Open Access Case Report

Journal of Renal Endocrinology

J Renal Endocrinol 2020;6:e03.

http://www.jrenendo.com

Nickan Research Institute

A case of Still's disease which complicated with macrophage activation syndrome

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Abstract

In this case report, we present a 21-year-old girl having 45 days of fever, which did not respond to any of the antibiotics. Even the patient's fever did not respond to intravenous acetaminophen. All efforts to find an infectious agent or malignancy were fruitless. Eventually, with suspicious to the macrophage activation syndrome (MAS), thus, bone marrow sampling was performed and the diagnosis was confirmed. In adult Still's disease (ASD) patients who are treated with the appropriate medications, MAS should be considered in case of resistant fever and hemoglobin loss.

Keywords: Adult Still's disease, Cyclophosphamide, Macrophage activation syndrome

Citation: Karimifar M, Karimifar M, Sanei MH. A case of Still's disease which complicated with macrophage activation syndrome. J Renal Endocrinol. 2020;6:e03.

Introduction

Adult Still's disease (ASD) is an inflammatory disorder characterized by two fever spikes per day lasting at least one week, arthritis or arthralgia, and an evanescent rash (a cutaneous evanescent salmon-pink maculopapular eruption, most often present during the febrile hours), leukocytosis with predominance of neutrophils and a marked elevation in serum ferritin. Other symptoms including pharyngitis, elevated hepatic aminotransferases, lymphadenopathy, elevated acute phase reactants, splenomegaly and thrombocytosis. Rare features that occur in a minority of patients include hepatomegaly, pleurisy, pericarditis, and abdominal pain. An infrequent but serious, potentially fatal complication is the macrophage activation syndrome (MAS) that is also referred to as hemophagocytic lymphohistiocytosis or reactive hemophagocytic syndrome. Transient pulmonary infiltrates, pericarditis and pleural effusions have been observed in 30% to 40% of patients with ASD (1-3). Affected individuals may complain of pleuritic chest pain, cough or mild dyspnea. Nevertheless, significant pulmonary interstitial disease has also been explained (4).

MAS can occur at any time during ASD, and simultaneous presentations of ASD and MAS are not unusual. Flares of ASD and the development of MAS can be similar clinically. Anemia and marked elevation of serum ferritin and C-reactive protein (CRP) may occur in either condition. Unlike ASD, patients with MAS may have leukopenia and/or thrombocytopenia, and very high levels of serum triglyceride. Additionally, despite elevations in ferritin and CRP, the levels of haptoglobin and fibrinogen may be normal or low in the patients with ASD who develop MAS, and some of these patients have normal or unexpectedly low erythrocyte sedimentation rates (ESR) (5-7). Pancytopenia is more common in ASD when it is associated with MAS.

Case Presentation

The patient was a 21-year-old girl who was a known case of ASD from 3 year ago. She was hospitalized for fever of 40.5°C. All of workups for finding a clue to an infection or a malignancy were fruitless. Lung examination and chest CT-scan showed interstitial lung disease. Patient tests are summarized in Table 1. The range of fever was 38 to 40.5°C and had two spikes per day but never return to normal temperature. Fever lasted 45 days and then after treatment of MAS recovered to normal temperature. After 45 days admission in hospital in clinical examination due to temperature greater than 38.5°C, splenomegaly, cytopenia affecting at least two of three cell lineages and ferritin greater than 500 ng/ml and bone marrow aspiration/biopsy (Figure 1), the diagnosis of MAS was made. Following diagnosis of MAS the patient treated with pulse methylprednisolone succinate 1 g daily for three consecutive days and 1 g cyclophosphamide

Received: 20 January 2019, Accepted: 19 March 2019, ePublished: 21 April 2019

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Table 1. Laboratory data

Parameter	Patient results	Normal range
WBC	2800	(4400-11000)/mm^3
RBC	3.28	(4.1-5.1) Mil/mm^3
Hb	8.4	(12.3-15.3) g/dL
Hct	27.2	(35.9-44.6) %
MCV	82.9	(79-96) fL
Platlets	229000	(150000-450000)/mm^3
Lymphoctes	3.7	(20-40) %
Neutrophils	93.8	(50-70) %
MIX	2.5	(3-12) %
Ferritin	>3000	(4-104.2) ng/mL
Iron	26	(37-145) micg/dL
TIBC	220	(228-428) micg/dL
Reticulocyte	1.3	(0.5-1.5) %
Amylase	45	(10-100) U/L
Lipase	31	(5-60) U/L
LDH	917	(100-480) U/L
CPK	35	(20-180) U/L
APTT	32	(28-40) seco
PT	12.8	(9-11) seco
INR	1.43	(1-1.2)
ALT	10	(10-33) U/L
AST	37	(10-33) U/L
ALK-P	224	(100-240) U/L
ESR	96	(0-20) mm/h
CRP	96	(1-6) mg/L
BUN	11	(7-18.6) mg/dL
Cr	0.9	(0.7-1.3) mg/dL
BS	87	(70-135) mg/dL
Bilirubin-Total	0.8	(0.1-1.1) mg/dL
Bilirubin-Direct	0.2	(0.12-0.3) mg/dL
Calcium	9.4	(8.6-10) mg/dL
Phosphorus	3.7	(2.6-4.5) mg/dL
Magnesium	1.9	(1.9-2.5) mg/dL
Natrium	145	(136-145) mEq/L
Kalium	4.2	(3.5-5.1) mEq/L
RF	Negative	
Anti-ccp	Negative	
ANA	Negative	
ds-DNA	Negative	
c-ANCA	Negative	
p-ANCA	Negative	
Wright	Negative	
Combs Wright	Negative	
2ME	Negative	
Widal	Negative	
Stool culture	Negative	
Blood culture	Negative	
Urine Culture	Negative	
Stool exam	Normal	
Urine analysis	Normal	

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, TIBC: total iron binding capacity, LDH: lactate dehydrogenase, CPK: creatin phosphokinase, ANA: anti-nuclear antibodies, dsDNA: anti-double stranded DNA, APTT: activated partial thromboplastin time, PT: prothrombin time, INR: international normalized ratio, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALK P: alkaline phosphatase, ESR: erythrocyte sedimentation rate, CRP: C-reactive Protein, BUN: blood urea nitrogen, Cr: creatinine, BS: blood Sugar, RF: rheumatoid factor, Anti-ccp: Anti–cyclic citrullinated peptide antibody, c-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies, 2ME: 2-Mercaptoethanol.

Implication for health policy/practice/research/ medical education

Macrophage activation syndrome can occur at any time during adult Still's disease.

intravenously stat every month for total of 6 months. One day after this treatment, fever returned to normal range and gradually after one week many of laboratory abnormality returned to normal ranges and the patient was discharged with 50 mg oral prednisolone, 200 mg hydroxychloroquine, 1000 mg calcium daily + 800 international units 25hydroxyvitamin D (25[OH]D) daily, 40 mg pantoprazole and 70 mg alendronate weakly. The dose of prednisolone was gradually reduced over the next few months and in the sixth month; prednisolone reached 5 mg per day. After 24 months follow-up, the patient is alive and fever free.

Discussion

MAS is a form of hemophagocytic lymphohistiocytosis that can occur in ASD or other rheumatologic diseases. Some authors call this "reactive hemophagocytic syndrome." Macrophages are professional antigen presenting cells derived from circulating monocytes; they present foreign antigens to lymphocytes. In MAS, macrophages become activated and secrete excessive amounts of cytokines, ultimately causing severe tissue damage that can lead to organ failure (8-13). MAS is a fatal condition in ASD. If you are not thinking about MAS, the MAS patient who was already in control gets worse. (14-16). One study suggests that MAS is particularly likely in patients with at least two of the following conditions; thrombocytopenia, anemia, and hepatomegaly (17). The diagnostic hallmark of MAS is the presence of numerous, well-differentiated macrophages that are engaged actively the hematopoietic elements in bone marrow (14,18).

Conclusion

In ASD patients who are treated with the appropriate medications, MAS should also be considered in case of fever and hemoglobin loss.

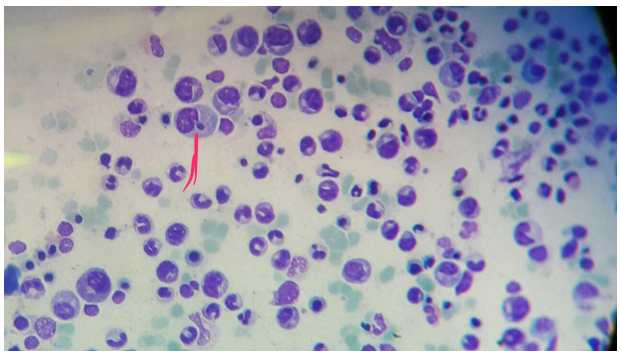

Figure 1. In bone marrow biopsy, a red blood cell is seen in cytoplasm of a macrophage (marked with red).

Authors' contribution

MK wrote the manuscript. MOZHK edited the manuscript. MHS reported the pathology of peripheral blood smear and bone marrow.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient has given her informed consent regarding the publication of this case report.

Funding/Support

None.

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