Macrophagic Activation Syndrome: A case report and literature review

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Abstract

A 73 years old man was admitted in a private surgical clinic for total hip prosthesis. After the surgical act, although there were no signs of infection, the patient received a large spectrum antibiotherapy and was, then, allowed to leave the clinic. He was hospitalized again 27 days latter; his general state had very badly deteriorated; pancytopenia spreads readily and the myelogram allowed the diagnosis of Macrophagic Activation Syndrome (MAS). Two days after his admission, the patient deceased.

Infection is the major cause of subsequent MAS. In the case of our patient, the administered antibotherapy may be had protected him against bacterial infections but was unsuccessful against viral, fungic or parasitic causes, which are aggravated in the case of an aged patient.

In this paper, we also gave results of the literature concerning clinical and biological features, as well as physiopathology and treatment.

Introduction

Macrophagic Activation Syndrome was initially described in 1950. It was individualized since the description of the post-viral hemophagocytosis by Risdall in 1979 (1).

In 1988, another study showed that its prevalence is estimated to 0.8% (2).

To our knowledge, no series were reported by researchers in the relevant literature, almost papers described individual cases (3, 4).

However, more recently, in 2000, 85 cases, including 55 of infectious, were reported in France during one single year (5). This suggests that this severe pathology is not very well elucidated. We, then, consider that any case reported with extensive description, including clinical and biological features, precise etiology if possible, will contribute to a better understanding of the pathology. We present, hereafter, a 73 years old man, MAS case treated in 2007.

Case Report

B.M, a 73 years old man, was admitted in March 2007 in a private surgical clinic for total hip prosthesis.

On admission, he was in a good general state; he weighed 80kg, and measured 175cm, his temperature was 37°2C; there was no pallor, cyanosis or jaundice; his blood pressure was 140/80mm Hg, the pulse rate was 80/min. There were no ganglions no splenomegaly and no hepatomegaly. The physical examination of other systems was unremarkable.

The pre operatory assessment was as follows: Absence of anaemia (haemoglobin = 13g/dl); leukocytes were normal (WBC 7,5x109/l) with normal distribution; platelet count was normal (190x109/l), Blood sedimentation rate was 2/6, Prothrombin time was at 90% and Activated Céphaline time was 28sec (control=30sec), Glycaemia: 0,89g/l, urea: 0,50g/l creatin : 12,2mg/l, Blood grouping revealed an O Rhesus positive group, Electrocardiogram and ultrasound Doppler were normal.

The patient was operated on 1st april. A systematic antibiotherapy, associating Bristopen, Gentamycine and Bactrim was started. The patient, also, received Fraxiparine and Di-antalvic against pain.

The following day, the patient presents an anaemia (Hb=9g/dl) which was related to the bleeding during surgery. He received red blood transfusions (three units); all the remaining of assessment was normal.

The patient left the clinic on April 8th, 2007.

He was hospitalized once again on April 27th, 2007 for luxation of the prosthesis.

The general state had very badly deteriorated: temperature at 39°C, he was obnubilated; blood pressure was 130/80 mm Hg and pulse 110/min.

There was a generalized cutanous rash; with no adenopathy, no hepatomegaly but tangible splenomegaly; crepitate rales were present in the two pulmonary bases.

The biological test showed anaemia (Hb = 9,4g/dl); leukocytes and platelets were normal; haemostasis assessment was normal; glycemia was at 1,10g/l, creatinine at 10,6mg/l; HBsAg, HCV, and HIV serology were negative.

Reanimation started, with antibiotic, urinary disinfectant and steroid therapy.

The patient, also, received red blood transfusions (two units).

On 29th april, despite blood transfusion, anaemia becomes serious (Hb=8g/dl); there was leukopenia (WBC 1x109/l) and thrombopenia (90x109/l).

A hematologic opinion is then required: in front of the deteriorated general state, with high fever, cutaneous rash, splenomegaly and pancytopenia: a macrophage activation syndrome is envisaged.

Myelogram confirmed this diagnosis; it revealed modularly infiltration by 7% of macrophages with benign cytological

aspect; they present intracytoplasmic vacuoles and blood cellular elements (erythroblast, leucocytes and platelets) (Figure 1)
Triglycerids were elevated at 4,50g/l; it was not possible to make dosage of ferritine.
The patient dies on May 1st, 2007.

Discussion

This pathology is present in childhood (family lymphohystiocytosis, Chediak-Higashi syndrome, Griscelli syndrome, Portillo syndrome (6). There is also reactional MAS in infectious pathology (7): bacterial infectious, viral infectious, fungic infectious and parasitic infectious.
MAS can be associated to aggressive lymphoma, acute leukaemia, myeloma, myelodysplasic syndrome, myeloproliferatif syndrome and solid tumours (8, 9).
It can also be associated with systemic diseases like lupus (10), connectivite, scleroderma and polyarthritis rheumatoid (11, 12).
MAS had been reported with some drug consummations like as phenytoine , valproique acid and parenteral nutrition of lipidic acqueous solutions; it can, also be seen after blood transfusion or vaccination(13).

On the clinical level, fever until 40°C is present in more than 90% of the observations; there is organomegaly (hepatomegaly, splenomegaly, peripheral adenopathy), cutaneous signs including papulous rash, nodules, lesions of vascularite, purpura, icterus related to the hepatic attack (14); digestive, neurologic and pulmonary signs can be observed. Visceral haemorrhage related to intravascular coagulation, with collapses, respiratory distress is possible (15, 16).

On the biological level, the anomalies are numerous but not specific, such as: Constant bi or pancytopenia; deep thrombopenia are the earliest anomalies. -Haemostasis disorders are found in 50-70% of the cases (hypofibrinogenemia, disturbed Quick time and activated cephaline time; sometimes there may be a real intravascular disseminated coagulation; it constitutes a factor of bad prognosis). -Hepatic disorders are found in 40% of the cases; they, generally, are signs of cytolysis. The positive diagnosis is cytological or histological: infiltration by 3% or more of macrophages; these macrophages contain in their cytoplasm blood cellular element (17).

On the physiopathological level, for most authors, this pathology seems to be caused by an abnormal activation of T-lymphocytes, which produce big quantities of inflammatory cytokines, which stimulate the macrophage answer (18). At the same time, the activation of macrophages is responsible for general inflammatory syndrome and fever (production of IL1, TNF and IL6).
Pancytopenia is related to the phagocytosis of blood cells, to the amplification of the lymphocytic answer (by production of IL2, IL1 and TNF) (19) and to the inhibiting action of erythropoiesis by IL1 and TNF (20).
Organomegaly is related to the tissue infiltration by activated macrophages.
High level of triglycerides, habitual in MAS, is related to the inhibition of the lipoprotein lipase by association TNF and IL1.
Hyperferritinemy would result from the erythrophagocytose, hepatic dysfunction and mainly from specific inflammation. Stimulation of the production of hepcidine by IL6 could play a predominant role, thus modifying the iron metabolism (13).
Some authors put the emphasis on the key role of TNF; it is an indicator in the MAS prognosis.
Viral infection, with herpes virus, CMV, EBV can conduct to a deregulation of TNF production, which would explain the frequency of MAS in this type of infection (21, 22). Other authors showed recently the role of the interferon gamma in the pathogenesis of MAS (23).

On the therapeutic level, the treatment is still badly codified; symptomatic treatment is important (correction of dyshydratation, transfusion if severe cytopenia).
In the family lymphohystiocytose, Etoposide (VP16) seems to give encouraging results (24). Lymphocyte T activation had led to try treatment by antilymphocytic serum, steroid and cyclosporine (25). Marrow transplantation had been also tested in child Lymphohistiocytose; it had completely modified the prognosis (26).
In reactional MAS, treatment of the cause is essential: anti-infectious treatment in case of post-infectious MAS, chemotherapy in the malignant hemopathies (Etopiside, steroids, cyclosporine) (27), polyvalent immunoglobulins in case of post-viral hemophagocytosis (28, 29).

Conclusion

Up to day, there is very little understanding about this serious pathology. Nothing could have predicted such a result for our patient. We think that all the medical staff must know the diagnosis criteria of Imashuku, established in 1997, which remains valid until this day, i.e: Fever more than 7 days with peaks to 38°5 C. cytopénia concerning at least 2 lines not caused by bone marrow disease (Hb ffi 9g/dl; Polynuclear Neutrophilffi 1x109/l; plateletsffi 100x109); ferritinemiaffl 1000 ng/ml; LDHffl 1000 UI/l; and hemophagocytosis in bone marrow, spleen, liver or ganglion.

Etiological diagnosis remains difficult, but infection represents the major cause and it is recommended to keep vigilant, particularly with aged patients.

Vital prognosis remains compromised in half of the cases.

Prospective studies are necessary; these include a better understanding of the physiopathology. It is necessary to gather precise information on the causes; it is the only way that, recommendations about the potential aggravating factors, as well as treatment, may be possible.

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FIGURES

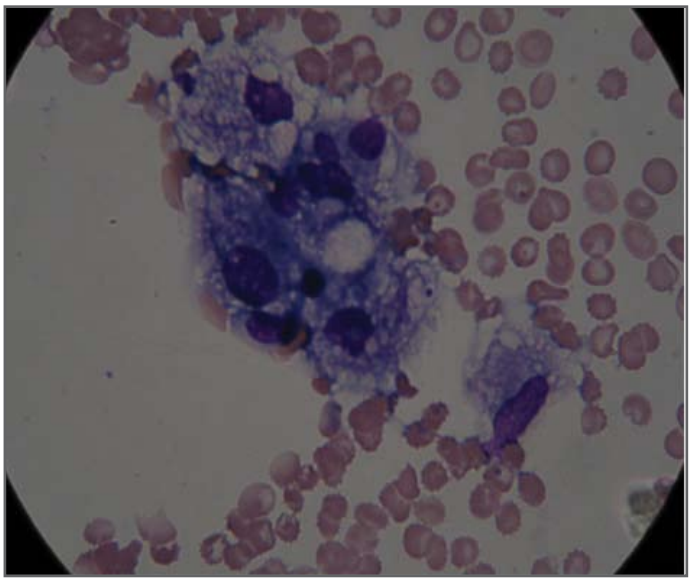

Figure 1. Bone marrow aspirate smear (May-Grünwald-Giemsa x100).

Meeting Highlights: Early Cancer From Prevention To Cure 2008

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Arab Medical Association Against Cancer (AMAAC) is committed to facilitating and disseminating the clinical and translational science that informs practice in cancer diagnosis, prevention, and treatment by encouraging communication and collaboration between professionals from diverse fields. The AMAAC Annual Meeting offers a unique opportunity for cancer professionals to learn, educate, and network.

The AMAAC meeting in Damascus – April, 2008 – was a collaborative effort among Al Bayroni Hospital, Italian Society of Oncology, and members of AMAAC from a variety of Arab countries. The meeting focused on themes that address the challenges and opportunities to treat and detect early cancer of breast, lung, prostate, colon, esophagus, and hepatocellular carcinoma (HCC)—how advances in clinical and translational science can reduce the burden of cancer.

Very interesting recent developments were presented on the topic of nutrition, diet, and food compounds. The effect of energy metabolism on cancer risk was explored. Risk is influenced by body mass index, caloric intake, birth weight, and exercise. All these factors influence serum levels of insulin and IGF-I, which mediate at least in part the effects of energy balance on risk. Anti-IGF-I-receptor drugs are in development, and Phase I/II trials are ongoing.

The role of tobacco was emphasized as the major preventable cause of death of humankind, and much of this preventable death involves cancer. Lung cancer, typically exhibiting an attributable risk of 75% to 85% for smoking, is by far the overriding issue, particularly in light of a 5-year survival rate of no more than 15%. It has also been recognized that smoking causes cancer of upper aerodigestive tract (oral cavity, nasal cavity, nasal sinuses, pharynx, larynx, esophagus), pancreas, stomach, liver, lower urinary tract (renal pelvis and bladder), kidney, and uterine cervix, and also causes myeloid leukemia.

Additionally, the impact of exposure to the sun – ultraviolet radiation including deliberate sun exposure in order to achieve «tanning» – on the development of both coetaneous melanoma and nonmelanocytic skin cancers was reviewed.

Central to prevention of cancer in many developing countries are two considerations: establishment of cancer registries and the institution of national cancer control programs (NCCP). In regards to cancer registries, most of our countries have established or working on establishing one, a testimony to the growing awareness in the region. One aspect of NCCP is screening in addition to prevention, early diagnosis, treatment, and palliative care. The French and Italian experience with establishing both programmes were reviewed, with particular focus on the Italian mammography screening program in Bologna. The importance of communication between referral hospital and surrounding community practices was emphasized to ensure proper follow up and dissemination of service to the community.

New techniques to guide biopsy of impalpable lesion in the breast were discussed. Annual mammography is advised for average risk women age 50 and older and biennial is recommended between ages 40 and 50 years.

Recent trends for hormonal therapy of breast cancer were reviewed. The pros and cons of aromatase inhibitors versus Tamoxifen were discussed. The issue of bone complications of therapy was explored and data to prevent and treat bone loss using bisphosphonate therapy was highlighted. The synergistic effect of combined hormonal blockade in the treatment of both breast and prostate cancer was analyzed.

In regards to lung cancer, systematic screening with either CT or chest x-ray is not unequivocally recommended by any major professional organization. Lung cancer screening has not been demonstrated to decrease deaths from lung cancer. Additionally, screening requires an ongoing commitment; cancers are detected on initial and annual studies, and a single baseline study is insufficient.

Those patients with early stages of lung cancer do benefit from adjuvant platinum based chemotherapy with significant improvement in overall survival.

When considering prostate cancer, there is no consensus on using any of the PSA modifications, and none of them has been shown to reduce the number of unnecessary biopsies or improve clinical outcomes. The total PSA cutoff of 4.0 ng/mL is still the most accepted standard because it balances the tradeoff between missing important cancers at a curable stage and avoiding both detection of clinically insignificant disease and subjecting men to unnecessary prostate biopsies.

Combined hormonal and radiation therapy for locally advanced node positive disease definitely improve survival (at least 2 years of hormonal therapy starting with or 2 months prior to radiation therapy).

An otherwise healthy individual, ages 50 and older needs to be screened for colorectal cancer. The following tests are options for screening: Annual occult blood test, flexible sigmoidoscopy every five years, annual occult test and flexible sigmoidoscopy every five years, double contrast barium enema (DCBE) every five years, or colonoscopy every 10 years. The decision about which option to select should