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Original Research Article

Diagnostic Interpretation and further evaluation of Extreme Hyperferritinemia (>10,000 microg/L) with reduced % Tsat (<50%) in pediatric patients in Tertiary care Hospital

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Abstract

Background*:** Ferritin is a soluble protein which provides intracellular storage of bioavailable iron. It is found primarily in Liver, bone marrow macrophages, spleen. Ferritin is measured by ELISA, RIA and Mass spectrometry. The main aim of this study is to etiologically categorise extreme hyperferritinemia (serum ferritin > 10000 microg/L). ***Methodology and Results*:** This is 05 years retrospective study (July -2018 to June 2023), conducted in hematology section, MMCH, KSA. Out of 34 cases of extreme hyperferritinemia, viral infection was the most common cause comprising 41% of all cases. Amongst the infectious etiology, 6 cases of EBV, 3 cases of ALF of suspected viral etiology, 2 cases of PIDS with secondary infection, 1 case each of Hepatitis A virus and CMV noted. 10 cases presented as Macrophage Activating syndrome comprising 29% of total cases of which 70 were Systemic Juvenile Idiopathic arthritis and remaining 30% includes SLE and juvenile rheumatoid arthritis. ***Discussion*:** Study conducted by Dondu *et al*., indicate that the most common causes of hyperferritinemia are rheumatologic diseases and infections, which were identified in 59.1 and 27.3%, respectively. Present study showed infective etiology as the most common cause of extreme hyperferritinemia. Reasons for differences in results are because other studies were conducted in Adult patients and in Rheumatologic department. ***Conclusion: Our study formulated a systematic investigating pathway for raised serum ferritin. If the laboratory screening tests, BMA and other sophisticated tests are done in systematic way, then challenging cases can be diagnosed easily.

Keywords: Macrophage activation syndrome, Haemophagocytic lymphohistiocytosis.

INTRODUCTION

Ferritin is a soluble protein which provides intracellular storage of bioavailable iron. It is an acute-phase reactant and coordinates the cellular defense against oxidative stress and inflammation. One microg/L of ferritin is equivalent to 8mg of stored iron. It is found primarily in Liver, bone marrow macrophages, spleen. Ferritin is measured by ELISA, RIA and Mass spectrometry

Role of Hepcidin and Iron Metabolism

- Hepcidin is produced by liver, It is imp IRP & regulates iron hemostasis.
- Carcinoma, Infection and Inflammation – stimulates IL-6 & Hepcidin is increased
- Hepcidin - Inhibits the absorbtion of Iron from GIT + Reduces the release of Iron from macrophages. Net effect is reduced iron level in serum.
- Transferrin delivers the iron to cells via Transferrin receptors.

Ferritin is a widely used test but there is no clear cut-off value specified for hyperferritinemia.

Normal Serum Ferrittin level in males is 40-340 microg/L and 14 -150 microg/L in females. Normal percentage Transferin Saturation (% Tsat) = 30-50%. As per BSH (2018) guidelines hyperferritinemia is defined as Serum Ferrittin level > 300 / 200 microg/L in male/ Female. The cut off value for raised % Tsat is > 50% and reduced % Tsat is < 30% [1].

Extreme Hyperferritinemia is defined as Serum ferritin level > 10,000 micrg/L [2, 3].

OBJECTIVES

1) To etiologically categorise extreme hyperferritinemia
2) To study rare disease like MAS, primary HLH
3) To formulate investigating pathway in cases of raised serum ferritin.

Materials and Method

This is 05 years retrospective study (July -2018 to June 2023), conducted in hematology section, MMCH, KSA. Institutional review committee provided ethical approval and permission. The local policy was followed for obtaining consent

Inclusion Criteria

1) As per the Hospital policy, children upto 14 years were included
2) By definition Hyperferritinemia = > 10,000 microg/L

Exclusion Criteria

1) COVID 19 infections
2) Gender was not included

Staining of Blood and BMA smears

Smears were stained with modified Romanowsky Wright- Giemsa stain. BMA smears were Fixed in wright stain for 5 min and stained with Giemsa stain for 10-15 min, washed with distilled water and studied under microscope

Statistical analysis of data

Mean +/- SD was used to express all data. Utilizing the unpaired students t test, statistical analysis was conducted. Statistically significant data has a p value less than 0.05.

RESULTS

Table 1: Etiologically categorise extreme hyperferritinemia

Primary HLH	Secondary HLH (24) (75%)		Hematological Malignancy (06) (17%)
04 (11%)	Viral infections (14) (41%)	MAS (10) (29%)	AML-M5 - 03 (09%) Burkitts L - 02 (06%) T –ALL - 01 (03%)
	EBV - 07 (20%) ALF - 03 (09%) PIDS - 02 (06%) HAV - 01 (03%) CMV - 01 (03%)	SJIA – 07(20%) SLE – 02 (06%) JRA - 01(03%)	

ALF- Acute liver failure, PIDS – Primary immunodeficiency syndrome, Hepatitis A virus CMV – Cytomegalovirus, SJIA – systemic Juvenile idiopathic arthritis, JRA – Juvenile rheumatoid arthritis

During 5 year period, total number 34 cases of extreme hyperferritinemia (serum ferritin > 10,000 microg/ L) cases studied, of which maximum serum ferritin level of 40,000 microg/L was noted in AML-M5

Out of 34 cases of extreme hyperferritinemia, viral infection was the most common cause comprising 41% of all cases. Amongst this infectious etiology, 6 cases of EBV, 3 cases of ALF of suspected viral etiology, 2 cases of PIDS with secondary infection, 1 case each of Hepatitis A virus and CMV noted.

10 cases presented as Macrophage Activating syndrome comprising 29% of total cases. 70% cases presenting as MAS are Systemic Juvenile Idiopathic arthritis and remaining 30% includes SLE and juvenile rheumatoid arthritis.

17% of extreme hyperferritinemia cases were due to Hemato-lymphoid malignancy. AML-M5 comprised of 3 cases, 02 cases of Burkitts lymphoma and 1 case of T-ALL.

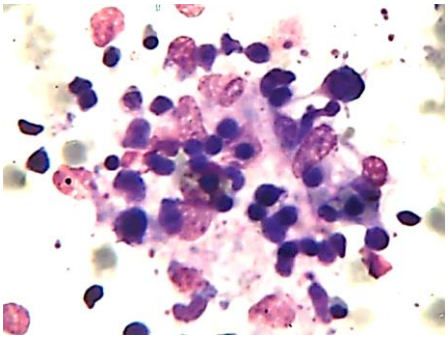


Fig 1: HLH (haemophagocytes engulfing erythroid cells)

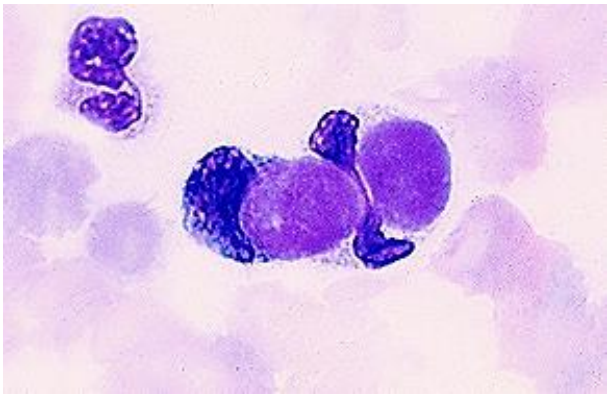


Fig 2: L.E cell (SLE)

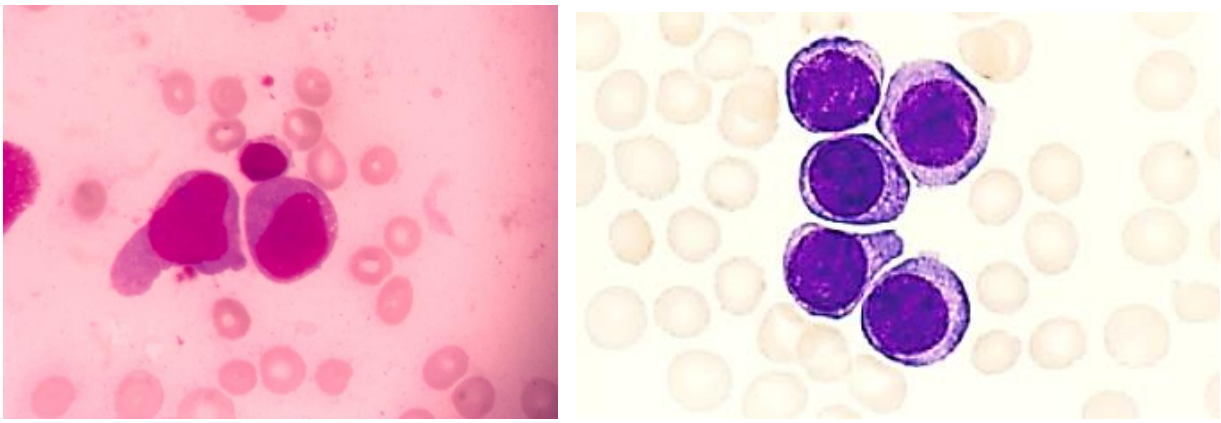


Fig 3 a & b): AML-M5 showing monoblasts and atypical monocytes

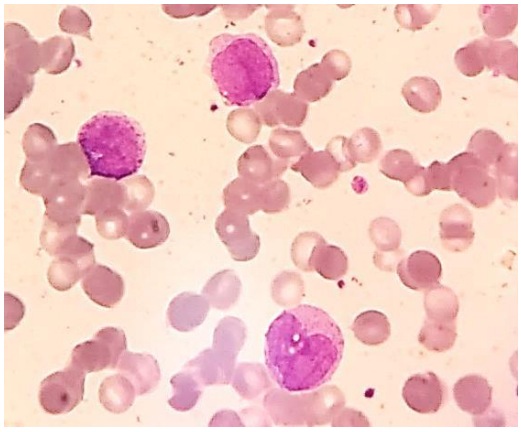


Fig 4: Promonocytes in AML

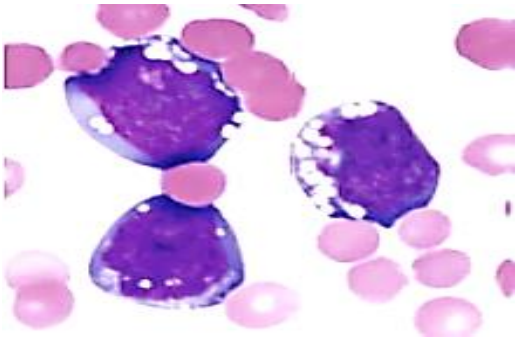


Fig 5: Burkitts Lymphoma

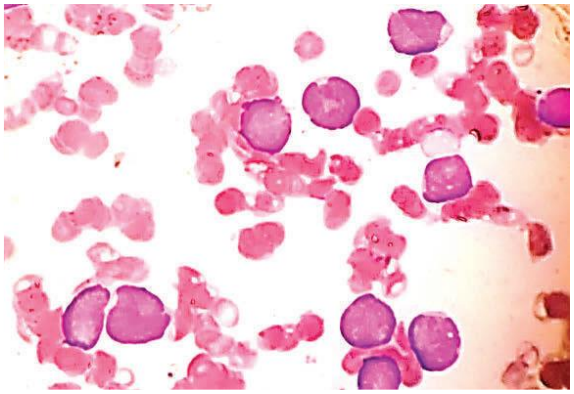
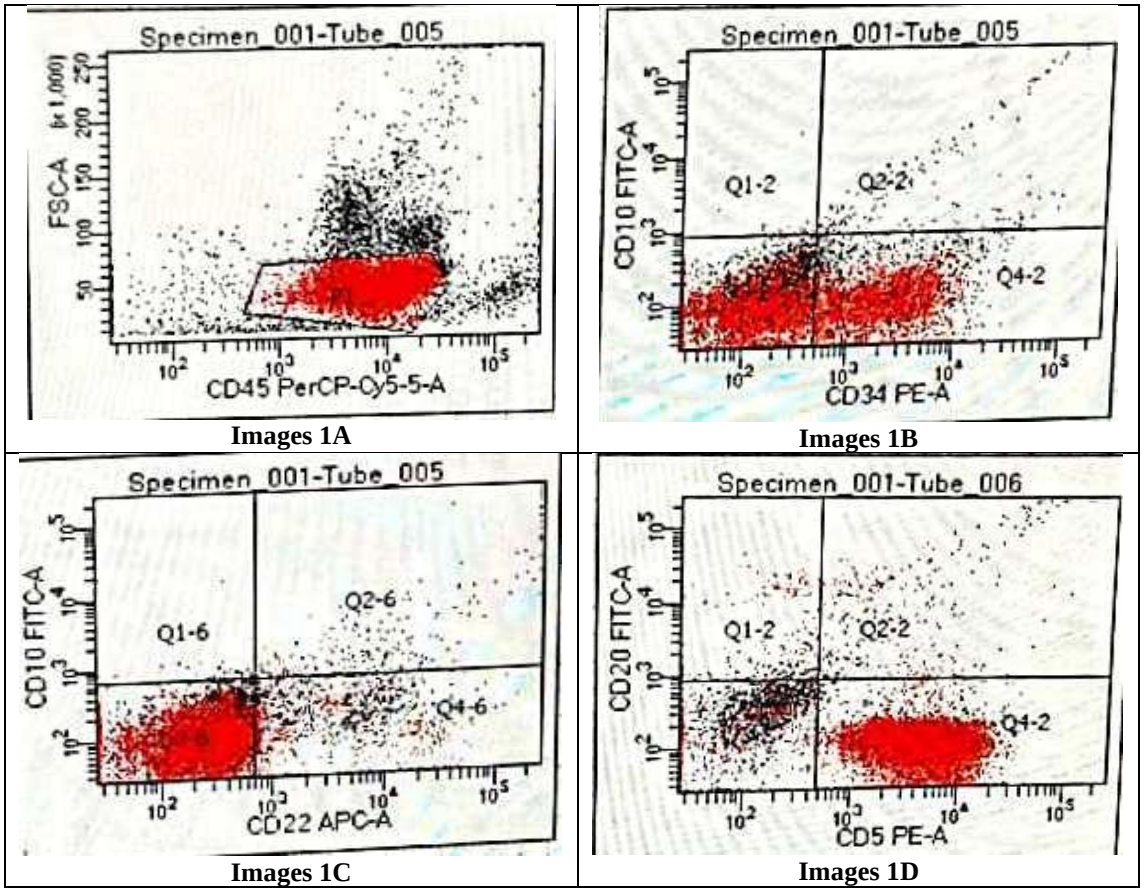


Fig 6: T-ALL showing Lymphoblsts

Flow cytometry images 1(A,B,C,D):- T-ALL (Strong +ve for CD5, CD34, CD45, -ve for CD19,CD22)



Images 1A **Images 1B**

Images 1C **Images 1D**

DISCUSSION

Increased ferritin Levels with low % Tsat excludes Hemolytic Anemias, Iron loading conditions (Hemoglobinopathies, sideroblastic Anemias, Transfusion related siderosis) and Hereditary Hemochromatosis.

The prevalence and causes of hyperferritinemia vary according to ethnic differences, gender, adult or pediatric age group, whether it was done in a general hospital or not, and the cut-off value for ferritin [4].

The most common causes of increased ferritin levels and reduced % Tsat in pediatric patients are Hematological malignancies, reactive histocytosis, HLH, Rheumatologic conditions, Gauchers disease, Acute and chronic infections, inflammatory conditions and auto-immune diseases [4].

Extreme Hyperferritinemia with serum ferritin > 10,000 microg/L is seen particularly in Primary HLH (hemophagocytic lymphohistiocytosis), secondary HLH like MAS & certain viral infections (EBV) [5-7].

The term Macrophage Activation Syndrome (MAS) identifies a potentially fatal complication of rheumatic diseases. It occurs usually in the context of systemic Juvenile Idiopathic Arthritis (sJIA), but it may occur also, albeit more rarely, in systemic Lupus Erythematosus and Kawasaki disease [8].

One UK based study conducted over a period of 1 year showed total ferritin samples measured were 53,81541 of which 41 cases of extreme hyperferritinemia with serum ferritin of ≥ 10,000 µg/L were noted giving a ratio of 0.08% [5].

In study conducted by Dondu *et al*., of 542 measurements from 242 patients, they identified the rate of hyperferritinemia (≥ 500 ng/mL) as 4.7%, and the rate of extreme hyperferritinemia (≥ 10,000 ng/mL) as 0.2%, that is, in line with the literature [2].

In Our study rate of extreme hyperferritinemia / total serum ferritin measured was 1.8% Which was in good correlation with literature.

Table 2: Comparison with studies by Dandu *et al*., [2]

Rheumatological diseases	*n* (%)	Ferritin, mean±SD, ng/mL	*P* value
AOSD	42 (29.4%)	9075±9191	<0.0001
RA	37 (25.6%)	946±505	
Vasculitis	18 (12.6%)	1042±547	
SLE	18 (12.6%)	1165±704	
Behçet's disease	8 (5.6%)	745±300	
Scleroderma	4 (2.8%)	873±201	
Gout disease	3 (2.1%)	1150±183	
PMR	3 (2.1%)	732±138	
Psoriatic arthritis	3 (2.1%)	611±46	
Ankylosing spondylitis	2 (1.4%)	682±1419	
Temporal arteritis	2 (1.4%)	1692±1409	
Dermatomyositis	2 (1.4%)	630±4384	
Retroperitoneal fibrosis	1 (0.7%)	1651	

AOSD adult-onset Still's disease, *PMR* polymyalgia rheumatica, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

Studies conducted by Dondu *et al*., showed 15 of the cases (88.2%) were due to Rheumatologic causes (SJIA) with mean ferritin of 19,183 ng/mL, one was due to HLH, and one was due to infection. There was a difference in results compared to other studies because Study by Dondu *et al.*, was done in rheumatology patients only. Study conducted by Dondu *et al*., indicate that the most common causes of hyperferritinemia are rheumatologic diseases and infections, which were identified in 59.1 and 27.3%, respectively [2].

In the literature, only a small number of studies investigated the cause of hyperferritinemia in the setting of the rheumatology department. Orbach *et al*., investigated the frequency of hyper-ferritinemia by considering only primary rheumatic diseases. They detected hyperferritinemia in 23% of SLE patients, 15% of dermatomyositis patients, and 4% of RA patients [9]. Other Studies with extreme hyperferritinemia showed only few cases of SJIA as etiology [9].

According to a newly published review, the rate of rheumatologic/ inflammatory diseases in patients with hyperferritinemia, which includes general hospital data, ranges from 1.8% to 32.6% [10]. Senjo H *et al*., have identified the most frequent of extreme hyperferritinemia causes as non-HIV infections, unlike the other studies [11].

Out of 34 cases of extreme hyperferritinemia, viral infection was the most common cause comprising 41% of all cases. Amongst this infectious etiology, 6 cases of EBV, 3 cases of ALF of suspected viral etiology, 2 cases of PIDS with secondary infection, 1 case each of Hepatitis A virus and CMV noted.

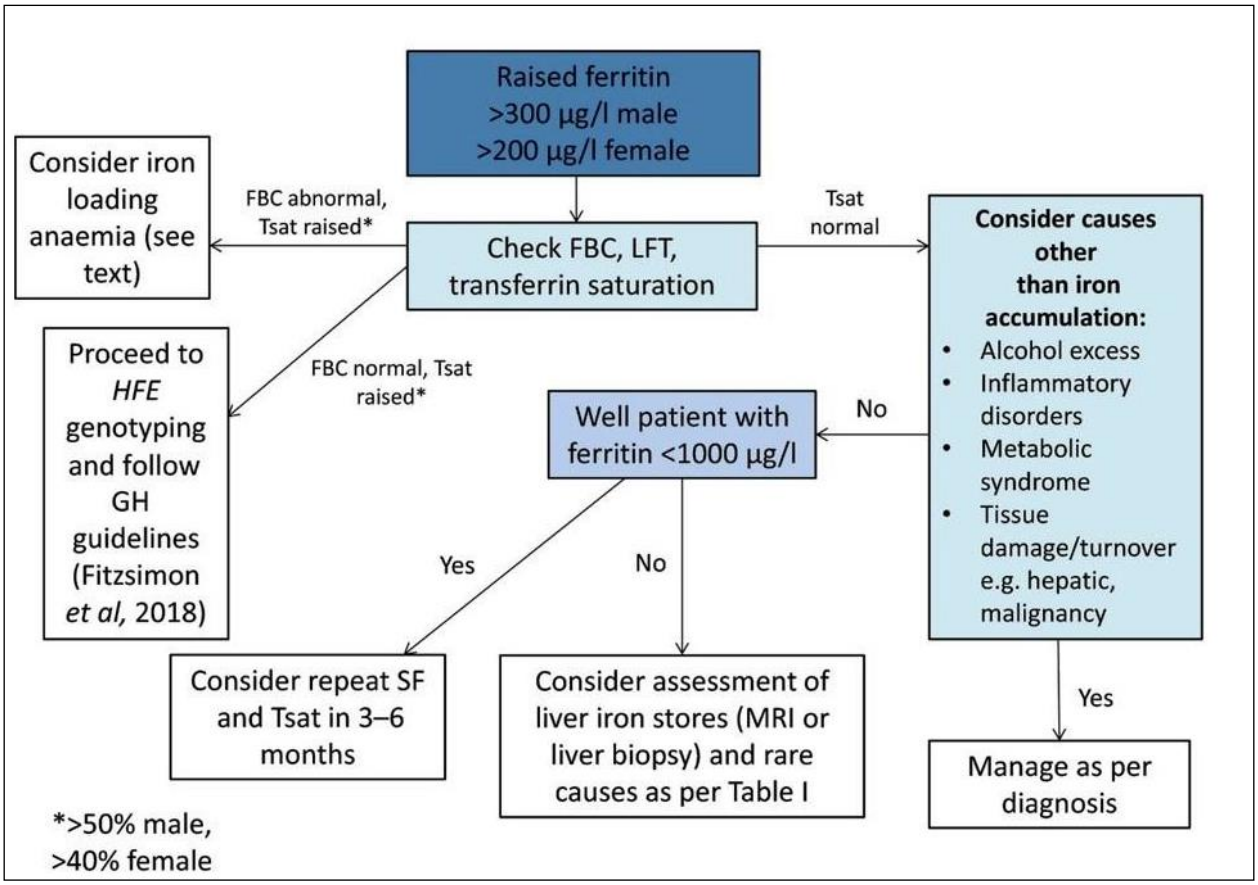
10 cases presented as Macrophage Activating syndrome comprising 29% of total cases. 70% cases presenting as MAS are Systemic Juvenile Idiopathic arthritis and remaining 30% includes SLE and juvenile rheumatoid arthritis.

17% of extreme hyperferritinemia cases were due to Hemato-lymphoid malignancy. AML-M5 comprised of 3 cases, 02 cases of Burkitts lymphoma and 1 case of T-ALL.

Primary HLH cases presented with positive family history, typical clinical and BMA findings one case was confirmed by perforin mutation studies.

Reasons for differences of present study with other studies

1) Majority of other studies were conducted in Adult patients and in Rheumatologic department.
2) Present study is conducted in pediatric tertiary care referral hospital so increased number of infective and Acute leukemia as etiology of extreme ferritinemia.
3) Our study has a retrospective design.



Investigating pathway in raised serum ferritin level

Interesting cases

1) 7 years boy with known sJIA presented with fever, severe arthralgia and arthritis involving elbow joints generalized seizures, hypotension, purpura splenomegaly and pancytopenia. Coagulation profiles and LFT were deranged. Serum ferritin was 24000 microg/L. patient was diagnosed as MAS.
2) 6 year old girl presented with Hepatosplenomegaly, deranged coagulation, serum ferritin of 40,000 microg/L. BMA showed predominant Monoblasts and myeloblasts which was subtyped as AML-M5 by flow cytometry

CONCLUSION

One of the limitations of our study is its retrospective design. Another limitation is that it includes pediatric patients. Other studies were conducted in rheumatology practice, so the most common causes of extreme hyperferritinemia are rheumatologic diseases (SJIA, RA, SLE, and vasculitis) and infections. Since our study was conducted in tertiary care pediatric referral hospital and not a primary Rheumatologic centre can lead to bias and can be the reason for increased number of infective causes of extreme hyperferritinemia. Also we noted that AML-M5 as the cause of serum ferritin

level of 40000 microg/L because this is also Leukemia specialist centre.

Our study formulated a systematic investigating pathway for raised serum ferritin. If the laboratory screening tests, BMA and other sophisticated tests are done in systematic way, then challenging cases can be diagnosed easily.

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