Macrophage activation syndrome: a life-threatening complication in a 44-year-old woman

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ABSTRACT

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of autoimmune diseases. A 44-year-old woman was admitted to the hospital for further evaluation due to swelling in the left latero-cervical region, a mild fever that persisted for two weeks, itchy papular skin lesions, oral ulcers, and diffuse joint pain. Her medical history reported hypertension, diffused painful joints, and a pauci-symptomatic recent SARS-CoV-2 infection. A severe, drug-resistant fever developed while the patient was in the hospital. Infectious diseases were excluded and blood cultures, swabs, and serum antibody dosages were carried out. In a patient with systemic lupus erythematosus, MAS was diagnosed due to the presence of fever, bilinear cytopenia, high ferritin, transaminase, and triglyceride levels with low fibrinogen levels. Methyl-prednisolone at immunosuppressive dosages and cyclosporine were started. Hematobiochemical parameters gradually returned to normal as the fever subsided. The patient's condition is being monitored while the cyclosporine therapy is continued and the steroidal therapy is gradually tapered off. It was not possible to show a potential link to the SARS-CoV-2 infection.

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Introduction

Macrophage activation syndrome (MAS) is a life-threatening hyperinflammatory condition that rarely complicates autoimmune diseases and belongs to the spectrum of hemophagocytic lymphohistiocytosis.[1] Its pathophysiological hallmark is a dysfunctional immune response, which leads to excessive activation and expansion of T-lymphocytes and macrophages, resulting in cytokine storm syndrome.[2,3] The main clinical features of this syndrome are: unremitting fever, hepatosplenomegaly, generalized lymphadenopathy, central nervous system dysfunction, and hemorrhagic manifestations. MAS is a relatively uncommon complication of systemic lupus erythematosus (SLE) in adults, with an occurrence ranging from 0.9 to 4.6%.[4] MAS mortality rate in SLE patients is high;[5] unfortunately, an early diagnosis is difficult because of the overlap of clinical characteristics and diagnostic criteria between active SLE and MAS-associated SLE.[5,6]

Case Report

A 44-year-old woman was hospitalized at the Internal Medicine Department for left latero-cervical region swelling, two weeks of continuous slight fever, and an itchy rash from the face to the trunk and upper limbs (Figure 1). The patient presented lymph adenomegalies at the neck, axillar, and inguinal chains. The latero-cervical swelling was painful, had elastic consistency, and was covered by red and warm skin. There were also diffused, itchy, papular skin lesions, worsening with exposure to light, painless oral ulcers, and diffused arthralgias. Chest and abdominal examinations were normal.

The patient referred to a medical history consisting of hypertension treated with irbesartan 300 mg/day, a single episode of thrombocytopenia treated with corticosteroids, diffused arthralgia, and a recent (2 months earlier) pauci-symp-

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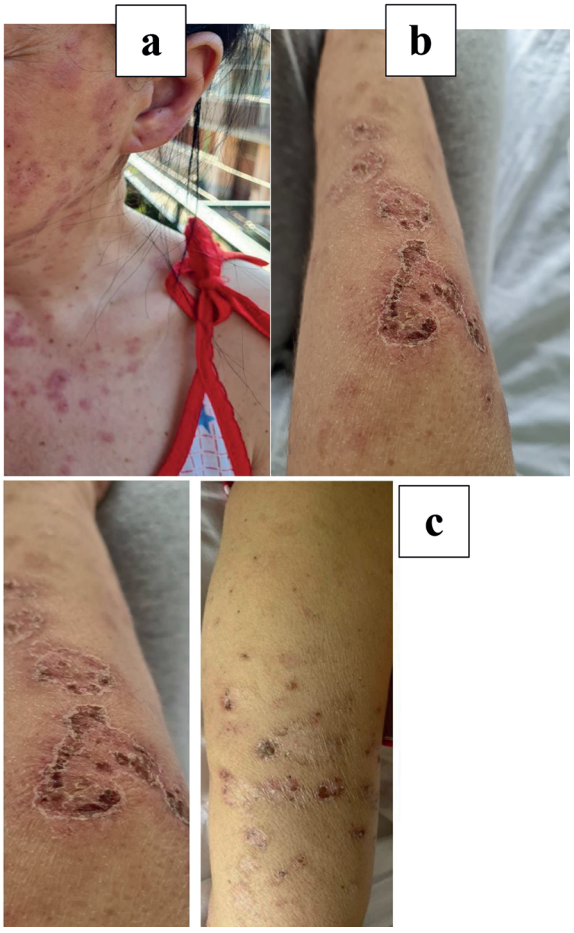

Figure 1. Skin lesions: a) face; b) arm; c) leg.

tomatic SARS-CoV-2 infection (the patient was not vaccinated for SARS-CoV-2). The patient was a current smoker.

Discussion

At admission, the patient presented mild anemia, high D-dimer, C-reactive protein (CRP), and β-2-microglobulin; white blood cell count and formula, lipid profile, cytolysis index, ferritin, and electrolytes were normal (Table 1). Autoimmunity profile was requested (Table 2).

A computed tomography (CT) scan showed slight hypertrophy of neck lymph nodes.

Fine-needle aspiration cytology of the latero-cervical lymph node was performed with sampling for cytomorphology and cytofluorimetry; a biopsy of an upper right arm skin lesion was also performed.

Because of the appearance of fever (38°C), serial blood cultures and swabs were performed with negative results. The search for antibodies for Leishmania, Treponema, Toxoplasma, Brucella, Salmonella, HIV, Cytomegalovirus, and SARS-CoV-2 was negative. Most common neoplastic markers were all negative.

In the following days, the fever reached 40.5°C and was not responsive to paracetamol and steroids. Laboratory tests worsened, showing a reduction of hemoglobin, white blood cells, and platelets (Table 1).

Suspecting a lymphoproliferative disease, a positron emission tomography scan was performed, evidencing an increased metabolic activity (SUV max 4.7) of the spleen and several supra and sub-diaphragmatic lymph nodes.

Microscopic examination of the peripheral blood smear showed discrete red blood cells, mild platelet anisocytosis and some hypo-segmented neutrophils.

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Table 1. Patient's laboratory values since admission.

Analyte	Normal range	Assessed value				
		At entry	14th day	16th day	20th day	30th day
Hb (g/dl)	12.0-15.5	11.1	9.3	9.0	7.5	8.4
RBC (×10⁶/ul)	4.0-5.0	3.65	3.00	2.91	2.44	2.60
Plt (×10³/ul)	150-450	153	107	112	162	276
WBC (×10³/ul)	4.5-11.0	6.20	3.60	3.96	6.70	7.31
Ferritin (ng/mL)	22-275	-	570	>2000	1583	277
CRP (mg/dl)	0.00-0.5	4.8	<0.33	1.28	-	<0.33
ESR (mm/h)	<10	-	-	35	-	-
D-dimer (ng/ml)	0-500	1075	-	11613	-	-
Fibrinog (mg/dL)	160-350	-	-	199	140	184
Tgc (mg/dl)	<150	163	200	393	333	127
AST (U/l)	0-34	24	27	396	153	9
ALT (U/l)	0-55	19	18	298	506	52
ALP (U/l)	50-116	55	43	166	206	115
GGT (U/l)	12-64	-	26	270	-	190
LDH (U/l)	125-243	177	179	751	299	131
CK (U/l)	30-200	43	31	54	20	9
Tbil (mg/dl)	0.20-1.20	0.41	0.26	0.49	1.81	0.76
Dbil (mg/dl)	0.00-0.50	0.21	0.21	0.29	1.31	0.42

Hb, hemoglobin; RBC, red blood cell count; Plt, platelets; WBC, white blood cell count; CRP, C-reactive-protein; ESR, erythrocyte sedimentation rate; Tgc, triglycerides; AST, aspartate amino-trasferase; ALT, alanine amino-transferase; ALP, alkaline phosphatase; GGT, gamma glutamyl-transpeptidase; LDH, lactate dehydrogenase; CK, creatine kinase; Tbil, total bilirubin; Dbil, direct bilirubin.

The lymph node fine needle cytology (FNC) did not show cellular atypia and skin lesion histology showed a not specific inflammatory infiltrate.

The autoimmunity evaluation showed a slight increase of immunoglobulin, and immunoglobulin G (IgG) levels, in particular IgG1 and IgG4 subclasses, and a modest C3 and C4 reduction. In addition, high levels of the antinuclear antibody (ANA) (immunofluorescence assay method) with granular pattern (1:1280) and anti-Sjögren's-syndrome-related antigen A (SSa) and anti-SSb (>640,0 AU/ml) were evidenced (Table 2). A direct poly-specific Coombs test for anti-IgG antibodies was positive.

Hypothetically, Sjogren's syndrome could have been consistent with high anti-SSa and anti-SSb values but was excluded by the lack of typical ocular and salivary symptoms, diagnostic histopathology, and radiological signs of salivary gland alterations.

Hyper IgG4 syndrome was also hypothesized, but the level of IgG4 was lower than the cut-off (135 mg/dl) and the typical radiological signs were not found.

The patient's clinical picture dramatically worsened, the 40°C body temperature persisted, and the fever did not respond to paracetamol and low-dose corticosteroids. The appearance of proteinuria (602mg/24h) led to the diagnosis of SLE.

According to the 2019 European League Against Rheumatism/American College of Rheumatology classification,[7] which requests at least 4 of 11 criteria be present for diagnosis of SLE, our patient presented: fever, ANA positivity, skin rash, photosensitivity, pancytopenia, hypocomplementemia, and proteinuria.

Furthermore, the presence of fever, bilinear cytopenia, and high levels of ferritin, transaminase, and triglyceride together with low fibrinogen levels, led to the diagnosis of MAS according to Ravelli's criteria.[8]

Table 2. Patient's main immunologic and autoimmunity parameters at entry.

Analyte Serumelectrophoresis	Assessed value	Normal range
Albumin (%)	42	55.8-66.1
Alpha 1 (%)	3.8	2.9-4.9
Alpha 2 (%)	8.2	7.1-11.8
Beta 1 (%)	4.2	4.7-7.2
Beta 2 (%)	3.9	3.2-6.5
Gamma (%)	37.9	11.1-18.8
A/G ratio	0.72	1.10-2.40
IgG (g/l)	27,900	7.37-16.07
IgG1 (g/l)	28,400	4.05-10.11
IgG2 (g/l)	3.830	1.69-7.86
IgG3 (g/l)	0.626	0.11-0.85
IgG4 (g/l)	7.240	0.03-2.01
IgA (g/l)	2.600	0.70-4.00
IgM (g/l)	0.821	0 40-2.30
IgE (KU/l)	115	<=100
C3 (g/l)	0.41	0.90-1.80
C4 (g/l)	0.08	0.10-0.40
ANA-ELISA (index)	19.20	0.00-1.00
ANA-IFI	1:1280, granular pattern	<1:80
PR3-ANCA (UI/ml)	0.0	<10
MPO-ANCA (UI/ml)	0.00	<10
ACPA (UA/ml)	0.0	<5.0
DsDNA – Ab (IU/ml)	27.5	<30
SSa – Ab (UA/ml)	>640.0	<10
SSb – Ab (UA/ml)	>640.0	<10
Sm-Ab (UA/ml)	0.0	<10
RNP-Ab (UA/ml)	0.0	<10
Scl 70-Ab (UA/ml)	3.6	<10
Jo-1-Ab (UA/ml)	0.0	<10
Anti-histones-Ab (EU/ml)	2.980	<20
Anti-centromere-Ab (UA/ml)	0.5	<10
Beta-2 microglobulin (ng/ml)	5523	609-2366

A/G, albumin/globulin; Ig, immunoglobin; ANA, antinuclear antibody; ELISA, enzyme-linked immunosorbent assay; IFI, immunofluorescence assay; PR3-ANCA, proteinase 3 antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase; ACPA, anti-citrullinated protein antibodies; Beta 2mic: DsDNA, double-stranded DNA; SSa/b, anti-Sjögren's-syndrome-related antigen A/B; Sm-Ab, Smith antibody; RNP, ribonucleoprotein; Scl 70- Ab, anti-scleroderma antibody; Jo-1-Ab, anti-synthetase antibody

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A course of intravenous methyl-prednisolone at immunosuppressive dosages (1000 mg) was started; 100 mg/day of cyclosporine was added the following day. Fever disappeared and hematobiochemical parameters gradually normalized. The steroidal therapy was gradually decreased until suspension, while the cyclosporine therapy continued. Due to the blood cell count trend, a blood transfusion was carried out.

Currently, the patient's clinical condition is being followed up at the rheumatology outpatient clinic, and is under satisfactory control.

Conclusions

MAS is a life-threatening hyperinflammatory condition that rarely complicates autoimmune diseases. It can be particularly deceptive because it can be initially misdiagnosed with infectious and/or neoplastic diseases; early diagnosis is essential to stop the cascade of potentially fatal autoimmune events.[8]

In our case, a possible correlation with the patient's recent SARS-CoV-2 infection remains in doubt.

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