Systemic lupus erythematosus-related macrophage activation syndrome inducing severe cytopenia successfully treated with anifrolumab: a case report

Sirs,

We report on a 50-year-old female diagnosed with SLE in 2011 for mucocutaneous, articular, serositic and severe haematologic involvement. At diagnosis, she presented ANA positivity, high anti-dsDNA, anti-Ro52 and anti-RNP/Sm positivity, with C3 and C4 consumption. She was treated with high dose glucocorticoid (GC) and azathioprine (2 mg/kg/day), with a poor response in terms of cytopenia. She was then enrolled in a phase-IIb clinical trial (NCT01283139) with sifalimumab, an anti-IFNα monoclonal antibody, which allowed a persistent clinical and laboratory remission during a 12-year follow-up.

In May 2023 she experienced a SLE flare, characterised by low-grade fever, weight loss, arthralgias, leukopenia (3.000/mm^3), C3 and C4 reduction (0.53 and <0.01 g/L, respectively), anti-dsDNA elevation (FEIA 326 UI/mL). At the time of disease flare, she was on low dose oral GC (2.5 mg/day) and azathioprine (1 mg/kg/day). For persistent high fever she was admitted to the Emergency Department where blood tests showed severe pancytopenia (Hb 7 g/dL, WBC 1.000/mm^3, PLT 80.000/mm^3), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) increase, hyperferritinaemia (2.800 ng/mL), hypertriglyceridaemia (174 mg/dL), and direct Coombs test positivity. Infectious diseases and malignancies were excluded after performing extensive laboratory and imaging tests. The HScore (1) for MAS risk was 232, corresponding to a 98–99% of MAS probability, and a bone marrow biopsy showed signs of haemophagocytosis. Intravenous 6-methyl-prednisolone (125 mg/day) for 6 days was administered with gradual tapering. The patient experienced a partial response, with resolution of fever and platelet normalisation, but persistence of anaemia (Hb 10,3g/dL) and leukopenia (WBC 3.810/mm^3), CRP and ESR increase, complement consumption (C3 0.87, C4 <0.01 g/L), high ferritin and triglycerides (522 ng/mL and 231 mg/dL, respectively). Given the response previously achieved with an anti-IFN treatment, anifrolumab was started at the dose of 300 mg every 4 weeks. After 2 months, the patient experienced a full blood count normalisation (Hb 13.8 g/dL, WBC 10.200/mm^3, PLT 191.000/mm^3), a significant decrease of ferritin (136 ng/mL), triglycerides (161 mg/dL), and ESR, CRP, and anti-dsDNA normalisation. After 12 months, she maintained persistent clinical and laboratory remission with low dose GC (methylprednisolone 4 mg/day) (Fig. 1). MAS is a rare, but severe complication of SLE and can potentially affect patients with long history of clinical stability. MAS and SLE share pathogenetic mechanisms, among which IFN may represent a common inflammatory mediator. In MAS, the sustained activation of CD8+ T-cells results in the release of large amounts of IFNγ, a potent activator of macrophages which, in turn, produces high levels of IL-1β, IL-6, IL-18, and TNFα (2). Furthermore, recent evidence in patients with Still disease-related MAS showed that type-I IFN stimulation could have an upstream role as compared with the IFNγ pathways (3).

In our case, we observed a partial response to GC, and the need for a better control of disease activity, with lower GC dose, led to the introduction of a GC-sparing agent like anifrolumab, whose choice was also guided by its suggested efficacy on haematologic activity. Indeed, a recent *post-hoc* analysis of the TULIP 1 and 2 trials showed a significant decrease of SLEDAI-2K organ domain score regarding haematologic activity from baseline to week 52 after anifrolumab therapy (4). Consistently, the MUSE trial showed that anifrolumab reversed lymphopenia and neutropenia in the whole population, irrespective of type-I IFN gene signature status (5). Intriguingly, the histologic analysis of bone marrow biopsies in SLE patients with cytopenia provide insights about the pathogenetic correlation between haematologic SLE and MAS considering that about 30% were found to have bone marrow abnormalities classifiable as haemophagocytosis (6). To the best of our knowledge, this is the first report of a SLE-related cytopenia induced by MAS successfully treated anifrolumab and it could help to broaden the spectrum of the potential clinical scenarios for anifrolumab effectiveness.

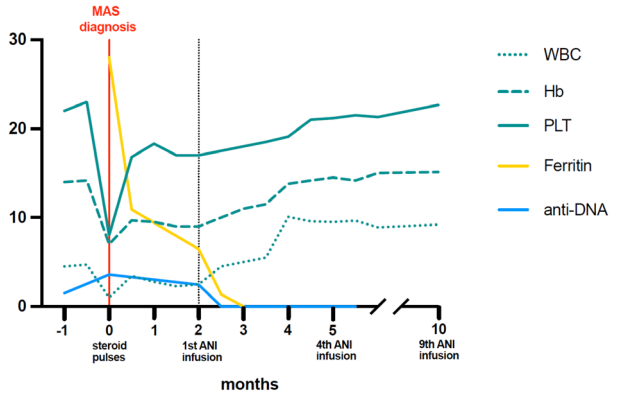

Fig. 1. The trend of laboratory parameters at MAS diagnosis, after steroid pulses and after anifrolumab therapy.

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