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Association of Macrophage Activating Syndrome with Castleman's Syndrome in Systemic Lupus Erythematosus

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ABSTRACT

Macrophage Activating Syndrome (MAS) is a life-threatening disease seen in autoimmune diseases including lupus erythematosus, rheumatoid arthritis, Still's disease, polyarteritis nodosa. It is characterized by fever, pancytopenia, liver failure, coagulopathy, and neurologic symptoms and high serum ferritin. A 27 yr. old female patient was admitted in shahid Mostafa Khomeini Hospital (Tehran-Iran) in May 2011 because of lower extremities edema and ascites and fever from 1.5 month ago. In physical examinations she had generalized lymphadenopathy, splenomegaly and pleural effusion. In laboratory tests she had pancytopenia, positive ANA and Anti DNA (ds), hypocomplementemia, hypertriglyceridemia and high ferritin level. Gradually she had signs of RPGN and ARDS. The patient had no skin and musculoskeletal signs of SLE and no liver failure nor coagulopathy of MAS. Her lymph node biopsy was reported as Castleman syndrome. Unlike other studies, the patient showed MAS before treatment with cytotoxic for lupus nephritis.

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Introduction

Macrophage Activating Syndrome (MAS) or secondary hemophagocytic lymphohistocytosis (HLH) is a life-threatening disease that follows lymphoma, viral infections and some auto immune disorders (1). Secondary HLH reported to occur in patients with systemic lupus erythematosus (SLE), steel disease, polyarteritisnodosa (PAN), mixed connective tissue disease, pulmonary sarcoidosis and sjogren syndrome (2-4).

There are no significant epidemiologic studies considering adult HLH and incidence is not known, yet. The average age of patients was 27 yrs. (5). In 23 patients with adult HLH, 14 patients with herpes simplex infections, 7 with rheumatologic diseases under treatment with azathioprine and steroid, and 7 suffering various malignant diseases such as lymphoma, leukemia, teratoma and breast cancer were reported (6).

In a cohort study in patients with adult steel disease fifteen percent had MAS symptoms including fever, pancytopenia, liver failure, coagulopathy, neurologic syndromes and all had high serum ferritin level (7). Main symptoms of MAS are similar to HLH and some authors consider it as acquired (secondary) form of HLH (8, 9). In some children with systemic juvenile rheu-

matoid arthritis (JRA), there were heterozygote genetic abnormalities along with primary HLH (10). Significant increase in soluble cytokines reported in MAS indicating uncontrolled cytotoxic T-cell (CD8+) proliferation (11). Typically MAS begins few days to weeks after receiving aspirin, NSAIDs, gold salts or sulfasalazine in systemic JRA. It may follows viral or bacterial infections or without any known cause. Easy bruising, spontaneous bleeding or even shock may be seen initially. Serum hemoglobin, platelet count, and fibrinogen usually decreased. Fibrin degradation products (FDP) is the first marker of disease (12). Death may occur in MAS with systemic JRA and renal failure (13). In MAS like HLH, proliferation of macrophages and T-lymphocytes leads to prolonged fever, purpura, and hepatosplenomegaly, mental disorders, increasing PTT, APTT, hypofibrinogenemia, and low ESR. There is increased soluble CD163, soluble IL-2R due to increased macrophages and T-cells (14). Natural killer cells (NK-cells) dysfunctions occur in MAS patients and perforin expression decrease similarly happen in HLH (15). Table 1 shows the diagnostic criteria of HLH (16).

Table 1
Diagnostic criteria for hemophagocyticnlymphohistiocytosis (HLH)

(1) Fever Peak temperature >38.5°C for seven or more days
(2) Splenomegaly Spleen palpated >3 cm below the left costal margin
(3) Cytopenia involving two or more cell lines (Hemoglobin <9.0 g/dL, Platelets <100,000/μL, Absolute neutrophil count <1000/μL)
(4) Hypertriglyceridemia or hypofibrinogenemia (Fasting triglycerides >2.0 mmol/L, Fibrinogen <1.5 g/L)
(5) Hemophagocytosis (demonstrated in bone marrow, spleen, or lymph node; no evidence for malignancy)
(6) Hepatitis
(7) Low or absent natural killer cell activity
(8) Serum ferritin level >500 μg/L
(9) Soluble CD25 (sIL-2 receptor) >2400 U/mL

The diagnosis of HLH requires the presence of five of the above criteria. Adapted from: Henter JI, et al. SeminOncol 1991; 18:29.

In SLE exacerbations, HLH syndrome presents with fever, hepatosplenomegaly, lymphadenopathy, liver dysfunction, increased serum ferritin and triglyceride, activated macrophages and phagocytosis of mature blood cells and their precursors in bone morrow or other tissues (17). Treatment of MAS consists of fresh frozen plasma (FFP), steroids, and palliation therapy. NSAIDs, rheumatologic drugs must be discontinued other than cyclosporine (2-5 mg/kg/d), prednisolone (4 mg/kg/d), dexamethasone (6 mg/kg/d)(18,19).

MAS is a relatively rare but potentially fatal complication of childhood rheumatic illnesses (20-23). A study in Iran on 120 patients with juvenile idiopathic arthritis and systemic SLE in Children Hospital Medical Center, Tehran University of Medical Sciences, from 1998 to 2007; showed only 5 children had MAS (24). MAS was very rare to be an initial presentation of systemic lupus erythematosus (22). Erythematosus plaques with macrophage infiltration as an initial manifestation of macrophage activation syndrome in a patient with systemic lupus erythematosus is reported (25). The difficulties in diagnosing MAS when multiple bone marrow biopsies fail to show hemophagocytosis in patient are showed; besides, PET scan in diagnosis and anaknra in treatment may be helpful (26). Kim et al. described a patient that bone marrow biopsy showed no evidence of hemophagocytosis and after splenectomy, the patient was improved and numerous hemophagocytic macrophages were proved in the splenic tissue (21).

Castleman's syndrome or angiofollicular lymph node hyperplasia is an unknown cause of lymphoproliferative disease characterized by lymphadenopathy and constitutional symptoms

and mimics malignant lymphoma. In Castleman's syndrome, three histologic types (vascular hyaline, plasma cell, mixed) and two clinical forms (localized, multicentric) have been reported (27). In multicertric form, the disease presents with collagen vascular like disease resembling RA, Sjogren, SLE (28). Besides, Castleman's disease may be developed in the progression of a connective tissue disease (29). In SLE patients with lymphadenopathy, 26% had castleman's syndrome in lymph node biopsy reports (30). There was not any case with SLE and castleman's syndrome and MAS in the literature.

Case Report

A 27 yr. old female patient complaining of exertional dyspnea, bilateral lower extremities edema, dry cough, from 1.5 month ago was admitted in shahid Mostafa Khomeini Hospital (Tehran-Iran) in May 2011. Swelling of abdomen, anorexia, and fatigue appeared. She had intermittent fever and no disease in her medical history except a laparoscopic surgery for right ovarian hemorrhagic cyst two months ago. In initial exam BP: 110/80 mmHg, PR: 88/min, T: 39

Table 2
Laboratory findings

Lab tests	15/06/2011	17/06/2011	27/06/2011	6/07/2011	13/07/2011
WBC/mm3	2400	2700	2500	2100	5900
Hb mg/dl	7.4	8.4	8.3	7.8	8.4
Platel/mm3	79000	64000	89000	44000	19000
Retic count %	1.5	-	-	-	-
ESR mm/1st h	50	-	25	-	40
BU mg/dl	67	140	159	193	192
Creat mg/dl	1.9	3.3	4.6	5.7	5.2
Uric acid mg/dl	10.2	-	-	-	-
CRP latex	Negative	-	-	-	-
RF latex	Positive	-	-	-	-
ANA (>10 positive)	>100	-	-	-	-
AntiDNA(ds) (>18 positive)	>333	>1000	-	-	-
ANCA (>18 positive)	-	>30	-	-	-
C3 (0.89-1.87)	0.43	0.46	-	-	-
C4 (0.16-0.38)	0.13	0.12	-	-	-
Lupus AntiCoagulant	-	-	-	-	Negative
HIV ab	Negative	-	-	-	Negative
Alb mg/dl	1.7	-	1.8	-	-
LDH	580	934	-	1349	1418
Urine protein	2+	-	-	-	-
Urine blood	1+	-	-	-	-
Urine RBC	6-8	-	-	-	-
Ferritin mg/dl (N-124)	267	-	535	-	-
Cholestrole mg/dl	-	-	211	-	230
TG mg/dl	-	-	909	-	652
AST IU/L	35	-	-	-	34
ALT IU/L	20	-	-	-	15

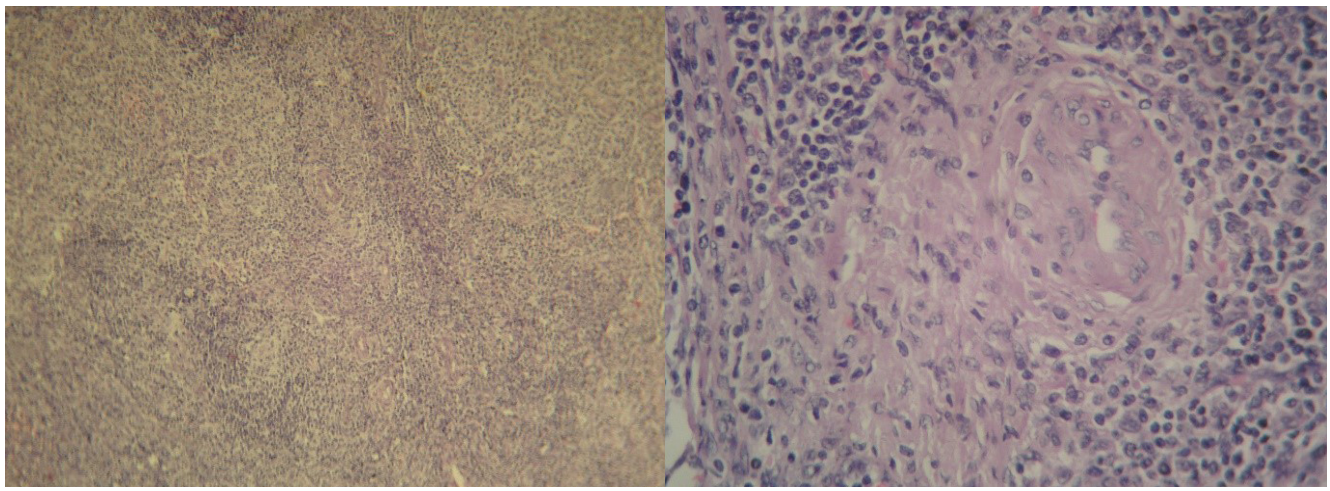

Fig. 1
lymph node biopsy shows follicular hyperplasia with variation in size and shape (A) and plasma cell with vascular proliferation (B) suggesting castlman syndrome(H&E ,a: x10 , b:x40). 1B: Chest CT scan shows alveolar fillings schema (ARDS) in lungs.

◦C. Skin was normal. There was multiple mobile non tender lymphadenopathy measuring 1 cm or more in posterior cervical, auxiliary, inguinal regions. Thyroid examination was normal. In heart, s1 and s2 were normal with a systolic murmur in left sternal border. Decreased bilateral basilar pulmonary sound and dullness was found in percussion. In abdomen distention and ascites, moderate splenomegaly and scar of previous surgery was found. There was a four plus pitting edema in lower extremities. Joint exam was normal. Table 2 shows the laboratory findings.

This study was approved by the Ethical Committee of the Medical Faculty, Shahed University, Tehran, Iran. Informed consent was taken from the patient.

The patient got worse with time. Intermittent high fever, nausea and vomiting were appeared. With the diagnosis of SLE and RPGN, methylprednisolone 500 mg for 3 days followed by oral prednisolone 1mg/kg/d and cyclosporine 100 mg/kg/d started. With no improvement mycophenolate mofetil 1gm/12 h was added to treatment. Lymph node biopsy showed microscopically, follicular hyperplasia with variation in size and shape, conspicuous interfollicular region, devoid of atypical changes. Vascular proliferation and few scattered hyalinaized areas were also seen. Findings were consistent with Castelman's syndrome (Fig. 1A). Bone morrow aspiration was dry tap. Subsequently uremia, dyspnea, ARDS symptoms with pleural and pericardial effusions on chest CT scan were developed (Fig. 1B).

Because of no improvement after mycophenolate mofetil and ongoing renal dysfunction, leucopenia, thrombocytopenia, anemia, one pulse of 500 mg cyclophosphamide was prescribed. Hemodyalysis started with improvement of peripheral edema, pulmonary crackles but cytopenia was continued. Mabthera (Rituximab) 500 mg was prescribed at this time. Diagnosis of MAS was made based on criteria (fever, splenomegaly, pancytopenia, nausea and vomiting, cough, generalized pulmonary coarse crackles, low serum albumin, hypertriglyceridemia, high serum ferritin, low ESR). Another dose of cyclosporine was given again but after one month of hospitalization the patient had a cardiopulmonary arrest and died.

Discussion

In patients that presenting with fever, lymphadenoathy, pancytopenia and polyserositis, in-

fectious disease (Tuberculosis), lymphoma and collagen disease must considered. SLE was a suitable diagnosis for our patient with pulmonary involvement, pancytopenia, polyserositis, renal failure, positive ANA and anti-DNAds, but she had no response to usual treatments. Fever, splenomegaly, cytopenia, hypertriglyceridemia, and serum ferritin above 500 mg/dl fulfilled five criteria of MAS diagnostic criteria. The patient had no articular, muscular, cutaneous problems, which is unusual for SLE and no liver test abnormalities, coagulopathy, neurologic symptoms are unusual for MAS. On the other hand hemophagocytosis was anticipated in bone morrow of MAS patients, while lymph node biopsy reported castleman's syndrome in this patient.

This is a case with SLE and MAS and castleman's syndrome not reported in the literature before. In cases of SLE and MAS described earlier, multiple bone marrow biopsies do not show hemophagocytosis. In lupus nephritis treated with cytotoxics, HLH may be seen with Epstein-Barr (EBV) virus activation (31). But in this case, HLH was present before treatment. Some reports advise IVIG and plasmapheresis (32, 33), since the patient had died, there was no opportunity for these options.

Conflict of interest

No conflict of interest.

Acknowledgements

The authors declare that there is no conflict of interests.

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