



## CASE REPORT

# Hemophagocytic lymphohistiocytosis with multifocal and multilevel involvement of the spinal cord: a case report

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### Abstract

**Introduction:** Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening hyperinflammatory syndrome caused by severe hypercytokinemia, due to highly stimulated, but ineffective immune response. In the central nervous system, it usually affects the leptomeninges, and very seldom affects the intramedullary spinal cord and brain parenchyma. We report a case of HLH with progressive spinal cord involvement.

**Case presentation:** A 62 year-old Filipino male with a history of laryngeal carcinoma, initially presented with constitutional signs and symptoms, which eventually developed progressive visceral and peripheral deterioration. Our patient's case was complicated with community-acquired pneumonia, followed by septic shock, which leads to his demise.

**Conclusion:** Spinal cord is a rare location for the development of HLH. Fulfilling the diagnostic clinical and laboratory criteria, supported by histopathologic findings through post-mortem examination, proved to explain the progressive neurologic deterioration of our patient.

### Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening hyperinflammatory syndrome caused by severe hypercytokinemia, due to highly stimulated, but ineffective immune response. Fever, pancytopenia, hepatosplenomegaly, lymphadenopathy, and rash often comprise the initial presentation. Certain forms of previous malignancies predispose some patients to develop the secondary form of HLH, most notable are of hematolymphoid origin, although certain solid organ tumors have also been reported. Some cases have also reported involvement of the spinal cord, but very rarely in the intramedullary. Clinical and laboratory diagnostic criteria have been developed for the diagnosis of this rare disease.

### Case presentation

This was a case of a 62 year-old male, with a history of laryngeal carcinoma, diagnosed clinically and treated as a case of hemophagocytic lymphohistiocytosis, presenting with fever, hepatosplenomegaly, pancytopenia (Hb 8 g/dL, WBC 100/mm<sup>3</sup>, Pl 14,000/mm<sup>3</sup>), hyperferritinemia (18,895 ng/mL), hyperfibrinogenemia (7.4 g/L), hyperlipidemia (Tg 551 mg/dL, VLDL 110 mg/dL), hyperbilirubinemia (TB 0.61, B2 0.25 mg/dL), elevated LDH (331 U/L), elevated D-dimer (4,847 ng/mL D-DU), markedly hypercellular bone marrow (>95%), who eventually developed progressive extremity weakness. Work up done included spinal MRI which revealed diffuse cord edema and multiple intramedullary enhancing lesions, the

largest is located at T3-T4 measuring 0.8x1.6 cm. (see images 1, 2, 3). He initially underwent spinal laminectomy and decompression with biopsy of the intramedullary lesion, which revealed non-specific perivascular and parenchymal lymphocytic and histiocytic infiltration. However, there was progression of paraparesis. Cranial MRI revealed subcentimeter nodular enhancing foci and irregular enhancement in the right frontal periventricular, right lentiform nucleus, and left temporal periventricular area, scattered foci of deep white matter and periventricular hyperintensity in both frontal, parietal, and left temporal lobes, hemosiderin deposits in the left frontal lobe and cerebellum. The patient continued to deteriorate and eventually expired.

### Post-mortem examination

Gross examination showed that the spinal column is straight with intact spinous processes and supporting bone and soft tissues. The previous dural incision scar is covered with blood clots measuring 2 cm. immediately superior to T1 vertebra. The spinal cord measures 42 cm. and weighs 62 grams. Cut sections of the cord show following lesions: Lesion (1) dark brown to black circumscribed area measuring 0.6x0.4x0.3 cm. located in the right anterior column of C2. Lesion (2) dark brown to black circumscribed area measuring 0.4x0.4x0.1 cm. located in the left posterior column of C2-C3. Lesion (3) dark brown to black circumscribed area measuring 0.3x0.3x0.2 cm. located in the right anterior column of T4-T5.

### Microscopic examination

Microsections disclose numerous infiltrating histiocytes in the parenchyma, singly and forming large nodules (see image 4), predominantly involving the white matter, and diffusely involving spinal cord levels C1 to T5. They are accompanied by perivascular and parenchymal lymphocytes, fibrinoid necrosis of small blood vessels, and calcifications. Meningeal infiltrates are not found. Adjacent neurons in the gray matter are viable. Nucleated cells including lymphocytes and red blood cells are noted inside many of the histiocytes (see images 5 & 6).

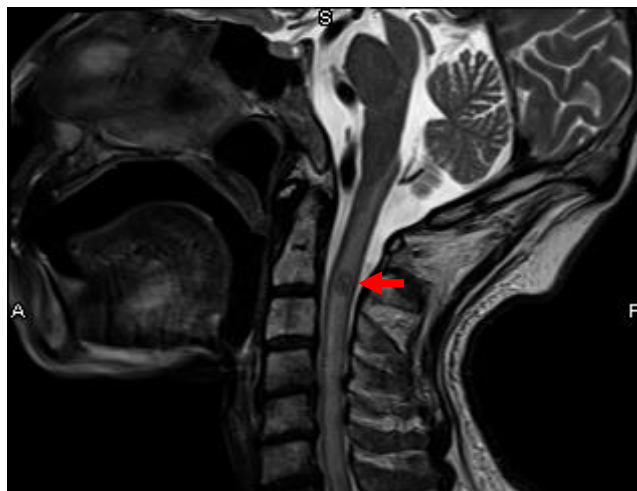


Image 1. T2 weighted MRI, sagittal cut of cervical region showing discrete intramedullary lesion.



Image 2. T2 weighted MRI, sagittal cut of lumbosacral region showing multiple discrete intramedullary lesions.

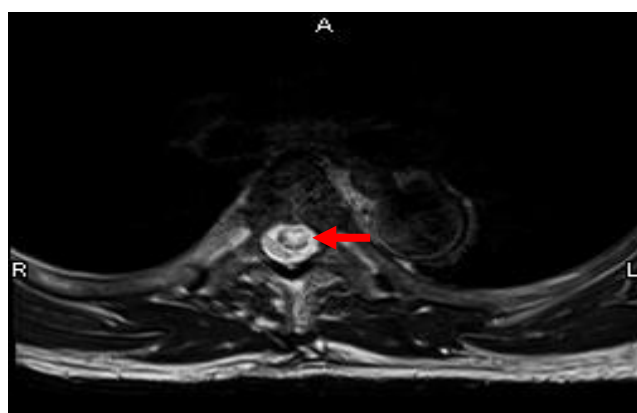


Image 3. Transverse cut showing an enhancing intramedullary lesion.

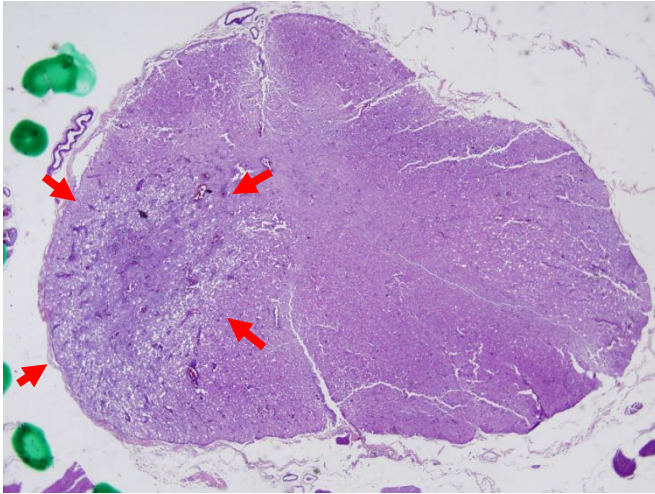
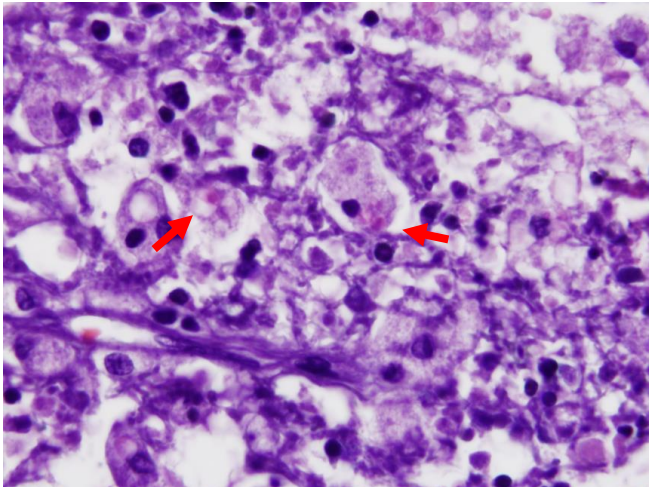
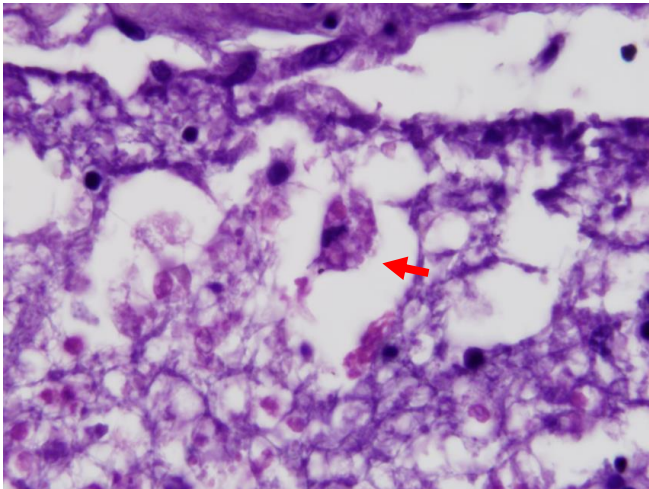


Image 4. Low power magnification showing a nodule composed of



Images 5 & 6. High power magnification showing hemophagocytosis.

### Immunohistochemical and special staining study results:

Kluver-Barrera stain highlights sharp demarcation between normal white matter and nodules. No engulfed myelin inside the cytoplasm of histiocytes (see images 7 & 8). Neurofilament immunostain shows disrupted but substantially preserved axons in the nodules (see images 9 & 10). CD56 stain highlights perivascular and parenchymal histiocytes in groups or singly-scattered (see images 11 & 12). Other special tests such as  $\beta$  Amyloid, and PAS are negative. EBER shows negative for EBV RNA, with positive for viable neuronal RNA.

### Discussion

Hemophagocytosis is defined as phagocytosis by the macrophages of other cellular elements like erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues. It is a non-specific phenomenon found in several conditions such as hemolytic anemia, malignant disease, infections and hemophagocytic syndrome.

Hemophagocytic syndrome (also known as Hemophagocytic Lymphohistiocytosis (HLH)) is a rare, life threatening hyperinflammatory syndrome caused by severe hypercytokinemia, due to highly stimulated, but ineffective immune process. It is not a single disease, but a clinical syndrome that can be associated with variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype with hypercytokinemia and excessive activation of lymphocytes and macrophages/histiocytes.

When the immune system is triggered in a healthy person, histiocytes, Natural Killer (NK) cells, and Cytotoxic T Lymphocytes (CTL) are all activated which then mutually stimulate each other by receptor interaction as well as by secretion of inflammatory cytokines and chemokines. This leads to killing of infected cells, removal of antigens, and then termination of the immune response. In HLH, there is an inherited or acquired defect of the NK cells and CTL that they are unable to cope effectively with the infectious agent or antigen.

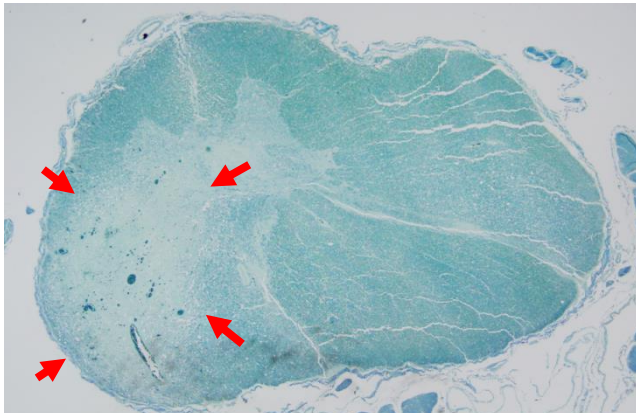


Image 7. Kluver-Barrera stain, scanning magnification.

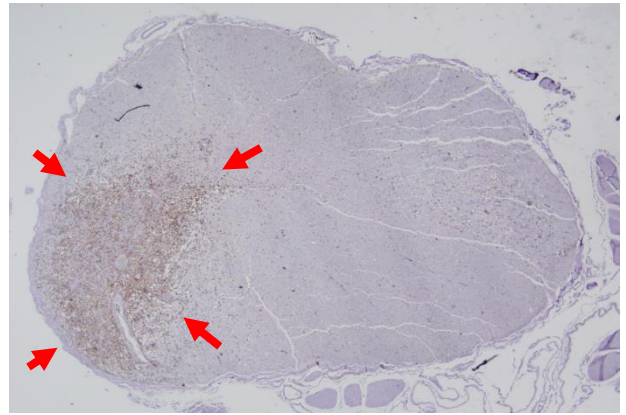


Image 11 CD68, scanning magnification.

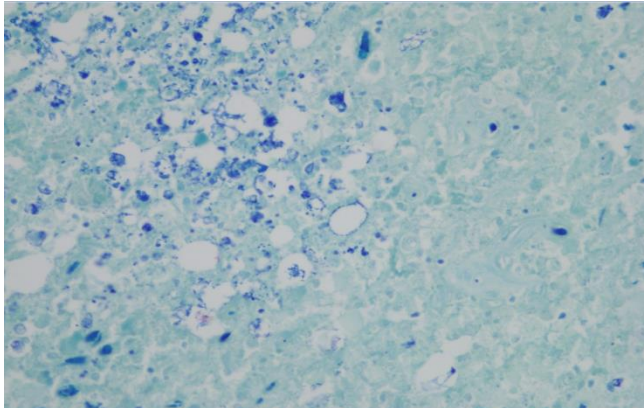


Image 8. Kluver-Barrera stain, high power magnification.

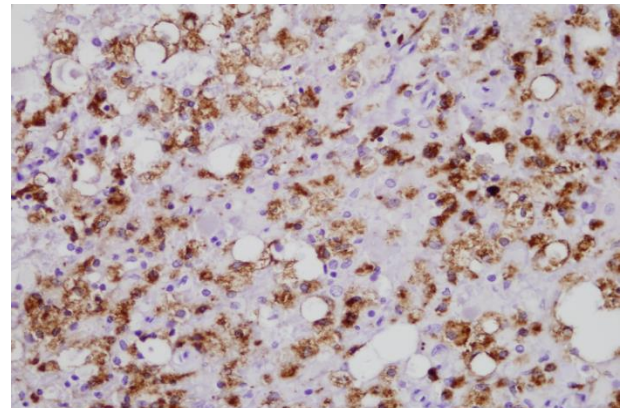


Image 12. CD68, high power magnification.

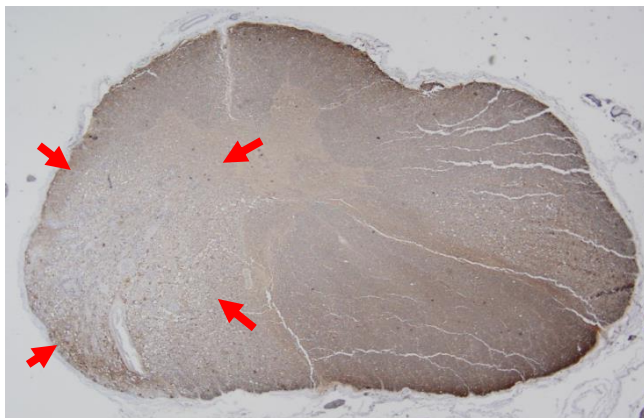


Image 9. Neurofilament, scanning magnification.

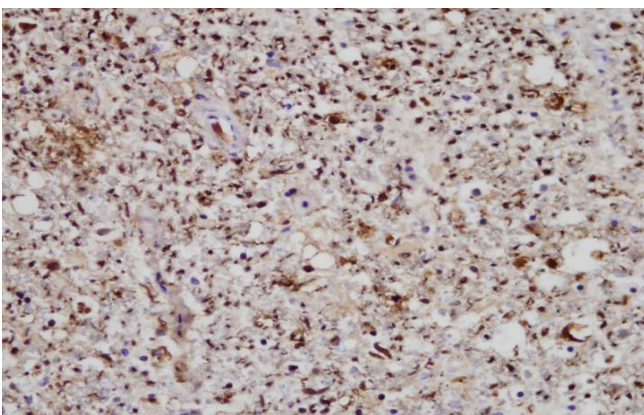


Image 10. Neurofilament, high power magnification.

This results in accumulation of activated T-lymphocytes and activated histiocytes with increasingly high levels of cytokines, especially interferon-gamma (IFN $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukins (IL-6, IL-8, IL-10, IL-12, IL-18, and soluble IL-2 receptor (CD25). The killing function of NK cells and CTL is mediated by a secretory pathway involving activation, polarization, and release of cytotoxic granules into the immunological synapse. This process is blocked in HLH, and results in tissue accumulation of activated T-lymphocytes and histiocytes with increasingly high levels of cytokines.

The clinical course of HLH is divided into two distinct forms, the primary and the secondary HLH. Primary HLH is an inherited form that exhibits an autosomal recessive mode of inheritance, and is restricted to infants and young children, with median survival of less than 2 months (if untreated). Most primary HLH episodes are triggered by infection. Primary HLH is also associated with mutation of several genes like Perforin (PFR1) gene, UNC13D gene, Syntaxin 11 (STX11) gene, FHLG-1 gene, Chediak-Higashi

syndrome (CHS-1, Griselly syndrome (GS-2), and X-linked lymphoproliferative syndrome (XLP).

In secondary (acquired) HLH (as in this case), is associated with several underlying conditions which include infections (like Epstein-Barr virus (EBV), Cytomegalovirus (CMV), measles, Human Herpes Virus-8 (HHV8), and Human Immunodeficient virus (HIV), tuberculosis, brucellosis, leishmaniasis, and certain types of fungus), autoimmune diseases, or Macrophage Activation Syndrome (MAS) (like systemic-onset Juvenile Idiopathic Arthritis (soJIA), lupus erythematosus, rheumatoid arthritis, Still disease, polyarteritis nodosa, mixed connective tissue disease, pulmonary sarcoidosis, systemic sclerosis, dermatomyositis, and Sjogren syndrome), malignancies (like lymphomas and solid tissue tumors), and immune suppression (after organ transplantation, and during immunosuppressive treatment.

As in primary HLH, the cytotoxic activity of NK cells and CTL are compromised. However, the mechanism that leads to this is not clear. Several hypotheses include: (1) Viruses that may interfere with CTL function, (2) high levels of cytokines that may impair NK cells and CTL, and (3) genetic polymorphisms for CD45 have also been described in several HLH cases. Perhaps certain individuals are more likely to deliver an HLH response to certain underlying conditions.

Hypercytokinemia and lymphohistiocytosis explain the majority of the signs and symptoms as well as laboratory findings in HLH. This is driven by an accentuation of the T-helper1 (Th1) response. With high levels of Th1-driven cytokines like TNF $\alpha$  and IFN $\gamma$ , macrophages become chronically activated and lead to its non-physiologic behaviour. These macrophages have been shown to ingest cellular elements without the involvement of typical receptor profile, and without induction of apoptosis of the ingested cells.

This will eventually cause pancytopenia, although TNF $\alpha$  and IFN $\gamma$  also act on hematopoietic precursors to suppress both early and late stages of hematopoiesis, and induce apoptosis of hematopoietic cells. Prolonged fever can also be explained by high levels of the endogenous pyrogens like IL-1, TNF $\alpha$ , and IL-16.

With highly proliferative histiocytes and activated lymphocytes, these cells tend to deposit into the liver sinusoids and splenic red pulp.

This explains the hepatosplenomegaly, hypertransaminemia and hyperbilirubinemia in HLH. These cells will also infiltrate neural organs (in this case, by microglial cells) like the brain and in very rare cases (as in this particular case), the spinal cord. This explains the progressive neurological deficit of this patient. Several case reports described the radiologic findings in HLH include diffuse white matter infiltrations, parenchymal atrophy, and calcifications, but the characteristics of these findings remain non-specific, especially in the immunocompromised. Other reports described diffuse white matter changes throughout the brain and the cervical spine, without mass effect, and with administration of contrast material revealed extensive leptomeningeal enhancement, with additional enhancement of the cerebral perivascular spaces. Very rarely that the lesion is seen intramedullary, which is seen in this particular case.

Other characteristic laboratory findings include elevated ferritin (which is likely secreted by activated macrophages), elevated triglycerides and LDH (due to suppressive activity of TNF $\alpha$  to lipoprotein lipase), hypofibrinogenemia (due to increased levels of plasminogen activator secreted by macrophages), impaired NK cell activity, and elevated soluble IL2 receptor (sCD25).

Less common clinical findings include lymphadenopathy, rash, and jaundice.

The histopathologic findings of HLH involvement of the CNS can be classified on the basis of the stages of the disease involvement microscopically, and the stages are characterized by increasing severity. Stage I, primarily show only leptomeningeal infiltrate of lymphocytes and histiocytes. Stage II, shows additional parenchymal involvement with perivascular infiltrations, and stage III, shows signs of cerebral tissue necrosis and demyelination in addition to the massive tissue infiltration that particularly affects the white matter. In this particular case, all the histopathologic findings, are compatible with stage III disease.

## Conclusion

Hemophagocytic lymphohistiocytosis is a rare progressive disease with multi-organ involvement. This rare case of HLH that involves the intramedullary spinal cord fulfils majority of the diagnostic criteria and is being supported by the histopathologic findings.

Table 1. The diagnostic criteria for HLH include the following:

1. Familial disease/known genetic defect
2. Clinical and laboratory criteria
  - a. Fever
  - b. Splenomegaly
  - c. Cytopenia (with at least 2 cell lines)
    - i. Hb <9
    - ii. Platelet count <100,000
    - iii. Absolute neutrophil count <1000
  - d. Hypertriglyceridemia and/or hypofibrinogenemia
    - i. Fasting TG >265 mg/dL
    - ii. Fibrinogen <150mg/L
  - e. Hemophagocytosis in bone marrow, CNS, or lymph nodes
  - f. Decreased/Absent NK cell activity\*
  - g. Ferritin >500 ug/L\*
  - h. sCD25 >2400 U/mL\*

\*Added in 2004

Criteria need to fulfil 5 of 8 above clinical/laboratory (do not need to fulfill this if have family history or molecular diagnosis that is consistent with HLH).

### Consent

Written informed consent of this case was obtained from the patient's next-of-kin for publication, which includes the accompanying images.

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