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Case Report

Tumor Lysis Syndrome Occurring During Treatment of Macrophage Activation Syndrome

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Abstract

Macrophage Activation Syndrome (MAC) is a form of Hemophagocytic lymphohistiocytosis (HLH) in patients with juvenile idiopathic arthritis and other rheumatologic conditions. Complication of treatment develop in various forms, however Tumor lysis syndrome is a very rare complication, which may occur during treatment of MAC. We herein present a rare case of MAC secondary to Systemic juvenile idiopathic arthritis, which was complicated by Tumor lysis syndrome at the initiation of treatment and was managed successfully.

Keywords

Macrophage Activation Syndrome; Hemophagocytic lymphohistiocytosis, juvenile idiopathic arthritis, tumor lysis syndrome

Abbreviations:

MAC : Macrophage Activation Syndrome;

HLH : Hemophagocytic Lymphohistiocytosis;

ESR : Erythrocyte Sedimentation Rate;

CRP : C-Reactive Protein

Case

A.U is a 2 years old girl, who was well, with no medical problems before she presented with history of 2 weeks fever that was associated with nonspecific rash, decreased activity, bony aches, joint pain and decreased feeding.

The child has normal developmental history, vaccination is up to date, no family history of concern and she is not allergic to any drug.

On initial examination, she was underweight, not dysmorphic, feverish, tachycardic, she had generalized lymphadenopathy with largest

Lymph node at the right axilla (1.5X1.3 cm), there was joint tenderness without obvious swelling, abdomen was lax, soft and the liver was palpable.

Initial investigations included (table 1); Blood counts that showed leukocytosis, normocytic anemia, and peripheral

blood smear showed atypical lymphocytes, all blood cultures came with no growth, ESR & CRP were high, both ANA & ds DNA were positive. Other bacterial and viral studies were all negative.

Table 1

White blood count	16.18	Immunoglobulin A	1.570 g/dl +
Hemoglobin	10.8 g/dl	**Immunoglobulin M**	1.600 g/dl +
Platelets	114,000	**Immunoglobulin G**	17.2 g/dl +
Erythrocyte sedimentation rate (ESR)	75 mm	**Immunoglobulin E**	1050 IU/ml +
C-reactive protein (CRP)	20 mg/dl		
LDH	1829 U/l	**Cytomegalovirus**	Negative
Anti-Nuclear antibodies (ANA)	Positive	**HIV Ab/Ag**	Negative
ds DNA	Positive	**Ferritin**	2365 ng/ml

She started on supportive measures and empiric antibiotics but with no improvement.

C.T chest and abdomen showed generalized lymphadenopathy, Bone Marrow Aspirate and biopsy revealed no evidence of malignancy.

Given the data from the clinical picture and initial investigation, the child was diagnosed as Systemic Juvenile Idiopathic Arthritis. She started on non-steroidal anti-inflammatory drug (indomethacin). The next day she became sicker, with high-grade fever, she developed pancytopenia, which required blood and platelets transfusion, she had also splenomegaly. The lab works (Table 2) showed very high serum ferritin level, hyper-triglyceridemia, hypo-fibrinogenemia, prolonged Prothrombin Time and Partial Thromboplastin Time, high d-Dimer, low Erythrocyte sedimentation rate.

Table 2

White blood count	1.2	d-Dimer	11
Hemoglobin	6.6 g/dl	**PT**	17 sec
Platelets	15,000	**PTT**	55 sec
Erythrocyte sedimentation rate	3 mm	**TGL**	550 mg/dl
Fibrinogen	120	**Ferritin**	13600 ng/ml

Bone Marrow Aspirate was repeated and showed mild hemophagocytosis and excisional right axillary lymph node biopsy revealed reactive hemophagocytosis with no evidence of malignancy; the picture which is highly suggestive of Macrophage Activation Syndrome (secondary HLH).

We decided to start her on Dexamethasone and Etoposide along with blood and platelets transfusion as well as fresh frozen plasma.

Following the initial doses of steroids and Etoposide, the child developed a full picture of Tumor Lysis Syndrome (Table 3) high level of serum uric acid, hyperphosphatemia, hypocalcemia, and elevated serum creatinine.

Table 3

White blood count	6.5	Uric acid	692 µmol/L
Hemoglobin	8.4 g/dl	**bicarbonate**	21 mmol/L
Platelets	24,000	**Phosphate**	2.8 mmol/L
Absolute Neutrophilic count	5.2	**Calcium**	1.68 mmol/L
LDH	4758 U/l	**Creatinine**	82 µmol/L
Sodium	142 mmol/L	**Urea**	17.2 mmol/L
Potassium	4.3 mmol/L		

She started immediately on hyper-hydration and alkalization, she received one dose of recombinant urate oxidase followed by oral Allopurinol and started on oral aluminum hydroxide. Electrolytes, ca, phosphorus, creatinine, BUN, urine PH, were carried out more frequently, strict measurement of intake and output was carried out regularly and urine output was maintained at 3 ml/kg/hr.

Her lab works started to improve markedly, with normalization of all electrolytes and uric acid.

The child continued on Dexamethasone, and full coverage by IV antibiotics due to the underlying septicemia and disseminated intravascular coagulation (DIC) until her general condition markedly improved with no more fever, no evident of hepatosplenomegaly, normal blood counts, triglycerides, fibrinogen, and ferritin. She was referred to a rheumatology center to continue the management of her initial disease.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive, life-threatening syndrome of excessive immune activation. Prompt initiation of treatment for HLH is essential for the survival of affected patients.

HLH is classified into primary, also known as familial hemophagocytic lymphohistiocytosis is a heterogeneous au-

tosomal recessive disorder found to be more prevalent with parental consanguinity and Secondary hemophagocytic lymphohistiocytosis, which occurs after strong immunologic activation that may occur with systemic infection, immunodeficiency, or underlying malignancy [1].

Both forms are characterized by the overwhelming activation of normal T lymphocytes and macrophages, invariably leading to clinical and hematologic alterations and death in the absence of treatment.

Macrophage Activation Syndrome is a form of HLH in patients with juvenile idiopathic arthritis and other rheumatologic conditions [2].

Early recognition of this syndrome and immediate therapeutic intervention to produce a rapid response are critical. Most clinicians start with intravenous methylprednisolone pulse therapy (30 mg/kg for three consecutive days) [3]. This might be followed by the HLH-2004 treatment protocol developed by the International Histiocyte Society.

Complications of initial treatment included severe myelosuppression, anemia, and thrombocytopenia, renal and liver impairment may occur. Severe infection as well may develop due to underlying pancytopenia and immune defects [4].

Renal impairment and/or acute renal injury can occur during treatment and are also frequently seen with Hemophagocytic lymphohistiocytosis as stated by Aulagnon et al, which are adversely affecting remission and survival [5].

Tumor lysis syndrome refers to the constellation of metabolic disturbances that might be seen after initiation of cancer treatment [6]. It usually occurs in patients with bulky, rapidly proliferating, treatment-responsive tumors [7].

It is typically associated with poorly differentiated lymphomas, such as Burkitt's lymphoma, and leukemias, such as acute lymphoblastic leukemia and acute myeloid leukemia. Other cancers such as Neuroblastoma, Germ cell tumors and melanoma have also been associated with TLS but are less common [8].

Clinically, the syndrome is characterized by rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute renal failure [9]. It could lead also to cardiac arrhythmias, seizures and sudden death.

The main principles of tumor lysis syndrome management are early detection and identification of patients at high risk and initiation of preventive therapy.

We presented a case of MAS secondary to Systemic juvenile idiopathic arthritis, which was complicated by Tumor lysis syndrome at the initiation of treatment, and to our knowledge, this is a very rare association, which should be kept in consideration while managing subsequent cases of either familial or acquired Hemophagocytic lymphohistiocytosis.

Conclusion

We recommend observing the parameters of Tumor lysis syndrome in every patient treated for familial or acquired Hemophagocytic lymphohistiocytosis besides the routine monitoring during the treatment.

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