# CASE 4

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**Under guidance of**

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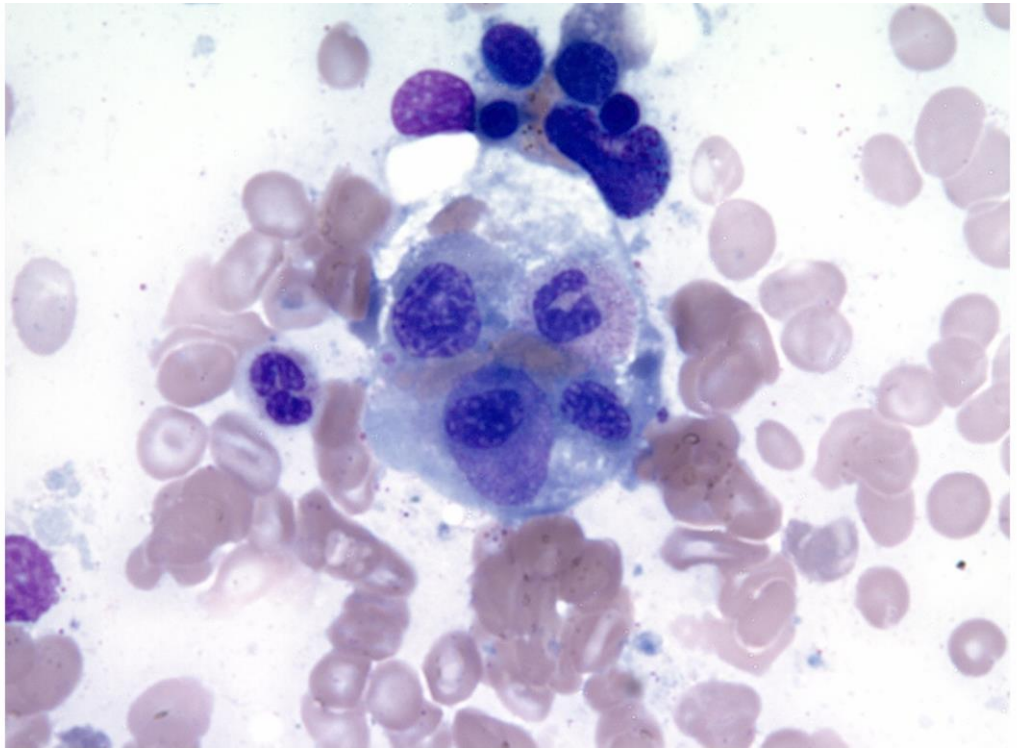
**Dr. Shiji Chalipat ( Pediatric Neurologist)**



# Chief complaints

-Eight-month-old male child
-Aundh, Pune
-Non consanguineous marriage
-First in birth order
. Cough - 1 month
. Fever - 1 month
. Blood in stools - one day
. Blood in vomitus - one day
This patient was admitted in our hospital 5 months ago

# History of presenting illness

- Patient was apparently asymptomatic **1 month** back when he developed **Fever** and cough for which he was taken to outside hospital and was received symptomatic medication
- Fever- **high grade**, not associated with chills and rigors, on and off, relieved on medication since 1 month

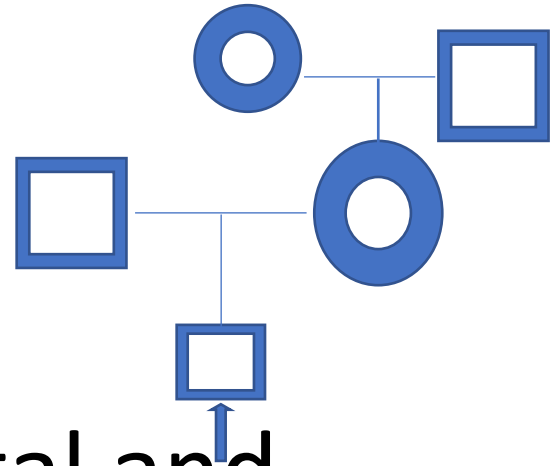
# History of presenting illness

- Complaints of **blood in stools**, 6 episodes/day, greenish coloured stools, associated with **frank blood and clots**
- Complaints of **Vomitings**, non projectile, non bilious,associated with food particles, 3-4 episodes/day since one day. Last episode was **blood tinged vomitus.**
- No history of rashes, seizures, altered sensorium and feeding abnormalities

# Past history

- No history of previous hospital admissions with similar complaints
- No history of previous blood transfusions

- Family history – No significant family history present.



- No Significant antenatal history, Natal and postnatal history
- Completely immunised according to age.
- Developmental and diet history are normal

# ANTHRAPOMETRY

| *PARAMETER* | *ACTUAL* | *DESIRED* | CENTILE |
|---|---|---|---|
| Weight | **7.5 kg** | 8.0 kg | 3rd and 50th |
| Length | **69cms** | 70cms | 3rd and 50th |
| Head circumference | **43 cms** | 44cms | 3rd and 50th |

- *Interpretation: Normal*

# Examination

## GENERAL EXAMINATION

**Child was conscious and irritable**

**Vitals on admission:**

- Temperature : 100F
- Pulse rate : 174/min( **Tachycardia +)**
- Respiratory rate : 34/ min
- Peripheral pulses : Feeble
- Capillary refill time 4 seconds( **Delayed)**
- SpO2: 91% on room air
- Bp -78/32 mmhg(at 5th Centile)(**Hypotension)**

- **Above clinical features suggest that patient was in compensated Hypotensive shock.**

# GENERAL EXAMINATION

Pallor present(Moderate)

No icterus

No cyanosis

No oedema

No lymphadenopathy

# SYSTEMIC EXAMINATION

•**Per abdomen examination :**

**Inspection:** flat, central umbilicus, no visible veins or scars seen**.**

**Palpation:** soft, non tender

**Hepatomegaly - liver span 9cms (palpable 4cms below right costal margin),firm in consistency non tender**

**Splenomegaly of 3cms(Mild) present below left costal margin, non tender and smooth margins**

**Percussion:** Palpatory findings are confirmed

**Auscultation:**Bowel sounds are present.

Other systems are normal

- **SEPTICAEMIC SHOCK**

Child was shifted to PICU and Septic profile was sent

# Investigations

- **Hb- 7.7 g/dl**
- **TLC-20,500/ul**
- **Platelets-44,000/ul**
- PVC- 22.4%
- N/L- 46%/34%
- RBC- 3.5 million
- MCV- 63.8fL
- MCH-21.8pgms
- MCHC-34.2g/dl

- Total.Bilurubin-2.99 mg/dl
- Direct- 2.21 mg/dl
- **AST-18261 U/lit**
- **ALT-7834 U/lit**
- **ALP-337 U/lit**
- **PT-40 sec**
- **INR-4.11**
- **APTT-75sec**

- **Covid IgG- Negative**
- **CRP- Negative**

- **2D-Echo- Normal**

- **2D-ECHO- Normal heart study**

- **Dengue NS1 Antigen- Positive**

- **2D-Echo- Normal**

- **DENGUE SHOCK SYNDROME WITH HEPATITIS**

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- **DENGUE SHOCK SYNDROME WITH HEPATITIS**

- After initial stabilization, fluid resuscitation and supportive treatment were started.Considering the symptomatic treatment received outside and severely deranged LFTs, IV N-Acetyl cystine was started along with Intravenous antibiotics.

- Due to less clinical improvement of the patient, and prolonged fever spikes after 24 hours of admission, markers of acute inflammation was sent.

- **Fibrinogen- 75.6mg/dl**
- **Ferritin- >40000 ng/dl**
- **Triglycerides-278mg/dl**

- **Dengue shock syndrome with secondary macrophage activating syndrome/Hemophagocytic lymphohistiocytosis was suspected**

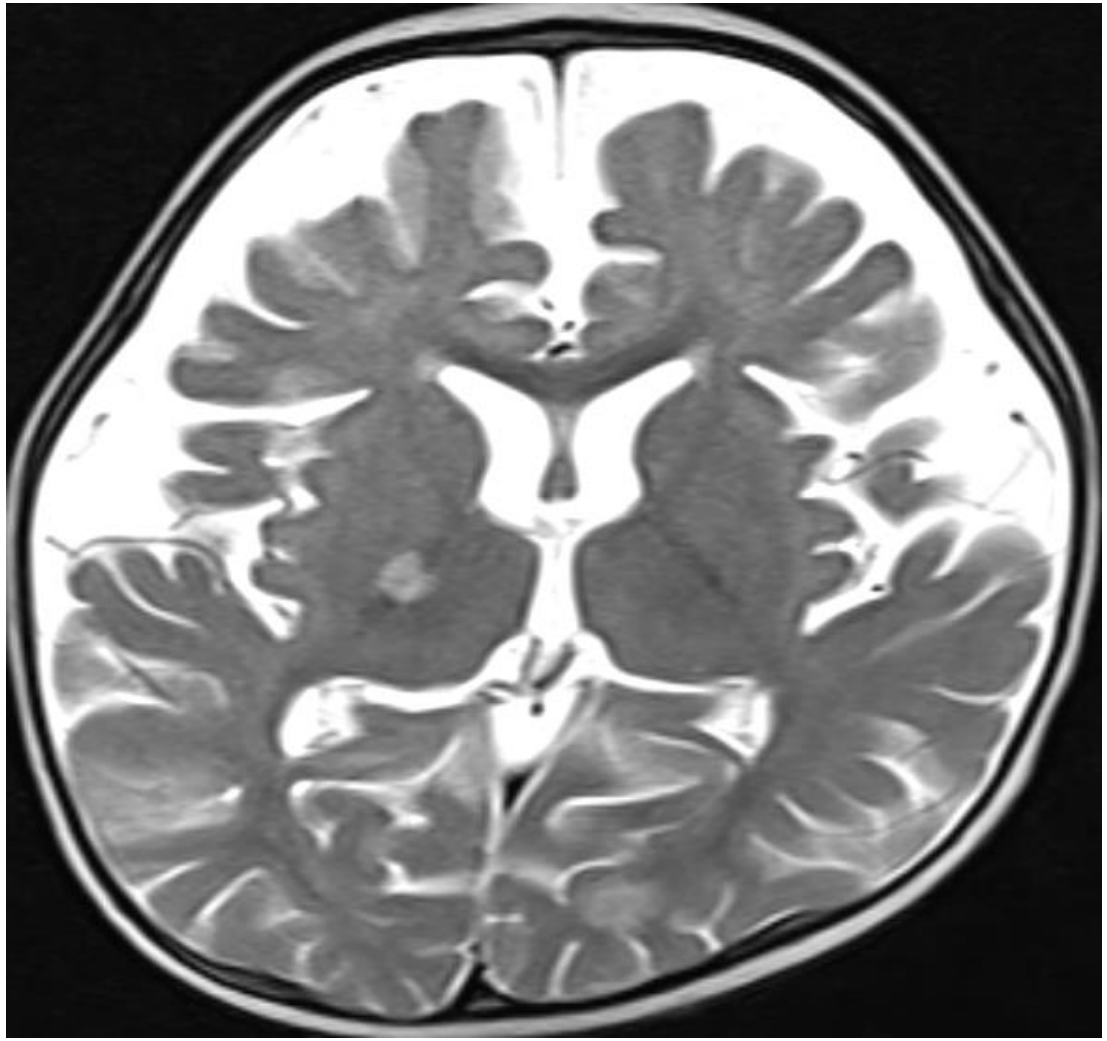
- After pediatric hematoncologist advice, DEXAMETHASONE was started at 10mg/m2 in view of Dengue triggered HLH.

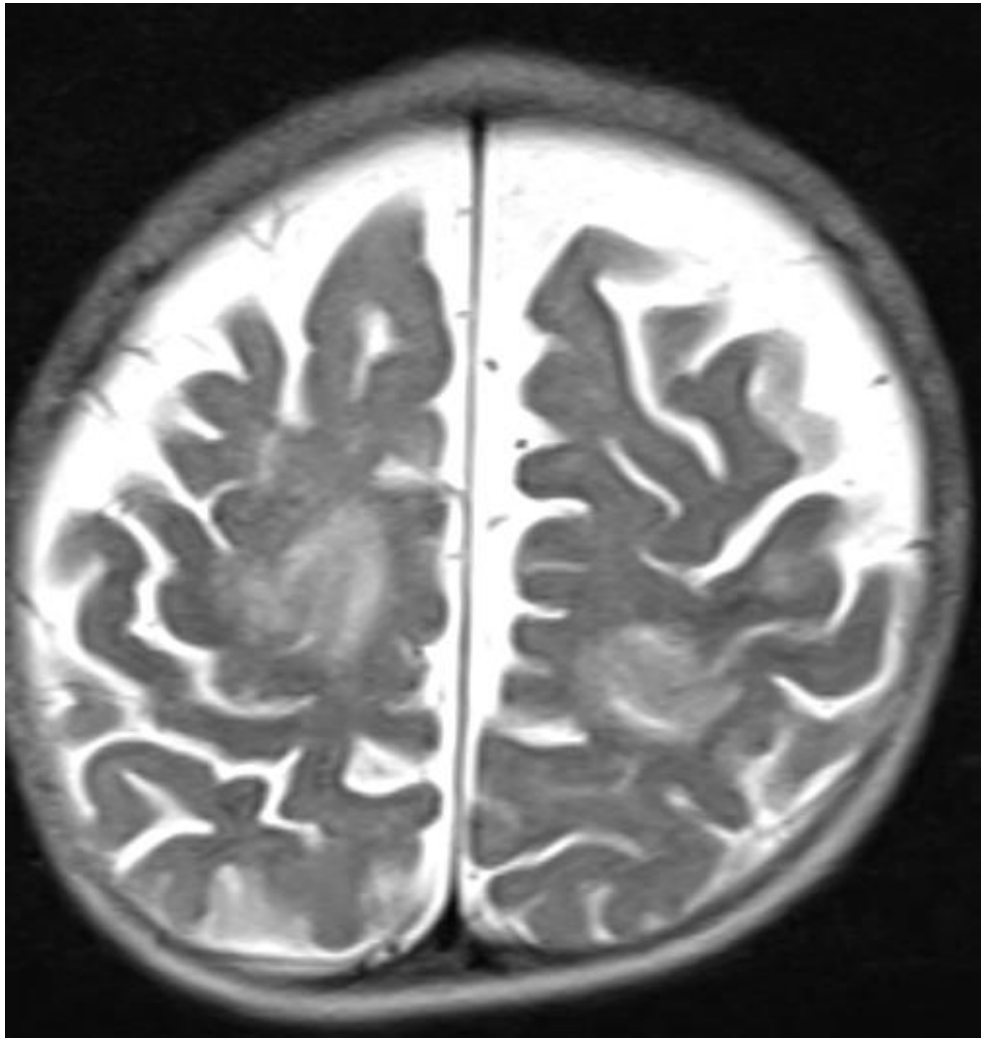
- A repeat hemogram showed an improvement in the platelet count and general condition of the child. The child became afebrile after 48 hours of dexamethasone and the blood indices improved with rising platelet count and total leukocytes. Hence, steroids with other supportive treatments were continued. The serum ferritin improved to 8125 ng/ml on Day 6 of dexamethasone.
- On D7 of admission, child was shifted out to the ward with off ionotropic and off IV fluid support.

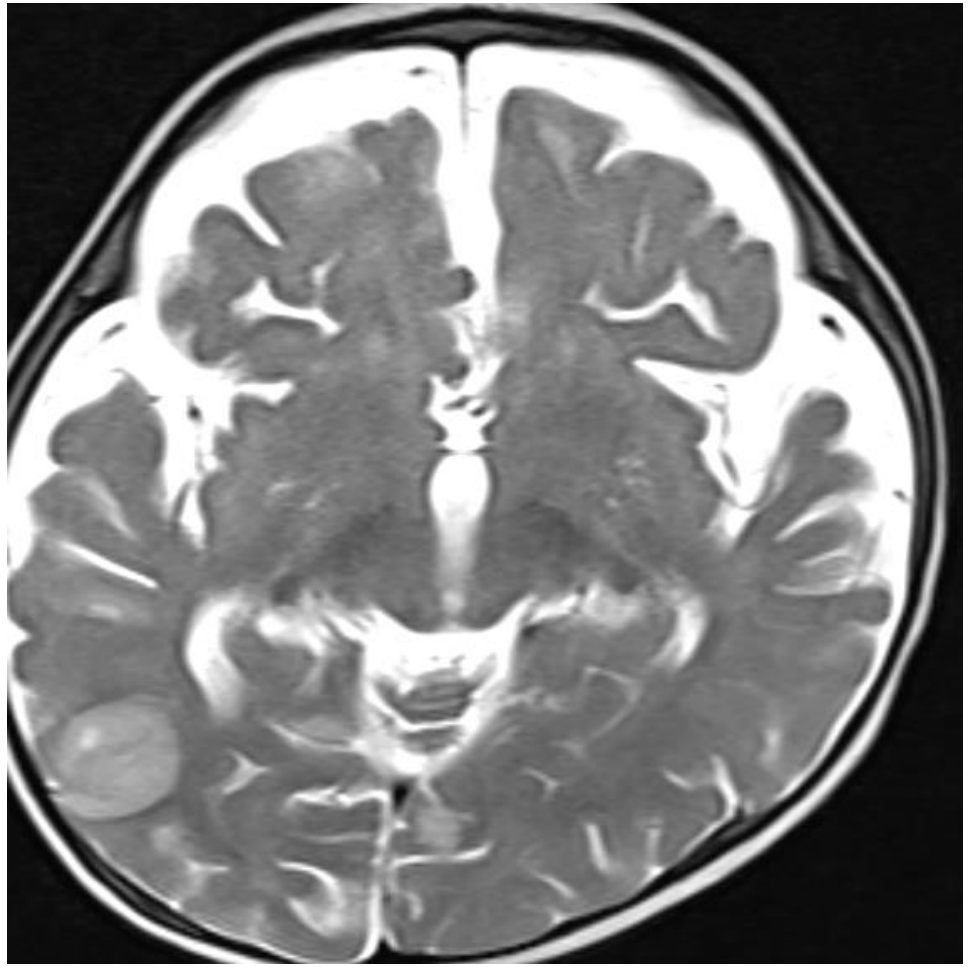
# Serial investigations

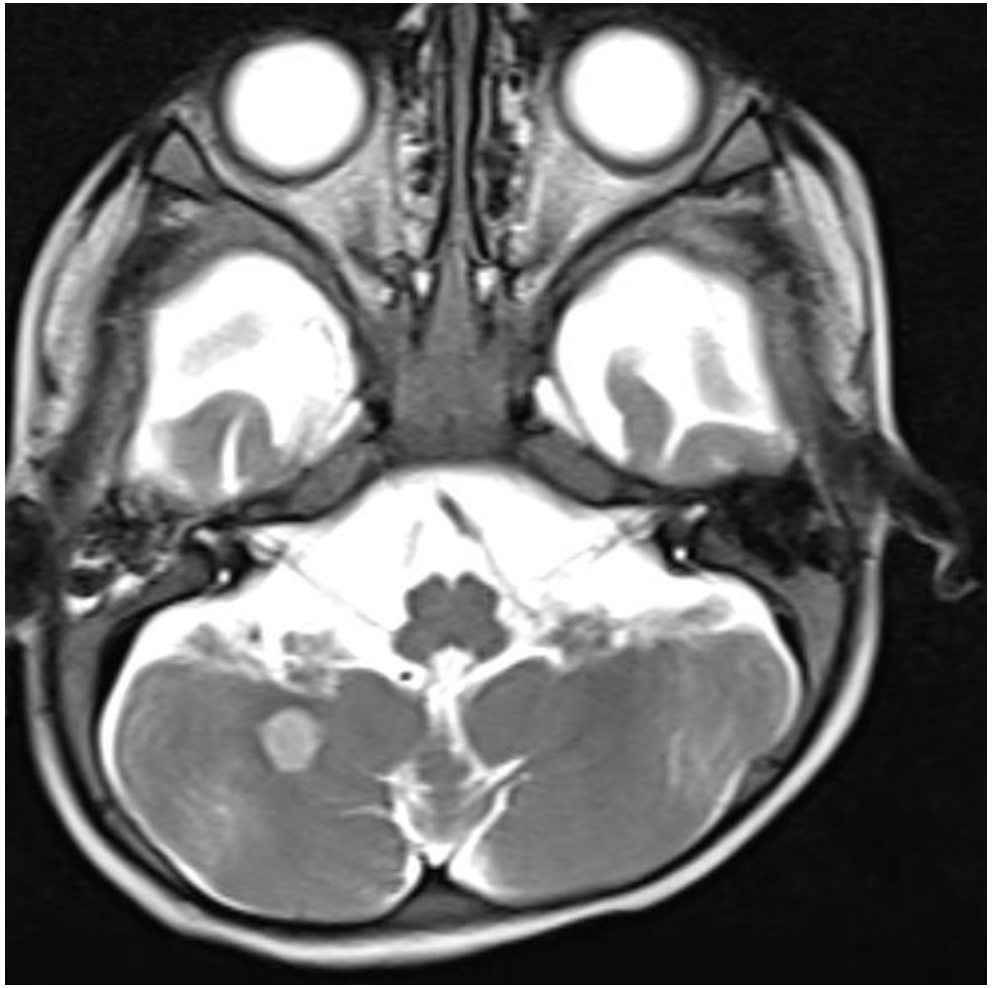
| DAY | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haemoglobin (g/dl) (Reference Range - 11.14-14.1g/dl) | 7.7 | 11.2 | 9.8 | 8.8 | 9.8 | 12 | 8.5 | 7.9 | 5.4 | 11.8 | 10.8 | 9.5 |
| Total Leukocyte Count ( per microliter) (Reference Range- 6000-11,000/microliter) | 20500 | 14300 | 8600 | 9300 | 8700 | 13300 | 12600 | 11100 | 7100 | 9300 | 8200 | 3400 |
| Differential leukocyte count (Neutrophil/Lymphocyte/Eosinophil) (%) Reference Range - Neutrophil (1500-8500/microliter), Lymphocytes (4000-10,000 /microliter), Eosinophils (50-700/microliter) | 46/34/20 | 51/34 | 46/41 | 47/40 | 56/29 | 76/15 | 77/15/8 | 79/15 | 66/25 | 76/16 | 79/18 | 70/30 |
| Platelets (per microliter) (Reference Range- 1,50,000-4,10,000/microliter) | 44000 | 78000 | 61000 | 62000 | 82000 | 42000 | 90000 | 78000 | 32000 | 49000 | 40000 | 14000 |
| Packed cell volume (%) (Reference Range -33.0-40.0%) | 22.4 | 33.4 | 28.1 | 26 | 29.3 | 36.1 | 27.1 | 24.7 | 17 | 36.2 | 33.4 | 29.4 |
| Aspartate transaminase (Units/Liter) (Reference Range 0-11 months-Not established, 1-13 years - 8 to 60 U/liter) | 18261 | 8404 | 7132 | 3134 | 2067 | 1374 | 549 |  | 231 | 186 |  | 183 |
| Alanine transaminase (Units/Liter) (Reference Range- 0 to 11 months-Not Established, 1-13 years - 8 to 60 U/Liter) | 7834 | 4113 | 4266 | 2680 | 2294 | 1863 | 1236 |  | 698 | 625 |  | 512 |
| Lactate dehydrogenase (Units/Liter) (Reference Range - 31 days to 11 months -180-435 U/Liter) | 9116 | 4921 |  |  |  |  |  |  |  |  |  |  |
| Ferritin (Nanogram/ml) (Reference Range - 21.81 to 274.66 ng/ml) | >40000 | 37964 | 23169 |  | 8125 |  |  |  | 3324 |  |  |  |

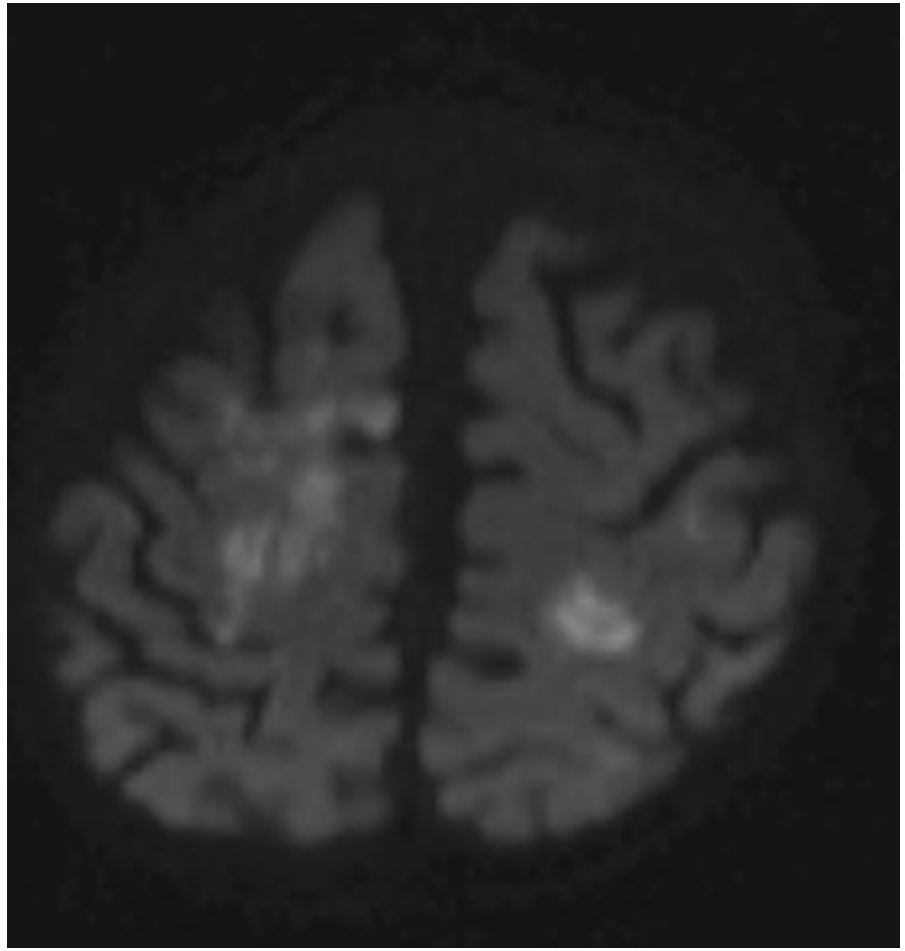
- On Day 9 of dexamethasone, the child had a rebound high grade fever spikes followed by right-sided focal status epilepticus.
- As per Pediatric neurologist advice,he was loaded with Anti epileptic medications and stabilised.
- Later he had right sided hemiparesis with right sided UMN facial nerve palsy and altered sensorium.
- Patient was shifted to PICU and after initial stabilisation; Neuroimaging(MRI) study was done.

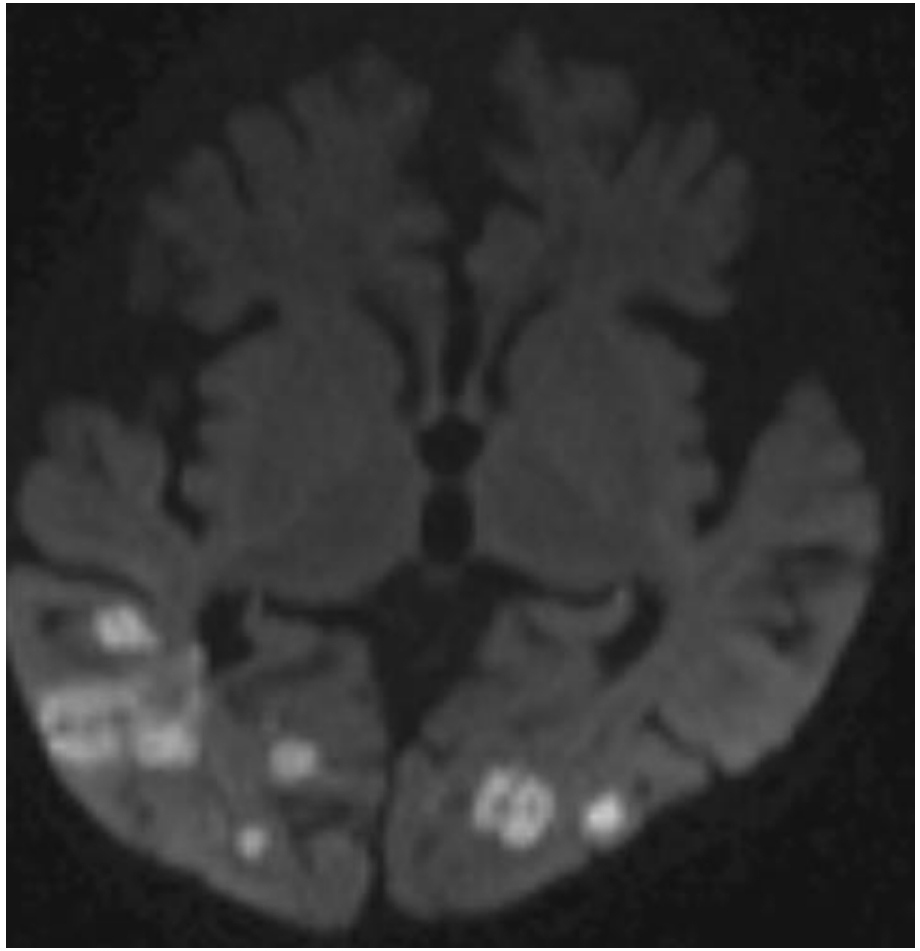


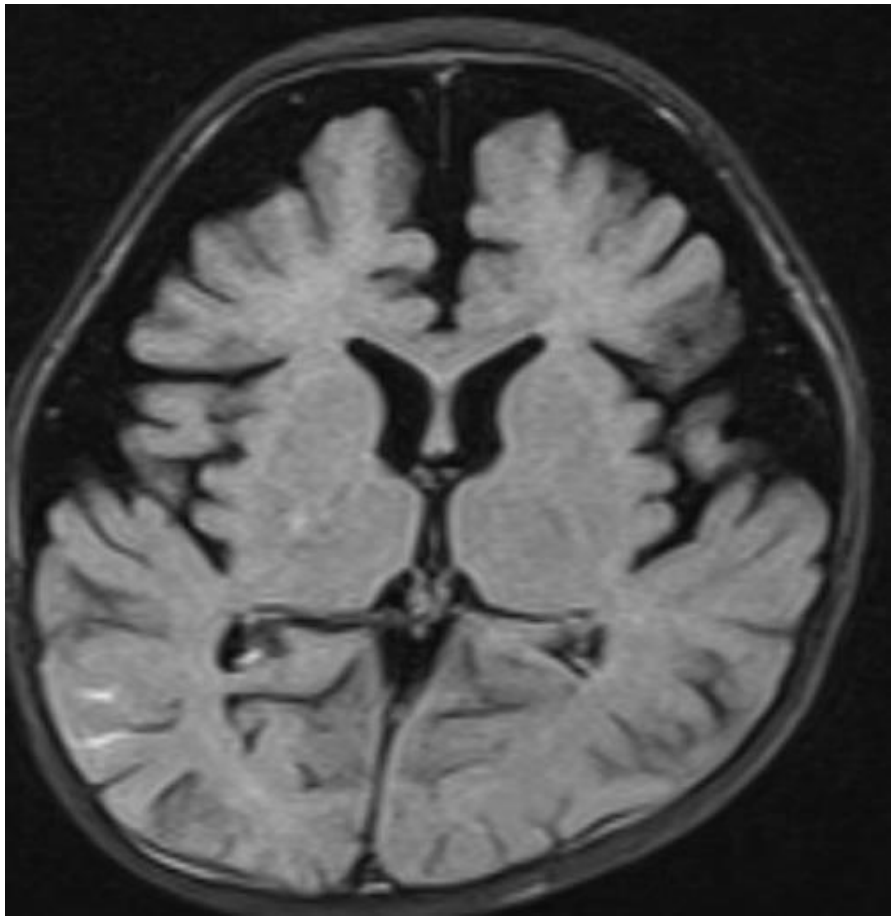


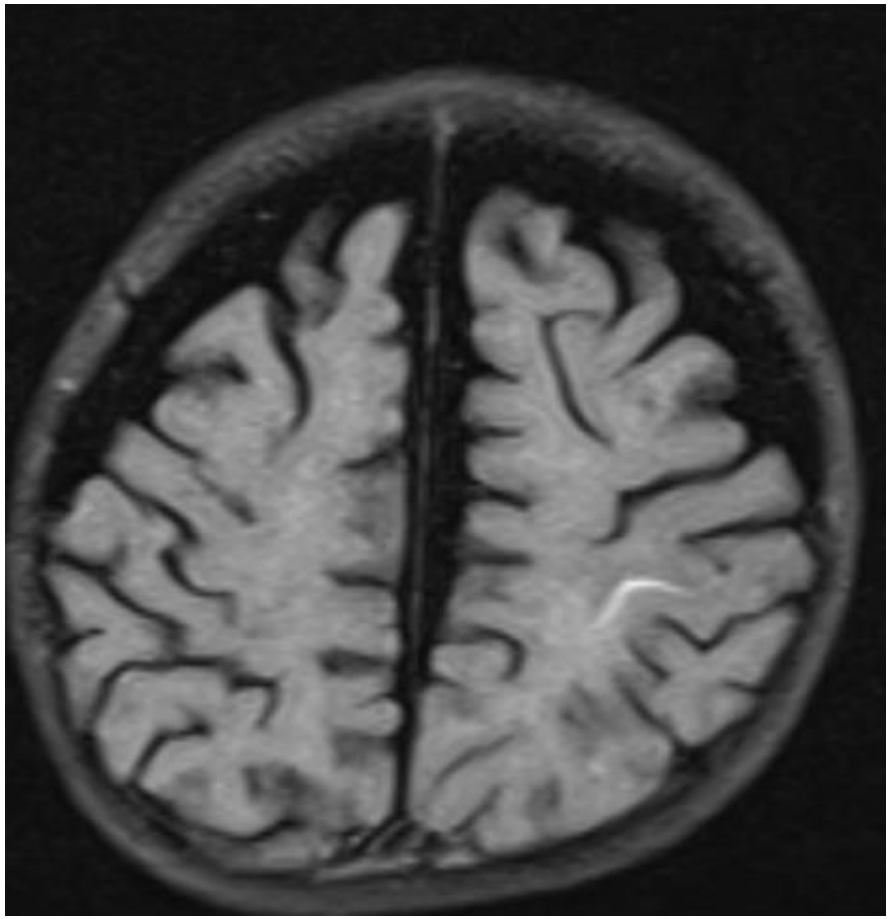












**Multiple well defined T2/FLAIR hyperintensities showing diffusion restriction with low ADC values are noted in right gangliocapsular region, bilateral temporal , occipital, bilateral frontal parietal lobes and bilateral cerebellum hemispheres -could be emboli infarcts**

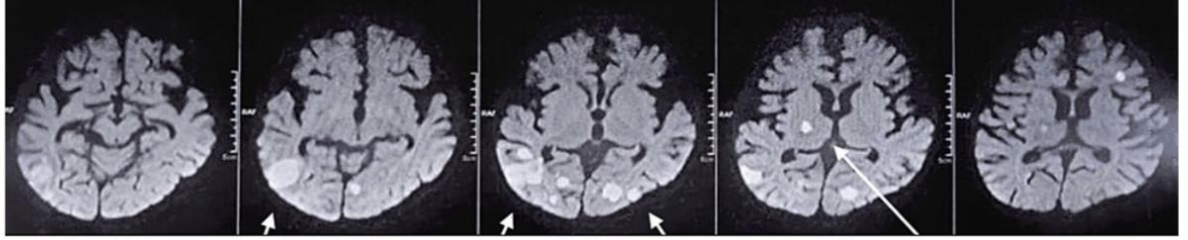
**FLAIR hyperintensities along sulcal spaces with leptomeningeal enhancement on contrast is noted in bilateral parietal lobes. It shows blooming on GRE**

**Benign_enlargement of sub arachnoid space in bilateral frontal lobes is noted**

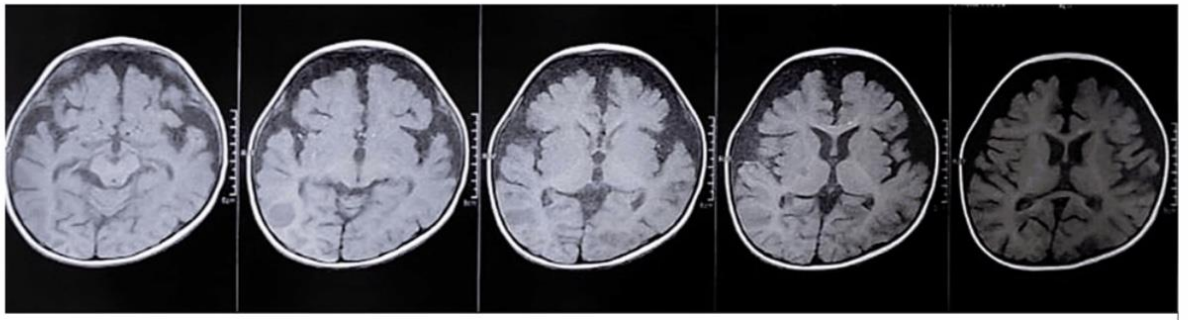
# MRI findings

- **Magnetic resonance imaging (MRI) brain revealed areas of diffusion-restricted embolic infarcts with diffuse leptomeningeal enhancement and mild cerebral edema**

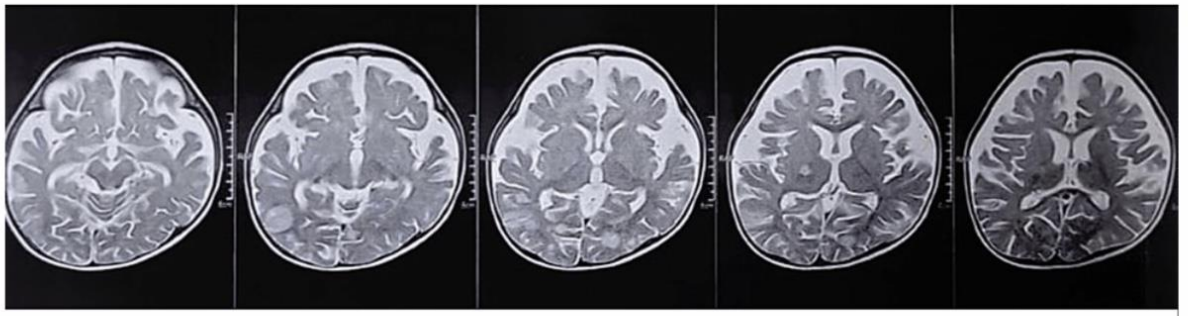
**CNS HLH was suspected and CSF routine microscopy was sent**



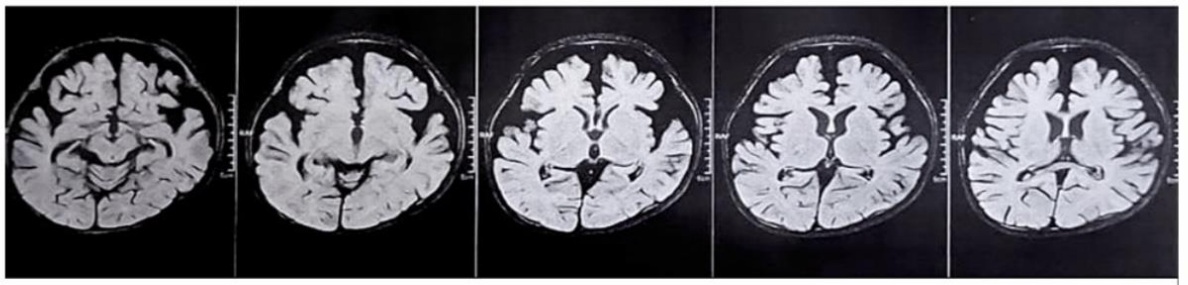
MRI BRAIN DIFFUSION RESTRICTION SUGGESTIVE OF EMBOLIC INFARCTS



MRI BRAIN T1



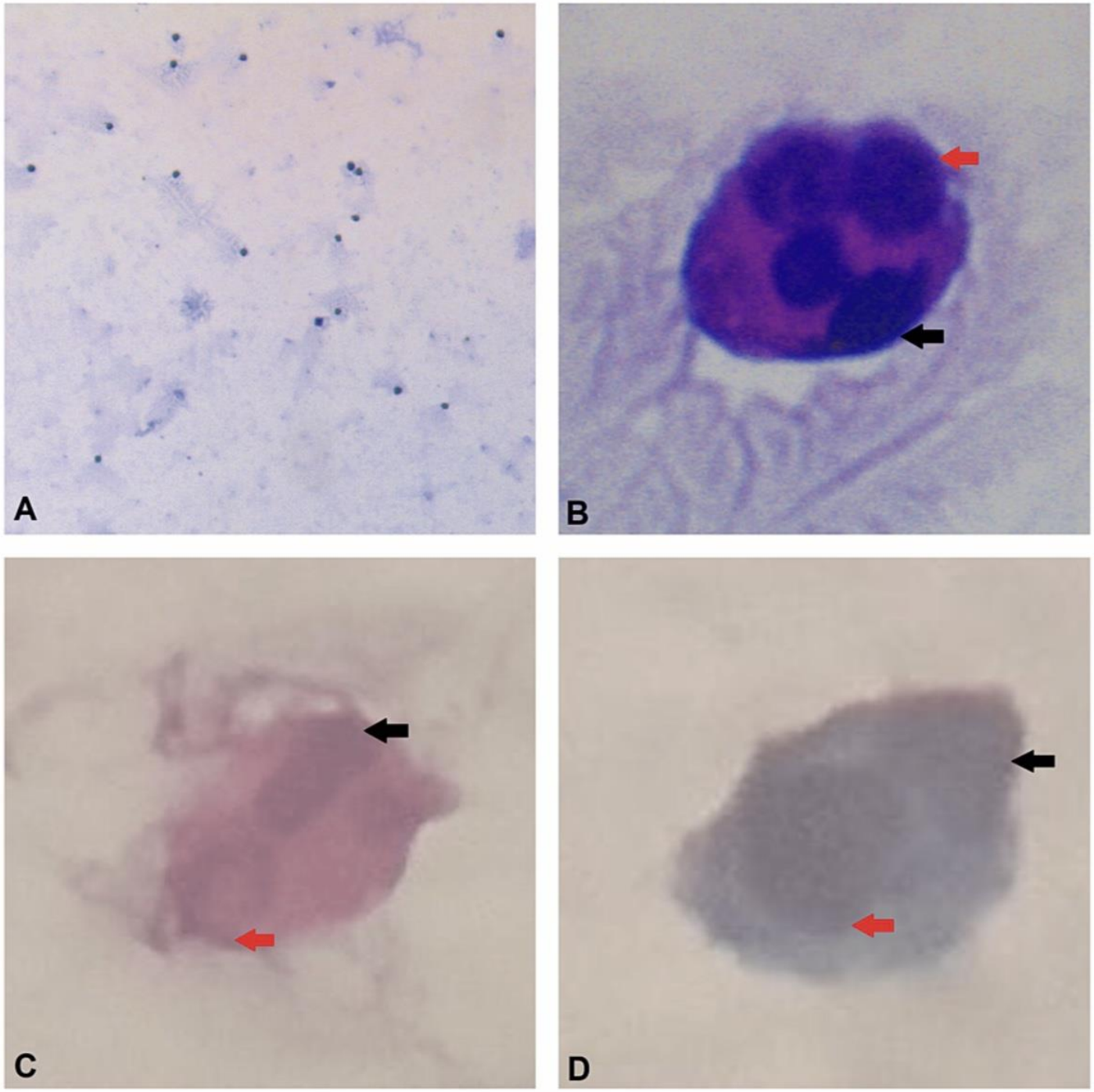
MRI BRAIN T2



MRI BRAIN FLAIR

# CSF Studies

- Histiocytes with hemophagocytes are seen



# FINAL DIAGNOSIS

**SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH CNS INVOLVEMENT WITH DENGUE SHOCK SYNDROME**

# CNS DIRECTED TREATMENT OF HLH

- **INTRATHECAL METHOTREXATE 6mg**
- **INTRATHECAL HYDROCORTISONE 10mg**
- **INTRAVENOUS ETOPOSIDE 150mg/m2**

-However, the patient remained persistently febrile and the pancytopenia worsened despite granulocyte colony-stimulating factor (G-CSF) support after 24 hours of Etoposide. The child also deteriorated hemodynamically and neurologically and required mechanical ventilation.

-Despite all resuscitative measures, the child succumbed to his illness 72 hours post receiving intrathecal chemotherapy.

# DISCUSSION

- **Definition: Hemophagocytic lymphohistiocytosis** is a form of histiocytosis characterised by accumulation of activated antigen presenting cells( Macrophages and lymphocytes) as a result of uncontrolled hemophagocytosis and uncontrolled upregulation of inflammatory cytokines.

# DISCUSSION

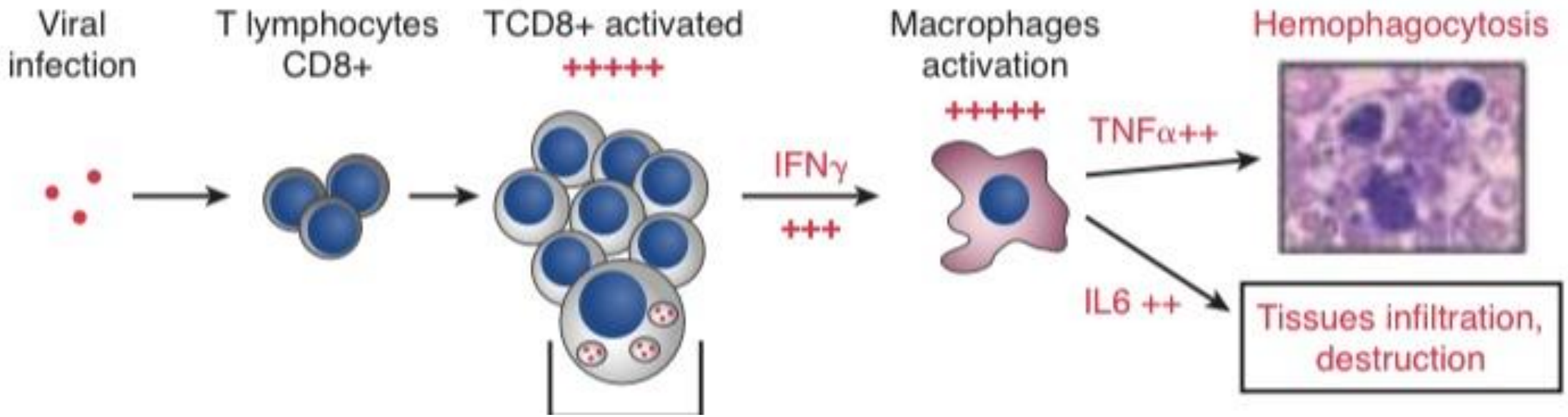
**PRIMARY HLH**

Familial type(AR)
<1-2 years old
Presentation: Fever(90%), Maculopapular rash(10%), petechial rash(60%), weight loss and Irritability.
Associated with severe immunodeficiency.

**SECONDARY HLH**

1. Infection associated
2. Older children
3. Hepatosplenomegaly(80%) lymphadenopathy(50%), Respiratory distress(90%), Jaundice and CNS involvement.
4. Myriad of both infectious and non infectious process( Phenytoin, ART) can trigger this.

# PATHOGENESIS



- **Diagnostic guidelines of HLH(One of two criteria)**

- **1) A molecular diagnosis consistent of HLH( PRF mutation or SAP mutation)**
- **2) 5 out of following 8 symptoms or lab investigations**
- ***Fever***
- ***Splenomegaly***
- ***Cytopenia (Hb <9gm%, Platelets< 1 lakh and Neutropenia <1000u/lit)***
- ***Hypertriglyceridemia(>265mg/dl) and/or hypofibrinogemia (<150mg/dl)***
- ***Hemophagocytosis in the bone marrow, spleen or lymph nodes with out evidence of malignancy***
- ***Low or absent NK Cell cytotoxicity***
- ***Hyperferritenemia***
- ***Elevated soluble CD25***

- **Dengue is a common tropical infection. Dengue triggered CNS HLH has not been reported. We hereby report a novel case of CNS HLH in an infant triggered by Dengue infection.**
- **Severe dengue infection complicated with HLH requires very prompt and aggressive treatment with steroids or intravenous immune globulin or chemotherapy.**

- Even though secondary HLH was suspected the genetic workup of Primary HLH couldn’t be done due to low social constraint, the possibility of Primary HLH precipitated by Dengue still remains a possibility in this Infant.

# AKNOWLEDGEMENT


- **THANK YOU**
- Pediatric Hematoncologist- Dr. Sarita Verma
- Pediatric Neurology- Dr. Shiji Chalipat
- Department of
- 1) Radiology
- 2) Microbiology
- 3)Pathology


Thank
you!