International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

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Macrophage activation syndrome: An unusual complication of brucellosis

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International Journal of Science and Research Archive, 2024, 13(01), 2046–2050

Publication history: Received on 18 August 2024; revised on 01 October 2024; accepted on 03 October 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.13.1.1839

Abstract

Introduction: During acute septicemic brucellosis, macrophage activation syndrome is a rare but serious complication. We report two cases of acute brucellosis complicated by macrophage activation syndrome (MAS).

Materials and methods: We conducted a retrospective study on the medical records of patients admitted for brucellosis complicated by SAM between February 2021 and January 2023. The diagnosis of brucellosis is based on the isolation of brucellosis in blood cultures and/or on positivity serology. The SAM was retained based on Henter's diagnostic criteria.

Results: During the study period, 30 patients were hospitalized for brucellosis. The average age is 46.7 years. Acute brucellosis complicated by SAM was noted in two immunocompetent male patients aged 47 and 46 years. Both patients were hospitalized for treatment of recent acute fever with deterioration in general condition, chills and diffuse arthromyalgia. The biological assessment revealed an inflammatory syndrome and pancytopenia in our patients. Blood cultures were requested returning positive for Brucella spp. Both patients presented more than five diagnostic criteria for SAM (fever, SPM, severe pancytopenia, hypertriglyceridemia and hyperferritinemia, histological signs of hemophagocytosis). Our patients improved only under antibiotic therapy.

Conclusion: Macrophage activation syndrome is a described but rare complication during brucellosis.

Keywords: Brucellosis; Complication; Macrophage Activation Syndrome; Pancytopenia

1. Introduction

1.1. Objectives

Infection-induced macrophagic activation syndrome is a rare but serious complication that can be life-threatening, warranting rapid and early diagnostic and therapeutic management. It is a reaction to viral, bacterial, fungal and/or parasitic infections. Some bacterial infections are rarely complicated by MAS, in particular tuberculosis, pyogenes and intracellular germs such as brucellosis. The expression of human brucellosis is highly polymorphous and varied, although hematological complications are rare, and the occurrence of true MAS is exceptional [1, 2]. The aim of our study is to report the cases of secondary MAS of brucellosis described in the infectious diseases department of Batna.

2. Materials and methods

Monocentric retrospective study conducted in a university hospital infectious diseases department (male hospitalization unit). We included all adult patients hospitalized for human brucellosis who presented with macrophagic activation syndrome. The diagnosis of brucellosis was based on the isolation of brucella from blood

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cultures and/or the positivity of Wright's serodiagnosis (a titre greater than or equal to 1/80 was considered positive) or ELISA serology. MAS was based on Henter's diagnostic criteria. Records were collected over a period from February 2021 to January 2023. Clinical information was collected from medical records using a standardized questionnaire. Epidemiological, clinical, cytological and biological data were evaluated.

3. Results

During the study period, 30 patients were hospitalized for brucellosis. The mean age was 46.7 years. 22 cases (73.33%) lived in rural areas. Clinically, 11 (36.66%) patients had presented with acute septicemic brucellosis. The focal forms were: neurobrucellosis 3.33% (n: 01), subacute orchitis 3.33% (n: 01), subacute endocarditis 3.33% (n: 01), spondylodiscitis 43.33% (n: 13), sacroiliitis 6.66% (n: 2), the association of these last two localizations was marked in a single patient 3.33% (n: 1). Acute septicemic brucellosis complicated by macrophagic activation syndrome was noted in two immunocompetent patients. The two patients were male, aged 46 and 47. They lived in rural areas. Both patients reported consumption of unpasteurized dairy products, with only one patient reporting contact with infected animals.

The first patient was 46 years old, a cattle breeder by profession, in moderately deteriorated general condition, presenting with fever, diffuse arthromyalgia and asthenia. Clinical examination revealed splenomegaly. Biological findings included cytolytic hepatitis, pancytopenia with leukopenia at 1800/mm3, anemia with Hb at 9.1 g/dl, thrombocytopenia at 40,000/mm3. Protein electrophoresis revealed hypoalbuminemia with hyperalpha-1 globulinemia. Hypertriglyceridemia of 3.43 mmol/L, LDH of 771 IU/L and very high ferritinemia of over 3,000 ng/ mL. Brucellosis serology was positive (IgM and IgG). Two blood cultures were positive for brucella spp. Abdomino-pelvic ultrasound revealed homogeneous splenomegaly. In view of this pancytopenia, a myelogram was performed, showing a bone marrow containing numerous activated macrophages. As the patient presented more than five diagnostic criteria of HLH (Hemophagocytic lympho histiocytosis), the diagnosis of brucellosis associated with macrophagic activation syndrome was retained. Our patient improved with curative antibiotic therapy based on Doxycycline, Gentamicin and Rifampicin. Corticosteroid therapy was not prescribed, given the rapidly favorable evolution at the time of diagnosis.

The second patient, aged 47, with no notable history, was hospitalized for diagnostic and therapeutic management of a recent acute fever that had been evolving for seven days, with deterioration in general condition, profuse sweating, chills and diffuse arthromyalgia. Physical examination was unremarkable, apart from stage 1 splenomegaly and purpura of the trunk and lower limbs. Investigations for urinary, digestive, ENT and respiratory infections were negative. Biological work-up revealed an inflammatory syndrome (elevated SV 70 h at the first hour and CRP 96 mg/l). Urine cytobacteriological examination was sterile, with no leukocyturia. Viral serologies (HIV, hepatitis A, B and C) were negative. Chest X-ray was borderline normal. Echocardiography was unremarkable. Given the epidemiological context of having consumed unpasteurized dairy products 15 days prior to the onset of symptoms, blood cultures were requested for brucella, which came back positive for Brucelles spp. Wright's serodiagnosis was positive at 1/2560 at the end of the second week of evolution.

A complete blood count showed pancytopenia with hemoglobin at 8.8 g/dl, leukopenia at 1800/mm3 and platelets at 36,000/mm3, following which a MAS workup was initiated returning as follows hypertriglyceridemia (2, 62 g/l), hyperferritinemia (950 U/L) and lactate dehydrogenase (634 U/L) were elevated, fibrinogen levels were low at 1.5g/L and bone marrow biopsy showed hemophagocytosis.

Gentamycin (5 mg/kg/d), Rifampicin (900 mg/day) j and Doxycycline (200 mg/day) were initiated. Clinical, hematological and biochemical evolution was favorable, with normalization of the blood count (leukocytes: 4500/mm3, Hb: 13 g/dl, platelets: 180000 /mm3) under antibiotic therapy.

4. Discussion

Macrophage activation syndrome (MAS) is a rare but serious and potentially fatal disease, caused by dysfunction of the natural killer T lymphocytes, resulting in uncontrolled, non-malignant lympho-histiocytic proliferation and excessive secretion of cytokines that promote macrophage activation, leading to multivisceral dysfunction [1, 2].

MAS may be primary, due to genetic inheritance, or secondary, due to malignancy, particularly lymphoma, autoimmune diseases (mainly lupus and Still's disease) or infectious pathologies. Secondary hemophagocytic syndrome was first reported in 1979 by Risdall et al [3]. Primary hemophagocytic syndrome, on the other hand, was described much earlier, in 1939 by Scott and Robb-Smith [4]. The infectious causes of MAS are varied (viral, bacterial, parasitic or fungal), but dominated by viral infections, in particular Epstein Barr virus and other herpes viruses, HIV, Covid-19 and parvovirus.

Parasitic infections such as leishmaniasis and toxoplasmosis are also sometimes implicated. Histoplasmosis is the most frequently implicated fungal infection. Bacterial etiologies of hemophagocytic syndrome are classically dominated mainly by Mycobacterium tuberculosis, rarely rickettsiosis, typhoid fever, leptospirosis, pyogenic Staphylococcus bacteria or enterobacteria. Brucellosis rarely causes haemophagocytosis syndrome [1, 2, 5].

In our study, we retained only those patients who fulfilled the diagnostic criteria established by Henter for the diagnosis of MAS. These were at least 5 of the 8 criteria listed in Table 01 [6].

Table 1 Diagnostic criteria for macrophagic activation syndrome [6]

Presence of at least 5 out of 8 diagnostic criteria:
Fever
Bi or pancytopenia - Hemoglobin <9 g/dl - Neutrophils <1000 /mm3 - Thrombocytes <100,000 mg/mm3
Hypertriglyceridemia (≥3 mmol/l) or hypofibrinogenemia (≤1.5 g/l)
Image of hemophagocytosis (marrow, liver, spleen, lymph nodes)
Ferritinemia ≥ 500 µg/l
Soluble CD 25 ≥ 2400 IU/ml
Low or no natural killer (NK) activity

Six of the diagnostic criteria classically used in MAS were present in our two patients: splenomegaly, fever, pancytopenia, hypertriglyceridemia, elevated ferritinemia and bone marrow hemophagocytosis.

Over the past three years, it seems that clinical forms of brucellosis with chills and altered general condition are on the increase. This may indicate a change in the virulence of Brucella species. To our knowledge, these are the first two reported cases of brucellosis-associated haemophagocytic syndrome in our region. However, there are no epidemiological data in Algeria on the incidence of this syndrome in brucellosis. Brucellosis is the most widespread zoonosis in the world, affecting several countries. It poses a real public health problem in developing countries, including our region. It is characterized by a combination of fever, sweating and arthromyalgia, with hepatomegaly, splenomegaly and/or adenopathy on physical examination. The expression of human brucellosis is highly polymorphic, a "disease of a hundred faces", but the most classic picture is that of undulating sweaty fever, with mainly osteo-articular and neurological complications. Hematological complications are rare in brucellosis, but true MAS is extremely rare [7].

Brucellosis-associated haemophagocytic syndrome most often occurs in the acute bacteremic phase. The hepatosplenomegaly and fever described in the classic brucellosis picture make it difficult to diagnose MAS. This can lead to delays in diagnosis and treatment. In our case, it was the pancytopenia that prompted us to perform a marrow aspiration and request the rest of the ASM work-up. In published studies, the rate of pancytopenia associated with brucellosis is low, ranging from 2 to 14%, compared with leukoneutropenia, which is common in acute brucellosis [8, 9, 10, 11]. Pathophysiologically, several mechanisms may explain this pancytopenia in brucellosis, namely histiocytic hemophagocytosis, hypersplenism, granulomatosis or bone marrow hypoplasia [12]. In our brucellosis patients, pancytopenia was secondary to MAS.

The occurrence of macrophagic activation syndrome (MAS) in Brucellosis remains a very rare and unusual situation. The number of cases of brucellosis complicated by MAS reported in the literature is rare. Cascio et al demonstrated through a PubMed search of human cases of MAS occurring during zoonotic diseases, that among bacterial infections, only 15 publications report cases of MAS secondary to brucellosis [14].

The treatment of secondary MAS of infectious origin is based on etiological treatment of the causative infectious agent and specific immunomodulatory treatment of hemophagocytosis with a combination of corticosteroids and etoposide. Intravenous immunoglobulins are not recommended. Disease prognosis remains dependent on the speed with which treatment is administered [15].

In Brucellosis, MAS is potentially reversible [13]. In both our cases, the clinical, haematological and biochemical course was favourable, with normalization of the blood count. Corticosteroid therapy was not prescribed, given the rapidly favorable evolution at the time of diagnosis under antibiotic treatment alone.

5. Conclusion

Brucellosis is an endemic zoonosis in our country. Most often benign, it can rarely lead to life-threatening complications. Macrophagic activation syndrome is a rare but serious complication. A finding of pancytopenia in the course of brucellosis should raise the suspicion of a hematological complication, including hemophagocytosis syndrome. MAS secondary to brucellosis does not always call for specific treatment, but only adequate, early and immediate anti-infectious etiological therapy can improve the prognosis. In our climate, the etiological investigation of secondary hemophagocytic syndrome must include a work-up for brucellosis.

Compliance with ethical standards

Acknowledgments

Thanks to all those who helped with this work.

Disclosure of conflict of interest

No Conflicts of interest to be disclsoed.

Author contributions

- Nabila Kalla: The creation and execution of the study, data collection, analysis and interpretation of the results.
- Ouanassa Hamouda, Nabila Kalla: drafted, revised and commented on the final version.
- All authors reviewed and approved the final version of the manuscript.

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