CASE REPORT

Extremely High Ferritinemia Associated with Haemophagocytic Lympho Histiocytosis (HLH)

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Abstract Hyperferritinemia (>10,000 ng/ml) is an important hallmark used as an indicator of infection triggered macrophage activation syndrome leading to hemophagocytic lympho histiocytosis (HLH). Measurement of serum ferritin can be used in diagnosis as well as disease monitoring indicator and prognosis related to HLH, cAPS, sepsis, neoplasm and inflammatory conditions. It is a major contributor to manage critically ill patients as predicting and monitoring indicator. It can be used as acute phase response in conditions of MAS, AOSD, cAPS etc. A case study in our hospital showed extremely high ferritin values along with low hemoglobin, elevated LDH and triglycerides with positive MRSA in sputum culture and macrophage proliferation and hemophagocytosis in the bone marrow examination. Patient showed definite inverse relation with steroid therapy and serum ferritin levels.

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Introduction

Hyperferritinemia (>10,000 ng/ml) is an important hallmark for using as an indicator of activity of phagocytic function of macrophages in hemophagocytic lympho histiocytosis (HLH)/macrophage activation syndrome (MAS).

Ferritin is a 24 subunit major intracellular iron storage protein. Within the cytosol it stores iron in a non soluble non toxic form and so protecting the cell. In the circulation it acts as delivery mechanism and its serum level reflect total iron body store [1]. It can be elevated in wide range of conditions such as malignancy, infection, septic shock, inflammation and chronic iron overload syndrome. It plays a role as acute phase reactant [2–7].

As per in vitro studies intracellular ferritin sharply increases during maturation of monocytes to macrophages. In the phagocytic process of erythrocytes ferritin accumulate rapidly. Phagocytic macrophages are important source of serum ferritin and play central role in iron circulation. Therefore ferritin levels sharply increase in histiocytic proliferative disorders [8]. So it is taken as a useful indicator of disease activity both in neoplastic and reactive conditions.

There are four uncommon medical conditions characterized by high levels of ferritin, namely the macrophage activation syndrome (MAS), adult onset still's disease (AOSD), catastrophic antiphospholipid syndrome (cAPS) and septic shock, that share a similar clinical and laboratory features. Markedly elevated ferritin levels are associated with inflammatory conditions such as adult onset still's disease (AOSD), Juvenile idiopathic arthritis and haemophagocytic lympho histiocytosis/MAS and septic shock [9].

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Case Report

A 50 years old female was admitted to Fortis Hospital Shalimar Bagh with high fever, vomiting and breathing difficulty. Patient came with septic shock (procalcitonin levels—73.79 ng/ml). Numerous investigations were done with the relevant findings (Table 1). Biochemical investigations (Triglycerides, AST, ALT, LDH) were processed on Dimension RxL Max, Siemens, GERMANY. Serum ferritin and Procalcitonin levels were done with ECLIA methodology on Cobas e 411, Roche Diagnostics, Mannheim Germany. Complete blood count was done by using fully automated hematology analyser Sysmex XT 1800i, USA. Fibrinogen levels were done on Star Compact Max, Diagnostica Stago platform via CLAUS methodology. The diagnostic criteria include fever, splenomegaly, cytopenias affecting at least 2 of 3 lineages in the peripheral blood, hyperferritinemia greater than 10,000 ng/ml, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen or lymph nodes, low or absent NK cell activity determined by 51cr release assay and high

levels of sCD25. The authors have considered at least 5 out of 8 criteria to be positive for diagnosis of HLH. (Table 2) [10] Common laboratory findings of our patient include extremely high ferritin values (ferritin—119,191 ng/ml), elevated LDH (LDH—545 U/l), high CRP (>180 mg/l) and mild triglyceridemia (TG—284 mg/dl). For serum ferritin levels a cut off of 10,000 ng/ml was found to be 90 % sensitive and 96 % specific for HLH [11].

Chest X ray showed bilateral fluffy shadows. Ultrasound report showed hepatomegaly and mild splenomegaly. Sputum culture was done which came positive for MRSA. Then bone marrow was done which confirmed hemophagocytic lymphohistiocytosis (Grade—+) and macrophage proliferation (Grade—++) (Fig. 1). Histopathologic findings of HLH typically include a prominent and diffuse accumulation of lymphocytes and mature macrophages, which occasionally exhibit hemophagocytosis. The microscopic visualisation of hemophagocytosis is simply one of the possible diagnostic criteria [10].

Keeping everything in mind diagnosis of hemophagocytic lymphohistiocytosis was made. Course of IV steroid

Table 1 Laboratory findings of patient at the time of admission

Parameter	Value	Units	Biological reference interval
Hb	10.1	g%	12.0–15.0
PT (mean—13.1)	15.2	secs	11.4–13.7
aPTT (mean—29.2)	35.2	secs	27.8–41.8
WBC	37.2 × 10 ⁹	/l	4.0–10.0
Neutrophils	89 × 10 ⁹	/l	2.0–8.0
Platelet	218	/cumm	150–410
AST	81	U/l	15–37
ALT	91	U/l	30–65
ALP	176	U/l	50–136
GGT	155	U/l	5–85
LDH	545	U/l	81–234
BUN	27	mg/dl	5–20
Creatinine	2.8	mg/dl	0.6–1.1
Triglycerides	284	mg/dl	<150—normal, 150–199—border line, >199 high
Fibrinogen	517	mg/dl	200–400
Ferritin	119,191	ng/ml	10.0–291.0
Procalcitonin	73.79	ng/ml	<0.5—low risk, >2.0 high risk
Leptospira	0.74	U/ml	<15.0—neg., 15–20 indeterminate, 20.0—positive
Complement C3	103	mg/dl	76–181
Complement C4	56.5	mg/dl	14–52
Sputum C/S	MRSA detected		No growth
Hb variant analysis	Normal		Normal
C-ANCA, P-ANCA	Negative		Negative
Clostridium difficile toxin	Not detected		Not detected
Myeloma band	Not detected		Not detected
Bone marrow aspirate	Hemophagocytic lymphohistiocytosis		Normal

Table 2 Description of patient according to probable criteria of HLH

Parameter	Criteria	Patient Detail
Fever	Non remitting high fever	Yes
Spleen	Enlarged	Yes (grade—++)
Neurologic symptoms	Present	Present
Medullar phagocytosis	Present	Present (grade—+)
Hemoglobin	<9.0	10.1 g%
Neutrophils	<1.0 × 10 ⁹ /l	31.9 × 10 ⁹ /l
CRP	>90 mg/l	>180 mg/l
Fibrinogen	low	517 mg/dl
Ferritin	>500 ng/ml	119,191 ng/ml (grade—severe)
Triglycerides	High	284 mg/dl (mild)
Peripheral smear	Cytopenia (2 of 3 lineages)	Normal
Bone marrow biopsy	Hemophagocytic syndrome	HLH (grade—+)

Fig. 1 Lymphocytic and macrophage proliferation with occasional haemophagocytosis (arrow)

was started and patient showed marked improvement within 2 days. Patient became afebrile and showed fall in serum ferritin levels and was shifted to ward with discontinuation of steroid. Trend of serum ferritin levels during admission period is depicted (Chart—1).

After shifting to ward patient showed sign of deterioration along with fever and serum ferritin levels also started rising. Then patient had to shifted back to ICU and put on steroids again. Patient condition improved, became afebrile, showed fall in Serum Ferritin levels and shifted to wards after recovery. Patient became clinically better, tolerating oral diet, able to walk with support and decreasing trend of serum Ferritin levels. Finally patient was discharged with follow up medication mainly on steroids.

Discussion

Hyperferritinemia is an important lab indicator for infection triggered macrophage activation syndrome leading to HLH. HLH also known as hemophagocytic syndrome is an

uncommon systemic inflammatory clinical syndrome associated with numerous conditions such as neoplastic, infectious, autoimmune or hereditary disease. HLH is caused by a defect in inflammatory signals that results in a setting of congenital or acquired defective natural killer (NK) T Cell function in the cytotoxic pathway [10].

In the present case patient presented with septic shock with extremely high ferritin value and elevated LDH. Bone marrow examination showed evidence of HLH with splenomegaly and hepatomegaly. Culture of sputum showed positivity for MRSA. Similar studies were done by other authors. During 7 months period Koduri et al. [12] studied four patients and diagnosed with RHPS. Of these three were diagnosed with acquired immunodeficiency syndrome. Their patient had elevated LDH (>1000 U/l), hyperferritinemia (range—34,976–425,984 ng/ml).

Four uncommon medical conditions characterized by high levels of ferritin namely MAS, AOSD, cAPS and septic shock that shows a similar clinical and laboratory features and also respond to similar treatments suggesting a common pathogenic mechanism [13]. In a study by Cofernils et al. [14] (1920) analyzed the scores of 40 patients with various severe inflammatory diseases aside from AOSD. No ferritin value was higher than 3300 ng/ml. In 3 of 10 consecutive patients ferritin value was higher than 3300 ng/ml. Among these three patients one patient showed a marked hyperferritinemia (3600 ng/ml) of mature appearing histiocytes and two patients had very high levels of serum ferritin (serum ferritin level—65,000 and 2,50,000 ng/ml). This study again suggest that very high serum ferritin levels encountered in AOSD reflect the presence of histiocytic hyperactivity that sometimes lead to HPS.

The clinical picture of MAS is generally acute and can be dramatic. Typically our patient was acutely ill with the sudden onset of non remitting high fever, splenomegaly. But leukocytes were raised in our case

contrast to clinical feature of MAS. Elevated liver enzyme including AST, ALT, LDH, GGT, high concentration of triglycerides and low levels of sodium are observed. There is usually an abnormal coagulation profile (PT, aPTT and fibrinogen).

The disorder of HLH is characterized by histiocytic proliferation in bone marrow, liver and spleen. It shows hematopoietic cellular phagocytosis. This disorder usually includes familial type of HLH, sporadic type of HLH and infection associated HLH and fourth is MAS [15]. Infection associated HPS is a reactive process related with viral/bacterial/fungal/parasitic infections. It is usually seen due to cytokines effect leading to marrow depression and disturbed clotting parameters. Bone marrow shows normal to hypo cellular appearance with suppression of erythrocytes and myelopoiesis. Macrophages are markedly increased and shows phagocytosis. The disease is treated with controlling the underlying ineffective agents and steroid therapy. Out of so many criteria for diagnosing HLH hyperferritinemia is an important parameter. Not only in malignant and MAS condition but elevated serum ferritin levels are independently and positively associated with the presence of the metabolic syndrome [16] and are associated with single cardio vascular risk factor [17].

Conclusion

Measurement of serum ferritin levels may be used in diagnosis and can be a useful indicator of disease activity, Therapy response and prognosis related to HLH, AOSD, cAPS, sepsis, neoplasm and inflammatory conditions. Serum ferritin levels in histiocytic proliferative disorders is a useful indicator of disease activity both in neoplastic and reactive disorders.

The concept of hyperferritinemia is a major contributor to manage critically ill patients, for guiding therapy and predicting prognosis. It can be used as reflection of acute phase response in condition (MAS, AOSD, SS). These disorders share similar clinical finding and respond to similar treatment which suggest that hyper ferritinemia is involved in common pathogenic mechanism.

Compliance with Ethical Standards

Conflict of interest Authors (Neelima, Jyoti, Pankaj, Alka, Leena and Manish) declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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