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Macrophage activation syndrome: A severe and frequent manifestation of acute pancreatitis in 362 childhood-onset compared to 1830 adult-onset systemic lupus erythematosus patients

Natali W.S. Gormezano[a,b], Carini I. Otsuzi[a], Diego L. Barros[a], Mariana A. da Silva[a], Rosa M.R. Pereira[a], Lucia M.A. Campos[b], Eduardo F. Borba[a], Eloisa Bonfá[a], Clovis A. Silva[a,b,*]

[a] Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo, no. 455, 3 andar, sala 3190-Cerqueira César, São Paulo 05403-010, Brazil
[b] Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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ABSTRACT

Objective: We previously reported a case series of acute pancreatitis (AP) and macrophage activation syndrome (MAS) in childhood (cSLE) patients; however, there are no data regarding the comparison of AP and MAS in large populations of cSLE and adult SLE (aSLE).
Methods: A study included 362 cSLE and 1830 aSLE patients. MAS was diagnosed according to preliminary diagnostic guidelines and AP according to the presence of abdominal pain or vomiting associated to an increase of pancreatic enzymes and/or pancreatic radiological abnormalities. Demographic data, clinical features, SLEDAI-2K, SLICC/ACR-DI, and treatment were assessed.
Results: Age in MAS patients was significantly lower compared with those without this complication [15 (8.8–55) vs. 33.5 (10.2–45.7) years, $p = 0.007$]. The frequencies of fever (94% vs. 37%, $p = 0.001$), leucopenia (82% vs. 19%, $p = 0.0001$), thrombocytopenia (65% vs. 19%, $p = 0.013$), hypertriglyceridemia (87% vs. 42%, $p = 0.037$), and hyperferritinemia (93% vs. 37%, $p = 0.011$) were also more frequently observed in AP patients with MAS compared in AP patients without MAS. Fever and hyperferritinemia concomitantly were more frequent in the former group (86% vs. 12%, $p = 0.0015$). Higher and significant frequency of AP in cSLE compared to aSLE patients [12/362 (3.3%) vs. 20/1830 (1.1%), $p = 0.003$], with similar AP duration [22 (6–60) vs. 15 (4–90) days, $p = 0.534$]. MAS (85% vs. 30%, $p = 0.003$) and death by MAS complication (31% vs. 0%, $p = 0.017$) were significantly higher in children compared with aSLE.
Conclusions: This study provides novel data demonstrating that MAS occur in the majority of cSLE with AP with a higher mortality compared to aSLE. In addition, we identified in AP patients, a cluster of MAS clinical and laboratorial parameters more associated with this complication.

Introduction

Macrophage activation syndrome (MAS) is a rare and severe complication in patients with infections and in rheumatic diseases with high mortality rate [1]. It has been reported in childhood-onset systemic lupus erythematosus (cSLE) [2–5], with a possible association with acute pancreatitis (AP) [6]. The latter is generally associated with disease activity in cSLE [7–9] and adult SLE (aSLE) [10–12] patients. However, the comparisons of specific clinical and laboratorial features of MAS in cSLE and aSLE populations with AP were not performed.

Therefore, the aim of this study was to compare, in a large population of cSLE and aSLE patients, the group of AP with and without MAS in order to identify demographic, clinical and laboratorial parameters associated with both complications in order to increase awareness to this rare condition.

Patients and methods

A retrospective study included 362 cSLE and 1830 aSLE patients followed at pediatric and adult lupus units of the same tertiary hospital, these two large data sets of cSLE and aSLE were generated from November 2012 to October 2014, and all were consecutive eligible patients. All of them fulfilled the American College of Rheumatology criteria for SLE [13]. We considered cSLE when

* Corresponding author at: Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo, no. 455, 3 andar, sala 3190-Cerqueira César, São Paulo 05403-010, Brazil.
E-mail address: clovisaasilva@gmail.com (C.A. Silva).

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disease onset was before 18 years of age and aSLE after 18 years of age.

Systematic analysis of medical charts was assessed regarding demographic data (age at AP diagnosis, disease duration until AP diagnosis, and duration of AP and gender), SLE clinical manifestations included: fever (38°C), hepatomegaly (> 3 cm below the costal arch), splenomegaly (> 3 cm below the costal arch) [2], vomiting, abdominal pain, arterial hypertension (> 140 × 90 mmHg), cutaneous lesions (malar or discoid rash, photosensitivity, mucosal ulcers, alopecia, or cutaneous vasculitis), articular involvement (arthritis or myositis), serositis (pericarditis or pleuritis), neuropsychiatry involvement (central nervous system and peripheral nervous system), nephritis (proteinuria ≥ 0.5 g/24 h, presence of cellular casts, hematuria, leucocituria excluding infection, or acute renal failure), hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding), antiphospholipid syndrome (thrombosis and/or obstetrics events in the presence of antiphospholipid antibodies) and hematologic complications (hemolytic anemia, leukopenia with a white blood cell count $< 4000/mm^3$ or lymphopenia $< 1500/mm^3$ on two or more occasions and thrombocytopenia with platelet count $< 100{,}000/mm^3$ in the absence of drugs).

MAS was diagnosed according to preliminary diagnostic guidelines, requiring the presence of at least one clinical (fever, hepatomegaly, splenomegaly, hemorrhagic manifestations, and central nervous system dysfunction) and two laboratorial criteria (cytopenia affecting two or more cell lineages, increased aspartate aminotransferase, increased lactate dehydrogenase, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia) [3]. Bone marrow aspiration for evidence of macrophage hemophagocytosis was performed when available.

AP was defined according to the presence of abdominal pain or vomiting associated to an increase, more than three-fold elevation, of serum pancreatic enzymes (amylase or lipase) and/or pancreatic radiological abnormalities (abdominal ultrasound or computer tomography) [6,7,11]. Death by MAS complication, necrohemorrhagic pancreatitis and type 2 diabetes mellitus after AP were observed. Data concerning the laboratory exams at AP and MAS diagnosis, treatment and outcome were also determined.

SLE disease activity and cumulative damage were measured in all patients, using the SLE Disease Activity Index 2000 (SLEDAI-2K) [14] and the Systemic Lupus International Collaborating Clinics/ACR—Damage Index (SLICC/ACR-DI) [15].

Erythrocyte sedimentation rate (ESR) was performed by Westergren method and C-reactive protein (CRP) by nephelometry. Anti-double-stranded DNA (anti-dsDNA) was detected by indirect immunofluorescence using *Crithidia luciliae* as substrate. Presence of anticardiolipin antibodies (aCL) IgG and IgM was analyzed by enzyme-linked immunosorbent assay (ELISA). Lupus anticoagulant (LAC) was detected according to the guidelines of the International Society on Thrombosis and Hemostasis [16].

Data concerning the use and current dosage of prednisone, methylprednisolone pulsotherapy antimalarials, methotrexate, azathioprine, cyclosporine and mycophenolate mofetil, intravenous cyclophosphamide, intravenous immunoglobulin, and plasmapheresis were determined.

Statistical analysis

Results are presented as the mean ± standard deviation or median (range) for continuous variables and as the number (%) for categorical variables. Data were compared by *t*-test or by the Mann–Whitney test for continuous variables to evaluate differences between AP in c-SLE and aSLE, as well as between MAS with and without AP. For categorical variables, differences were assessed by Fisher's exact test and Pearson chi-square. $P < 0.05$ were considered significant.

Results

Analyses of AP patients showed a higher and significant frequency of AP in cSLE compared to aSLE patients [12/362 (3.3%) vs. 20/1830 (1.1%), $p = 0.003$], with similar AP duration [22 (6–60) vs. 15 (4–90) days, $p = 0.534$]. Recurrence of AP occurred in one of 12 cSLE (13 episodes) and none in aSLE.

Demographic data, clinical features, disease activity, disease damage, outcomes, laboratory, and treatment of AP patients are in Table 1. cSLE patients had significantly higher fever (92% vs. 50%, $p = 0.002$), mucocutaneous involvement (85% vs. 30%, $p = 0.003$), alopecia (46% vs. 5%, $p = 0.008$), serositis (69% vs. 30%, $p = 0.037$), arterial hypertension (62% vs. 20%, $p = 0.027$), acute renal failure (58% vs. 15%, $p = 0.018$), and SLEDAI-2K at AP diagnosis [22 (8–41) vs. 10 (0–40), $p = 0.007$]. MAS (85% vs. 30%, $p = 0.003$) and death (31% vs. 0%, $p = 0.017$) were significantly higher in children compared with aSLE.

Thrombocytopenia (77% vs. 20%, $p = 0.003$), anti-ds DNA (92% vs. 50%, $p = 0.023$) and IgM anticardiolipin autoantibodies (43% vs. 0%, $p = 0.023$) were significantly higher in cSLE vs. aSLE. No differences were evidenced in glucocorticoid use at AP diagnosis in cSLE compared to aSLE groups (92% vs. 100%, $p = 0.394$). None of cSLE and aSLE patients used trimethoprim–sulfamethoxazole at AP diagnosis. Intravenous immunoglobulin was significantly used for AP treatment in cSLE compared to aSLE (62% vs. 10%, $p = 0.005$) (Table 1).

The frequencies of pancreatitis in cSLE-associated MAS were significantly higher compared to those without MAS [11/20 (55%) vs. 2/342 (0.6%), $p = 0.0001$]. The frequencies of pancreatitis in aSLE-associated MAS were also significantly higher compared to those without MAS [6/13 (46%) vs. 14/1817 (0.8%), $p = 0.0001$].

Further analysis of SLE patients with AP with and without MAS showed that age in MAS patients with AP was significantly lower compared with those without this complication [15 (8.8–55) vs. 33.5 (10.2–45.7) years, $p = 0.007$]. The frequencies of fever (94% vs. 37%, $p = 0.001$), leucopenia (82% vs. 19%, $p = 0.0001$), thrombocytopenia (65% vs. 19%, $p = 0.013$), hypertriglyceridemia (87% vs. 42%, $p = 0.037$) and hyperferritinemia (93% vs. 37%, $p = 0.011$) were also more frequently observed in AP patients with MAS compared in AP patients without MAS. The median of aspartate aminotransferase (AST) [121 (23–1156) vs. 30 (13–1446) U/L, $p = 0.018$], triglyceride [271 (163–526) vs. 172 (61–357) mg/dL, $p = 0.018$] and ferritin [1804 (28–24,511) vs. 409 (25–4282) ng/mL, $p = 0.041$] were significantly higher in AP patients with MAS, as showed in Table 2. Macrophage hemophagocitosis in bone marrow aspirate were observed in four patients. For the treatment of MAS patients, 76% received methylprednisolone pulsotherapy during MAS episodes, 47% intravenous immunoglobulin and less than 20% cyclosporine ($p > 0.05$). Fever and hyperferritinemia concomitantly were more frequent in AP patients with MAS compared to AP patients without MAS (86% vs. 12%, $p = 0.0015$).

The frequency of MAS was significantly higher in cSLE compared to aSLE patients [20/362 (5.5%) vs. 13/1830 (0.7%), $p = 0.0001$.

The comparison of SLE-MAS with and without pancreatitis revealed that SLEDAI-2K ≥ 6 at MAS diagnosis was significantly higher in SLE-MAS with pancreatitis compared to those without pancreatitis (100% vs. 75%, $p = 0.04$) (Table 3). All cSLE and aSLE patients were promptly treated at AP and MAS diagnosis. The treatments, outcome and cause of deaths are included in Table 3.

Discussion

To our knowledge, this was the first study to show that MAS is a very frequent and severe complication in childhood SLE with AP