Epstein-Barr Virus-associated Hemophagocytic Lymphohistiocytosis in Adults: A Retrospective Analysis of 23 Patients in China

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ABSTRACT: **Background:** Epstein-Barr virus (EBV)-associated hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disease with poor prognosis despite intensive therapy.

Objectives: To discuss the ideal therapy of EBV-associated HLH for adults.

Methods: We retrospectively studied 23 adult patients with EBV-associated HLH at our institution between January 2000 and June 2015. The clinical characteristics, treatment, and prognosis of adult EBV-associated HLH were analyzed. The median age was 38 years (range 18–72).

Results: All patients were found to have high fever, thrombocytopenia, abnormal liver function, elevated ferritin, and lactate dehydrogenase. Leukopenia, anemia, coagulopathy, hypofibrinogenemia, and splenomegaly were found in more than 80% of patients. Ten patients were treated with HLH-2004 protocol. Eventually, 95.7% of patients died of EBV-associated HLH. Non-HLH-2004 treatment and bone marrow suppression may predict early relapse independently, and the poor performance status and high lactate dehydrogenase level can be poor prognostic factors. It was also validated in comprehensive analysis of published articles.

Conclusions: Adult EBV-associated HLH occurs most often in people of Asian descent who are older than 35 years. These patients had a disappointing outcome despite intensive treatment, especially with high lactate dehydrogenase levels, poor performance status, and bone marrow suppression. HLH-2004 protocol has shown a glimmer of hope in the adult populations.

IMAJ 2018; 20: 80–85

KEY WORDS: hemophagocytic lymphohistiocytosis (HLH), Epstein-Barr virus (EBV), prognostic factors

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Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a rare immune-mediated but life-threatening disease. Adult HLH has rarely been reported, because many studies and clinical guidelines have focused on pediatric HLH.

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Usually, Epstein-Barr virus (EBV) is a harmless passenger residing in B cells. However it may cause severe diseases, including HLH and lymphoma, depending on the immunological response of the individuals [1]. EBV accounted for 43% of viral patients in adult HLH [2]. Unfortunately, given the rarity of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH), there were not enough data to guide treatment decisions in adults, therefore it was uniformly fatal.

To characterize EBV-HLH and improve outcomes in adults, we retrospectively analyzed 23 adult EBV-HLH patients who came to our institution during 15 consecutive years. We validated the results in a systematic analysis of published articles.

PATIENTS AND METHODS

PATIENTS

After obtaining institutional review board approval, the database query of patients was performed with ICD-10 code (D76.2) and EBV-HLH from January 2000 to June 2015 at the Affiliated Drum Tower Hospital of Nanjing University Medical School, China. Medical records were manually reviewed. Patients < 18 years with chronic active EBV infection were excluded.

The diagnosis of HLH was based on HLH-2004 guidelines [3], with five of the following eight criteria:

- fever ≥ 38.5°C
- splenomegaly
- peripheral blood cytopenia
- hypertriglyceridemia
- hemophagocytosis in bone marrow (BM), spleen, lymph node, or liver
- low or absent natural killer (NK) cell activity
- ferritin > 500 ng/ml
- elevated soluble CD25 (soluble IL-2 receptor alpha)

Furthermore, the EBV-HLH was selected according to the point system [4], including:

- EBV load (polymerase chain reaction [PCR]) > 5000 copies/ml

- duration of EBV viremia > 1 month
- presence of EBV in tissues
- no evidence (history, serologies, PCR) of exposure to other viruses associated with HLH
- no alternative etiologies for HLH

Demographics, etiology, clinical features, laboratory findings, treatment, and outcomes were collected for all eligible patients. The data were analyzed anonymously.

Moreover, it should be emphasized that we made differential diagnoses with viral capsid antigen-immunoglobulin M (VCA-IgM) and early D antigen-immunoglobulin G (EA-D-IgG) antibodies, excluding chronic active EBV infection. The VCA-IgM revealed whether the EBV infection was initial or chronic, and the EA-DR-IgG confirmed the reactivation. EBV-HLH was associated with activated CD8+ T-cells in most cases, while NK or CD4+ T-cell subpopulations tended to improve in chronic active EBV infection. However, there were some limitations to differentially diagnose the EBV infection using serological methods. Therefore, we also detected the EBV genomic DNA in whole blood.

THE HLH-2004 PROTOCOL

The HLH-2004 protocol suggested 8 weeks of initial therapy, including etoposide, dexamethasone, and CSV. If the disease was persistent after the initial therapy, continuation therapy was recommended for those without familial and genetic disease. Broad spectrum antibiotics, antiviral therapy, and antifungal therapy are recommended to prevent reactivation after reduction in therapeutic intensity, infections, or vaccinations. It was also feasible to restart intense therapy from week 2, and then the modified continuation therapy. Intrathecal therapy was recommended in cases of central nervous system (CNS) reactivation. Hematopoietic stem cell transplantation (HSCT) remained a high priority.

CLINICAL ENDPOINTS

Clinical response and EBV-HLH-specific markers (e.g., serum ferritin, triglycerides, EBV-DNA, NK cells) were assessed twice weekly. BM suppression was the decrease of leukocytes, erythrocytes, and/or thrombocytes. Moreover, complete clinical response was defined as the disappearance of all clinical symptoms, with normalization of EBV-HLH-specific markers; worsening of the symptoms or specific markers was considered disease progression [5]. Progression-free survival (PFS) was measured from clinical response to progression or death. Indeed, overall survival was defined from diagnosis to death or the last contact.

FLOW CYTOMETRY FOR T/NK CELL COUNTS

Peripheral blood (5 ml) was collected before treatment. Blood cells were preserved and incubated with CY5-anti-CD3/CD8, FITC-anti-CD4, and PE-anti-CD56/CD16 at 18–25°C for 20 minutes, protected from light. After erythrocyte lysis and a washing step, the flow cytometry analysis was performed immediately on a Coulter XL flow cytometer (Beckman Coulter, USA). NK cells were characterized as CD3-CD56+ and/or CD16+.

QPCR FOR EBV DNA IN WHOLE BLOOD

DNA was extracted from whole blood using the QIAamp DNA Blood miniKit (Qiagen, USA). Real-time quantitative PCR of the *EBNA1* gene, with 250 nM sense (5'-TGATAACCATGGACGAGGAC-3') and antisense 5'-GCAGCCAATGCAACTTGGAC -3') primers were obtained using the ABI Prism 7500 system (Taqman, Applied Biosystem, UK) [6]. Each sample was assayed in triplicate. Finally, relative gene expression was calculated with the comparative threshold cycle. Furthermore, the detection limit of the EBV DNA assay was 500 copies/ml of blood.

SEARCH STRATEGY FOR PUBLISHED ARTICLES

Medline and Embase were searched for articles in English from January 1, 1974 to June 10, 2016, using the term, or in combination: "hemophagocytic lymphohistiocytosis," "histiocytic medullary reticulosis," "haemophagocytic lymphohistiocytosis," "haemophagocytic syndrome," "Epstein-Barr virus," "EBV," "Epstein-Barr virus-associated," "EBV-associated," and "adult." The references cited in the identified studies or reviews were also enrolled. Duplicate publications, age < 18 years, experimental studies, and incomplete/irrelevant information were excluded. The exact diagnosis of EBV-HLH and survival data were detailed.

STATISTICAL ANALYSIS

All data were listed as median (range) if not otherwise specified. Fisher's exact test was used to identify the correlation. Moreover, prognostic factors associated with EBV-HLH were evaluated by univariate and multivariate analyses using the Cox regression model. Furthermore, overall survival was visualized with the Kaplan–Meier curves. All *P*-values were two-sided, and $P < 0.05$ was considered to be significance. Statistical analysis was performed using SPSS software version 13 (SPSS Inc., Chicago, IL, USA).

RESULTS

BASELINE CHARACTERISTICS

This study was comprised of 23 EBV-HLH patients. In the 15 years of the study, 90 HLH patients were not enrolled in the study according to the strict diagnostic criteria: 44 patients due to probable EBV-HLH (3-4 points) or possible (1-2 points) diagnoses (points were awarded according to the point system of EBV-HLH, set by Kelesidis et.al. [4]); 23 malignant tumors,

9 chronic active EBV infections (negative VCA-IgM or positive EA-D-IgG), 6 other infections, 3 autoimmune diseases, 3 transplantation-related, and 2 incomplete medical records.

The median age was 38 years (range 18–72) and 73.9% patients were from rural towns and cities with a low population density. The median time from onset to diagnosis was 20 days (range 0–60). Moreover, the Karnofsky performance score [7] was 70–90 in 12 patients. All patients had persistent high fever (39–40.5°C) for more than 7 days. Splenomegaly and hepatomegaly was found in 82.6% and 47.8% of patients, respectively. Thrombocytopenia, leukopenia, and pancytopenia was found in 100%, 95.7%, and 43.5% of patients, respectively. All patients had elevated lactate dehydrogenase (LDH) and liver impairment. Coagulopathy was found including prolonged clotting times, partial thromboplastin (PT) 47.8%, activated partial thromboplastin time (aPTT) 87.0%, and hypofibrinogenemia (87.0%). Ferritin > 1500 μg/L was found in all patients and > 10000 μg/L in 66.7% (10/15) of patients. Moreover, hyperbilirubinemia, atypical lymphocytes, and hypertriglyceridemia was present in 60.9%, 43.5%, and 52.2% of patients, respectively.

The median EBV viral load was 1.05×10^6/ml (range 7.69×10^3/ml–1.34×10^9/ml) in blood, compatible with EBV activation. In addition, EBV was detected in all BM samples of patients. Cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and Paul–Bunnell test were serologically negative in all patients.

The T-cell subpopulation was evaluated in 19 patients, and the low CD4+/CD8+ ratio was found in 8/19 peripheral blood samples. It was also shown that the number of NK cells (CD3-CD56+ and/or CD16+) decreased significantly in 10/19 patients.

Bone marrow biopsy was performed in 21 patients, and BM hemophagocytosis was detected in 19/21 patients, with 3% (1%–8.4%) macrophage in the total nucleated BM cells. BM suppression without malignant infiltration was found in four patients. Non-clonal T-cell receptor (TCR) gene rearrangement and leishmaniasis were detected in all patients. The biopsy and positron emission tomography/computed tomography (PET/CT) scans confirmed co-existing one peripheral T-cell lymphoma, one angioimmunoblastic lymphoma, one nasal T/NK cell lymphoma, and six reactive lymphoid hyperplasias.

TREATMENTS

Ten patients were treated according to the HLH-2004 protocol, another 11 patients were given steroids alone (10 mg/d dexamethasone intravenously) because of performance status or bacterial infections. Otherwise, a chemotherapy regimen (2 CHOP and 1 ECHOP) was administered to the other two patients. Antiviral therapy was performed in five patients with ganciclovir, foscarnet, and acyclovir, respectively. Five patients were treated with intravenous immunoglobulin. Antibiotics were commonly prescribed after bacterial infections were confirmed (*Streptococcus mitis*, n=13). One patient received rituximab, leading to weakening inflammation, and relapsed on day 91 and died on day 114. Supportive care with blood transfusion of washed red blood cells, plasma, and/or apheresis platelets was given in 19/23 patients.

OVERALL OUTCOMES

Eventually, 95.7% of patients died of EBV-HLH after a median follow-up of 51 days (range 10–456). The median overall survival was 57.5 (29.0–456.0) and 41.0 (10.0–114.0) days with HLH-2004 and non-HLH-2004 treatment, respectively. The inflammatory process had ceased in 18/23 patients after treatment. Unfortunately, 17/18 patients, who had ceased inflammatory process, experienced relapse after complete clinical response to initial treatment. The median PFS was 29.5 (8.0–456.0) days and 9.0 (0–90.0) days with HLH-2004 and non-HLH-2004 treatment, respectively. The EBV load fell below the detection limits (n=4) or < 1000 copies/ml (n=5) after HLH-2004 treatment. No EBV negative conversion was found with steroids alone. One death was related to allogeneic HSCT.

PROGNOSTIC FACTORS

After univariate and multivariate analysis of the EBV-HLH cohort [Table 1], we found that non-HLH-2004 treatment ($P = 0.023$) and BM suppression ($P = 0.035$) may predict early relapse independently. The poor performance status ($P = 0.000$) and high LDH level ($P = 0.004$, median LDH level [1172 U/L] as the cut-off to divide into high and low LDH level), can be independent poor prognostic factors [Figure 1].

Table 1. Multivariate Cox regression analysis in adult EBV-HLHs

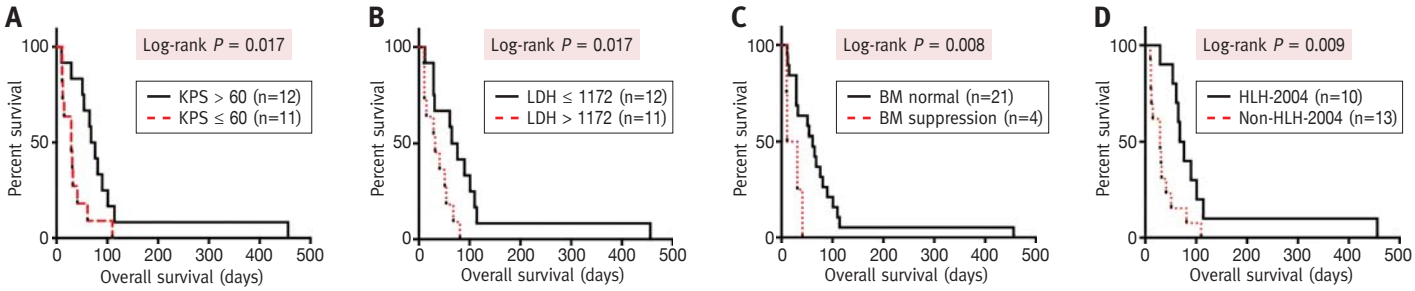
Covariate	Cox HR	Mean	*P*-value
PFS			
Gender	0.719	0.739	0.396
KPS	3.341	65.652	0.068
Time to diagnosis	0.966	20.304	0.326
Initial treatment	0.264	0.084–0.830**	0.023*
Liver failure	0.008	0.130	0.930
Renal failure	0.188	0.130	0.664
LDH	2.262	1618.348	0.133
BM suppression	2.240	1.058–4.742**	0.035*
Overall survival			
Gender	0.401	0.739	0.074
KPS	0.948	0.921–0.976**	0.000*
Time to diagnosis	0.789	20.304	0.374
Initial treatment	1.004	0.435	0.316
Liver failure	1.925	0.130	0.165
Renal failure	1.211	0.130	0.762
LDH	1.000	1.000–1.001**	0.004*
BM suppression	0.194	0.522	0.660

*Covariate (gender, KPS, time to diagnosis, initial treatment, liver failure, renal failure, LDH, BM suppression) may be of direct interest or it may be a confounding or interacting variable

**95% confidence interval

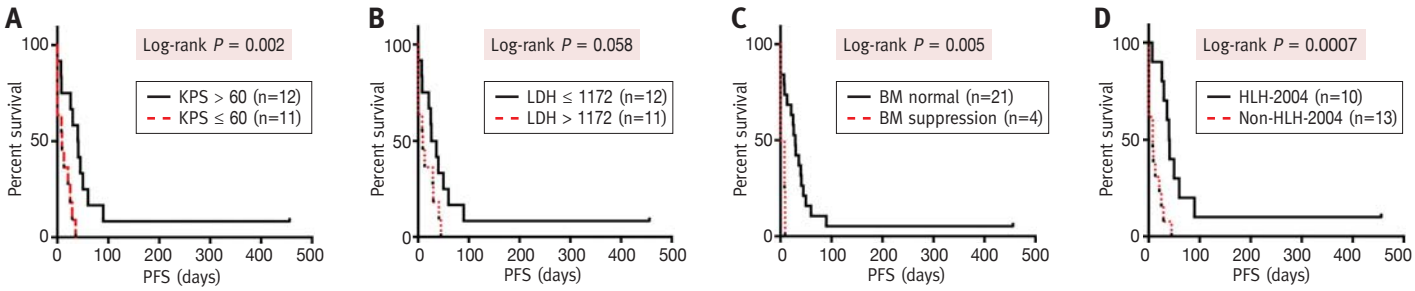
PFS = progression-free survival, HR = hazard ratio, KPS = Karnofsky performance score, LDH = lactate dehydrogenase, BM = bone marrow, EBV = Epstein-Barr virus, HLH = hemophagocytic lymphohistiocytosis

Figure 1. K-M estimates of the percentage of PFS for 23 patients with EBV-HLH **[A]** based on low KPS ≤ 60, **[B]** elevated levels of the LDH › 1172 U/L (median), **[C]** BM suppression, and **[D]** treated with non-HLH-2004 protocol. Statistical differences between groups were evaluated using the log-rank test



BM = bone marrow, EBV-HLH = Epstein-Barr virus-hemophagocytic lymphohistiocytosis, KPS = Karnofsky performance scores, LDH = lactate dehydrogenase, OS = overall survival, PFS = progression-free survival

Figure 2. K-M estimates of the percentage of overall survival for the 23 patients with EBV-HLH **[A]** based on KPS ≤ 60, **[B]** LDH ›1172 U/L, **[C]** BM suppression, and **[D]** treated with non-HLH-2004 protocol. Statistical differences between groups were evaluated using the log-rank test



BM = bone marrow, EBV-HLH = Epstein-Barr virus-hemophagocytic lymphohistiocytosis, KPS = Karnofsky performance scores, LDH = lactate dehydrogenase, PFS = progression-free survival, PFS = progression-free survival

REVIEW OF PUBLISHED ARTICLES

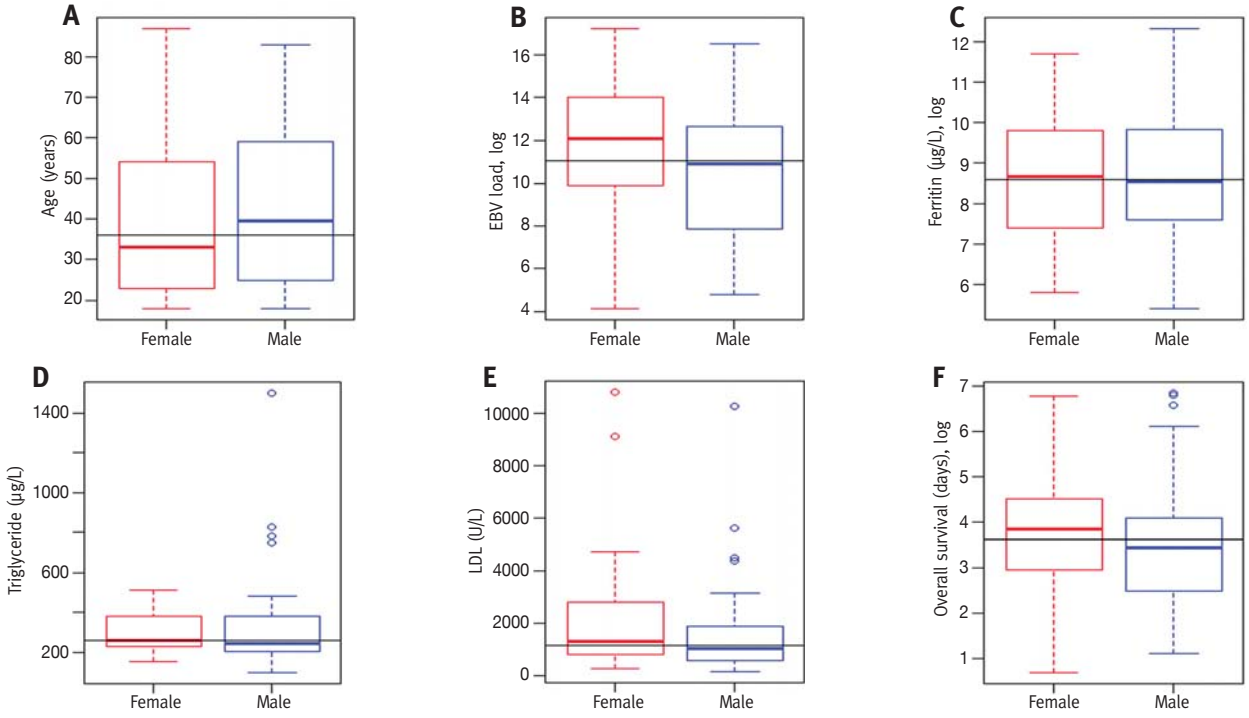
Clinical characteristics of 255 patients in 124 articles were reviewed. The median age at diagnosis of EBV-HLH was 35 years (18–87), and a spike incidence was in 2012. More importantly, a remarkable geographic variability was found (66.2% Asian, especially 32.9% Japanese). In these studies 77.1% of patients had fever, 51.5% had splenomegaly, 34.6% had hepatomegaly, 58.9% had pancytopenia, 51.5% had elevated LDH (1130, 160 over 5000 U/L), 47.2% had elevated ferritin (5462, 225 over 90000 µg/L), 22.1% had hypertriglyceridemia, and 19.0% had hyperbilirubinemia. In addition, 132 patients were diagnosed with high EBV DNA load and others with antibody/in situ hybridization. The co-morbidity included 46 lymphomas, 19 primary immunodeficiencies, and 11 secondary immunodeficiencies. As for treatment, 24 patients were treated with HLH-2004, 30 patients with HLH-94, and 25 patients with steroids alone. Eventually, 72.3% of patients died, with the median overall survival of 37.5 (2–930) days. For HLH-2004/94 and non-HLH-2004/94, the median overall survival was 51 days (41–107, interquartile) and 31.5 days (12.75–78.75), respectively.

DISCUSSION

The epidemiology of EBV-HLH is not well understood at present. We described the clinical characteristics of the largest series in the recent decade with EBV-HLH in adults. A specific geographical distribution of EBV-HLH was found in Asia [2]. It was shown that the median age of adult EBV-HLH was 35–38 years in our series and published articles. All EBV-HLH were found after 2002 due to greater awareness of the disease, or possibly new environmental triggers or the introduction of laboratory tests. Moreover, no difference of incidence was found before and after 2009, even though there was a spike in 2012. Based on our findings, tural residents (73.9%) may be more prone to EBV-HLH than those living in urban areas. The male/female ratio of pediatric EBV-HLH was 0.64, and adult patients comprised 35% of our study.

As for clinical features, high EBV DNA load might suggest EBV association and the definite EBV-HLH was 5–6 points in our hospital because serum viral load by PCR might be more helpful than serological antibody. High fever, thrombocytopenia, abnormal liver function, elevated ferritin, and LDH

Figure 3. Boxplots of the distribution of clinical features of 255 cases of EBV-HLH in female/male adults. **[A]** Age, **[B]** EBV load (log), **[C]** ferritin (μg/L, log), **[D]** triglyceridemia (mg/dl), **[E]** LDH (U/L), and **[F]** overall survival (days, log). In visualization, blood concentrations were higher in females. Boxes represent the 25th and 75th percentiles, lines inside the boxes are medians, whiskers represent values within the 1.5 IQR of the 25th and 75th percentiles, and circles represent outliers. Each thick black horizontal line reflects the median value



EBV = Epstein-Barr virus, LDH = lactate dehydrogenase

were found in all patients. Splenomegaly, coagulopathy, and hypofibrinogenemia were found in more than 80% of patients. Hyperferritinemia was found in all of our patients, with >10000 μg/L in 66.7% of patients, although it might not be specific for adult HLH [8]. The significant decline of $CD4^+/CD8^+$ T and NK cells was found in almost half of patients. Clonal TCR gene rearrangements may be detected in EBV-HLH patients [9]; however, only polyclonal features were found in the current study. In fact, the most common symptoms and laboratory findings were also found in comprehensive analysis of published articles [Figure 3] [10].

Currently, the ideal therapy for patients with EBV-HLH remains unknown. Most of the patients experienced relapse and death, although HSCT could offer hope. In our series and review 95.7% and 72.3% of patients died due to EBV-HLH, respectively. HLH-94, the first protocol for HLH, has increased the survival rate to 54% in children dramatically in the past 2 decades [11]. Although the results of new HLH-2004 protocol clinical trial (children only) have not been shown, 10 patients were treated with the HLH-2004 protocol in our series. Interestingly, the difference of PFS and overall survival was shown with and without HLH-2004 treatment in our adult series [Table 1, Figure 1, Figure 2]. HLH-2004 treatment may predict late relapse rather than survival. The survival benefit (51 vs. 31.5 days) was also confirmed in our review.

Past studies found poor prognostic factors of EBV-HLH to be older age, underlying lymphoma, low platelet count, and high levels of aspartate-aminotransferase and LDH level [12]. In our study, the high LDH level and poor performance status were independent poor prognostic factors. Furthermore, BM suppression and treatment with non-HLH-2004 protocol may also predict early relapse

However, these findings should be interpreted with caution because high loads might also be identified in patients with EBV-associate lymphomas [13], although we excluded chronic active EBV infection with VCA-IgM and EA-D-IgG antibodies. In our series, there were three cases with T/NK cell lymphoma and one extranodal disease in the nasopharynx with negative PET finding. Similarly, 20% of patients also were diagnosed with lymphoma in our review. Therefore, consideration of lymphomas are important considerations [10,14].

CONCLUSIONS

Adult EBV-HLH occurs most often in people of Asian descent who are older than 30 years of age. These patients had poor prognoses despite intensive therapy, especially those with high

LDH level, poor performance status, and BM suppression. Although HLH-2004 protocol has shown a glimmer of hope, further investigation is needed to develop better treatment in the adult population.

Acknowledgements

This work was supported by National Natural Science Foundation of China (81472782), Natural Science Foundation of Jiangsu Province (BK20141491), Six Talent Peaks Foundation of Jiangsu Province (2012-WS-026), "333" Talents Project of Jiangsu Province, and PAPD (the Priority Academic Program Development of Jiangsu Higher Education Institutions).

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References

1. Kuppers R. B cells under influence: transformation of B cells by Epstein-Barr virus. *Nat Rev Immunol* 2003; 3: 801-12.
2. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; 383: 1503-16.
3. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011; 118: 4041-52.
4. Kelesidis T, Humphries R, Terashita D, et al. Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in Los Angeles County. *J Med Virol* 2012; 84: 777-85.
5. Imashuku S, Kuriyama K, Teramura T, et al. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *J Clin Oncol* 2001; 19: 2665-73.
6. Jabs WJ, Hennig H, Kittel M, et al. Normalized quantification by real-time PCR of Epstein-Barr virus load in patients at risk for posttransplant lymphoproliferative disorders. *J Clin Microbiol* 2001; 39: 564-9.
7. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol* 1984; 2: 187-93.
8. Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. *Blood* 2015; 125: 1548-52.
9. Toga A, Wada T, Sakakibara Y, et al. Clinical significance of cloned expansion and CD5 down-regulation in Epstein-Barr Virus (EBV) infected CD8+ T lymphocytes in EBV-associated hemophagocytic lymphohistiocytosis. *J Infect Dis* 2010; 201: 1923-32.
10. Shah MV, Go RS. EBV-positive peripheral T-cell lymphoma with extensive hemophagocytosis. *Blood* 2014; 124: 3329.
11. Trottestam H, Horne A, Arico M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood* 2011; 118: 4577-84.
12. Arca M, Fardet L, Galicier L, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br J Haematol* 2015; 168: 63-8.
13. Sano H, Kobayashi R, Tanaka J, et al. Risk factor analysis of non-Hodgkin lymphoma-associated haemophagocytic syndromes: a multicentre study. *Br J Haematol* 2014; 165: 786-92.
14. Mayson E, Saverimuttu J, Warburton P. Two-faced haemophagocytic lympho-histiocytosis: comparative review of two cases of adulthaemophagocytic lymphohistiocytosis. *Intern Med J* 2014; 44: 198-201.

Capsule

Smoking behavior changes in the early rheumatoid arthritis period and risk of mortality during 36 years of prospective follow-up

Sparks and co-authors investigated whether rheumatoid arthritis (RA) diagnosis influences smoking behavior changes and whether these changes were associated with mortality. The authors identified an incident RA cohort in the Nurses' Health Study (NHS 1976–2012). Behavioral data were collected through biennial questionnaires. The authors created a comparison cohort, matching RA cases to women without RA by age and calendar year at the index date of RA diagnosis. To investigate smoking behavior changes in the early RA period, sustained cessation was defined as permanently quitting within 4 years of the RA/index date. Among 121,700 women in the NHS, the authors identified 938 with incident RA matched to 8951 non-RA comparators. Among current smokers, 40.0% with RA permanently quit smoking in the early RA period, compared to 36.1% of comparators (odds ratio for sustained cessation 1.18, 95% confidence interval [95%CI] 0.88–1.58). There were 313 deaths (33.4%) in the RA cohort and 2042 (22.8%) among comparators. Compared to continued smoking, sustained cessation was associated with similarly decreased mortality in both the RA (HR 0.58, 95%CI 0.33–1.01) and comparison (HR 0.47, 95%CI 0.39–0.58) cohorts. Women with RA had higher mortality for › 5 post-RA pack-years (HR 3.67, 95%CI 2.80–4.81) than comparators with › 5 post-index pack-years (HR 1.88, 95% CI 1.62, 2.17; P ‹ 0.001 for interaction; reference: ever-smoker non-RA women with 0 post-index pack-years). The conclusion was that sustained smoking cessation within 4 years of RA diagnosis reduced mortality risk, with a similar effect observed among non-RA comparators. Smoking › 5 pack-years after RA diagnosis significantly increased mortality beyond the risk of non-RA comparators.

Arthritis Care & Res 2018; 70: 19

Eitan Israeli

"When I despair, I remember that all through history, the way of truth and love has always won. There have been murderers and tyrants, and for a time they can seem invincible. But in the end they always fall. Think of it, always"

Mohandas Karamchand Gandhi, (1869–1948), Leader of the Indian independence movement against British rule. Employing nonviolent civil disobedience, he led India to independence and inspired movements for civil rights and freedom across the world