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Disseminated Multifocal Tuberculosis: An Unusual Presentation with Macrophagic Activation Syndrome

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Abstract:- Macrophage activation syndrome (MAS) is a rare but severe entity, associated with inappropriate stimulation of macrophages in the bone marrow and lymphoid organs, the diagnosis is based on the association of clinical, biological and cyto-histological signs, this syndrome can be primary or secondary, it is rarely described in association with tuberculosis. We tend to report an uncommon case of a young immuno-competent patient with disseminated tuberculosis complicated by MAS, the prognosis is poor, with a mortality of nearly 50%; thus, it is necessary to focus on MAS as the result of its prevalence may be an issue of poor prognosis with critical implications.

Keywords:-*Disseminated tuberculosis / Macrophagic activation syndrome / Pancytopenia / Antibacterial therapy /immunosuppressive treatment.*

I. INTRODUCTION

Macrophage activation syndrome (MAS) could be a rare *[1]* however severe entity, caused by inappropriate stimulation of macrophages. It can be primary or secondary, the pathologies involved can be hematological (T lymphoma), tumoral or infectious: viral (especially EBV), or bacterial (more rarely tuberculosis) *[2]*; the prognosis is poor, with a mortality rate of nearly 50%.

We report an unusual presentation of a young immunocompetent patient with disseminated tuberculosis complicated by MAS.

II. PRESENTATION OF CASE

The study case is about a 23-year-old woman, who has been smoking for 6 years, without any medical or surgical history, including no personal or family history of tuberculosis or known tuberculosis contagion. She did not travel abroad for the past few years.

She complains of having intermittent fever associated with dry cough and night sweats for more than three months. Four weeks before admission, the patient had increased fatigue, body weight loss of about 15 kg and right hypochondrial pain.

The clinical examination traces the patient's extremely cachectic, icteric, febrile at 40°C, the respiratory examination was normal with an oxygen saturation of 95% in room air, the right hypochondrium was found to be sensitive during an abdominal examination without defence with hepatosplenomegaly.

A cardiovascular examination showed cyanosis distally of the two lower limbs with an absence of distal pulses (posterior tibial pedal), without sensorimotor impact. *(Figure 1)*

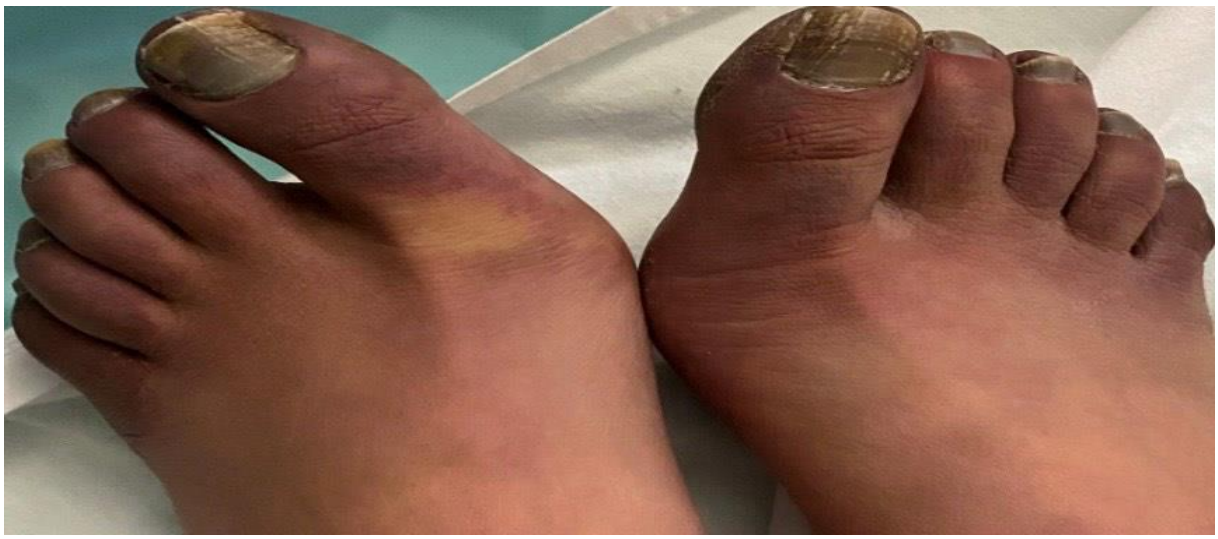

Fig. 1: Clinical aspect of distal ischemia of both lower limbs

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The biological examination showed a pancytopenia: normocytic normochromic anemia at 8.7 g/dl, leukopenia at 2000/µL, with lymphopenia at 700 /µL and thrombocytopenia at 100,000/µL, mild hepatic cytolysis (AST 54 IU/L, ALT 75 IU/L), and cholestatic (PAL 143 IU/L, GGT 64 IU/L, hypertriglyceridemia at 2.4 g/L, hyperferritinemia at 1900 ng/ml, LDH: 437 U/ L, fibrinogen level at 1.3 g/L. In addition, the immunological assessment was negative as well as the HIV and CMV serologies.

Based on the clinical and biological signs, the diagnosis of macrophage activation syndrome was suspected, requiring a medullogram, which revealed multilineage dysplasia. The bone marrow biopsy showed a granulomatous myelitis with caseous necrosis in favor of hematopoietic tuberculosis.

A search for BK in the sputum test came back positive on direct examination, and the Chest X-ray showed well-limited and diffuse micronodular opacities in both lung fields creating a miliary pattern. *(Figure 2)*

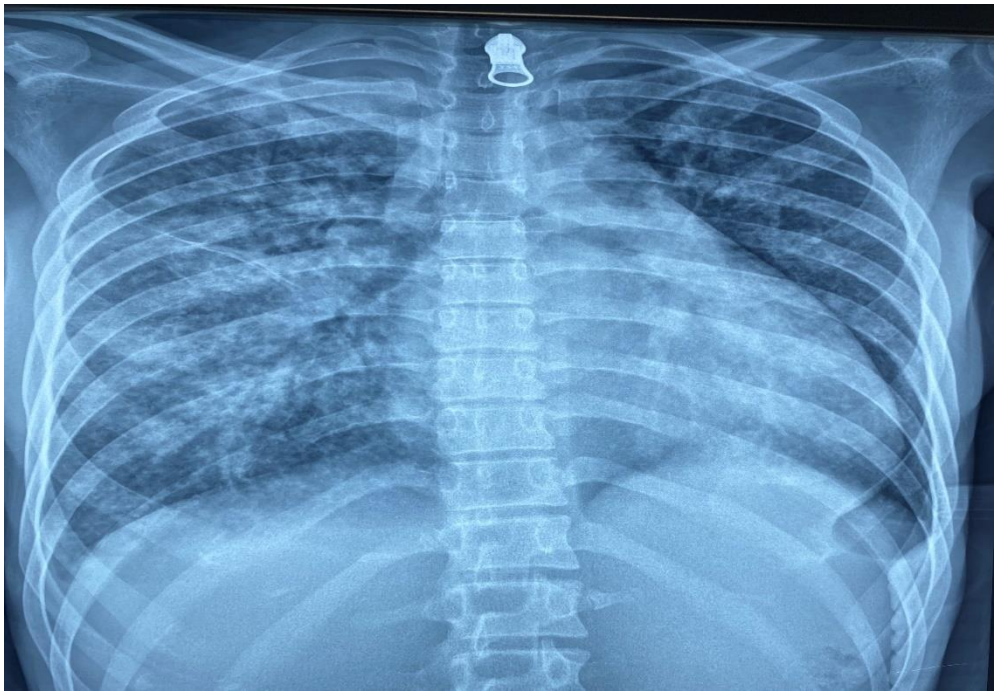

Fig. 2: Chest X-ray showed diffuse micronodular opacities in both lung fields creating a miliary pattern

Chest-abdomen-pelvis CT showed multiple bilateral parenchymal micronodules in the thoracic area *(Figure 3)*, which were diffuse and gave a miliary appearance, associated with a small pleural effusion in the right lateral and posterior basal areas. At the abdominopelvic level *(Figure 4)*, micronodules are scattered over the entire splenic parenchyma with the presence of two foci of parenchymal infarction in the subcapsular region and lymphadenopathy flows in the hepatic mesenteric hilar and perigastric regions.

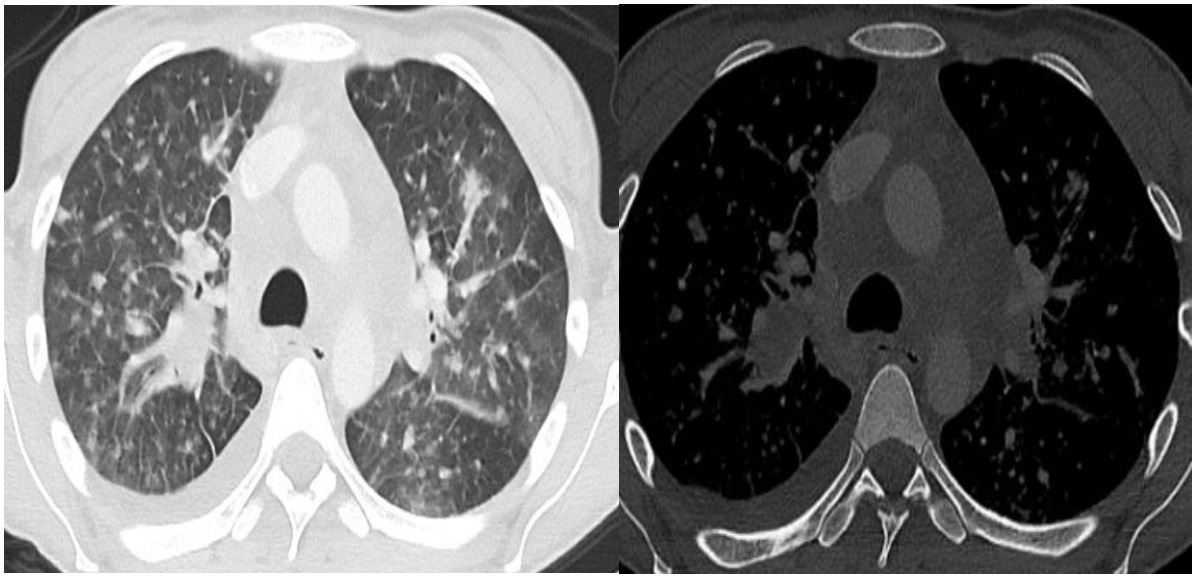

Fig. 3: Axial chest CT scan showing multiple diffuse, bilateral parenchymal micronodules suggestive of miliary tuberculosis associated with a small pleural effusion on the right.

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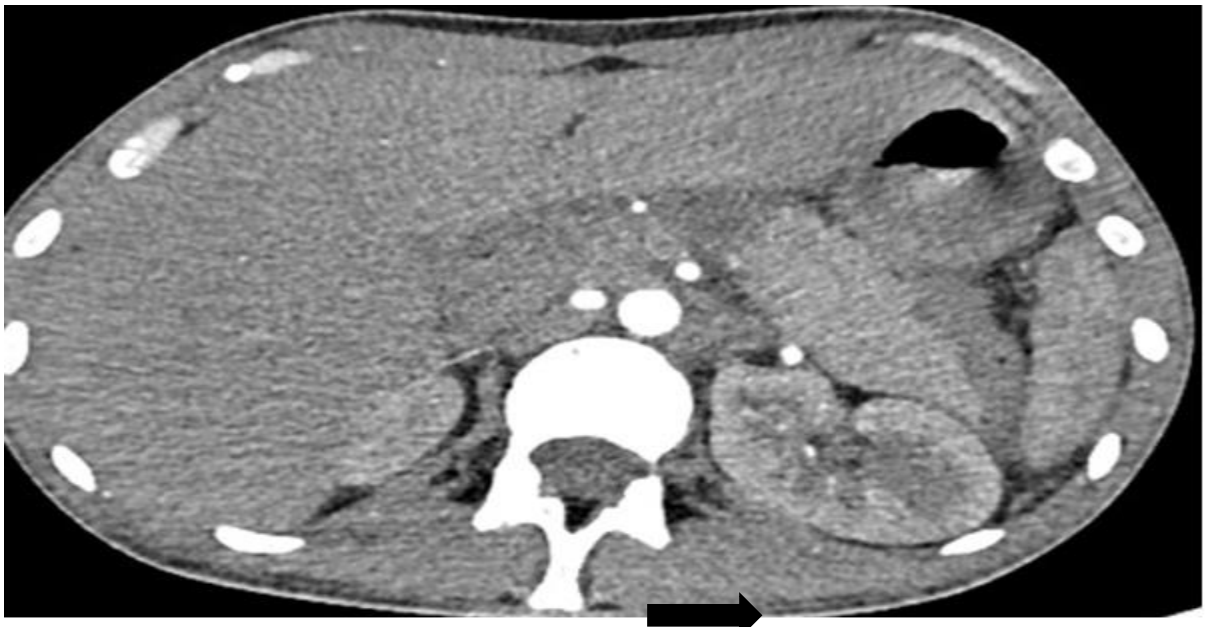

Fig. 4: An abdominal CT scan in axial section after contrast product injection reveals micronodules scattered throughout the splenic parenchyma, as well as two foci of parenchymal infarction

The diagnosis of multifocal tuberculosis (Miliary tuberculosis associated with splenic tuberculosis) in an immunocompetent patient revealed by macrophage activation syndrome was retained. The patient was treated with antibacillary treatment (two months of quadruple therapy associating Rifampicin, Isoniazid, Ethambutol and Pyrazinamide "intensive phase", and seven months of dual therapy associating Rifampicin and Isoniazid "maintenance phase») for a total period of nine months with vitamin B6 supplementation at a preventive dose of 25 mg/dr and cotrimoxazole prophylaxis.

Three weeks after the beginning of the anti-tuberculosis treatment the patient presented a deterioration of the hepatic cytolysis (AST 3282 UI/L [108 times the normal], ALT 736 UI/L [13 times the normal]), a cholestasis PAL 286 UI/L, GGT 120 UI/L, Due to the severe form of tuberculosis, the anti-tuberculosis treatment was stopped and replaced by a non-hepatotoxic treatment (Kanamycin, Ethambutol, Levofloxacin).

Unfortunately, the outcome was unfavourable leading to the patient's death because of hepatic encephalopathy secondary to an acute liver failure.

III. DISCUSSION

Macrophage activation syndrome (MAS) is also known as lymphohistiocytic activation syndrome (LHAS), hemophagocytic syndrome. It is a rare but potentially fatal disease; it can occur at any age, with a slight male predominance in adults (sex ratio I, 5 to 2.5) and an annual incidence of approximately four cases per year [1].

The pathophysiology is still poorly understood, possible cytokine hypersecretion (including TNF-alpha, IFN-gamma, and IL-6) by activated macrophages is responsible for clinical and biological manifestations. [3].

The diagnosis of MAS is based on the combination of clinical, biological and histological or cytological signs. Currently, Henter's criteria are those accepted as diagnostic criteria for MAS. the presence of five of the eight criteria allows the diagnosis to be retained (Table 1) [4].

1. Fever
2. Cytopenia involing 2 or more lines:
➢ Hb < 9 g/dL
➢ Platelets < 100000/mm3
➢ Neutrophils < 1000/mm3
3. Hypertriglyceridemia and/or hypofibrinogenemia: ➢ Triglycerides>3mmol/L ➢ Fibrinogen<1.5g/L
4. Hemophagocytosis in marrow, spleen, or lymph nodes
5. No evidence of malignancy
6. Decreased or absent Natural killer (NK) cell activity (according to local laboratory references)
7. Ferritinemia≥500mg/L
8. elevated soluble CD 25 (IL-2Rα chain ≥2,400 IU/mL)

Table 1: Henter's criteria for the diagnosis of macrophage activation syndrome [4]

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The major clinical signs are constant fever (>38.5°C). Marked asthenia, icterus, hepatosplenomegaly and lymphadenopathy. A morbilliform skin rash or neurological signs (convulsions, localization signs) are more uncommon. (Table 2) [5].

Clinical signs	Frequency
Fever	70-100%
Splenomegaly	70-100%
Hepatomegaly	40-95%
Lymphadenopathy	15-50%
Skin rash 5-65%	5-65%
Neurological signs	20-50%

Table 2: frequencies of clinical signs of macrophage activation syndrome [5]

The biological manifestations are found early on in the haemogram test with pancytopenia, hypertriglyceridemia, hepatic cytolysis and hyperferritinaemia (secreted by activated macrophages). Our patient presents all these criteria.

The combination of these clinical and biological signs suggests the diagnosis of MAS, which must be confirmed by cytological and/or histological diagnosis based on a myelogram or even a bone marrow biopsy. According to some studies *[6]* the prevalence of hemophagocytosis varies between 25 and 100% of SAM, but is neither sensitive (70–83%) nor specific (60%). *[7]* It can be found in cases of blood transfusion, autoimmune disease or sepsis *[8]*. Osteo-medullary biopsy may often underestimate active hemophagocytosis and seems less efficient than myelogram.

There are 2 forms of MAS: primary and hereditary forms, often found in children under two years of age, such as familial hemophagocytic lymphohistiocytosis; and secondary forms due to hematological pathologies, , including T-cell lymphomas, autoimmune diseases, or infections such as tuberculosis [9], as it is in this case.

The association of hemophagocytic syndrome with tuberculosis remains very rare; in 1995 and 1996, Quinquandon et al [10] and Undar et al [11] respectively reported two cases of hemophagocytosis associated with tuberculosis; Brastianos et al in 2006, were able to retrospectively collect only 37 cases in the literature, proof of the rarity of this association. Among these 37 patients, 29 had extrapulmonary tuberculosis and 27 had involvement of a hematopoietic organ, as in our case. Ten patients had no hematopoietic localization but still had macrophagic activation syndrome. Data regarding the site of the tuberculosis were missing for three patients [12].

According to published reports [13], extrapulmonary tuberculosis represents an increasing proportion of all cases of tuberculosis, reaching 20 to 40%. Splenic tuberculosis remains a rare location, especially in an immunocompetent subject; it represents approximately 1% of all tuberculosis and 10% of extra-pulmonary forms [14]. Usually, it is not associated with hemophagocytosis [15] and should be considered in the presence of any splenomegaly with fever and anti-tuberculosis treatment should be discussed.

There are currently no specific recommendations for the management of MAS in the context of tuberculosis [16]; corticosteroids or immunosuppressants raise concerns about the risk of mycobacterial infection worsening at first.

Brastianos et al. [15], in their retrospective series had constituted two arms: one arm with treatment : subdivided into an arm with anti-tuberculosis treatment alone and an arm combining anti-tuberculosis treatment with immunosuppressants; and an arm without any treatment; According to the HAS [17], treatment with intravenous immunoglobulin for MAS due to infectious causes is not recommended due to lack of evidence, so the place of immunoglobulins in the treatment of hemophagocytosis remains to be clarified before this treatment can be proposed in the context of tuberculosis [12], early anti-tuberculosis treatment is the most important: In this case, our patient was put on anti-tuberculosis treatment but the evolution was unfavourable and death occurred in a context of severe hepatic damage.

The prognosis of MAS is poor, and MAS-related mortality associated with reported tuberculosis represented 50% [18]. The severity of cholestasis also correlates with a fatal prognosis for Kerguenec et al [19] in their series comprising 30 patients with MAS and liver disease.

IV. CONCLUSION

The uncommon but severe condition known as Macrophage activation syndrome (MAS), the diagnosis is based on a combination of clinical, biological and histological or cytological criteria's; it can also be due to an infectious pathogen, notably tuberculosis.

The association of hemophagocytic syndrome with tuberculosis is still highly unusual, and the prognosis is terrible. This necessitates an aggressive diagnostic strategy, early therapeutic care and multidisciplinary treatment.

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