CASE REPORT

Sepsis and Macrophage Activation Syndrome: Two Successive Complications of *Staphylococcus aureus* Infection

Niariantsoa Rakotomalala[1]*, Hobynomena Rakotomalala[1], Irina Mamisoa Ranaivo[2], Stéphane Ralandison[3]

Abstract

The macrophage activation syndrome (MAS) and the sepsis are both a condition of hyperinflammation. The differential diagnosis can be difficult. The two pathologies can succeed with each other. The purpose of this literature review is to illustrate these diagnostic and therapeutic difficulties through a reported case of a macrophage activation syndrome secondary to infection (MASI). It was a 42-year-old diabetic man, hospitalized for an acute myositis due to an infection of *Staphylococcus aureus*. These germs caused a septic shock requiring antibiotic therapy. After an initial clinical improvement, the diagnosis of MASI post-*Staphylococcus aureus* was retained with a persistence of the inflammatory syndrome and appearance of fever with splenomegaly associated with hepatic cytolysis a 30% decrease in prothrombin time, a mild regenerative anemia without hemophagocytosis. An inflammatory syndrome may have several completely opposite etiologies and pathophysiology. Our case fulfilled both of the criteria of sepsis and MAS. Several signs were common for the two pathologies, but a detailed analysis of the clinical and biological elements lead to the diagnostic orientation.

Keywords: Diagnostic difficulty, Macrophagic activation syndrome, Sepsis.

International Journal of Health and Biological Sciences, (2020); DOI: 10.46682/ijhbs.3.1.2

Introduction

Macrophagic activation syndrome (MAS) is a condition of pathological hyper-inflammation leading to benign hystio-lymphocytosis hyperprolifération.[1] Sepsis is defined as an inappropriate systemic response due to infection with multivisceral organ failure.[2] It can be difficult to distinguish a SAM and sepsis, as the boundary between inflammation and infection can be blurred. In both cases, the prognosis may be affected; they are life-threatening dydisease, especially since the treatment is practically the opposite between these two diseases. The difficulty is even ugreater when it is knew that MAS can be secondary to infectious reactive sepsis (MASI), and a MAS can become complicated by sepsis. Saim is to illustrate these diagnostic and therapeutic difficulties through a case report.

Observation

We reported a case of a 42- year- old man who presented with a post-traumatic muscle pain of the left thigh. During his hospitalization, we discovered a type 2 diabetes complicated by ketoacidosis. The patient had no specific history other than repeated furunculosis. Initial biological check-up showed inflammatory syndrome with a high CRP level at 109 mg /L, hyperleukocytosis with a large amount of polymorphonuclear cells (18 G/L and 14 G/L). The platelet count was 62G /L. The creatinine and serum electrolytes were normal.

The soft tissue ultrasound revealed a musculo-aponevrotic disinsertion of the left vastus lateralis muscle in his proximal insertion. Thus, the patient received ketoprofen as treatment with icing and rest, as well as insulin therapy and hyperhydration in relation to his diabetes.

After a marked initial clinical improvement, the patient had a fever at 39.5°C on the four's day of hospitalization with re-emergence of myositis sign. On day 5, his condition had rapidly deteriorated following a septic shock. The computed tomography scan of the soft tissue objectified multiple micro-abscesses in the pectineus, left external obturator, and iliopsoas muscles. In view of this infective myositis, he received Ceftriaxone 2g/d, Ciprofloxacin 800 mg/d and Gentamycin 3 mg/kg/d targeting *Staphylococcus aureus* identified in the blood culture. The progression was marked at day 10 of hospitalization and Day 5 of antibiotic therapy by the lifting of the shock state and the disappearance of the signs of myositis. On the other hand, the fever persisted in a plateau at 40°C, accompanied by splenomegaly.

Biologically, the blood culture control and the urinalysis were negative, but there was an appearance of normocytic and normochromic anemia poorly regenerative at 8.5 g/dL, hyperleukocytosis at 25 G/L (85% of polymorphonuclear cells), thrombocytopenia at 98 G/L. CRP remained elevated at 139 mg/L.

This picture of a persistent clinico-biological inflammatory syndrome with bicytopenia prompted us to carry out a medullo-gram showing a bone marrow of normal richness without hemophagocytosis. There was markedly raised ferritinemia at 100,000 IU/mL, hypertriglyceridemia at 4mmol/L (N < 1.7 mmol/L), elevated transaminases (AST at 2xN, ALT at 4xN), anicteric cholestasis with total bilirubinemia at 24µmol/l (n < 17.1 µmol/L), Gamma-GT at 105 IU/L (N = 15 to 55 IU/L), normal alkaline phosphatases 400

[1]Department of Rheumatology, Faculty of Medicine, Univesity Hospital of Morafeno Toamasin , University of Ankatso, Antananarivo Madagascar.

[2] Department of Dermatology, Faculty of Medicine, University Hospital of Morafeno Toamasina, University of Barikadimy Toamasina, Madagasacar

[3]Department of Rheumatology, Faculty of Medicine, University Hospital of Morafeno Toamasina, University of Barikadimy Toamasina, Madagascar,

Corresponding Author: Niariantsoa Rakotomalala, University of Ankatso Antananarivo Madagascar, Faculty of Medicine, Univesity Hospital of Morafeno Toamasina Department of Rheumatology, e-mail: ntsoakewl@gmail.com

How to cite this article: Rakotomalala N, Rakotomalala H, Ranaivo IM, Ralandison S. Sepsis and Macrophage Activation Syndrome: Two Successive Complications of *Staphylococcus aureus* Infection. International Journal of Health and Biological Sciences 2020; 3(1):3-5

Source of support: Nil

Conflict of interest: None

Received: 07/01/2020 **Revised:** 24/02/2020 **Accepted:** 09/03/2020

IU /l (N = 30 to 100 IU/L), with a 30% decrease in prothrombin time. Doppler echocardiography eliminated endocarditis. Abdominal-pelvic ultrasound confirmed splenomegaly but did not show any other abnormalities.

We have mentioned the diagnosis of macrophage activation syndrome secondary to *Staphylococcus aureus* infection in front of this intense and persistent clinico-biological inflammatory syndrome with cytopenia. After 3 days of systemic corticosteroid (methylprednisolone) therapy with 120 mg/d, followed by prednisone per os at 1 mg/kg/d, fever and biological inflammatory syndrome disappeared in 3 days. The patient came out asymptomatic one week after corticosteroid therapy.

Discussion

An intense inflammatory syndrome may have multiple aetiologies and pathophysiology completely opposite. This is the case for our patient in whom sepsis, MASI, and MAS were triggered by the same causative agent: *Staphylococcus aureus*. Moreover, there is no defined chronology or established continuity of events between these three pathological entities, which makes diagnosis very difficult.

Sepsis is a life-threatening organ dysfunction caused by an inappropriate host response to infection. The diagnosis is made in front of a sequential organ failure assessment (SOFA) score of > 2.[2] This score has been filled-in our case (hyperbilirubinemia, thrombocytopenia, and cardiovascular collapse). This is a diagnostic and therapeutic emergency. Any acute inflammatory syndrome should be investigated, and its etiological treatment initiated promptly.

The MAS or Hemophagocytic lymphohistiocytosis (HLH) is a benign proliferation of lympho-hystiocytosis cells, resulting from a state of hyper-inflammation, secondary to an abnormality of CD8+ T-cell (LT CD8).[1,3] This is due to the inability of the LT to remove a given antigen, including infectious agents. This permanent stimulation of LT will lead to hyperproliferation with hyper inflammation state (phagocytosis, hyperproduction of pro-inflammatory cytokine). There are two types of MAS: primary MAS and secondary or acquired MAS.[4] Reactive MAS may be secondary to several pathologies: hemopathy, neoplasia, and infectious disease. To diagnose the MAS, several diagnostic criteria were established, including the HLH 2004 criteria (HemophagocyticLymphoHistiocytosis), including clinical, biological, and histological parameters.[5] MAS diagnosis is retained when the score is > 5. Our patient met these diagnostic criteria with a score of 5, which allowed us to diagnose MAS secondary to *Staphylococcus aureus* septicemia.

The MASI is a bridge between the two diseases. This is actually a MAS that is reactive to an infection. Clinically there is no obvious difference between the manifestations of MAS and MASI outside the fact that MASI occurs in adults rather than in primitive MAS. And also, the presence of a severe infection that should be sought before all MAS and during its evolution. The main agents involved are viruses, which account for almost half of the aetiologies of the MASI, followed by bacteria in about 16% of cases, and mainly common germs (13.7%).[3] *Staphylococcus aureus* was twice the infectious agent found by *Bourkis*and al during its study of 11 cases of MASI.[6] The diagnostic criterion remains that of HLH 2004.

There are no pathognomonic signs for each of these three pathological entities, but the diagnosis is made mainly on a fine analysis of the clinical-biological elements. Indeed, some diagnostic elements may be useful to evoke MAS. Ferritinemia, a marker of macrophage activity, was higher during MAS than in a sepsis. In a review of the literature by *Machowiz* and al., the mean ferritinemia value was 3171 ng/mL with a maximum of 210170 ng/mL compared with a median value of 590 ng/mL in the sepsis.[7] Our patient had severe hyperferritinemia at 100,000 IU/L (Table 1).

CPR is a protein of IL-6-mediated inflammation. A CPR value of > 100 mg/L is typically considered secondary to bacterial infection. This rise in CPR is less marked in the MAS.[8] However, failure to degrade CRP after proper antibiotic therapy led us to look for another non-infectious cause of the manifest inflammatory syndrome.

Cytopenia was more frequent and deeper in the MAS than in the sepsis. It is secondary to the production of Interferon-gamma and TNF-alfa, which inhibit hematopoiesis, cytopenia being aggravated by the hemophagocytosis. Pancytopenia in MAS is mostly due to high levels of TNF-alfa and IFN-gamma (ineffective erythropoiesis), with hemophagocytosis playing a minor role. *Kaihlembergand al* found median hemoglobin of 7.8-8.5 g/dl in patients with MAS.[8] For sepsis, the median is 10.4 g/dl of hemoglobin.[9] For platelet count, *Li*and et al. reported an average of 27-53 G/L in patients with MAS, and 93% of patients had platelet counts <100G/L.[10] In the course of sepsis, the presence of thrombocytopenia is mostly secondary to DIC (disseminated intravascular coagulation) or evolution to a state of septic shock, the value usually found as below <150G/L. The frequency of thrombocytopenia in severe sepsis was 14.5% in a prospective registry of over 1200 patients and platelet count exceeds 100 × 109/L in the majority of patients, even with severe sepsis and septic shock.[11] This bicytopenia was present in our patient, which didn't add up to the diagnosis.

The level of trygliceridemia also has a diagnostic orientation value. Hypertriglyceridemia in SAM is due to inhibition of lipoprease by TNF alfa. Triglycerides are higher in sepsis than in MAS with values of 440 mg/dL versus 180 mg/dl in serial studies.[12,13]

The same applies to the value of fibrinogenemia, the fibrinogen being cleaved by plasmin produced by activated macrophages. This

Table 1: commonalities between MAS and sepsis reported according to the HLH 2004 diagnostic criteria for the diagnosis of MAS

HLH criteria	*MAS*	*Sepsis*	*Case*
Fever	100%	90–100%	Present
Hepatosplenomegaly	70–100%	79%	Present
Cytopenia :			
Anemia	90–100%	51,6%	Hb 8,5 G/dL
Thrombopenia	86%–100%	14,5%– 26%	Platelets 98G/L
Hypertriglyceridemia	60–70%	81%	4mmol/L
Hypofibrinogénemia	65–80%	7%–76%	Not dosed
Lowactivity NK*	36%	96%	Not dosed
Ferritinémia>50µg/L	55–70%	33,3%	100.000 UI/L
Soluble Il 2 receptor *	93%		Not dosed
Hémophagocytosis	66,6%–100%	83%	Not dosed

value is lower in MAS; the median value is 105ng/dL. In contrast, in the sepsis, except in the case of DIC, fibrinogenemia would readily exceed 500 ng/dL.[14]

Finally, the presence of hemophagocytosis is not a discriminatory element. The sensitivity of this sign is 75–100% in MAS's series. However, hemophagocytosis can occur in many other conditions besides MAS, for example, after a blood transfusion or influenza. Hemophagocytosis reported to be present in 64% of patients hospitalized for resuscitation and thrombocytopenia[15] and in 80% of patients who died as a result of sepsis.[16,17]

Table 1 compares the frequency of the clinical and biological components found in the MAS and the severe sepsis, and also what was found in our patient. The strong points that led to the diagnosis in our patient were the identification of *Staphylococcus aureus* as the causal agent of the entire event. It was responsible for septicemia following myositis. The well-conducted antibiotic therapy eradicated the infection, but the secondary intensification of the inflammation corresponding with the diagnostic criteria of the HLH 2004 allowed us to make the diagnosis of MAS. The diagnosis was supported by the clinical-biological improvement of the patient on corticosteroid therapy, which could have aggravated the disease in the event of infection.

Conclusion

A hyper-inflamed state has multiple etiologies, sepsis and MAS are part of it. These two pathologies can succeed each other, and one can be the cause or the consequence of the other. The presence of MAS should be investigated for the absence of improvement in an infectious state despite adequate antibiotic therapy. In the absence of pathognomonic signs for each disease, fine analysis of clinical-biological components such as ferritinemia, CRP, trygliceridemia, and cytopenias are valuable aids in diagnostic guidance.

References

1. Carter SJ, Tattersall RS, Ramanan A V. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. Rheumatology [Internet]. 2018;(February):1–13. Available from: https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/key006/4898122
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama. 2016 Feb 23;315(8):801-10.
3. Créput C, Galicier L, Oksenhendler E, Azoulay E. Syndrome d'activation lymphohistiocytaire: Revue de la littérature, implications en réanimation. Reanimation. 2005;14(7):604–613.
4. Karras A, Hermine O. Syndrome d ' activation macrophagique. Rev Med Int 2002;23:768–778.
5. Larroche C. Le syndrome d'activation macrophagique acquis de l'adulte : comment le reconnaître et le traiter ? Rev rhum. 2012;79:194–200.
6. N-ingeHenter J. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(February 2006):124–131.
7. Boukhris I, Kechaou I, Fekih Y, Cherif E, Kaouech Z, Azzabi S, et al. Syndrome d'activation macrophagique : une urgence hématologique en médecine interne. Rev Méd Interne [Internet]. 2014;35:A101–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0248866314008194
8. Machowicz R, Janka G, Wiktor-jedrzejczak W. Similar but not the same : Differential diagnosis of HLH and sepsis. Crit Rev Oncol / Hematol [Internet]. 2017;114:1–12. Available from: http://dx.doi.org/10.1016/j.critrevonc.2017.03.023
9. Lehmberg K, Pink I, Eulenburg C, Beutel K, Maul-pavicic A, Janka G. Differentiating Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis from Other Forms of Hemophagocytic. J Pediatr [Internet]. 2013;162(6):1245–1251. Available from: http://dx.doi.org/10.1016/j.jpeds.2012.11.081
10. Vincent JL, Reinhart K, Gattinoni L, Webb A, Meier-hellmann A, Nollet G. Anemia and Blood Transfusion in Critically Ill Patients. JAMA. 2012;288(12):1499–507.
11. Li F, Yang Y, Jin F, Dehoedt C, Rao J, Zhou Y, et al. Clinical characteristics and prognostic factors of adult hemophagocytic syndrome patients : a retrospective study of increasing awareness of a disease from a single-center in China. Orphanet J Rare Dis. 2015;10:1–9.
12. Venkata C, Kashyap R, Farmer JC, Afessa B. Thrombocytopenia in adult patients with sepsis : incidence , risk factors , and its association with clinical outcome. J intensive care. 2013;1(9):1–10.
13. Janka GE. Hemophagocytic syndromes. Bloodd Rev. 2007;21:245–53.
14. Besset S, Schnell D, Azoulay É. Hemophagocytic Lymphohistiocytosis Mimicking Septic Shock. Chest [Internet]. 2012;141(3):835. Available from: http://dx.doi.org/10.1378/chest.11-2717
15. Lavigne GL. Simple coagulation tests improve survival prediction in patients with septic shock. J Thromb Haemost. 2008;6(October 2007):645–653.
16. François B. Thrombocytopenia in the Sepsis Syndrome : Role of Hemophagocytosis and Macrophage Colony-stimulating Factor. Am J Med. 1997;103(2):114–120.
17. Strauss R, Neureiter D, Westenburger B, Wehler M, Kirchner T, Hahn EG. Multifactorial risk analysis of bone marrow histiocytic hyperplasia with hemophagocytosis in critically ill medical patients— A postmortem clinicopathologic analysis. Crit Care Mes. 2004;32(6):1316–1320.