Chronic active EBV infection associated with NK cell lymphoma and hemophagocytic lymphohistiocytosis in a 27-year-old woman
A case report

Ya-Dong Wang, MD, PhD, Ling-Ling Wu, MM, Lu-Yuan Ma, MM, Xiao-Bo Shang, MM, Zi-Yue Li, MM, Wei Wang, MD, Chuan Shen, MD, Jing-Jing Yang, BD, Li-Xia Sun, MD, Cai-Yan Zhao, MD, PhD.

Abstract

Rationale: Chronic active Epstein-Barr virus infection (CAEBV) is a common infectious disease that often affects multiple organs or systems. However, it is liable to be neglected and misdiagnosed owing to its insidious onset, lack of specific findings in the early phase, and a general lack of awareness among clinicians.

Patient concerns: A 27-year-old woman case has been described who was initially misdiagnosed as drug-induced liver injury due to onset presentation of mild splenomegaly, recurrent liver dysfunction, and disputable pathological evidence of liver biopsy.

Diagnoses: CAEBV complicated with natural killer (NK) cell lymphoma and hemophagocytic lymphohistiocytosis (HLH) was diagnosed by in situ hybridization of liver tissue section with EBV-encoded RNA -1 probe and flow cytometry of bone marrow.

Interventions: After admission, the patient received symptomatic treatment and antiviral therapy (combination of acyclovir and foscarnet sodium) as well as adjuvant treatment (thymosin alpha 1 and methylprednisolone); later, the patient received etoposide and dexamethasone for diagnosis of EBV associated HLH. Subsequently, the disease progressed to NK cell lymphoma and the patient received the revised EPOCH chemotherapy regimen [etoposide (100mg/d, d1–5), dexamethasone (7.5mg/d, d1–5; 5mg/d, d6–14), cyclophosphamide (0.8g/d, d1–2), and pegaspargase (3750u/d, tid, d1–2)].

Outcomes: Although the patient received a series of therapies and other comprehensive measures, finally she died of gastrointestinal hemorrhage and multiple organ failure.

Lessons: Liver is one of the main target organs of EBV infection. In the clinical setting of unexplained fever and liver injury, it is necessary to be aware of CAEBV, as well as its fatal complication such as EBV associated NK cell lymphoma and HLH.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate transaminase, CAEBV = chronic active EBV infection, CD = clusters of differentiation, CMV = cytomegalovirus, CRP = C-reaction protein, DBIL = direct bilirubin, DIC = disseminated intravascular coagulation, DILI = drug-induced liver injury, EBER = EBV-encoded RNA, EBV = Epstein-Barr virus, EBV-Ca = EBV capsid antigen, EBV-EA = EBV early antigen, FDG = fluorodeoxyglucose, HLH = hemophagocytic lymphohistiocytosis, HSCT = hematopoietic stem cell transplantation, IFN = interferon, IL = interleukin, LDH = lactate dehydrogenase, LY = lymphocyte, NK = natural killer, PET/CT = positron emission tomography/computed tomography, SSC = side scatter, TB = tuberculosis, TBIL = total bilirubin, TCR = T cell receptor, WBC = white blood cell.

Keywords: allogeneic hematopoietic stem cell transplantation, chronic active EBV infection, Epstein-Barr virus, hemophagocytic lymphohistiocytosis, NK cell lymphoma

1. Introduction

Epstein-Barr virus (EBV) infection, which is a common infectious disease, is easily neglected and misdiagnosed. Most cases of acute EBV infection present as infectious mononucleosis (IM). However, in a few cases, EBV infection would eventually develop to chronic active EBV infection (CAEBV); this phenomenon is attributable to the failure to evolve into latent infection after primary infection or to the transition from latent infection to productive infection, which may increase the total number of latently-infected cells and thus is an essential aspect of EBV-associated multiple organ injuries and even malignancies. Many deaths from EBV infection are attributable to the complications of lymphoproliferative disorders [e.g., T/natural killer (NK) cell lymphoma] and secondary hemophagocytic lymphohistiocytosis (HLH), which eventually results in bleeding, infection, multiple organ failure, and disseminated intravascular coagulation (DIC). In the present case, liver dysfunction of the patient was initially misdiagnosed as drug-induced liver injury.
injury (DILI); however, a diagnosis of CAEBV complicated with NK cell lymphoma and HLH was eventually established by in situ hybridization of liver tissue section with EBV-encoded RNA (EBER)-1 probe and flow cytometry of bone marrow. This can remind the clinicians that in the clinical setting of unexplained fever and liver injury, it is necessary to be aware of CAEBV, as well as its fatal complications such as EBV associated NK cell lymphoma and HLH.

2. Case presentation

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Hebei Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the individual participant included in the study.

The patient was a 27-year-old woman with no relevant medical history or family history. In June 2016, she presented at our hospital for 4 months of intermittent fever with 3 and half months of fatigue and dark-colored urine. The patient developed fever (38.5°C) 4 months ago with no apparent cause. The fever type was irregular; it was accompanied by myalgia and occasional headache. She denied any history of chills, pharyngalgia, cough, and expectoration, abdominal pain, diarrhea, localized joint pain, or rash. The patient was prescribed anti-infection therapy for 4 days in a local hospital because of increased white blood cell (WBC) counts and neutrophils. However, her body temperature persisted in the range of 38.5°C to 39.1°C. About 3 and half months ago, the patient was referred to the superior central hospital owing to development of anorexia, fatigue, and dark-colored urine. Results of lab investigations were as follows: serum alanine aminotransferase (ALT) 1187 U/L; serum aspartate transaminase (AST) 1243.7 U/L; total bilirubin (TBIL) 165.4 μmol/L, direct bilirubin (DBIL) 92.2 μmol/L. She tested negative for antigen and antibody markers of hepatotropic hepatitis A–E virus with the exception of hepatitis B surface antibody, and undetectable for viral nucleic acid. She received glycoprotein remedies for hepato-protection and to lower transaminase levels, and cefoperazone-sulbactam antibiotic therapy for about 1 month; however, there was no improvement in clinical manifestations. About 2 and half months ago, the patient was transferred to another local hospital for specialized infectious diseases. Liver biochemistry tests showed ALT 374 U/L; AST 164 U/L; TBIL 84.2 μmol/L, DBIL 57.3 μmol/L. Besides, her anti-streptolysin “O” was 201 U/mL, rheumatoid factor was 156.2 IU/mL, and C-reactive protein (CRP) level was 1.9 mg/L. EBV- capsid antigen (CA)-IgM, cytomegalovirus (CMV)-IgM, rubella virus-IgM, toxoplasmosis-IgM, herpes simplex virus 2-IgM, as well as Widal, Weil-Felix test, and Brucella agglutination test were all negative. The anti-extractable nuclear antigen antibodies were all negative. Liver biopsy was performed and then the diagnosis of DILI was considered based on liver pathology (Fig. 1). The patient received symptomatic treatment along with methylprednisolone (starting at 28 mg/day and reduced by 4 mg per week). The patient’s temperature and liver function were restored during treatment. However, there was recurrence of fever after 1 week of methylprednisolone withdrawal. When she came to our hospital, she was still febrile (temperature 39.5°C); however, the general physical examination was unremarkable.

At admission, the results of blood tests were: WBC 3.95 × 10^9/L; platelet 142.00 × 10^9/L; plasma prothrombin time 13.5 s; and fibrinogen 1.86 g/L. Liver biochemistry tests were: ALT 1577 U/L; AST 2354 U/L; TBIL 80.5 μmol/L; DBIL 51.2 μmol/L; albumin 33 g/L; alkaline phosphatase 468 U/L; gamma-glutamyl transferase 215 U/L; lactate dehydrogenase (LDH) 1032 U/L; triglycerides 2.67 mmol/L; erythrocyte sedimentation rate 27 mm/h; procollatin 0.06 ng/mL; and CRP 8.80 mg/L. Tuberculin skin test, anti-tuberculosis (TB) antibody, T-Spot TB test, as well as (1,3)-β-D-Glucan and Galactomannan tests were all negative. A series of blood, urine, stool, and marrow culture were repeatedly negative. CMV DNA level was <500 copies/mL; Multi-tumor markers were all within normal range. However, EBV DNA level was 2.837 × 10^6 copies/mL. The EBV antibody spectrum showed EBV-CA-IgG (+), EBV nuclear antigen (EBNA1)-IgG (+), and EBV-early antigen (EA)-IgG (+). T cell subsets: clusters of differentiation (CD)3+ 21.05%, CD3+CD4+ 8.83%, CD3+CD8 + 11.53% and CD4/CD8 0.77. On ultrasound, the size of spleen was 12.0 cm × 5.6 cm; however, there was no hepatomegaly or lymphadenecasis in neck, armpits, mediastinum, or along the abdominal blood vessels.

After admission, the patient received symptomatic treatment and antiviral therapy with a combination of acyclovir and Foscarnet Sodium. Thymosin alpha 1 and methylprednisolone were prescribed to regulate immunity and as an adjuvant to antiviral therapy. The patient’s liver biochemical profile recovered to normal range while intermittent fever continued to persist. Furthermore, an increase in EBV DNA level was also noted (4 weeks after admission: 3.01 × 10^6 copies/mL; 6 weeks after admission: 1.32 × 10^7 copies/mL). Bone marrow immunophenotyping for hematological malignancy by flow cytometry with CD45/side scatter (SSC) gating and normal cells as internal reference showed that: lymphocytes (LYs) accounted for about 31.8% of nucleated cells, of which CD3-CD56+ NK cells accounted for about 79.8% and the cells were CD2, CD38, CD56, CD94 positive, and CD7 negative (Fig. 2). Repeat evaluation of the pathologic section of the liver (borrowed from the local hospital) showed mildly expanded hepatic sinusoids with beaded arrangement of LYs; severe lymphocytic infiltration in portal tracts, mixed with occasional atypical LY with dark cytoplasm, prominent nuclei, and vacuolar nucleus (Fig. 1). EBER-1 probe in situ hybridization of hepatic pathologic section (+). One month after admission, the patient developed hematochecia but colonoscopy showed no abnormality. At this time, blood tests showed WBC 6.54 × 10^9/L (neutrophils 2.13 × 10^9/L; LYs 3.84 × 10^9/L), red blood cell 3.80 × 10^12/L; hemoglobin 106.60 g/L; platelet 234 × 10^9/L; plasma prothrombin time 12.8 s; prothrombin activity 82.00%; international normalized ratio 1.14; fibrinogen 1.03 g/L; and D-dimer 0.89 mg/L. The bleeding resolved after symptomatic treatment. Two months after admission, the patient passed away. Urine test showed red blood cells 67.3 μL and occult blood (+++). The symptoms improved after hemostatic therapy; laboratory tests showed plasma fibrinogen level of 0.77 g/L and ferritin >1200 mg/L. sCD25 in serum was 20312 pg/mL (Ref 400–2700 pg/mL). Based on the above results, the patient received treatment with etoposide and dexamethasone for diagnosis of EBV associated HLH; subsequently, her temperature, liver biochemical profile and blood lipids were restored to normal range. Repeat flow cytometry of bone marrow showed that 11.01% bone marrow cells exhibited an abnormal phenotype of mature NK cells, which accounted for 17.17% of nucleated cells and 64.13% of LYs; the cells were CD56, CD2, CD7dim, CD8dim, CD161, CD94bri,
CD159a positive, and CD3, CD4, CD5, CD16, CD159c, CD158b, CD158a/h, Ki67, CD30, CD57, CD10, T cell receptor (TCR) ab, TCRd, CD158e, CD117 negative; granzyme B positive rate was 91.51% and perforin positive rate was 93.83%; bone marrow chromosome karyotyping: 46, XX [20]; gene rearrangements of IgH and TCRγ/δ were negative. Bone marrow cytomorphologic features: 3 cell-lineage of erythrocyte, granulocyte and thrombocyte in bone marrow showed active proliferation with toxic change in some granulocytes. The proportion of LYS was within the normal range; occasionally, atypical LYS characterized by dense chromatin and purple-red particles in cytoplasm. The mononuclear-macrophage showed active proliferation and phagocytic red blood cells, platelet fragments, and coarse particles were scattered within the cytoplasm. Bone marrow pathology showed clusters or cord-shaped cells distributed in hematopoietic tissues, with large cell volume and deep nuclear staining. Reticular fiber staining: myelofibrosis-1 (Fig. 3). According to these results, the patient was eventually diagnosed as a case of EBV associated NK cell lymphoma accompanied by HLH. In September 8, 2016, the patient received the first course of revised EPOCH chemotherapy with etoposide (100 mg/d, d1–5), dexamethasone (7.5 mg/d, d1–5; 5 mg/d, d6–14), cyclophosphamide (0.8 g/d, d1–2), and pegaspargase (3750 u/d, tid, d1–2). Fifteen days later, the patient developed hematochezia again; colonoscopy showed that the location of gastrointestinal hemorrhage was in cecum.

Figure 1. Histopathological examination of liver tissue sections: multiple focal hepatocytes necrosis and apoptosis in hepatic lobule; ballooning degeneration and fatty degeneration of some hepatocytes; mildly expanded hepatic sinusoids with beaded arrangement of lymphocytes; and patches of severe piecemeal necrosis and severe lymphocytic infiltration in portal tracts, mixed with occasional atypical lymphocyte with dark cytoplasm, prominent nucleoli, and vacuolar nucleus. A) Hematoxylin-eosin staining (200×); B) Masson-trichrome staining (200×); C) Reticular fiber staining (200×); D) Periodic acid-Schiff staining (200×); E) Cytokeratin 19 staining (200×); F) CD38 staining (200×).
and ascending colon. Unfortunately, the patient died of gastrointestinal hemorrhage and multiple organ failure.

3. Discussion

EBV is a double-stranded DNA oncogenic herpesvirus which belongs to γ subfamily of herpesvirus family. Clinical manifestations and prognosis tend to vary depending on the immune status of the hosts. EBV infection rates are believed to exceed 90% and the latent infection can persist throughout the life span.[6] Decline in host cellular immunity is an important inducing factor which triggers activation of latent EBV infection. Clinical reports of CAEBV first appeared in 1948, and it was defined as a lymphoproliferative disease with chronic or repeated IM, and accompanied by increased levels of VCA-IgG, EA-IgG, and NA-IgG. Okano et al improved the diagnostic criteria of CAEBV in 2005:[7]

(1) Persistent or recurrent IM-like symptom;
(2) unusual pattern of anti-EBV antibodies with raised anti-VCA and anti-EA, and/or detection of increased EBV genomes in the affected tissues, including peripheral blood;
(3) chronic illness which cannot be explained by other known disease processes at diagnosis.

A case of CAEBV must fulfill all criteria. An EBV-associated disease such as HLH or lymphoma mainly derived from T-cell or NK-cell lineage often develops during the course of illness. The clinical manifestations are diverse with considerable inter-individual variability, because the pathological injury due to EBV infection can involve almost all organ systems, including lymph nodes, liver, spleen, blood, heart, and kidney, as well as cutaneous lesions, such as hypersensitivity reaction to mosquito bites.[8] Persistent or intermittent fever, hepatosplenomegaly, and abnormal liver biochemistry are particularly common manifestations of CAEBV, which suggests that the liver dysfunction is one of the most important manifestations of chronic EBV infection and may even lead to acute liver failure.[9] The common accepted mechanism is that the virus induces activation of cytotoxic T cells, which can synthesize and release cytokines as perforin/T cell intracellular antigen-1 and cytotoxic granules and then mediate immune hepatocyte

Figure 2. The proportion of NK cells was increased and the phenotype was abnormal based on immunophenotyping for hematological malignancy analysis (bone marrow) detected by flow cytometry with CD45/SSC gating and normal cells as internal reference. Cell population proportion in total 10^5 cells: lymphocyte (green) 31.8%, monocyte (purple) 2.3%, granulocyte (blue) 57.6%, blast cell (red) 2.0%, erythroblast (gray) 6.3%. Results: CD34+ cells accounted for 0.1% of nuclear cells, and lymphocytes accounted for about 31.8% of nucleated cells, of which CD3-CD56+ NK cells accounted for about 79.8% and the cells were CD2, CD38, CD56, CD94 positive, and CD7 negative. CD = clusters of differentiation, NK = natural killer, SSC = side scatter.
In most patients with persistent CAEBV infection, the key step in the pathogenesis is infection of T cells or NK cells by EBV, which causes clonal proliferation; the subsequent potent cytotoxic LY responses participate in EBV-associated pathologies. In addition to comprehensive adaptive T cell responses, several innate LY populations seem to target different stages of EBV infection and are compromised in primary immunodeficiencies that render individuals susceptible to symptomatic EBV infection. The consequent production of large amounts of cytokines triggers a cascade of immune inflammatory reactions. Studies have shown elevated serum levels of inflammatory factors interleukin (IL)-1β, IL-10 and interferon (IFN)-γ in CAEBV patients who have T or NK clonal proliferation, and the increase of IFN-γ is accompanied by an increase in IL-13 levels. Detection of peripheral blood mononuclear cell also confirms that the above inflammatory factors are upregulated at the gene transcription level. CAEBV patients with B cell clonal proliferation also have abnormal expressions of helper T (Th) cell subsets 1 (Th1) (tumor necrosis factor-α, IFN-γ) and Th2 (IL-6, IL-10) cytokines, as well as increased Th1/Th2 ratio. In this case, the patient with liver dysfunction was misdiagnosed as DILI. The main reason was the failure to monitor EBV DNA and antibody spectrum timely; in particular, the liver pathology showed no typical histological changes of EBV infection, especially owing to overlapping characteristics with those of DILI, along with lack of recognition by initial clinicians and pathologists. After the clinical diagnosis of EBV infection, in situ hybridization of liver tissue section with EBER-1 probe confirmed the definite diagnosis. Therefore, in the clinical setting of unexplained fever and liver injury, it is necessary to be aware of CAEBV, especially in conditions which cannot be explained by other diseases, and then detect the EBV DNA and EBV antibody spectrum in blood or affected tissue in a timely manner for a definitive diagnosis.

HLH is characterized by hyperinflammatory response to various underlying conditions such as severe infectious diseases, autoimmune diseases, malignancies, and acquired immune deficiency syndrome. EBV is the most common etiological agent that can trigger infection-related HLH. Based on the research by Cohen, mutations in 3 genes (PRF1, STXBP2, and UNC13D) are associated with HLH and can also predispose to severe chronic active EBV disease. It is important to identify these proteins which may help to identify new targets of immunosuppressive therapies to control EBV infection. HLH comprises 2 different conditions that may be difficult to distinguish from one another: a primary and a secondary form. Primary HLH is an
autosomal recessive disease with family history and juvenile onset; PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 and other genetic mutations can be found on genetic screening, which was not applicable to this patient. Secondary HLH may have many causes, including infection, cancer, and autoimmune diseases. According to the HLH diagnostic criteria revised by the International Organization of Histiocyte Societies in 2004,[13] this patient qualified 5 out of the 8 diagnostic criteria for secondary HLH. In this case, abnormal EBV DNA and antibody spectrum made the etiology of HLH clear.

In addition to EBV-associated HLH, some patients with CAEBV may even develop lymphoma or leukemia due to T cell/NK cell hyperproliferation and malignant infiltration.[16] Considering the clinical features, symptoms and laboratory test results, EBV-associated HLH was diagnosed and aggressive NK cell lymphoma was also highly suspected in this patient. EBV mainly infects the B cells and can also infect T/NK cells. CD21 transfer through immune synapses from B cells to T/NK cells provides an opportunity for EBV to infect NK cells. EBV transcription and related protein replication are detected in almost 95% of NK/T cell lymphoma cases, which demonstrates that EBV infection is associated with NK/T cell lymphoma. In this patient, we found co-existing evidence of EBV infection, HLH and NK cell lymphoma. It is entirely conceivable that EBV infection was the basic reason for HLH and NK cell lymphoma. However, given the overlapping clinical features of lymphoma and HLH (such as fever, hemophagocytosis, hepatosplenomegaly, elevated ferritin, elevated LDH), it is difficult to determine whether HLH was secondary to lymphoma or was a late complication of CAEBV. According to published literature, presence of hemophagocytosis in lymphoma patients is highly suggestive of lymphoma-associated HLH. Moreover, a high sIL-2R/ferritin ratio is a useful diagnostic marker for lymphoma-associated HLH.[17] Both these points are applicable to this case. Unfortunately, no lymph node biopsy was performed because the patient had no superficial lymph node enlargement. Fluorodeoxyglucose (FDG)- positron emission tomography/computed tomography (PET/CT) may be a useful tool for some selected cases based on clinical need. Hypermetabolic FDG foci in the liver, spleen, and bone marrow, as well as multiple FDG-avid lymph nodes, are highly suggestive of EBV-associated lymphoma. Lesions of CAEBV exhibiting FDG uptake also demonstrated the development of overt lymphoma[19] even though this patient did not receive FDG-PET/CT because of financial constraints. Although liver biopsy was performed at an early stage, the possibility of NK cell-related proliferative diseases was not in consideration; moreover, there were not enough tissue samples for special immunophenotyping and pathogen detection. After the occurrence of HLH in the late stage, hepatic puncture could not be performed for the second time due to the increased risk of internal bleeding. After the death, no autopsy was performed because of the refusal from patient’s families. If more histological evidence was obtained to confirm abnormal NK cell infiltration in multiple organs, the diagnosis could have been more conclusive.

CAEBV is a kind of rare systemic infection characterized by an aggressive clinical course and poor prognosis. Early diagnosis and treatment, and fundamental reconstruction of antiviral immunity, along with the complete removal of EBV-infected LYs or clonal proliferative LYs are key to alter the disease course and improve the prognosis. The entire disease course in this patient exhibited chronic active progress, and the treatment included antiviral therapy, immunomodulatory therapy, chemotherapy, and other comprehensive measures. The response was still not ideal, which confirms the poor effect of routine treatment in this disease.[19] Many deaths from EBV infection are due to complications of lymphoproliferative disorders derived from T/NK cells (e.g., malignant lymphoma and leukemia), and secondary HLH associated with EBV,[20] which eventually results in bleeding, infection, multiple organ failure, and DIC. Kimura et al[20,21] have demonstrated that liver dysfunction, thrombocytopenia, fever (more than once a week), splenomegaly, anemia, and age of onset more than 8 years are important predictors of poor prognosis in patients with CAEBV. The prognosis of patients with T cell clonal proliferation is even worse than that of the NK cell type. A retrospective analysis by Cohen et al[19] on 28-year CAEBV treatment in the United States showed that although antiviral and immunomodulatory treatment could relieve symptoms in the short term, these did not work well in the long-term; eventually, patients who do not receive more definitive treatment would die of complications such as infections or lymphoproliferative diseases. Immunoglobulin therapy may play a role in blocking the binding of receptor on the IgG Fc segment with phagocytes, restore the function of T cells, B cells and help recover the CD4/CD8 ratio. Therefore, it can retard the progress of the disease. EBV-specific adoptive cell therapy can be effective in some patients. Savoldo et al[22] reinfused in vitro cultured EBV-specific cytotoxic T LYs in 8 CAEBV patients; in 5 patients, this led to resolution of fever, hepatosplenomegaly and lymphadenopathy along with a decrease in serum EBV antibody levels. Only 1 case relapsed 1 year later, while the remaining 4 cases did not relapse within the next 36-month follow-up period. Allogeneic hematopoietic stem cell transplantation (HSCT) is one of the radical treatments of CAEBV, which can not only eliminate EBV-positive cells but also help reestablish anti EBV-specific cellular immunity of the recipients. However, this treatment has also been shown to be effective in only a certain proportion of patients, and its complications are potential cause of death in patients with CAEBV.[23] EBV positivity in peripheral blood was shown to be another poor prognostic factor for patients with NK/T cell lymphoma-associated HLH.[24] In addition, pre-HSCT immune-suppression also has a significant impact on the response and prognosis of patients. Kawa et al[25] found that compared with myeloablatative preconditioning regimen, a regimen of reduced pretreatment dose could improve patient tolerance. Both the 3-year overall survival and event-free survival associated with the latter were significantly higher than that associated with the former, which provided a more optimized solution for patients who had the opportunity to receive HSCT. Unfortunately, due to recurrent gastrointestinal bleeding, liver damage, and unstable condition, the patient, in this case, was not able to prepare for pretransplantation. In addition, a donor with suitable matching type was not screened in time and she had lost the chance of early bone marrow transplantation.

Author contributions

Conceptualization: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Data curation: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Investigation: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Methodology: Ya-Dong Wang, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li.
Supervision: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Cai-Yan Zhao.

Resources: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Validation: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Visualization: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Writing – original draft: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

Writing – review & editing: Ya-Dong Wang, Ling-Ling Wu, Lu-Yuan Ma, Xiao-Bo Shang, Zi-Yue Li, Wei Wang, Chuan Shen, Jing-Jing Yang, Li-Xia Sun, Cai-Yan Zhao.

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