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# SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: CASE SERIES FROM A TERTIARY CARE CENTER

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**ABSTRACT**

We report three cases of secondary hemophagocytic lymphohistiocytosis (HLH) with diverse etiologies including malignancy-associated, inflammatory, and viral-triggered HLH. Detailed clinical features, laboratory investigations, bone marrow findings, management, and outcomes are presented.. Clinical manifestations, laboratory parameters, bone marrow aspiration results, treatment regimens, and outcomes were documented in detail.

## CASE -1

Severe Secondary Hemophagocytic Lymphohistiocytosis in an Adolescent Male Presenting With Fever, Shock, Cytopenias, and Hepatic Injury: A Case Report.

## CASE PRESENTATION

A 15-year-old male from Ooty presented with 15 days of persistent high-grade fever (104°F), chills, rigors, generalized weakness, and altered mental status. On admission he was conscious but disoriented, with irritable and irrelevant speech. No neck stiffness, rash, or focal deficits were noted.

### Initial Examination

Temperature: 104°F, Tachycardic,
Blood pressure: 70/50mmHg,
CNS: Disoriented, no meningeal signs,
Skin: No rash,
Abdomen: Mild hepatomegaly

## INITIAL LABORATORY FINDINGS

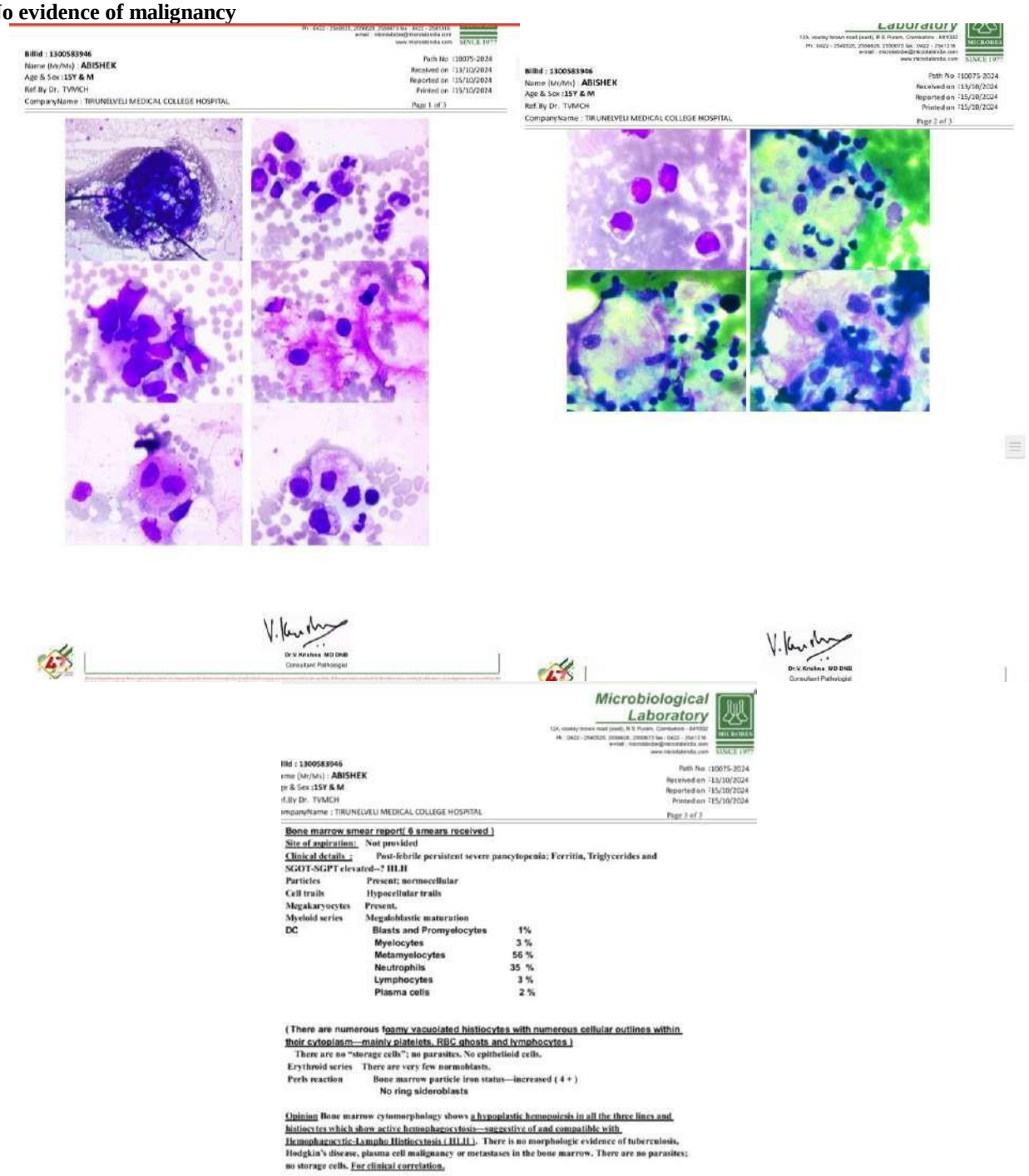
| Parameter | Value |
|---|---|
| Hemoglobin | 8.8 g/dL |
| Platelets | 25,000/µL |
| WBC | 3.7 ×$10^9$/L |
| SGOT | 744.8 U/L |
| SGPT | 142.3 U/L |
| Albumin | 2.22 g/dL |
| Total Bilirubin | 0.92 mg/dL |
| LDH | 1583 U/L |
| CRP | 60.9 mg/L |
| Triglycerides | 540 mg/dL |
| Fibrinogen | 82 mg/dL |

S.ferritin-2500 (elevated)---

## CLINICAL COURSE

The patient was initially managed with fluid resuscitation and empirical ceftriaxone + doxycycline for suspected tropical infections. Artesunate was administered due to high persistent fever and suspicion of malaria, but he showed no clinical response. By day 2, he developed persistent septic-like shock, requiring noradrenaline infusion. Because of persistent fever, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and worsening shock, HLH was strongly suspected. Bone Marrow Aspiration- Numerous activated macrophages. Prominent hemophagocytosis.

**No evidence of malignancy**




Diagnosis: Secondary Hemophagocytic Lymphohistiocytosis

**TREATMENT**

Dexamethasone 8 mg IV twice daily,Within 3 doses, the patient had a dramatic improvement in shock, allowing tapering of noradrenaline.

**OUTCOME**

Day 6: Became afebrile

Day 10:

Hemoglobin ↑ to 10.1 g/dL Platelets ↑ to 108,000/µL LDH ↓ to 788 U/L

Day 14:

**Clinically stable**

Liver enzymes normalized Inflammatory markers improved

**Complete resolution of symptoms**

The patient was discharged with steroid taper and follow-up.

**Conclusion-** HLH must be considered in any adolescent presenting with prolonged fever, cytopenias, shock, and

elevated inflammatory markers. Prompt diagnosis and early initiation of corticosteroid therapy can be life-saving.

**Case -2**

Classical Hodgkin Lymphoma Presenting as Secondary Hemophagocytic Lymphohistiocytosis: A Case Report with Serial Laboratory and Radiologic Trends.

**Clinical Presentation (January 2025)**

A 33-year-old woman presented with intermittent high-grade fever for 15 days, associated with progressive weakness, anorexia, and abdominal discomfort. There was no history of weight loss, night sweats, or prior chronic illness.

On examination, the patient was pale with low-grade icterus. Abdominal examination revealed mild hepatosplenomegaly. No palpable peripheral lymphadenopathy was detected at the time of admission.

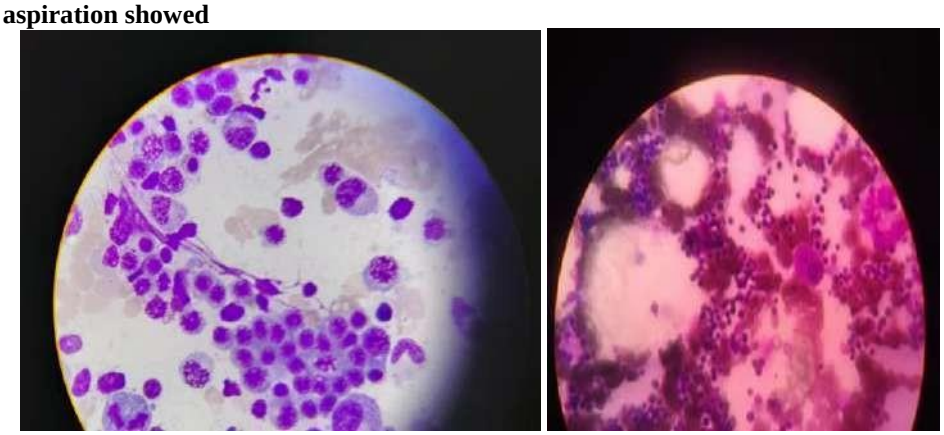
Initial Laboratory Findings (18 January 2025)

Hematological Parameters
White blood cell count: 1.4 $\times 10^3/\mu L$
Hemoglobin: 5.7 g/dL
Platelet count: 49,000/µL
Peripheral smear: Dimorphic anemia with pancytopenia
Biochemical Parameters
Serum ferritin: Markedly elevated
C-reactive protein: 178 mg/L
Lactate dehydrogenase (LDH): 3165 U/L
Total bilirubin: 1.16 mg/dL
AST/ALT: 45/34 U/L

**Imaging Studies**

Ultrasound abdomen revealed:
Mild hepatosplenomegaly
Mild ascites
Gallbladder wall edema
Bone Marrow Examination (January 2025)

**Bone marrow aspiration showed**



**Erythroid hyperplasia**
Increased histiocytes with active hemophagocytosis
No blasts or atypical lymphoid cells
The findings fulfilled ≥5 HLH-2004 diagnostic criteria, confirming secondary HLH.
Evaluation for Underlying Etiology

**CT Abdomen**

Multiple para-aortic and aortocaval lymph nodes,Mild hepatosplenomegaly

**CT-Guided FNAC**

FNAC from a retroperitoneal lymph node yielded scant cellularity and was non-diagnostic.

Excisional Lymph Node Biopsy (February 2025)
As clinical suspicion for malignancy remained high and cytology was inconclusive, a cervical lymph node that became palpable during follow-up was excised.

**Histopathological Findings**

Partial effacement of lymph node architecture
Presence of Reed–Sternberg cells and Hodgkin variants
Mixed inflammatory background comprising lymphocytes, eosinophils, plasma cells, and histiocytes
Fibrous bands suggestive of nodular sclerosis areas

**Immunohistochemistry**

CD30: Positive
CD15: Positive
PAX5: Weakly positive
CD20: Negative
CD45: Negative

Final Pathological Diagnosis
Classical Hodgkin Lymphoma (cHL)

This established Hodgkin lymphoma as the underlying trigger for secondary HLH.

Final Diagnosis
Secondary Hemophagocytic Lymphohistiocytosis triggered by Classical Hodgkin Lymphoma
Treatment
Supportive Management During HLH Phase
Packed red blood cell transfusions
Intravenous fluids, Antipyretics

Empirical broad-spectrum antibiotics, Serial monitoring of ferritin, LDH, and blood counts
Definitive Therapy

Following confirmation of cHL, ABVD chemotherapy was initiated:
Adriamycin
Bleomycin
Vinblastine
Dacarbazine
The patient tolerated treatment well.

Follow-Up and Outcome

**Serial Hematological Trends**

**Serial Hematological Parameters Over Time**

| Date | Hemoglobin (g/dL) | WBC (×10³/µL) | Platelets (/µL) |
|---|---|---|---|
| 18 Jan 2025 | 5.7 | 1.4 | 49,000 |
| 24 Jan 2025 | 6.3 | 9.2 | 48,000 |
| 01 Feb 2025 | 7.4 | 4.3 | 17,800 |
| 19 Sep 2025 | 10.5 | 12.4 | 290,000 |
| 06 Oct 2025 | 10.2 | 10.8 | 282,000 |
| 24 Oct 2025 | 11.0 | 9.8 | 309,000 |

**Biochemical Response**
LDH decreased from 3165 U/L → 404 U/L CRP decreased from 178 mg/L → <20 mg/L Liver function tests normalized
Renal function remained normal Radiologic Response

**Repeat CT imaging demonstrated**
Reduction in lymph node size Resolution of hepatosplenomegaly No new lesions
The patient remains in clinical remission at latest follow-up.

**DISCUSSION**
This case illustrates that HLH may precede the diagnosis of Hodgkin lymphoma and serve as its initial manifestation. FNAC may be inadequate, particularly for deep-seated or small lymph nodes, and excisional biopsy remains the diagnostic gold standard. Definitive treatment of the underlying lymphoma led to complete resolution of HLH, underscoring the importance of etiologic diagnosis.

**Case -3**
Mumps Meningoencephalitis Complicated by Secondary Hemophagocytic Lymphohistiocytosis in an Adolescent Boy:

**A CASE REPORT**
A 13-year-old previously healthy boy presented with a history of high-grade fever for eight days, associated with bilateral parotid swelling, which resolved spontaneously over a few days. Three days after resolution of parotitis, he developed severe headache, projectile vomiting, and altered sensorium.

At presentation, the patient had been afebrile for 48 hours, and parotid swelling had completely subsided.

**Clinical Examination**
**Neurological examination revealed**
Delirium
Positive Kernig sign
Exaggerated deep tendon reflexes
Sustained ankle clonus
Extensor plantar responses bilaterally
Systemic examination showed no rash or lymphadenopathy. External genitalia were normal.

**Investigations**
Hematological Parameters
Total leukocyte count: 4,300/µL
Hemoglobin: 8.5 g/dL
Platelet count: 54,000/µL
Peripheral smear: Microcytic and normocytic anemia

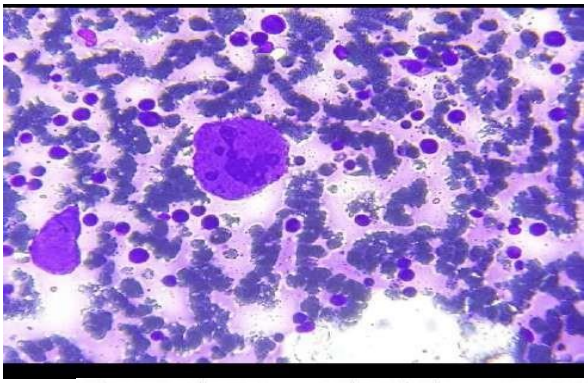
**Biochemical Parameters**
Serum sodium: 132 mEq/L
Serum potassium: 3.5 mEq/L
Random blood sugar: 95 mg/dL

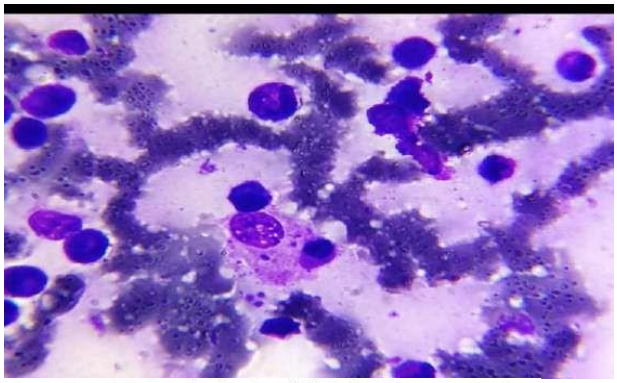
**Liver function tests**
Total bilirubin: 2.0 mg/dL
AST/ALT: 182/154 U/L
Total protein: 6 g/dL
Serum albumin: 3 g/dL
Serum globulin: 3 g/dL

**Inflammatory and metabolic markers**
Triglycerides: 591 mg/dL
ESR: 40 mm/hr
CRP: 194 mg/L
Serum LDH: 1400 U/L
Serum ferritin: >2000 ng/mL

**Pancreatic enzymes**
Serum amylase: 117 U/L
Serum lipase: 98 U/L
Cardiac Evaluation
ECG: Sinus arrhythmia
Imaging
Ultrasound abdomen: Borderline splenomegaly
MRI brain: Normal study

**Cerebrospinal Fluid Analysis**
Appearance: Hemorrhagic, watery consistency
Protein: 3944 mg/dL
Globulin: Positive
Cells: Scattered RBCs, no inflammatory cells
Bone Marrow Examination
Cellularity: Cellular marrow
Myeloid-to-erythroid ratio: ~3:1
Erythropoiesis: Mixed microcytic, normocytic, and megaloblastic
Leukopoiesis: Normal maturation
Megakaryocytes: Present
Special finding: Prominent hemophagocytosis





**Patient name :** Madhan Kumar **Age/Sex :** 13 / Male **MPIN :** 315010250366465 **Date of sample collection :** 11/11/2025 ( CSF & Serum specimen )

**Work up :** Department of Virology, Tirunelveli Medical College

**King Institute of Preventive Medicine & Research**
**Department of Virology**

| S.No | Name | Age | Sex | KIPM NO | Hospital | District | Received Date | Sample Type | Test | Virus | Results | Report Date |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Madhan Kumar | 13 | Male | 11906 | Tirunelveli GH | Tirunelveli | 12-Nov-25 | CSF | PCR | Herpes simplex virus (HSV) | Negative | 14-Nov-25 |
| | | | | | | | | CSF | PCR | VZV/Varicella Zoster Virus | Negative | 14-Nov-25 |
| | | | | | | | | CSF | PCR | Mumps Virus | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Herpes simplex virus (HSV) | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Cytomegalovirus (CMV) | Equivocal | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Rubella Virus | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Epstein-Barr virus (EBV) | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | VZV/Varicella Zoster Virus | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Parvovirus | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Japanese Encephalitis(JE) | Negative | 14-Nov-25 |
| | | | | | | | | CSF | IgM | Japanese Encephalitis(JE) | Negative | 14-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Mumps Virus | Positive | 13-Nov-25 |
| | | | | | | | | Blood - Serum | IgM | Dengue | Negative | 13-Nov-25 |

**Diagnosis**
Secondary Hemophagocytic Lymphohistiocytosis triggered by mumps meningoencephalitis

**Treatment**
**The patient was managed with**
Intravenous fluids Dexamethasone Antipyretics
He showed a prompt clinical response to corticosteroid therapy.

**Outcome**
The patient's neurological status and systemic condition improved gradually over one month. Hematological and biochemical parameters normalized, and he was subsequently discharged in stable condition.

**TABLE 1. Clinical details and hematological parameters of the cases**

| Parameter | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Age / Sex | 33/Female | 15/Male | 13/Male |
| Presenting complaints | Fever, weakness | Fever, shock, AMS | Fever, parotitis, AMS |
| Duration of fever | 15 days | 15 days | 8 days |
| Significant findings | Pallor, HSM | Shock, hepatomegaly | Meningeal signs |
| Hemoglobin (g/dL) | 5.7 | 8.8 | 8.5 |
| Total leukocyte count (/μL) | 1400 | 3700 | 4300 |
| Platelet count (/μL) | 49000 | 25000 | 54000 |
| Bone marrow | Hemophagocytosis | Hemophagocytosis | Hemophagocytosis |

**TABLE 2. Biochemical parameters of cases at admission**

| Parameter | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Total bilirubin (mg/dL) | 1.16 | 0.92 | 2.0 |
| AST (U/L) | 45 | 744.8 | 182 |
| ALT (U/L) | 34 | 142.3 | 154 |
| Triglycerides (mg/dL) | - | 540 | 591 |
| Ferritin (ng/mL) | High | High | >2000 |
| LDH (U/L) | 3165 | 1583 | 1400 |
| CRP (mg/L) | 178 | 60.9 | 194 |

**TABLE 3. Final diagnosis, treatment, and outcome**

| Case | Final diagnosis | Diagnostic test | Treatment | Outcome |
|---|---|---|---|---|
| Case 1 | Hodgkin lymphoma-associated HLH | Excisional biopsy | ABVD chemotherapy | Recovered |
| Case 2 | Inflammatory secondary HLH | Bone marrow | IV dexamethasone | Recovered |
| Case 3 | Mumps-associated HLH | Bone marrow | Steroids + supportive care | Recovered |

## DISCUSSION

This case series illustrates the heterogeneous presentation of secondary HLH in a tertiary care setting. All three patients presented with prolonged fever and cytopenias but differed in underlying etiology— malignancy-associated, inflammatory, and viral-associated HLH.

Malignancy-associated HLH poses a diagnostic challenge, particularly when lymphadenopathy is minimal or deep-seated. FNAC may be inconclusive, and excisional biopsy remains the gold standard. Infection-associated HLH, especially viral-triggered HLH, can mimic severe sepsis or meningoencephalitis.

Recognition of hyperinflammatory markers such as hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia is critical.

Early initiation of corticosteroids or definitive disease-directed therapy led to favorable outcomes in all cases, underscoring the importance of timely diagnosis.

## CONCLUSION

Secondary HLH is an under-recognized but potentially fatal condition with diverse etiologies. Clinicians should maintain a high index of suspicion in patients presenting with prolonged fever, cytopenias, and hyperinflammatory laboratory features. Early diagnosis and etiology-specific treatment significantly improve survival.