Extranodal NK/T cell lymphoma-associated hemophagocytic syndrome: where do we stand?

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Comment on: Wen H, Ma H, Cai Q, *et al.* Recurrent ECSIT mutation encoding V140A triggers hyperinflammation and promotes hemophagocytic syndrome in extranodal NK/T cell lymphoma. Nat Med 2018;24:154-64.

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Hemophagocytic lymphohistiocytosis (HLH), first reported as "*familial hemophagocytic reticulosis*" by Farquhar JW in 1952, is a rare life-threatening disorder characterized by overwhelming immune and inflammation activation, and "cytokine storm" (1-5). HLH can be roughly categorized as primary HLH (pHLH), which is inherited, or secondary HLH (sHLH) occurring in a context of infection, autoimmune diseases or malignancies. Patients with pHLH harbor biallelic mutations in genes encoding proteins critical to granule-dependent cytotoxicity pathway which lead to defect of cytotoxic function of cytotoxic T cells (CTL) and NK cells (1). Identification of these mutations has driven the development of animal models for primary HLH which are genetically engineered to mirror the mutations found in human. Extensive studies from these animal models clearly demonstrated that $CD8^+$ CTL cells and IFN-γ secreted by CTLs play essential role in pathogenesis in primary HLH (6-8). Thus, an anti-IFN-γ monoclonal antibody, NI-0505, that binds to and neutralizes human IFN-γ was tested in clinical trial and showed promising efficacy (9). Although presented with the common features of activated macrophages and "cytokine storm", unlike pHLH, sHLH is a more heterogenous disorder, its mechanism remains largely unknown.

Lymphoma-associated hemophagocytic syndrome (LAHPS), a fatal disease, accounts for about half of sHLH, among which extranodal NK/T cell lymphoma (ENKTL) is the most frequent subtype that develops LAHPS (10). Patients of ENKTL who developed LAHPS had extremely poor prognosis, with 6-month and 1-year survival rate being 23.0% and 15.4%, respectively (10). Thus, it is critical to clarify the underlying mechanisms and explore some valuable biomarkers to predict patients who are more likely to develop LAHPS during the disease course. Previous studies found that patients of ENKTL with younger age, bone marrow involvement and reduced serum albumin were independent risk factors for developing LAHPS (11), which needs to be validated in larger cohort of patients with ENKTL.

Although there are few cases of ENKTL reported to be EBV negative (12), it has been demonstrated that EBV infection plays an important role in the lymphomagenesis of almost all patients of ENKTL. Patients with ENKTL usually present with systemic symptoms, such as high fever and weight loss, and about 20% of ENKTL cases may develop HPS. A valuable marker for active HPS is serum level of sIL-2Ra, and in our previous study, we found the level of serum sIL-2Rα in ENKTL was significantly higher than that in normal healthy controls (2,964±1613.6 ng/L *vs.* 562.1±141.2 ng/L, $P<0.05$), and the sIL-2Rα level significantly correlated with B symptoms (13). Thus, we proposed that patients of ENKTL are more prone to develop HPS, which may partially relate to the EBV infection. EBV latent proteins like latent membrane protein-1 (LMP-1), can selectively activate NF-κB signaling pathway (14), which may mediate the upregulation of IL-2Rα expression in ENKTL (data not published yet), resulting in high level of serum sIL-2Rα. However, not all

patients of ENKTL develop HPS. Thus, mechanisms other than EBV infection underlie ENKTL-associated HPS (NK/T-LAHPS).

Like patients with pHLH in whom high levels of IFN-γ, TNF-α, IL-6, IL-12, and IL-10 were observed, patients with LAHPS have similar cytokine pattern. Although aberrant secretion of proinflammatory cytokines by lymphoma cells due to constitutively activation of immune/inflammatory related pathway due to somatic mutations, is expected as a trigger in LAHPS, the direct evidences and detailed mechanisms are lacking. Haijun Wen and his colleagues recently published their intriguing findings in *Nature Medicine* which sheds light for a potential detailed mechanism for LAHPS with their elegant research of *in vitro* and *in vivo* data on ENKTL (5). First, they identified a recurrent somatic mutation as ECSIT-T419C encoding V140A in 19.3% of 88 ENKTL samples by whole-exome sequencing in 5 ENKTL tumors and subsequent targeted sequencing validation in 83 tumor samples. Interestingly, the *ECSIT*-T419C mutation was significantly enriched in ENKTL patients with HPS, as 9 out of 17 individuals with HPS (53%) harbored this mutation, while only 5 out of 36 individuals (14%) who lack presence of HPS in the same cohort harbored it. Further molecular and chemical biology experiment confirmed ECSIT-V140A potently activates NF-κB signaling pathway and its downstream cytokines such as TNF, IFN-γ, and IL-1β. More importantly, ECSIT-T419C transfected ENKTL cells secreted IFN-γ and TNF-α to activate macrophage to produce massive cytokines both *in vitro* and in mouse xenografts, which supports the concept that the cytokines aberrantly produced by tumors drive the HPS pathogenesis in LAHPS.

T/NK cell lymphomas make up the largest type of lymphoma with LAHPS, accounting for about 46% (15). It's well-known some driver mutations, including STAT3 and STAT5B, in T/NK lymphoma are able to constitutively activate JAK/STAT signaling pathway, which is used by normal T/NK cells to transduce cytokine signaling, resulting in producing type 1 cytokines, including IL-6, IL-18, IFN-β by an autocrine or paracrine manner (16). However, the cytokines secreted due to these somatic driver mutations may not be strong enough to activate systemic resident macrophages to develop HPS. Additional factors are needed to amplify the immune response. One possible tumor-intrinsic factor might be somatic mutation in gene that regulate immune or inflammatory signaling pathway, like JAK/STAT, NF-κB (17), as Haijun Wen *et al.* showed ECSIT-V140A or ENKTL driver mutation alone can't elicit HPS in vivo, unless the NK/T cells acquire both mutations in the same clone, which synergistically activate NF-κB signaling pathway to produce massive IFN-γ and TNF-α to drive HPS (5). Further DNA sequencing to T/NK cell lymphoma with HPS may identify more such kind of "second hit" mutations. Another lymphoma intrinsic factor is EBV. EBV frequently associated with lymphomas and HPS in Eastern Asia. EBV is able to invade B cells and T/NK cells. Classically, EBV infects B cells, and induces infectious mononucleosis, and less frequently EBV directly invades T/NK cells or indirectly from B cells. Interestingly, in most of the EBV-associated HPS, T/NK cells are infected instead of B cells (18). A mount of evidences demonstrates LMP-1 can selectively activate NF-κB signaling and up-regulate TNF-α and IFN-γ. Similarly, EBV-associated T/NK lymphomas frequently show NF-κB signaling activation and hypercytokinemia (18). Thus, it's plausible EBV infection in T/NK lymphoma cells contribute to NF-κB signaling activation and downstream cytokines production.

LAHPS also develops in B cell lymphomas, and diffuse large B cell lymphoma (DLBCL) is identified as the largest defined subtype associated with HPS (15). Interestingly, it's known that MYD88 mutations in ABC-DLBCL activate NF-κB and STAT3 signaling pathway resulting in secreting cytokines as IL-6, IL-10, and IFNβ (19). It's not clear whether these B lymphoma cells can produce only local inflammation or systemic elevated cytokines. However, it's more likely that these malignant B cells secrete immunomodulatory cytokines to activate DCs or T cells diffusely in the microenvironment to predispose to HPS (20). Additional tumor extrinsic factors may be needed for HPS development in the setting of B lymphomas.

Recent findings support the concept that the distinction between primary HLH and secondary HLH is blurred (3). A substantial population of secondary HLH is found to harbor heterozygous mutations in genes associated with primary HLH (21,22). In addition, polymorphisms in immune and inflammation related genes such as cytokine production and signaling, TLR signaling, inflammasome activation or NK cell receptors contribute to secondary HLH susceptibility (3). On the other hand, genetic defects can't be detected in about 80% of secondary HLH patients, in whom infection, rheumatologic disease, or malignancy otherwise account for the development of HLH (3). Thus, HLH is proposed as a 'threshold' disease (4,6). Different predisposing factors as mutations in genes involved in lymphocyte cytotoxicity, infection, background

inflammation are superimposed to reach a certain threshold, beyond which HLH develops (3,23). Thus, in the context of lymphoma associated HLH, besides lymphoma associated mutation and latent EBV infection, extrinsic factors including germline mutations in immune/inflammatory related genes, newly infected infection, may all add up to contribute to full blown HLH development. Further *in vivo* and *in vitro* studiesare warranted.

As for the treatment of ENKTL, asparaginase-based chemotherapy regimens have significantly improved the survival outcomes for both early and advanced stage patients. However, the prognosis of patients with NK/T-LAHPS is still dismal. Although previous studies have indicated that PD-1-targeted therapy is highly effective in relapsed/refractory ENKTL (24), the role of these novel agents in NK/T-LAHPS needs to be explored in clinical trials. In this study reported by Wen *et al.* (5), combination of dexamethasone and thalidomide could effectively relieve NK/T-LAHPS both *in vitro* and *in vivo* studies, which mainly through inhibiting degradation of IκBα and IκBβ as well as NF-κB (p65 and p52) nuclear translocation and impairing the binding of NF-κB (p65 and p52) to the transcription start site (TSS) of TNF and IFNG, while the efficacy of adding dexamethasone and thalidomide to conventional therapy regimens needs to be clarified in future large cohort studies. As we have shown previously, sIL-2Rα or sCD25 is typically elevated in either patients of HPS or ENKTL and can serve as a valuable biomarker of disease activity, although its role in the pathophysiology of HPS or ENKTL is unclear. There was an anecdotal case report that daclizumab (a monoclonal anti-CD25 antibody) successfully treat an adult patient with steroid-dependent HLH (25). Coincidentally, a 42-year-old male patient of stage IV NKTCL relapsed after 6 cycles of GELOX (gemcitabine, oxaliplatin, and asparaginase), and did not respond to 2 cycles of EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin) and 2 cycles of SMILE (dexamethasone, methotrexate, ifosfamide, asparaginase, and etoposide), but after 2 cycles of pegaspargase and Basiliximab (anti-CD25 antibody), partial remission (PR) was achieved with tolerable toxicities (data not published). Thus, we speculate that CD25-targeted therapy may be effective in patients of NK/T-LAHPS, which needs to be investigated further.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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