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(CASE REPORT)

MULTIFOCAL TUBERCULOSIS COMPLICATED WITH MACROPHAGE ACTIVATION SYNDROME (MAS): A CASE REPORT

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ABSTRACT

Macrophagic activation syndrome is a rare, severe and often fatal immunological complication associated with a wide range of conditions such as: infections, cancers and auto immune diseases. We report a case of a young patient of 22 years old, admitted for acute pancreatitis in a febrile context and poor general condition. Later we confirmed the diagnosis of multifocal tuberculosis (pulmonary, ganglionic and peritoneal) complicated by Macrophagic Activation Syndrome. The diagnosis has been established upon clinical, biological and radiological criteria with a microbiological confirmation of tuberculosis. The treatment administered consisted of adapted antitubercular antibiotics and high-dose corticosteroid therapy, which lead to a favorable clinical evolution. This case report illustrates the importance of considering a Macrophagic Activation Syndrome in front of unexplained biological anomalies in a tuberculosis patient, even with no known history of immunodepression.

Keywords: Macrophagic activation syndrome; Multifocal tuberculosis; Hemophagocytosis; Pancytopenia;

1 INTRODUCTION

Macrophagic activation syndrome (MAS) also referred to as hemophagocytic lymphohistiocytosis is a rare potentially fatal pathological entity first described by Farquhar and Claireaux in 1952 [1]. We can distinct 2 categories of MAS: primary and secondary. The primary form is due to defects in genes involved in lymphocyte granule-dependent cytotoxicity, inflammasome activation, or other immune functions [2], the secondary form can be met in a variety of conditions such as : infectious diseases, whether viral (Epstein-Barr Virus for example), fungal, parasitic, or bacterial (like in our case : Tuberculosis), Neoplasms (Haematological and solid) and autoimmune diseases [3]. It usually presents with fever, splenomegaly, Cytopenia affecting at least two blood cell lineages in addition to other biological findings like hypertriglycerdiemia/hypofibrinogenemia and hyperferritinemia. Histologically, we find hemophagocytosis in bone marrow, spleen, lymph nodes or liver. Hemophagocytosis is the ingestion of cellular blood

components and their precursors by macrophages [4]. We can find this image in bone marrow, spleen, liver and lymph nodes, in addition to bodily fluids [5]. Our case today treats secondary macrophage activation syndrome complicating multifocal tuberculosis in a 22 year old male young adult.

2 CASE PRESENTATION

A 22-year-old male student with a history of undocumented abdominal surgery at the age of 6 months, with no other medical or toxic history, presented to the emergency department with dorsal oppressive epigastric pain associated with fever and nocturnal chills, and a dry cough. The diagnostic of acute pancreatitis has been taken on radiological criteria: inflammatory changes in pancreas and peripancreatic fat, biological criteria: Lipasemia at 246 UI/L and clinical criteria: the typical pancreatic pain. The pulmonary clinical exam was normal. The chest X-Ray (figure 1) was unremarkable.

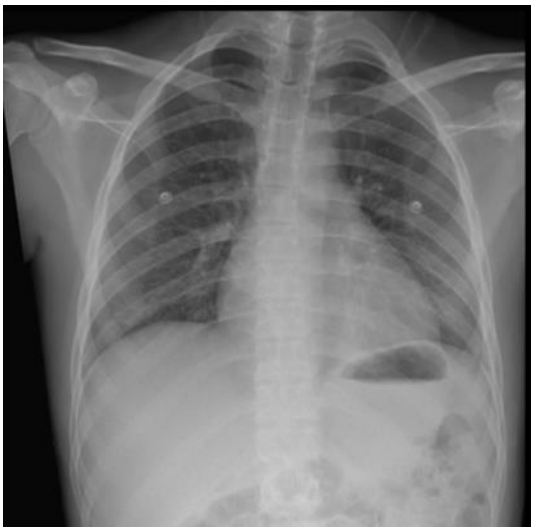

Figure 1: Chest X-Ray of the patient

The thoracoabdominal-pelvic computed tomography (TAP-CT) (figure 2 A-D) showed multiple lymphadenopathies in the celiac mesenteric, common iliac, and ileocecal regions, grouped together in a magma that most likely indicates peritoneal and ganglionic tuberculosis with no other anomaly.

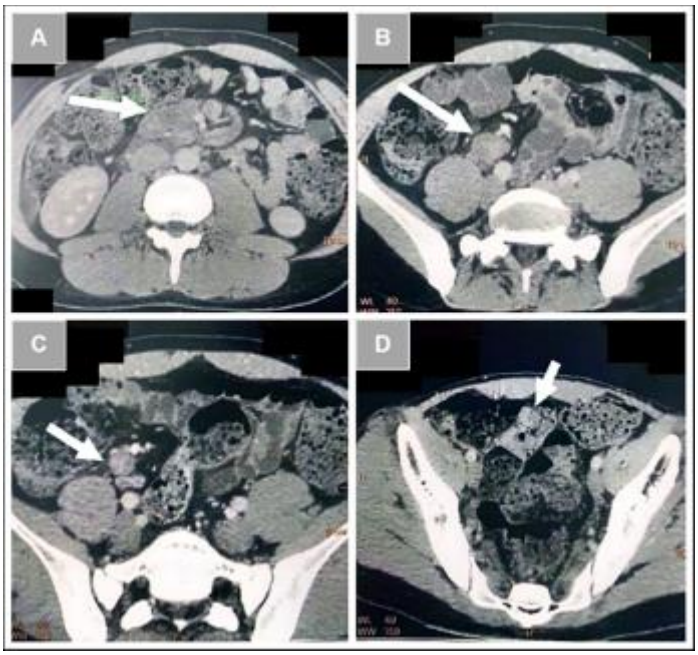

Figure 2: TAP-CT showing group of lymphadenopathies favor of peritoneal and ganglionic tuberculosis

Pulmonary tuberculosis has been confirmed using molecular biology study (GeneXpert MTB/RIF) in the sputum.

The patient's laboratory findings at admission and during the eighth day of hospitalization are presented in Table 1.

Table 1: Laboratory findings at admission and during the eighth day of hospitalization

Parameter	Initial value	Day 8	Reference range
Hemoglobin(HGB)	9.2 g/dL	8.6 g/dL	13-17 g/dL
Mean Corpuscular Volume(MCV)	88.5 fL	87.6 fL	79-99 fL
Mean Corpuscular Hemoglobin (MCH)	33 pg	33 pg	27-32 pg
Platelets	53 $x10^9$ /µL	38 $x10^9$ /µL	150-400 x 10^9/µL
Leukocytes	3880 $x10^9$/µL	920 $x10^9$ /µL	4-10 $x10^9$/µL
Neutrophils	2680 $x10^9$/µL	520 $x10^9$ /µL	1.5-7 $x10^9$/µL
Lymphocytes	1090 $x10^9$/µL	290 $x10^9$ /µL	1-4 $x10^9$/µL
Monocytes	90 $x10^9$/µL	110 $x10^9$ /µL	0.3-1 $x10^9$/µL
Eosinophils	20 $x10^9$/µL	10 $x10^9$ /µL	0.1-0.4 $x10^9$/µL
Basophils	0 $x10^9$/µL	0 $x10^9$ /µL	0-0.1 $x10^9$/µL
C reactive protein	78 mg/dL	66 mg/dL	0-6 mg/L
Urea	0.3 g/L	0.3 g/L	0.15-0.45 g/L
Serum Creatinine	11.4 mg/L	8 mg/L	6-11 mg/L
Serum Lipase Level	246 U/L	-	13-60 U/L
Aspartate aminotransferase(AST)	262 U/L	531 U/L	< 31 U/L
Alanine aminotransferase(ALT)	157 U/L	417 U/L	< 34 U/L
Total bilirubin	0.9 mg/dL	-	0.3-0.12 mg/dL
Alkaline Phosphatase (ALP)	110 IU/L	-	44-147 IU/L
Prothrombin time	75%	41%	80-100%
Fibrinogen	-	1.9 g/L	2-4 g/L
Serum ferritin	-	3600 ng/mL	30-300 ng/mL
Lactate deshydrogenase (LDH)	-	310 U/L	140-280 U/L
HIV serology	-	Negative	-
Hepatitis C and B serology	-	Negative	-

Initial laboratory investigations revealed normocytic normochromic anemia associated with thrombocytopenia, while the leukocyte count remained within the normal range. Inflammatory markers were elevated, with increased C-reactive protein levels, and liver function tests demonstrated marked hepatocellular injury characterized by significant elevations in AST and ALT.

By the eighth day of hospitalization, the patient had developed pancytopenia, including leukopenia, neutropenia, lymphopenia, worsening anemia, and thrombocytopenia. Coagulation studies showed a reduced prothrombin time, whereas fibrinogen levels remained within the normal range. Serum ferritin and lactate dehydrogenase levels were markedly elevated, and hepatic cytolysis had further worsened. Serological testing for HIV and viral hepatitis was negative. Abdominal ultrasonography showed no hepatomegaly or splenomegaly.

Throughout hospitalization, the patient experienced persistent high-grade fever (39.5°C), which resolved progressively within three days after initiation of treatment.

The diagnosis of multifocal tuberculosis (pulmonary, peritoneal and ganglionic) was retained and in front of the pancytopenia, the hyperferritinemia and the prolonged fever we have retained the diagnostic of macrophagic activation syndrome (MAS). Hepatoprotective anti-tuberculosis antibiotherapy was initiated to prevent progression of cytolysis: 15 mg/kg/day of Amikacine + 750 mg/kg/day of Levofloxacine + 15 mg/kg/day of Ethambutol and high-dose

corticosteroid therapy was initiated at 240 mg/day(4mg/kg/j), gradually tapered. The patient's clinical condition began to improve within the first three days of treatment, with laboratory abnormalities gradually normalizing over the course of his 20-day hospitalization. He was subsequently discharged without any sequelae and continued to be followed regularly in the outpatient clinic.

3 DISCUSSION

Due to the clear clinical improvement and the regression of the biological inflammatory syndrome, the pancytopenia and the hepatic cytolysis under the anti-tuberculosis antibiotherapy associated with high-dose corticosteroid therapy, we have retained that we were in front of a case multifocal tuberculosis complicated with macrophagic activation syndrome.

Macrophagic activation syndrome is a very rare, potentially fatal disease with a mortality rate at almost 50%. In 2014, Ramos-Casals et al [3] analyzed the etiologies of macrophage activation syndrome (MAS) in a cohort of 2,197 patients and identified three main categories: infections (50%), malignancies (48%), and, to a lesser extent, autoimmune diseases and other causes such as organ transplantation or drug exposure. Among infectious etiologies, viruses accounted for 68% of cases. The most common viral triggers were Epstein–Barr virus (43%), human immunodeficiency virus (HIV; 22%), and cytomegalovirus (9%). Bacterial infections represented 18% of infectious causes, with Mycobacterium tuberculosis being the most frequent bacterial trigger, identified in 78 patients from the 2,197-case cohort. Parasitic infections were the third most common infectious etiology, accounting for 5% of cases, and included Leishmania spp., Plasmodium spp., and Toxoplasma spp. Malignancy-associated MAS was predominantly related to hematological neoplasms, mainly T-cell or natural killer (NK)-cell lymphomas and B-cell lymphomas.

Autoimmune diseases constituted the third etiological category, with systemic lupus erythematosus (48%) and adult-onset Still's disease (20%) being the most frequently associated conditions.

More rarely, MAS was triggered by kidney or hematopoietic stem cell transplantation, medications, surgical procedures, biopsies, or vaccination.

Finally, in 81 cases (3.6%) of the 2,197-patient cohort, no underlying etiology was identified, corresponding to idiopathic macrophage activation syndrome.

The pathophysiology of macrophage activation syndrome has not yet been clearly elucidated in the literature. One prevailing hypothesis suggests that MAS is caused by excessive production of pro-inflammatory cytokines, such as TNF-α, (IFN-γ), and IL-6, by inadequately regulated activated macrophages. This results in an uncontrolled cycle of mutual activation between macrophages and lymphocytes, which underlies the various clinical and biological manifestations of the syndrome [6].

Macrophage activation syndrome is clinically characterized by the onset of prolonged fever, hepatosplenomegaly, and enlargement of hematopoietic organs in approximately two thirds of cases. Pulmonary involvement may be present, as well as neurological manifestations ranging from focal neurological deficits to acute confusional states or coma [7].

Biologically, we find that in almost all of the cases a pancytopenia is present, with a quarter of the cases having agranulocytosis [3]. Hepatic cytolysis, hyperferritinemia and hypertriglyceridemia are present in approximately all patients.

Histologically, we find hemophagocytosis which is the phagocytosis by histiocytes of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues. However it's neither sensible (70-83%) neither specific (60%) [7].

The diagnosis of macrophage activation syndrome was established according to the HLH-2004 diagnostic criteria, which require either a molecular diagnosis consistent with HLH or the fulfillment of at least five of eight diagnostic criteria. These include persistent fever, splenomegaly, cytopenias affecting at least two hematopoietic cell lineages (hemoglobin <9 g/dL, platelet count $<100 \times 10^9$/L, and/or neutrophil count $<1.0 \times 10^9$/L), hypertriglyceridemia (fasting triglycerides ≥3.0 mmol/L) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L), evidence of hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver, low or absent natural killer (NK) cell activity, hyperferritinemia (ferritin ≥500 ng/mL), and elevated soluble interleukin-2 receptor (sCD25) levels (≥2,400 U/mL) [8].

Regarding tuberculosis-associated macrophage activation syndrome, Brastianos et al. analyzed 37 cases reported in the literature. They found that 50% of patients had a history of immunosuppression, 83% presented with extrapulmonary tuberculosis, and 49% had associated hepatomegaly. Among the 35 cases for which data were available, 21 patients were male and 14 were female. The mean age was 46 ± 22 years (median age, 44 years), with a wide age range extending from 14 days to 83 years [9] .

To date, no study has established a standardized treatment protocol for macrophage activation syndrome. Nevertheless, most authors recommend a combination of high-dose corticosteroid therapy (>1 mg/kg/day) and etoposide (VP-16) at a dose of 100–150 mg/m^2 [10]. This immunosuppressive treatment should be combined with management of the underlying etiology, such as anti-infective therapy for infectious triggers, including anti-tuberculosis treatment in cases of tuberculosis, as in our patient.

Poor prognostic factors in macrophage activation syndrome were studied by Kaito K. et al. in a cohort of 34 patients, of whom 14 survived and 20 died. The authors concluded that the following factors are associated with a poor prognosis: age over 30 years, presence of disseminated intravascular coagulation (DIC), hyperferritinemia, elevated β2-microglobulin levels, the combination of anemia and thrombocytopenia, and jaundice. The presence of these factors should prompt aggressive management, including adequate chemotherapy and appropriate supportive care [11].

4 CONCLUSION

Macrophage activation syndrome constitutes a diagnostic and therapeutic emergency, which is why early recognition can significantly influence prognosis. This is particularly true in the context of multifocal tuberculosis, especially when suggestive laboratory findings such as pancytopenia, hyperferritinemia, and hepatic cytolysis are present. The favorable response observed in our patient to corticosteroid therapy combined with anti-tuberculosis treatment highlights the importance of rapid and targeted management of the underlying etiology. This case underscores the need for vigilance, even in immunocompetent patients, to prevent this rare but potentially life-threatening complication.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

The study was conducted in accordance with ethical standards

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Author contributions

All authors contributed to the conduct of this work and to the writing of the manuscript. All authors read and approved the final version of the manuscript.

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