Original Research Paper

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General Medicine

CASE SERIES : HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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ABSTRACT Hemophagocytic lymphohistiocytosis is an aggressive and life threatening syndrome. It is consequence of severe uncontrolled hyperinflammatory reaction that in most cases is triggered by infectious agent. It may be inherited (primary) or acquired (secondary). It is associated with high mortality if not treated early. We describe a case series of three pateints with secondary HLH,where all 3 pateints presented with different clinical symptoms and were diagnosed to be HLH based on standard approved HLH criteria.

KEYWORDS :

INTRODUCTION:

HLH is life threatening hyperinflammatory syndrome characterised by an unremitting activation of CD 8+T lymphocytes and macrophages that induce cytokine mediated BM suppression and features of intense phagocytosis in BM and liver. It may be inherited (primary) or acquired (secondary). It is associated with high mortality if not treated early.

The diagnosis is established by HLH diagnostic criteria 2009. Molecular confirmation (pathogenic mutations in PRF1,MUNC18-2,RAB27A,BIRC4 etc)
Five or more of following clinical finding

Fever >38.5 Celsius , Hepatospleenomegaly,Cytopenia impacting at least two blood cell lines (hemoglobin <9gm/l, Platelet count <1lakh, absolute neutrophil count <1000b/l, Ferritin >500ug/dl, Hemophagocytosis in bone marrow biopsy, Elevated CD25Low /absent NK cells activity Hypertriglyceridemia ,Hyperfibrinogenemia, Hyponatremia.

Case 1 : HLH associated with Spotted Fever Group Rickettsia

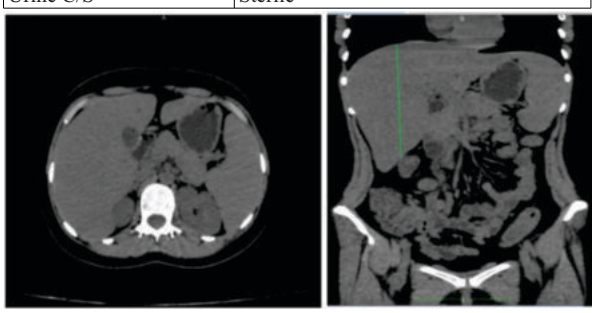
26 year old female, housewife, recent interstate travel, not k/c/o any comorbidities was admitted with complaints of fever, loose motions, abdominal pain, vomiting ,giddiness and generalised weakness since 2 days, and decreased urine output and breathlessness since 1day. Past history and family history were not significant. Personal history married and has one child ,patient had no addiction. Patient was febrile with temperature of 101°F, pulse-140/min, BP 60systolic ,RR-34/min, with acidotic breathing, spo2-90%RA. No pallor, icterus, clubbing, cyanosis, edema and lymphadenopathy.

CVS-S1S2, Tachycardia +,RS-B/L NVBS,PA-minimal epigastric tenderness and hepatomegaly, CNS-conscious lethargic, intermittently following oral commands. Ultrasound/CT abdomen Liver -18cm in size and normal echotexture. Spleen -11.8cm in size and echotexture.Both kidneys normal in size and echotexture .Para aortic few subcentimetric lymph nodes.Circumferential wall thickening involving terminal ileum (8mm), ileocaecal junction ,caecum(10mm) and asc3nding colon (11mm).Raised echogenicity is noted in right iliac fossa.Multiple enlarged mesenteric lymph nodes are noted in the right ilac fossa,largest measuring 2cm some showing central fatty hilum within.Imaging features are likely to represent infective / inflammatory etiology. Bone Marrow Aspiration increase in the number of macrophages and showing hemophagocytosis. Patient was started on iv doxycyline and meropenem, was on single inotropes, stat dose of steroids was given. Over the day patient shock worsend and was on triple inotropes and then scummbed within 24 hours of admission due to shock.

Parameters	Value
Haemoglobin	8g/dl
TLC	5960
DC	56/39.1/3.63/0.14/0.17
MCV	63.7fL
MCH	20pg
MCHC	31.4g/dl
RBC	5.5million/cu.mm
Platelet count	33,000

LFT -Bilirubin	Wnl
SGOT/SGPT/ALP	Increased (579/115/118)
Hypoalbuminemia	2.5g/dl
RFT	Deranged (BU-83.46%, SC-4.7mg%)
Hyponatremia	129mmol/L
Amylase/lipase	Increased (512/692U/L)
Lipid profile	TG-882mg%
Ferritin	>40,000ng/ml
Plasma D- Dimer	12626ng/ml
ABG	pH-7.143 Pco2-8.8mmhg Hco3-2.9mmo/ Po2-116mmhg

Serology	
Dengue NS1Ag	Negative
IgM lepto	Negative
HIV/HCV/HBsAg	Negative
Weil Felix	Proteus Antigen OX 19- Positive (1:320) OX 2-Positive (1:320) OX K-Negative
Blood C/S	Sterile
Urine C/S	Sterile



Case report 2 Hemophagocytic lymphohistiocytosis associated with Dengue

14 year old male student, not k/c/o any comorbidities was admitted with complains of fever associated with headache since 15 days,vomiting and rash since 5 days and abdominal pain since 1 day.Patient was tested postive for Dengue NS1 and IgM on 3rd day of fever.

Clinical examination

Patient was febrile with temperature of 100°F, Pulse -92/min, BP-120/70 mmhg, No postural drop, RR-16/min.Icterus +, No pallor, no clubbing, no cyanosis, no Lymphadenopathy, No edema.RS- B/L clear, CVS- No murmur, PA- liver palpable 3cm below coastal margin

and Spleen just palpable, tenderness in B/L Hypochondruim and epigastric region.

CNS- conscious oriented, no deficit. Abdominal USG Liver-20cm in size and normal echotexture. Spleen-14cm in size and normal echotexture. Right and left kidney normal in size and echotexture. Free fluid in perihepatic, in between bowel loops and in pelvis.Bone Marrow Aspiration-. Megakaryocytes are increased in number with immature nuclei. Marrow macrophages are increased in number and show evidence of hemophagocytosis.

The patient was managed with antibiotic, intravenous fluids and steroids.Patient improved and was discharged.

Parameters	Value
Haemoglobin	12.1
TLC	9360
DC	47/44/04/05
MCV	88.6fl
MCH	30.6pg
MCHC	34.6gm/dl
RBC	3.95million/cu.mm
Platelet count	80,000
Peripheral smear	Normocytic Normochromic

LFT-Bilirubin	Increase
SGOT/SGPT/ALP	Increased (234/234/349)
RFT	WnL
Lipid profiles	TG-177mg/dl
Ferritin	5816.8ng/mlT

Dengue NS1 Antigen IgM	Positive Positive
IgM Lepto	Negative
Malaria	Negative

Case Report 3 Hemophagocytic lymphohistiocytosis associated with sepsis

44 year old female k/c/o psychiatric illness sice 6 years had presented with complaints of generalised weakness in form of easy fatigability , decreased appetite since 1 month, alterd sensorium since 15 day and fever on and off since 1 week.

Clinical examination Patient was febrile with temperature 100 F, Pulse-120 min, BP- 90/60mmhg. Icterus +, No pallor, no clubbing, no cyanosis, no Lymphadenopathy, No edema. Pateint appeared dehydrated and cachexic. RS -B/L conducted sounds, CVS- S1S2, with no murmur.,P/A - soft non tender, no organomegaly.CNS- Conscious confused, tone increased in all 4 limbs, reflex -Normal, plantar - flexor.

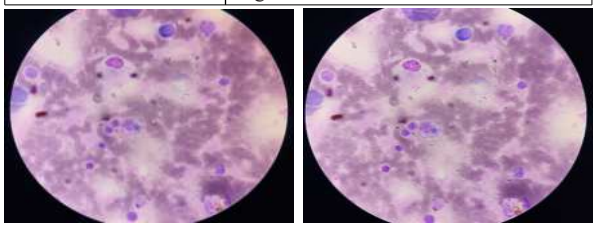
Abdominal USG Liver -15.4 cm with fatty echotexture and Spleen 12.3 cm with normal echotexture.Both kidneys normal in size and echotexture. CT brain normal.

Blood C/S- growth of coagulase negative staphylococcus species. BMA report -increase in number of macrophages with evidence of hemophagocytosis. Patient was started on iv antibiotic depending on sensitivity of blood culture , and IV fluids and steriods however during stay patient developed septic shock and succumbed.

Parameters	Value
Haemoglobin	6.5 gm%
TLC	14,200
DC	73/41/01/03
MCV	76.7fl
MCH	28.9pg
MCHC	37.6gm/dl
RBC	2.26 million /cumm
Platelet count	58,000

LFT-Bilirubin	Wnl
SGOT/SGPT/ALP	600/206
RFT	Wnl
Lipid profile	TG-161mg%
LDH	2519U/L
Ferritin	>40000 ng/ml
Procalcitonin	2.77ng/ml

Dengue NS1 IgM	Positive Positive
IgM Lepto	Negative
Malaria	Negative



Bone marrow smear showing macrophage engulfing polymorphs

DISCUSSION

We describe a case series of three pateints with secondary HLH,where all 3 pateints presented with different clinical symptoms where fever pancytopenia and hyperferritinemia were common features and were diagnosed to be HLH based on standard approved HLH criteria. Of which two cases were associated with Dengue of which one had secondary superadded infection causing sepsis and 1 with scrub typhus infection as secondary cause , where in only 1 of 3 pateint survived.

Case specific clinical features

Case	Sex	Age (Yr)	Comorbidities	Fever	Rash	CNS	Hepatomegaly	Splenomegaly	Cause
1	F	26	None	Y	No	No	Y	Y	Scrub typhus
2	M	14	None	Y	Y	No	Y	Y	Dengue
3	F	44	None	Y	No	Y	No	No	Dengue + sepsis

Case specific morbidity and outcome

Case	Hb	TC	Platelet	Ferritin (ng/ml)	TG (mg./.)	ALT	AST	BMA	Outcome
1	8	5960	33,000	>40,000	882	115	579	Positive	Expired
2	12.1	9360	80,000	5816	177	234	234	Positive	Survived
3	6.5	14,200	58,000	>40,000	161	161	600	Positive	Expired

Several studies have reported that elevated Ferritin levels and fever are the most common finding in pateints with HLH.,these findings were present in all of 3 pateints.

CONCLUSION

Concluding that physicians must possess a high index of suspicion for diagnosing HLH as diverse range of symptoms and signs may be observed in case of secondary HLH. Early diagnosis and intervention play crucial role in improvement of pateints outcome. A delay in diagnosis and management can lead to fatal outcomes. The management of such cases necessitates expeditious treatment of underlying disease in conjunction with ameliorate of cytokine storm with immunosuppressive agents. Once underlying cause of cytokine storm is treated lethal progression of diseases to end.

REFERENCES

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