# NK/T-cell non-Hodgkin's lymphoma with secondary haemophagocytic lymphohistiocytosis treated with matched unrelated donor allogeneic stem cell transplant

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## DESCRIPTION

A 39-year-old Hispanic man who was recently diagnosed with stage IV NK/T-cell lymphoma nasal type from paratracheal lymph node and bone marrow biopsy (figures 1 and 2) presented to the emergency department with fever, chills and general weakness for 2 weeks. The patient was tachycardic, tachypneic and hypotensive. Physical examination showed marked hepatosplenomegaly and complete blood count revealed pancytopaenia. Liver function test demonstrated total bilirubin 19.1 mg/dL, asparate aminotransferace 144 IU/L, alamine transaminase 92 IU/L, alkaline phosphatase 595 IU/L and fibrinogen 54 mg/dL (figure 3). Iron panel revealed iron 203 µg/dL, serum ferritin 48 900 ng/mL and transferrin saturation 94%. Subsequent positron emission tomography (PET) and MRI demonstrated marked hepatosplenomegaly and multiple mediastinal and retroperitoneal lymph node enlargement with avid fluorodeoxyglucose update (figure 4), meeting the diagnostic criteria of haemophagocytic lymphohistiocytosis (HLH; table 1).[1]

Infectious work up was all negative except Epstein-Barr virus (EBV) quantitative PCR measure at $1.7\times10^9$ IU/mL, for which high-dose valacyclovir was initiated. Induction chemotherapy with an ESHAP, EPOCH regimen[2] and combination chemotherapy with L-asparaginase, methotrexate, dexamethasone followed by matched unrelated donor allogeneic stem cell transplant were performed for the treatment of HLH and NK/T-cell

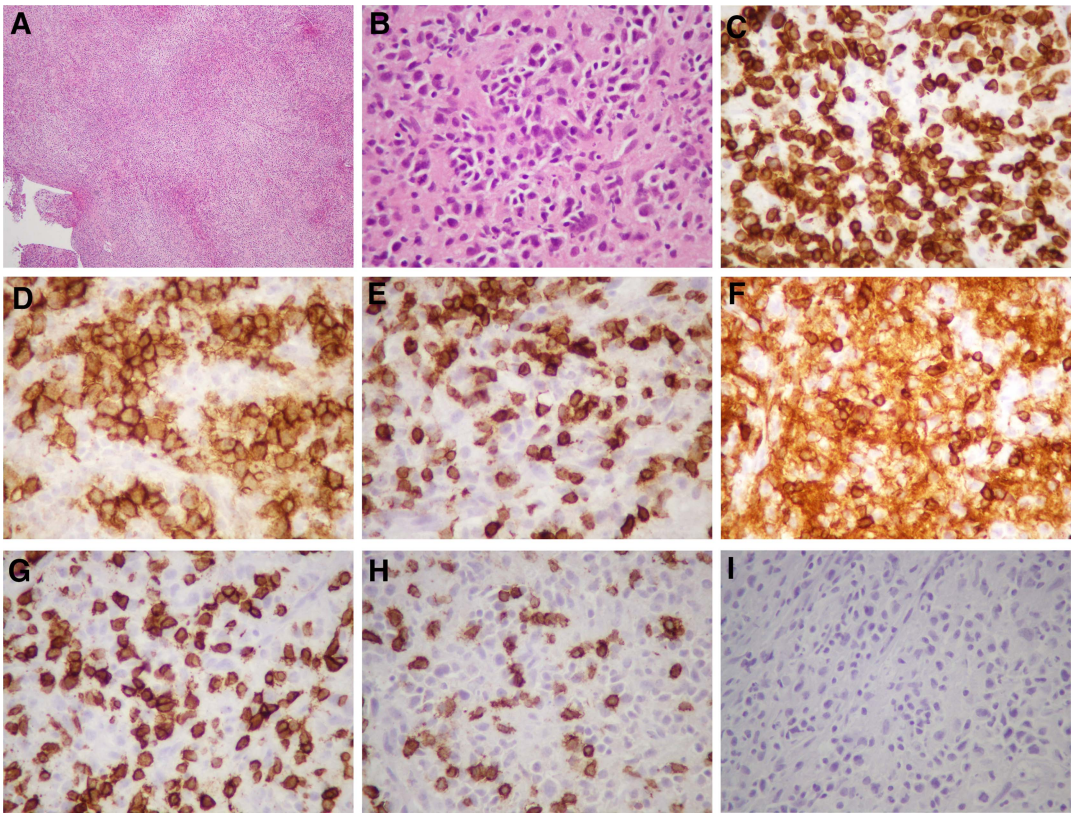


**Figure 1** Paratracheal lymph node biopsy showing diffuse infiltration by large atypical cells with coarse chromatin, prominent nucleoli and abundant eosinophilic cytoplasm intermixed with a smaller number of small mature lymphocytes and histiocytes (A and B). Apoptotic bodies and numerous mitotic figures are noted. There is no necrosis, granulomata or vasculitis present. Immunohistochemical stains demonstrated malignant cells positive for CD3 (C), CD56 (D) and EBER-ISH (E), but negative for the rest of the T-cell markers including CD4 (F), CD5 (G) and CD8 (H). The background small lymphocytes are mostly T cells and only a few CD20 B cells are observed (I).

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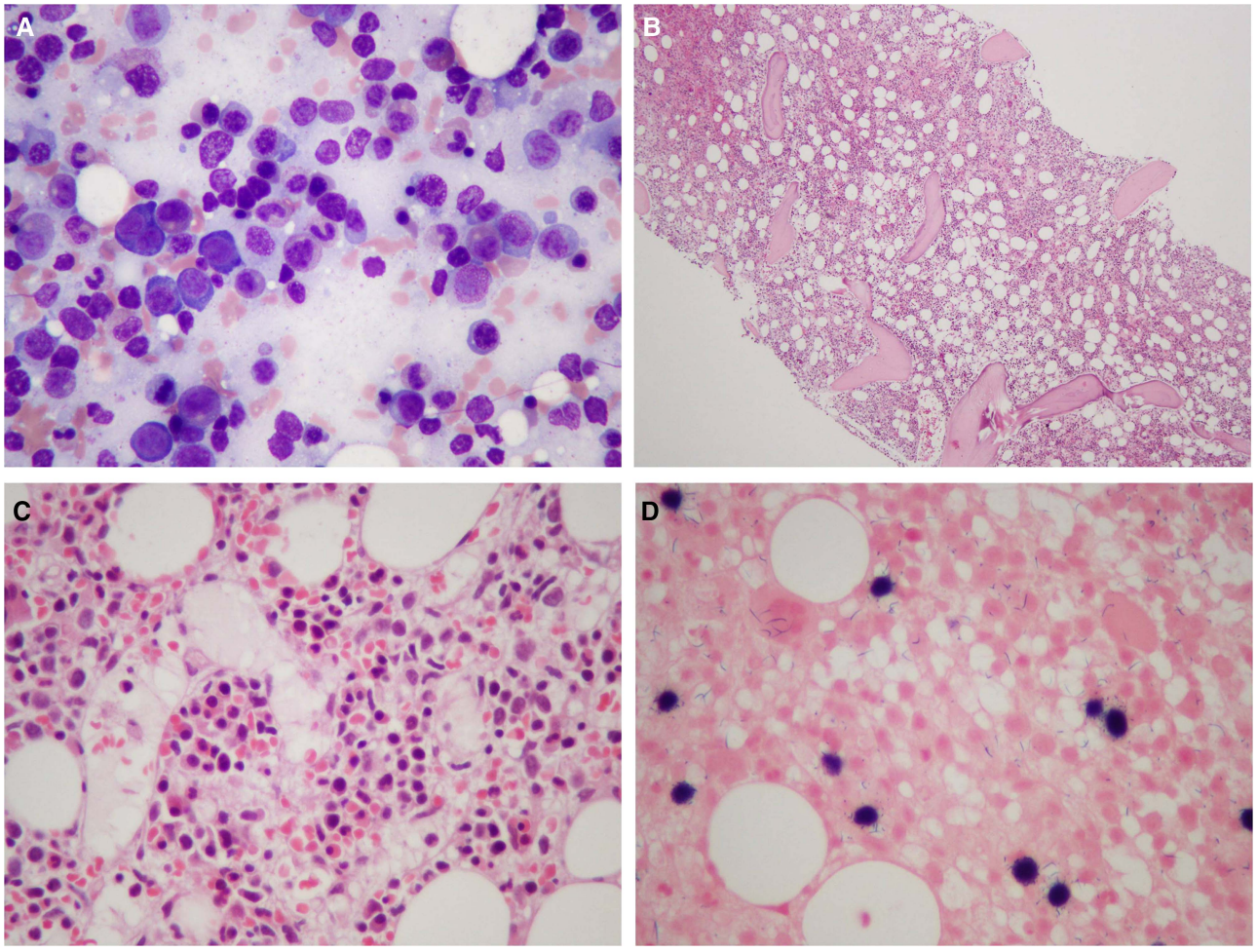


**Figure 2** Bone marrow aspirate and core biopsy. Bone marrow aspirate (A) and biopsy (B and C) demonstrated cellularity of 60%, trilineage haematopoiesis with myeloid:erythroid ratio of 1.04, 5.4% of lymphocytes and 1–2% of CD56 and EBER+large atypical lymphocytes (D) suggesting low level of bone marrow involvement with NK/T-cell lymphoma. No clusters of abnormal cells are observed. Megakaryocytes are normal in their morphology and number. No granulomata or fibrosis is observed.

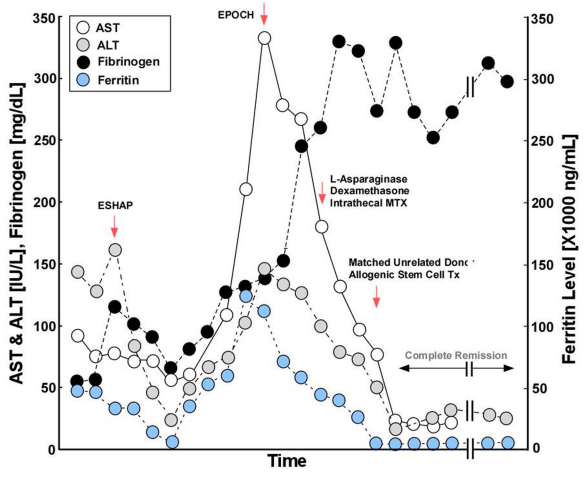


**Figure 3** Laboratory values during the hospital course. The patient presented with elevated liver enzymes and ferritin levels, which became normalised on induction chemotherapy with an ESHAP and EPOCH regimen. The patient achieved complete remission with subsequent combination chemotherapy with L-asparaginase, dexamethasone and intrathecal methotrexate followed by matched unrelated donor allogeneic stem cell transplant with normal laboratory values (AST, aspirate aminotransferase; ALT, alamine transaminase; MTX, methotrexate).

lymphoma, respectively.[3] Bilirubin, transaminase and ferritin levels became normalised (figure 3) and EBV PCR became undetectable over the treatment course. Bone marrow biopsy on post-transplant day 72 demonstrated no evidence of haemophagocytes or abnormal NK/T-cell population, specifically CD56/EBER+ atypical lymphoid cells. Subsequent PET scan on post-transplant day 75 confirmed complete remission (figure 5).

HLH is a syndrome with clinical manifestation of fever, splenomegaly, transaminitis and cytopaenia (table 1). It is frequently associated with underlying malignancy, rheumatoid disease, infection, genetic defect of cytotoxicity or reduced NK cell function leading to macrophages activation.[4] Etoposide including combination regimen as well as intrathecal methotrexate in patients with central nervous system (CNS) involvement are current treatment recommendations.[5] In the familial, relapsed or progressive HLH, stem cell transplant is an alternative option with 50–60% of long-term disease-free survival.[5] NK/T-cell non-Hodgkin's lymphoma (NHL) is one of the most common malignancies associated with secondary HLHs. L-asparaginase including concurrent chemoradiation treatment is the treatment of choice for NK/T-cell NHL and stem cell transplant can be considered in refractory disease or young patients who achieve complete remission.[3]

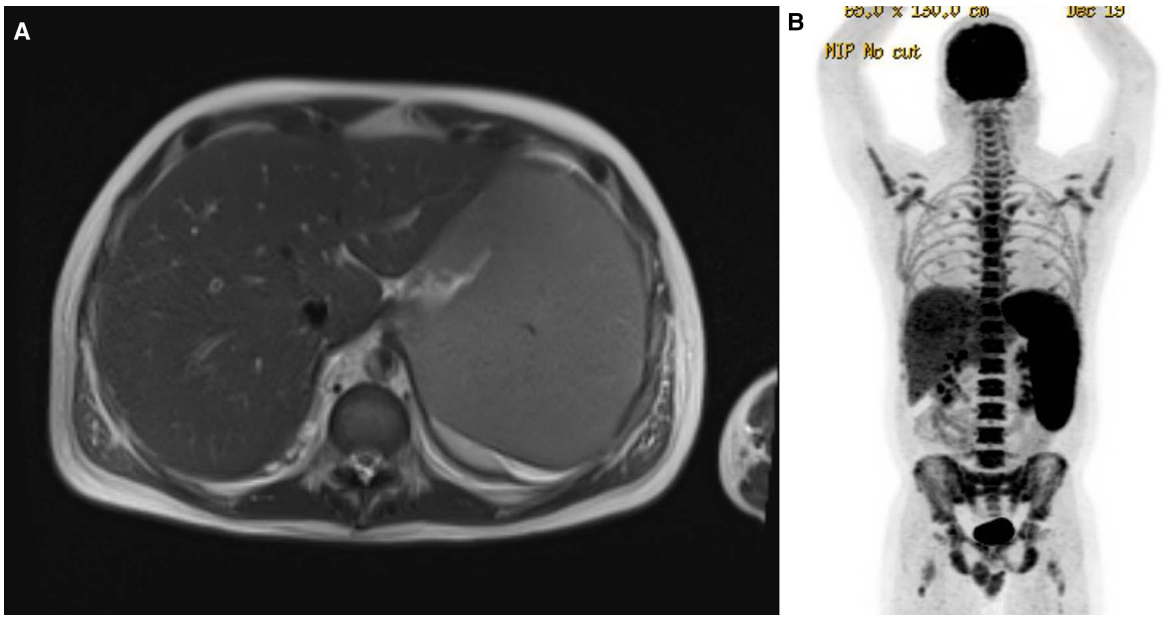


**Figure 4** Pretransplant MRI and positron emission tomography (PET) scan. MRI of the abdomen (A) showing marked splenomegaly, multiple retroperitoneal lymph nodes including aortocaval adenopathy and mesenteric mass. Heterogeneous hepatic parenchymal enhancement with periportal oedema is observed. PET scan (B) demonstrated avid fluorodeoxyglucose (FDG) uptake with max standardised uptake values (SUV) 17 in the spleen. Also, hypermetabolic mesenteric and retroperitoneal lymph nodes are observed. Pancreas, adrenal glands and kidneys are unremarkable.

**Table 1** Diagnostic criteria of HLH[1]

| Molecular diagnosis of FHLH | Clinical diagnosis of HLH |
|---|---|
| Mutation ins<br>1. BIRC4 (Baculoviral IAP repeat containing protein 4) or XIAP (X linked inhibitor of apoptosis protein)<br>2. PRF1 (Perforin-1/Pore forming protein-1)<br>3. Rab27a (Ras-related protein Rab-27a)<br>4. SH2D1A (SH2 domain-containing protein 1A)<br>5. STX11 (Syntaxin 11)<br>6. STXBP2 (Syntaxin-binding protein 2)<br>7. UNC13D (Protein unc-13 homolog D) | Five of the eight criteria fulfilled<br>1. Fever ≥38.5°C<br>2. Splenomegaly<br>3. Cytopaenia of at least two lineage<br>4. Haemophagocytosis in the tissue<br>5. Triglyceride >265 mg/dL or fibrinogen <150 mg/dL<br>6. Ferritin >500 ng/mL<br>7. Elevated CD25<br>8. Low or absent NK cell activity |

FHLH, familial haemophagocytic lymphohistiocytosis; HLH, haemophagocytic lymphohistiocytosis.

## Learning points

- Macrophage activation plays a pivotal role in haemophagocytic lymphohistiocytosis (HLH) syndrome and thorough investigation for the underlying pathology including malignancy, rheumatoid disease, infection and genetic disorder are important.
- Pathological confirmation of haemophagocytosis in tissues is only one of the eight current clinical criteria for the diagnosis of HLH. Its demonstration is not mandatory if sufficient numbers of other criteria are met.
- NK/T-cell non-Hodgkin's lymphoma is the most common underlying malignancy associated with secondary HLH. L-asparaginase including combination chemotherapy is the current recommendation and allogeneic stem cell transplant can be considered in patients with refractory disease or young patients who achieve complete remission.


**Figure 5** Post-transplant positron emission tomography scan showing no evidence of lymphoadenopathy. Liver, spleen, pancreas, adrenal glands and kidneys are unremarkable and there is no fluorodeoxyglucose avid osseous disease.

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**Patient consent** Obtained.

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## REFERENCES

1 Henter JI, Horne A, Aricó M, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
2 Jordan MB, Allen CE, Weitzman S, *et al*. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;118:4041–52.

3 Tse E, Kwong YL. How I treat NK/T-cell lymphomas. *Blood* 2013;121:4997–5005.
4 Fisman DN. Hemophagocytic syndromes and infection. *Emerg Infect Dis* 2000;6:601–8.
5 Trottestam H, Horne A, Aricò M, *et al*. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood* 2011;118:4577–84.