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Brief report

Secondary Macrophage Activation Syndrome Due to Autoimmune, Hematologic, Infectious and Oncologic Diseases. Thirteen Case Series and Review of the Literature☆

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ABSTRACT

Objective: Describe the demographic characteristics and disorders of patients with diagnosis of macrophage activation syndrome (MAS) in the December 2008–January 2014 period.
Methods: Medical records were reviewed from diagnosis of MAS and after discharge until January 2014. Patients were divided into 4 groups according to the primary disease: autoimmune (AI), hemato-oncologic (HO), infectious (Inf) and oncologic (Onc). The variables were analyzed among the 4 groups and between AI and HO.
Results: Thirteen patients [7 men, with a median of 54 years (32–63)] were studied. The etiologies were: 5 AI, 5 HO, 2 Inf and 1 Onc disease. Hemophagocytic cells were found in the ascitic fluid of one patient. A patient with MAS secondary to IgG4-related disease was found.
Conclusions: Mortality, prognosis and disease progression may be influenced by the delay in diagnosis, treatment initiation and etiology of MAS. HO ill patients had a worse prognosis.

Síndrome de activación macrofágica secundario a enfermedades autoinmunes, hematológicas, infecciosas y oncológicas. Serie de 13 casos clínicos y una revisión bibliográfica

Palabras clave:
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RESUMEN

Objetivo: Describir las características demográficas y trastornos de pacientes con diagnóstico de síndrome de activación macrofágica (SAM) en el periodo comprendido entre diciembre de 2008-enero de 2014.
Métodos: Se revisaron las historias clínicas desde el diagnóstico de SAM y tras su alta hospitalaria hasta enero de 2014. Los pacientes se agruparon en 4 grupos: autoinmunes (AI), hemato-oncólogicas (HO), infecciosas (Inf) y oncológicas (Onc). Las variables fueron analizadas entre los 4 grupos y entre AI y HO.
Resultados: Trece pacientes (7 hombres, con una mediana de 54 años [32-63]) se estudiaron. Las etiologías encontradas fueron: 5 AI, 5 HO, 2 Inf y una Onc. Se encontraron células hemofagocíticas en el líquido ascítico en uno de los pacientes. Se encontró un paciente con SAM secundario a enfermedad relacionada con la IgG4.
Conclusiones: La mortalidad, el pronóstico y la evolución de la enfermedad puede verse influida por el retraso en el diagnóstico, el inicio del tratamiento y la etiología del SAM. Los pacientes con enfermedades HO presentaron peor pronóstico.

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Introduction

Macrophage activation syndrome (MAS) is a group of diseases characterized by a severe acute inflammatory syndrome, usually underdiagnosed.[1] The usual clinical manifestations are fever, *rash*, enlarged organs and central nervous system alterations. Laboratory analysis usually shows pancytopenia, hepatitis, coagulopathy, hyperferritinemia and hypertriglyceridemia, and histologically the presence of hemophagocytic cells (HC) on bone marrow (BM), spleen and/or lymph node biopsy.[1,2]

This disease is caused by proliferation and activation of T cells and macrophages, causing an inflammatory response characterized by hypersecretion of cytokines such as interferon-gamma, tumor necrosis factor alpha, interleukin 1 (IL-1), IL-6, IL-10, IL-12, IL-18, and macrophage colony stimulating factor.[1,2] Secondary MAS is the result of an immunological reaction caused by autoimmune disease, infection, exposure to drugs and neoplasms.[2,3]MAS secondary to autoimmune diseases (AD) has certain differences from the other types such as very high hyperferritinemia, a decrease in erythrocyte sedimentation rate, a mild cytopenia and a more pronounced initial[3] coagulopathy. It can occur at any age, but especially at the beginning of juvenile idiopathic arthritis (JIA) and adult Still's disease (ASD), and during the development of systemic lupus erythematosus (SLE). It is estimated to occur in 7% of the patients with JIA, with a mortality rate ranging between 10 and 20%.[2–4]

In recent years we have witnessed an increased incidence of this disease, probably because before it was underdiagnosed due to lack of knowledge regarding it. It is for this reason that we decided to conduct a review of the cases to date in our hospital.

Objective

To describe the demographic, clinical and laboratory data, treatment strategies, mortality and underlying disorders during hospitalization and after discharge of patients diagnosed with MAS during the period of December 2008–January 2014 in the Hospital Universitario Donostia, Gipuzkoa, Spain.

Materials and Methods

In order to describe the clinical characteristics of patients diagnosed with MAS we reviewed paper and computerized medical records. Following data collection patients were grouped into 4 groups according to the underlying disease: AD, hemato-oncologic (HO), infectious (Inf) and oncologic (Onc).

Nominal variables were diagnosis, possible triggers of MAS and treatments used during admission and currently. Dichotomous variables were gender, fever, organomegaly, hospital mortality after discharge, admission to the intensive care unit (ICU) and recurrence of MAS. Quantitative variables were age, analytical findings, hospital stay in days, days from admission to BM biopsy, days after the BM biopsy until discharge or death of the patient and the evolution time after discharge hospital in months. Quantitative variables with a skewed distribution are represented as median and interquartile range.

Results

13 patients were found 5 with AD, 5 with HO diseases 2, with Inf diseases and one with Onc disease. Table 1 shows demographic characteristics, etiology, possible triggers of MAS, mortality, treatments used during admission and currently as well as clinical outcomes after hospital discharge.

Fever was the only common criterion. Organomegaly (splenomegaly and/or hepatomegaly) was present in all patients except for patient 13. Tables 2–4 show the descriptive analysis of patients with secondary MAS shown by type of disease. Patients 6, 7 and 8 underwent more than one BM biopsy and patient 3 also presented HC and ascites.

With regard to treatment strategies, all patients received glucocorticoids (GC), 8 patients (3 AD and 2 HO, 2 Inf and 1 Onc) received immunoglobulin (IG), 8 patients (5 AD and 3 HO) received cyclosporine (CSP), 4 patients (2 AD and 2 HO) received anakinra, 2 patients (2 HO) tocilizumab and chemotherapy. All patients received broad spectrum antibiotics, except patient 11. Most patients received maintenance therapy and transfusions of red blood cells and platelets, colony stimulating factor, erythropoietin and vasopressors. Patient 5 required three hemodialysis sessions during hospitalization due to fluid overload, and clinicians, during admission, did not reach a definite etiologic diagnosis but seven months after discharge identified it as an IgG4-related disease.

Patients 7, 8 and 9 died during admission with a diagnosis of multiple organ dysfunction syndrome (MODS) and patient 12 presented massive hemoptysis; 13 patients died after discharge due to their underlying disease. Five patients were admitted to the ICU, all for MODS. Patients 4 and 7 had 2 admissions to the ICU each, with the second admission diagnosis being, in patient 7, MODS and sepsis as well as bacterial peritonitis in patient 4 due to *Pseudomonas aeruginosa*, *Enterococcus faecallis* and *Bacteroides fragillis*, requiring up to 4 surgical cavity lavages. No patient had a recurrence of MAS after discharge.

Discussion

The main diseases related to MAS in our study were AD and HO, these being the most frequent. With respect to AD, we found 3 patients who started with MAS and one that presented the ethological diagnosis after hospital discharge, which was associated with IgG4 disease, the first case reported of this association with MAS.

In a series of 18 patients in the US, one case was found after bone marrow transplantation.[4,5] In a series of 58 patients with HIV in France, other infectious agents were described, including HIV, acting as triggers of MAS.[6]MAS cases secondary to *Pneumocystis jirovecii* have been reported in patients with HO disease and not in HIV.[9] Patient 12 could be the first case of MAS secondary to *P. jirovecii* in a patient with HIV, although HIV could also be the cause of MAS.

The most common bacteria related to MAS are *Salmonella*, *Tuberculosis* and *Pseudomonas*,[5] and within the Enterobacteriaceae isolated cases of *Serratia*, *Klebsiella* and *Campylobacter* have been reported.[7–9] In 2001, the first described case of MAS secondary to *Campylobacter fetus* was reported in a patient with acquired immunodeficiency syndrome. Patient 11 is the first case of MAS secondary to *Campylobacter jejuni*.

Regarding MAS secondary to chemotherapy, cases have been rarely described. In 2012 a patient with neuroblastoma was associated to MAS after starting chemotherapy.[10] Patient 13 is probably the first case of MAS secondary to chemotherapy with temozolomide, although MAS could also be attributed to the tumor itself, albeit less likely.

None of the patients underwent quantification of *natural killer* cells and sIL-2 receptor because these tests are not performed in our hospital. These tests are not available in all hospitals, and when performed, the results are often slow to come. It is for this and the high mortality related to MAS that these tests should not be decisive for the diagnosis, let alone onset of treatment, provided there is a high suspicion of MAS.[1,10,11]