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Macrophage Activation Syndrome:A case series;From Sepsis to Malignancy:Early diagnosis and treatment

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ABSTRACT

INTRODUCTION:- Haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome(MAS) is a syndrome of fulminant cytokine storm leading to multiorgan dysfunction and high mortality rate.HLH may be Familial or Primary(fHLH) and Secondary (sHLH).FHLH is due to mutation in gene coding for perforin or NK cell of CD8 lymphocytes. sHLH may be associated with hematological malignancies,autoimmune disorders like SLE,Still's diseae,kawasaki disease, infections and sepsis of various etiology starting from bacteria ,viral protozoal ,fungal and zoonotic infection.Main presenting features are fever,hepatospleenomegly,cytopenia,high ferritin level,high serum triglyceride and haemophagocytosis in bone marrow spleen or lymphnode.

MATERIAL AND METHOD: In this series we describe Five cases ,(two cases of SLE,one B-Cell lymphoma,one case of scrub typhus,one case of kleibsiella pneumoniae presenting as sepsis) with their clinical,laboratory investigations,management and outcome with special correlation of ferritin level and HS score with the prognosis.All patients managed with I.V.Methyl prednisolone 30 mg/kg/day for three consecutive days and out come is assessed.

CONCLUSION: MAS in SLE and sepsis is a lifethreatening unrecognised condition,early diagnosis and treatment can increase the survival rate by many folds . a drop of ferritin level by 15% after 48 hrs of treatment is a surrogate marker of good prognosis.From H scoring cut off value 169 corresponds to sensitivity of 93% and specificity of 86%.

Keywords: haemophagocytois lymphohistiocytosis,(HLH),Macrophage activation syndrome,hypertriglyceredemia

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Introduction

MAS is a rare potentially life threatening multisystemic inflammatory syndrome caused by excessive immune activation and cytokine storm from excessively activated lymphocytes and macrophages.Cardinal features include fever,hepatospleenomegaly,cytopenias,high ferritinemia,and histological lymphophago-cytosis.

HLH may be Primary and secondary .Primary genetic HLH is caused by specific genetic homozygous or heterozygous loss of function mutation in perforin mediated cytotoxicity pathway protein(PPF1,SDX11)and may present early in infancy as familial or associated with genetic immune deficiency syndromes like Chediak Higashi,Griselli syndrome type 2.It commonly affects infants and triggered by certain infections like EBV.Acquired or secondary HLH occurs in adults sporadically with conditions like chronic immune dysregulation like rheumatological disorders like systemic juvenile idiopathic arthritis,kawasaki disease,or malignancies like Tcell and B cell leukemias or infections like scrub typhus or periodic fevers[1].

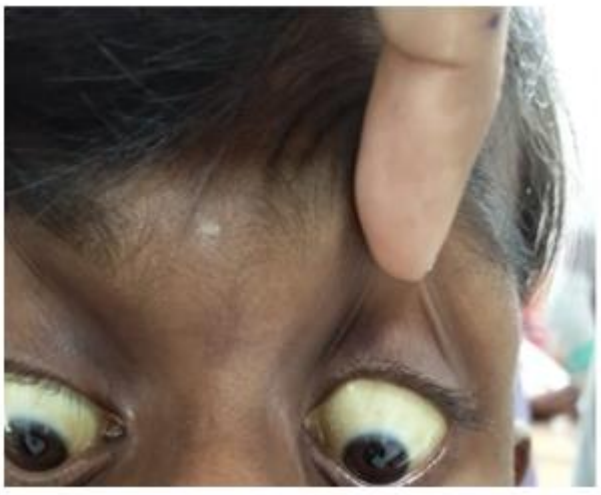
Current concept of pathogenesis of MAS in sepsis- overproduction of IL-1*B* is effected through the stimulation of TLRs by ferritin and HMGB1 .this leads to cytokine stotm and shredding of soluble CD 163.These interleukins lead to overproduction of IFN gamma By NK cell leading to haemophagocytosis.[2]

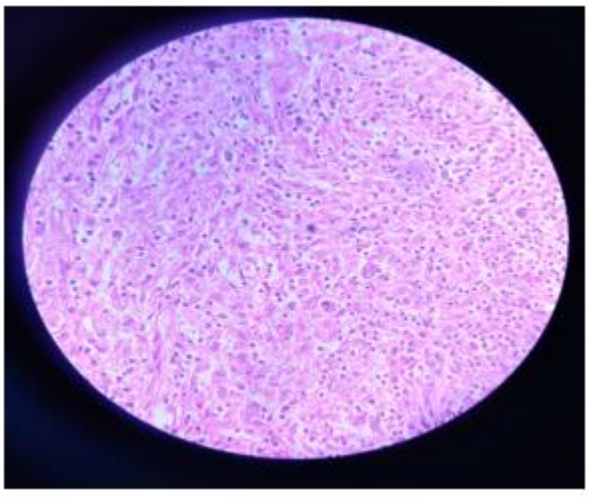
Case series

Here we present a case series of 5 young cases presenting to PG DEPARTMENT OF MEDICINE SCB MEDICAL COLLEGE AND HOSPITAL,CUTTACK, , one with lymphoma, two with SLE and two with infections who were later diagnosed as developing MAS during admission in the ward and improved with early intervention with high dose of steroid.

CASE 1

A 26 yr male presented with on and off fever with pain abdomen weight loss and generalised lymphadenopathy.fever was not associated with cough ,chills ,rash arthralgia with negative viral markers, dengue serology ,MP ict,scrub serology.He also had hepatosplenomegaly , pitting pedal edema and icterus.Investigation reports revealed pancytopenia ,high ferritin,high triglyceredemia increased transaminase and bone marrow study revealed haemophagocytic cell with HS SCORE 200 and LN biopsy finally revealed the underlying B- CELL LYMPHOMA.During the development of MAS the patient was having high grade fever and vitally very much unstable he was given inj. methylprednisolone and his ferritin and LDH level decreased and he was then started with chemotherapy for B CELL LYMPHOMA in dept of haematology.

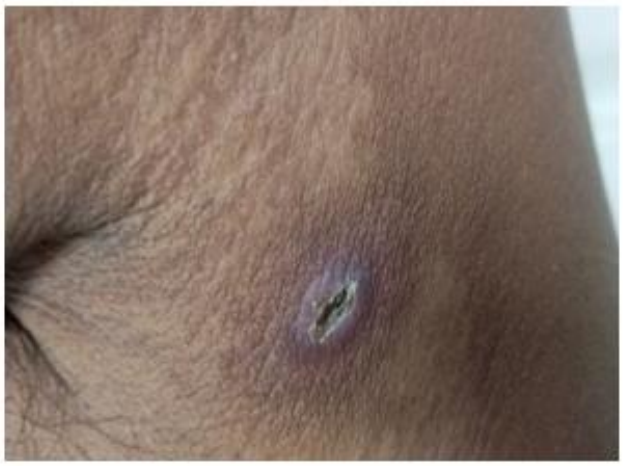


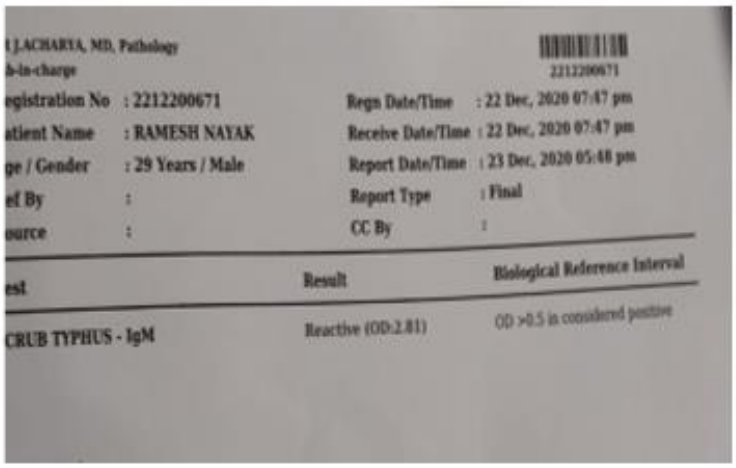


Picture 1-icteric tinge of b/l bulbar conjunctiva, picture 2- LN BIOPSY suggesting RS CELL

CASE 2

A 32 yrs male with history of visit to nearby jungle in last 15 days presented to us with fever,malaise and in shock.On thorough clinical examination revealed a painless eschar in left axillary area which was painless and almost unnoticed by him.His igM scrub typhus was found positive in high titer.After two days of admission he deteriorated with high ferritin, pancytopenia ,high triglyceride high LDH with bone marrow revealing haemophagocytic cells..He was on Doxycycline and azithromycin,and after addition of inj methylprednisolone for 2days he gradually revived and discharged afebrile on day 10 of admission.Hence this was a case of scrub typhus presented with MAS and early intervention with steroid saved him from this devastating outcome.





J LACHARYA, MD, Pathology
-In-charge

egistration No	: 2212200671	Regn Date/Time	: 22 Dec, 2020 07:47 pm
atient Name	: RAMESH NAYAK	Receive Date/Time	: 22 Dec, 2020 07:47 pm
ge / Gender	: 29 Years / Male	Report Date/Time	: 23 Dec, 2020 05:48 pm
ef By	:	Report Type	: Final
ource	:	CC By	:

est	Result	Biological Reference Interval
CRUB TYPHUS - IgM	Reactive (OD:2.81)	OD >0.5 is considered positive

Painless eschar on left axilla with high titer of scrub typhus igM

SUMMARIZING THE INVESTIGATION REPORTS OF ALL FOUR CASES:-

	CASE 1	CASE 2	CASE 3	CASE 4
Haemoglobin	6.1	8.0	7.4	4.9
Total leucocyte count	4000	3200	4000	2610
Total platelet count	13000	30000	39000	15000
ESR	20	16	30	45
S.ferritin	37700	2200	2600	3060
S.LDH	1615	1506	2450	1800
S.Triglyceride	271	300	396	338
LFT	Total-12.5,direct-8.4,sgot-108,sgpt-63,ALP402	Total-4.5, direct-2.8,sgot-66 sgpt-60,ALP-365	Total-5.2,direct-3.4,sgot200 sgpt165 ALP-346	Total-12.0 direct-8.6AST-679,ALT-139ALP-450
Hepatosplenomegaly	Yes	Yes	Yes	Yes

.

CASE 3

A 18 yr presented with high grade fever, cough, breathlessness, shock and decreased urination.Physical examination revealed course crepitationts in left lower lobe and hepatosplenomegaly.His sputum culture revealed kleibsiella pneumoniae sensitive to polymyxin.his other investigations revealed pancytopenia ,high ferritin hypertriglyceredemia High LDH bone marrow revealed haemophagocytic cells with HS score of 201.His s.ANA was negative ,so we thought of it as a case of Klebsiella pneumonia sepsis progressing to MAS ,Hence we started polymyxin along with addition of steroid and he gradually improved and discharged stable.

CASE 4

A 15yr female being a known case of SLE presented to us with weakness for 2months with fever ,black stool,shortness of breath ,arthralgia and later developed altered sensorium and 2 episodes of convulsion.Clincal examination revealed pallor and hepatosplenomegaly,and investigation reports revealed features of pancytopenia, high ferritin, hepatopathy and high triglyceridemia with very low Serum C3,C4 and normal CSF study with normal CT scan .Hence suspecting as a case of 'SLE WITH FLARE WITH MAS' we started on inj methylprednisolone 1gm per day for 5 days and she gradually improved and discharged with oral steroid and hydroxychloroquine with advice for follow up.

Discussion

According to 2016 EULAR classification [3], MAS Can be diagnosed when the following criteria are met like fever and ferritin >684ng/ml with >2 criteria

1.platelet count≤18100/ml

2 .AST>48u/l

3.Triglyceride>156 mg/dl

4.fibrinogen ≤360 mg/dl

And according to 2005 preliminary diagnostic guidelines for MAS, the diagnosis of MAS required the presence of at least two laboratory criteria or the presence of one laboratory criteria with one clinical criteria,

LABORATORY CRITERIA- decreased platelets≤ 262000/ml,AST>59u/l, WBC count ,<4.0×10 9 hypofibrinogen≤250 mg/dl

CLINICAL CRITERIA-central nervous system dysfunction, haemorrhage , hepatomegaly and hemophagocytosis in bone marrow in doubtful cases.

2004 HLH diagnostic criteria[4] if one of the two criteria is met.

A- molecular diagnosis of HLH,reported mutation of PRF1

B-five out of eight criterias

1.persistent fever.

2.hepatospleenomegaly

3.cytopenias,bicytopenia or pancytopenia

4.hypertriglyceridemia> 265mg/dl

5. Hypofibrinogenemia

6.ferritin≥500ng/ml

7.soluble CD 25≥2400UNITS

8. low or absent NK cell activity.

Infectious causes triggering MAS

Viral: DNA-EBV,CMV,HHV 6,HSV 1,HSV 2,HHV; RNA-Hep A, Hep C, measles, rubella, HTLV; Zoonotic virus-RNA-dengue(flavivirus), SARS, hanta virus, influenza A virus(H5N1)

Bacterial: Mycoplasma pneumoniae, salmonella typhi, Klebsiella pneumoniae, mycobacterium tuberculosis

Zoonotic bacteria: rickettsiae, Oientia tsutsugamushi, coxiella, Bartonella, salmonella

Protozoal. Leishmaniasis, Plasmodium falciparum, Plasmodium Vivax

Fungal. Aspergillosis, Pneumocystis jirovecii, cryptococcus neoformans

Treatment options for MAS

- Treatment of underlying cause like infection along with high dose of corticosteroids and cyclophosphamide.

- ATG(antiyhymocyte globulin) and IVIG is not given in infection associated MAS but may be a treatment choice of option in SLE, AOSD probable MAS
- in MAS with Systemic juvenile Idiopathic Arthritis(SJIA)[5] IL-1 receptor antagonist Anakinra was shown to be highly effective but it may convert the subtle MAS to overt MAS.
- IL-6 blockade via anti IL-6 receptor monoclonal antibody (toclizumab) also has been proven helpful in JIA.

Conclusion

All the four cases admitted for fever with some other underlying cause like SLE ,LYMPHOMA , developed fulminant cytokine storm leading to MODS ,,but early intervention with high dose steroid could reduce the mortality.Ferritin is an useful marker .28 day mortality for patients having ferritin >4420 ng/ml was 66.7%,and it's level decreases within 48 hrs points to good prognosis.A devastating situation like Mas exists in critically ill patients in sepsis

A new novel laboratory marker of MAS is soluble CD163.Its expression is restricted to macrophages monocyte lineage unlike ferritin and soluble CD25(IL 2 receptor alpha chain)which can be produced by liver, spleen etc.Another novel marker is follistatin related protein 1 which is elevated along with ferritin andCD25 in MAS related to JIA.Ferritin to ESR ratio-As ferritin rises due to inflammation in MAS and ESR tends to drop due to hypofibinogen due to coagulopathy,a,simpler ratio of ferritin to ESR may Be a simple valuable tool in diagnosing MAS in febrile hospitalized patients which is quite evident in our case series.Ferritin measurement plays an important role in both diagnosis and therapeutic prognosis.[6]

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none

Declarations:

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ethics approvals and consent to participate

Ethics approvals and consent to participate: consents were obtained from the patients after ensuring confidentiality of their information

Conflicts of interest:

the authors declare that there is no conflict of interest

References

[1]. Preeti Sharma, Shailza Shreshtha, Pradeep Kumar and Rachna Sharma, A Review on Macrophage Activation Syndrome, J Pure Appl Microbiol., 2019; 13(1):183-191 doi: 10.22207/JPAM.13.1.19

[2]. Schram AM ,Comstock P,CampoM,Gorovets D MullayA,Bodio K et al.Haemophagocytic lymphocytosis in adult:amulticentercase series over 7yrs.*Br J Haematolo.(2016)172:412-9.doi:10.1111/bjh.13837.*

[3]. Ravelli A Minoia F ,DaviS,et al.2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis:a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International TTriasOrganisationCollaberation.ArthritisRheumatol. 2016;68(3): 566-576

[4]. Henter JI ,Horne A Arico M ,et al.HLH-2004:diagnostic and therapeutic guidelines for hemophagocyticlymphohistiocytosis.Pediatric Blood Cancer.2007;48(2):124-131

[5]. Schulert GS ,Grom Aa ,Macrophage activation syndrome and cytokine-directed therapy;BestPract Res Clin Rheumatol.2014;28(2):277-92

[6]. Vilaiyaku S ,Sirachainan N ,Wanitkun S ,Pirojsakul K ,Vaewpanich J. Recurentmacrohage activation syndrome as primary manifestation in sysemic lupus erythmatous and benefits of serial ferritin measurement:a Case based review.ClinicalRheumatol.2013;32(6):899-904

[7]. Ravelli A et al.Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis.J Pediatr.2005;146(5):598-604

[8]. Davi S et al;Paediatric Rheumatology international trials organisation;childhoodArhritis Rheumatology Research Alliance ; paediatric Rheumatologycollaberative study group;Arthritis Rheumatol.2014;66(10):2871-80