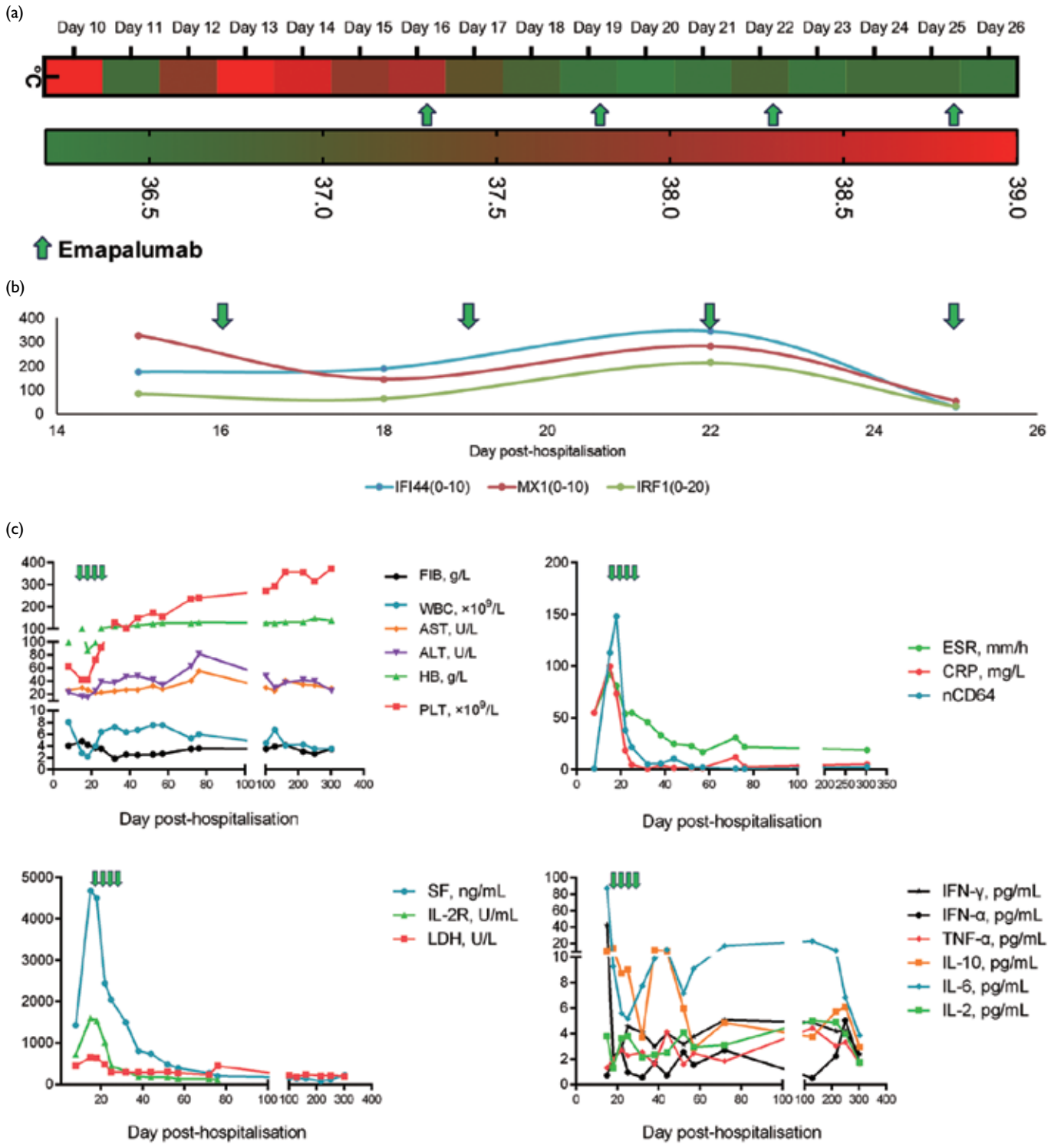

FIG 1. Inflammatory state and interferon (IFN) gene changes before and after emapalumab. (a) Body temperature fluctuations. (b) IFN-related gene changes. (c) Changes in inflammatory and biochemical indices. Green arrows indicate emapalumab administration

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FIB = fibrinogen; Hb = haemoglobin; *IFI44* = interferon induced protein 44; IFN-α = interferon alpha; IFN-γ = interferon gamma; IL-2 = interleukin 2; IL-2R = interleukin-2 receptor; IL-6 = interleukin 6; IL-10 = interleukin 10; *IRF1* = interferon regulatory factor 1; LDH = lactate dehydrogenase; *MX1* = interferon-induced GTP-binding protein Mx1; nCD64 = CD64 on neutrophils; PLT = platelet count; SF = serum ferritin; TNF-α = tumour necrosis factor alpha; WBC = white blood cells

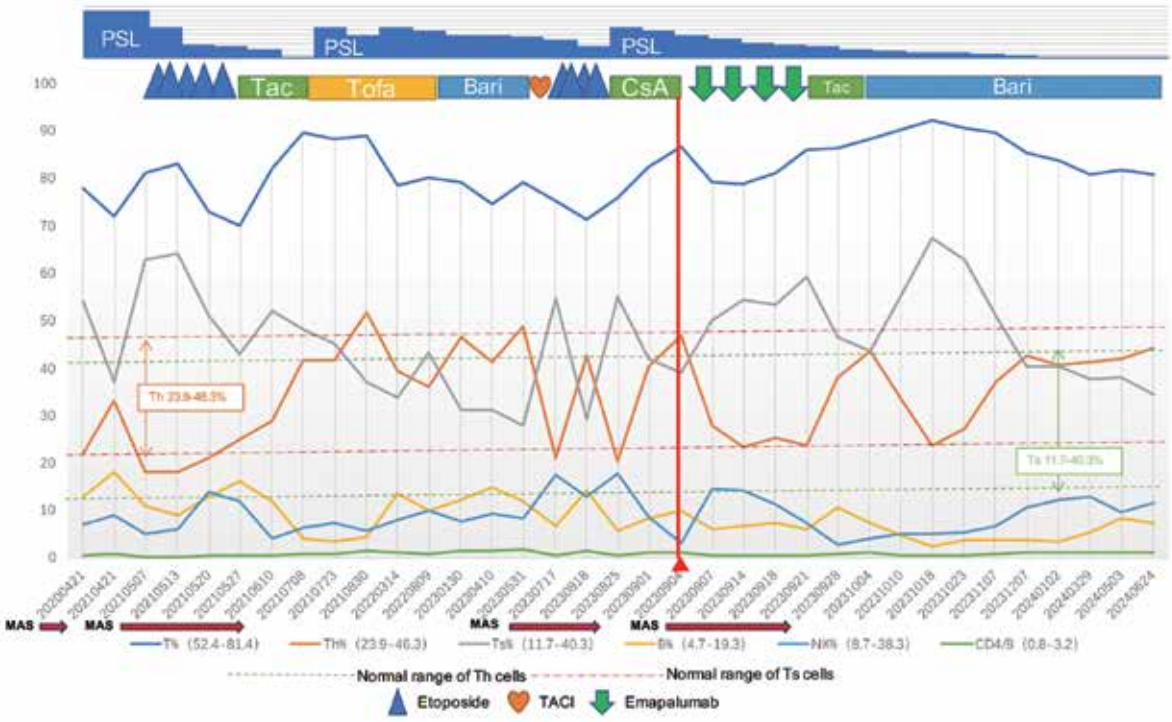

FIG 2. Clinical course and immune endotype fluctuations. The top panel shows medication use. The middle section displays immune endotype changes, revealing recurrence of macrophage activation syndrome whenever CD8⁺ T cells predominated. Long-term use of baricitinib restored the normal CD4⁺/CD8⁺ balance

Abbreviations: B = B cells; Bari = baricitinib; CsA = cyclosporin A; MAS = macrophage activation syndrome; NK = natural killer cells; PSL= prednisolone; T = T cells; Tac = tacrolimus; TACI = telitacicept; Th = T helper cells; Tofa = tofacitinib; Ts = suppressor T cells

the patient was discharged on oral prednisolone (60 mg/day) and tacrolimus (1 mg twice daily). One month later, tacrolimus was switched to baricitinib due to severe hair loss. At 9-month follow-up, inflammation and organ function normalised, enabling tapering of prednisone to 7.5 mg/day with baricitinib (Fig 2). The immune endotype changes, particularly CD8⁺ T-cell proliferation, were identified as a risk factor for MAS in this patient.

Discussion

Emapalumab has been successfully administered in children with primary haemophagocytic lymphohistiocytosis and relapsed/refractory haemophagocytic lymphohistiocytosis.[1] In our case, we jointly assessed the inflammatory state, interferon gene expression, and immune cell fluctuations to quickly identify this patient with SLE-MAS.

Patients with SLE and MAS have a high mortality rate,[2] partly due to the difficulty in reaching an early MAS diagnosis since clinical features overlap with those of other conditions. Identifying immune endotypes may help detect MAS early. Interferon gamma plays a key role in SLE by activating neutrophils, CD8⁺ and CD4⁺ T cells, and macrophages, with its dysregulation contributing to MAS pathogenesis.[3] In our patient, MAS presented as severe inflammation unresponsive to steroids or immunosuppressants but was effectively controlled by emapalumab. We observed elevated IFN-stimulated genes (*IFI44*, *MX1*, and *IRF1*) that normalised following emapalumab treatment.

Before treatment, the patient exhibited increased CXCL10 and CCL5 levels. Inflammatory markers were elevated, with cell analysis showing increased CD64⁺ neutrophils and CD8⁺ T cells, alongside reduced CD4⁺ T cells. In MAS, the percentage of CD8⁺ T cells outnumbers that of CD4⁺ T cells. Following emapalumab treatment, these abnormalities resolved, suggesting that excessive type II IFN signalling and CD8⁺ T cell overactivation drive SLE-MAS, potentially defining it as a distinct SLE subtype rather than a mere complication.

This case provides initial clinical evidence for the efficacy of emapalumab in refractory SLE-MAS although these findings are limited by the single-case nature and require validation in larger cohorts. The case highlights the importance of precise immune profiling in SLE-MAS and supports the use of emapalumab as a potential therapeutic strategy for refractory cases.

Author contributions

Concept or design: L Gu.
Acquisition of data: R Guo.
Analysis or interpretation of data: R Guo, S Ye.
Drafting of the manuscript: R Guo, L Gu.
Critical revision of the manuscript for important intellectual content: S Ye, L Gu.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study was supported by Renji Hospital, School of Medicine, Shanghai Jiao Tong University, China (Grant Nos.: 2019NYLYCP0202 and RJTJ24-MS-020). The funder had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Ethics approval

The study was approved by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University, China (Ref No.: 2016-083). The patient was treated in accordance with the Declaration of Helsinki. Informed patient consent was obtained for publication of this case report, including the accompanying clinical images.

Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2512876).

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