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Case Report

Addressing the treatment of macrophage activation syndrome: A challenging balance between immune suppression and infectious risk

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Background

Hemophagocytic Lymphohistiocytosis (HLH) is a rare and potentially life-threatening syndrome related to a dysregulation of cytolytic function of Natural Killer (NK) cells and cytotoxic T cells (CTLs), which in turns leads to an inappropriate immune stimulation and hyperinflammatory state, resulting in hypercytokinemia, accumulation of activated lymphocytes and macrophages [1,2].

HLH can be primary or secondary. Primary HLH is related to genetic defects leading to abnormal lymphocyte cytotoxicity and is usually diagnosed in children and infants; secondary HLH mainly affects adults, and is related to infections (i.e., Epstein-Barr virus), malignancies (especially haematologic), primary immunodeficiencies and autoimmune diseases.

Macrophage Activation Syndrome (MAS) is a subset of secondary HLH complicating chronic inflammatory autoimmune conditions, such as Systemic Lupus Erythematosus (SLE), Kawasaki Disease (KD) and juvenile idiopathic arthritis (JIA).

The most common clinical features of MAS consist of unremitting fever and hepato-splenomegaly. Laboratory findings include cytopenia, hyperferritinemia, fibrinolytic consumptive coagulopathy, liver dysfunction, and hypertriglyceridemia [3].

A definite characteristic of MAS is the histopathological

finding of hemophagocytosis, related to an abnormal macrophage activation, which can be observed in bone marrow, liver, and spleen biopsies. Although typical, this finding is not diagnostic, as it usually occurs in late stages, and can also be found especially in critically ill patients with sepsis [4,5].

Currently, no diagnostic criteria have been validated for adults, as the mainly used HLH-2004 criteria are derived from a paediatric cohort [6]. Recently, HScore, which estimates the probability of HLH, was developed on an adult cohort, but still needs validation [7].

Moreover, due to the lack of therapeutic guidelines, treatment regimens are mainly based on protocols for paediatric and familial HLH and case series.

Therefore, MAS represent a diagnostic and therapeutic challenge, thus leading to a poor prognosis [8].

Case description

Here we report the case of a Caucasian 67 years-old woman who was admitted to our Department due to persistent fever (Tc 39,5 °C) unresponsive to multiple antibiotic regimens administered by her General Practitioner (Beta lactamic antibiotics and macrolides). The patient was affected by SLE (anti-SSA positivity, anti-dsDNA positivity, arthritis and pericardial effusion), treated with hydroxychloroquine 200 mg/day and low dose prednisone (5 mg/day). On admission she didn't report any significant symptoms and didn't show any

sign of reactivation of SLE. Blood tests revealed pancytopenia with marked neutropenia (White blood cells, WBC, $1120 \times 10^3/\mu\text{L}$, Neutrophils $650 \times 10^3/\mu\text{L}$; Hemoglobin, Hb, 9,99 g/dL, Platelets $84200 \times 10^3/\mu\text{L}$), hepatic cytolysis (aspartate aminotransferase, AST, 5 x upper limit normal, ULN; alanine aminotransferase, ALT, 5,6 x ULN), normal renal function, normal complement levels, mild increase of C-Reactive Protein (CRP 140 mg/L) along with hyperferritinemia (5045 ng/ml) and low fibrinogen (289 mg/dl). Peripheral blood smear was negative for schistocytes. Anti-dsDNA Antibodies were not detected on Indirect Immunofluorescence (IFI).

Initially, empiric antibiotic therapy with meropenem and vancomycin was started, after collecting blood and urine cultures, which afterwards resulted negative. Moreover, thoracic contrast-enhanced CT scan, echocardiography and total body positron emission tomography (PET) were performed, but didn't show significant abnormalities, apart from mild splenomegaly (longitudinal diameter 13 cm). Due to the finding of pancytopenia, the patient underwent bone marrow biopsy and needle aspiration, which showed hypocellular bone marrow along with hemophagocytosis.

After discussion of the case along with a multi-disciplinary team (rheumatologist, immunologist and haematologist), the diagnosis of MAS was formulated and high dose steroid therapy was initiated with methylprednisolone 1 g/day for three days, followed by dexamethasone 1 mg/kg/day. A panel of tests to rule out an infectious trigger turned out negative (antibodies against Parvovirus B19, HIV, HSV, HBV, HCV, Borrelia and direct detection of DNA of CMV, EBV, HHV-6). As high-grade fever persisted along with pancytopenia, the IL-1 antagonist anakinra (100 mg subcutaneous once daily) was initially associated to steroid therapy, followed by immunoglobulin infusion (500 mg/kg/day) for four days. In view of the absence of significant clinical benefit, finally, intravenous ciclosporin (180 mg/day) was added. The patient began to show clinical improvement and a slow but constant raise of neutrophils, platelets and haemoglobin. She was finally discharged on prednisone 37,5 mg/day and ciclosporin 120 mg twice a day.

During follow up, the patient complained dysphagia and odynophagia and oral candidosis was found, therefore intravenous caspofungin was administered in day hospital regimen, then shifted to oral fluconazole, while steroid tapering was carried on.

Three weeks later, the patient presented to the Emergency Room (ER) complaining low appetite and fatigue. Blood tests revealed leucocytosis with neutrophilia (white blood cells, WBC, $10,600 \times 10^3/\mu\text{L}$, neutrophils $9,720 \times 10^3/\mu\text{L}$), acute kidney injury (eGFR 39 ml/min), increased CRP and hyperferritinemia (10,952 ng/ml).

Lung CT-scan was performed and revealed a focal subpleural flogistic lesion. Therefore, empiric antibiotic therapy with meropenem was started, along with fluconazole and immunosuppressive therapy with ciclosporin and prednisone. Blood cultures were collected and direct detection of EBV and CMV-DNA was performed.

After 48 hours in the ER, the patient was admitted to our Department, where she rapidly worsened due to the onset of Clostridium Difficile colitis. Therefore, fidaxomicin 200 mg twice daily was added, obtaining a prompt regression of diarrhoea and a clinical and laboratoristic improvement.

Moreover, direct detection of CMV DNA showed an amount of 13,711,385 copies/ml, consequently, ganciclovir was administered (5 mg/kg twice daily for 14 days, followed by valganciclovir 900 mg once daily. Immunosuppressive therapy was gradually tapered, up to the discontinuation of ciclosporin and maintenance of low dose prednisone (15 mg once daily).

The patient initially showed mild clinical improvement, but then developed respiratory failure and chest HRCT showed multifocal pneumonia and pleural effusion, requiring chest drainage and a further cycle of antibiotic therapy (initially linezolid with meropenem, then ceftobiprole), along with fluconazole and valganciclovir.

Fidaxomicin was also re-administered due to the reappearance of C. Difficile diarrhoea.

Despite maximised therapy, the patient didn't show any significant improvement, and eventually died. A few days after, pleural fluid cultures resulted positive for Aspergillus fumigatus.

Discussion

As our case points out, diagnosing MAS can be arduous, as this condition might mimic signs and symptoms of other systemic illnesses, thus leading to a late diagnosis, correlating with a poor prognosis [2].

However, even in case of a prompt diagnosis, as in our case, choosing a correct treatment regimen can be equally challenging, mainly due to the absence of therapeutic guidelines, especially in adults.

The first therapeutic protocol, defined by HLH-94 guidelines, and later updated in 2004, consists of an association of intravenous steroids, etoposide, and ciclosporin A (CSA), and it drastically improved survival. However, it is just validated on a paediatric cohort, therefore, adult treatment can only be inferred. In this context case reports and case series do have a role in choosing therapeutic regimens [6].

Concerning high dose steroid therapy, it appears to be the main and first treatment as highlighted by most studies. HLH-94 guidelines suggest dexamethasone, but this is only related to its better ability to penetrate blood brain barrier. Most recent studies also suggest methylprednisolone as a reliable alternative [2]. In our patient, treatment regimen was selected after team discussion along with an immunologist, a rheumatologist and a haematologist. There was strong consensus about starting with intravenous steroids, and methylprednisolone was the chosen drug.

As it turned out to be ineffective, more difficulties were found selecting following therapy.



A second line treatment which appears to be effective especially in patients affected by MAS is CSA, whose main immunosuppressive effect consists of depressing T-cell activation and inhibiting their proliferation [8,10]. HLH-2004 suggest starting CSA (2–7 mg/kg/day) together with steroids, while, following HLH-94, CSA should be administered after 8 weeks due to its potential side effects. Recent studies seem to support HLH-94 protocol, both due to contraindications and side effects, and to the apparent absence of significant improvement [2,6].

Another agent which seems to have shown valuable results in HLH patients, especially those with MAS, is the IL-1 inhibitor anakinra, whose anti-cytokine effect appears to be particularly valuable in the cytokine storm characterizing MAS. Moreover, since its introduction in 2001 this drug has always shown a favourable safety profile [2, 11]. The optimal time to start this drug remains unclear, although an early use seems advisable, in order to obtain a prompt and effective inhibition of cytokine activity; recommended dosing is 2 – 6 mg/kg/day to a maximum of 10 mg/kg/day [8,9].

Treatment regimen might also include Intravenous Immunoglobulin (IVIG) infusion, which can be considered due to the ability of immunoglobulin to inhibit complement activation, therefore resulting in anti-inflammatory activity. At present, only few data are available, mainly consisting of case reports, but IVIG use in association with methylprednisolone seems a favourable option, also considering the absence of significant side effects [6].

In our case, considering the absence of a standardised treatment, we preferred anakinra and IVIG over CSA both due to potential side effects of this drug, especially in such a frail patient, and due to the absence of clear signs and symptoms of reactivation of SLE. Moreover, our choice was mainly influenced by the anti-cytokine effect of anakinra and the potentially adjuvant anti-inflammatory effect of IVIG.

Despite expectations, we didn't achieve benefits, therefore shifting to CSA, and finally obtaining clinical response.

In this case, we didn't consider etoposide, which in HLH-guidelines appears to be a cornerstone in therapeutic approach, and whose use is suggested since the beginning [6]. Our choice was related to the fact that this chemotherapeutic agent seems to be primarily effective in HLH related to oncohematological conditions; in addition, some studies highlight a possible use in patients with MAS triggered by EBV infection, which in our case was promptly ruled out [2]. Moreover, as La Rosée, et al. suggest, etoposide may have important side effects in elderly and multimorbid patients, and therefore its use in adult patients should be evaluated carefully [2,8].

Finally, supportive therapy, especially broad-spectrum antibiotics, antimycotic and antiviral therapy, should be administered on a case-by-case basis. This is particularly true, mainly due to the infectious complications of immunosuppressive therapy, which might lead to a poorer outcome [8].

In our patient, broad spectrum antibiotics, along with antimycotic and antiviral treatment were administered during hospitalisation. Moreover, following discharge, a multi disciplinary team continued taking care of the patient and different therapies were proposed in order to treat infectious complications, which appeared to be the most relevant issue, and, which, eventually, led to the patient's death.

In conclusion, as our case highlights, even in case of a multidisciplinary approach with a strict follow up and a dedicated team, MAS is still burdened by a poor prognosis, not only due to the absence of standardised and efficacious treatment regimens, but also due to the potentially fatal complications, especially infectious ones.

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