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CASE REPORT

Successful management of infection and macrophage activation syndrome patient using low-dose etoposide: A case report

Shu-Pei Gao, Xiao-Fang Luo, Mohammadreza Kosari, Wen-Juan Li, Liu Yang, Wei Tu, Ji-Xin Zhong

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Abstract

BACKGROUND

Macrophage activation syndrome (MAS), a sub-type of hemophagocytic lymphohistiocytosis (HLH) secondary to autoimmune rheumatic diseases, is a critical and potentially fatal condition characterized by an excessive inflammatory response. Despite the established efficacy of the HLH-2004 guideline in diagnosing and treating HLH over the years, ongoing discussion persists regarding its application, especially for HLH secondary to complicated conditions, such as autoimmune rheumatic diseases combined with severe infection. Etoposide (VP-16), a topoisomerase II inhibitor that effectively induces DNA damage and subsequent apoptosis in hyperactivated immune cells, has been widely used for the treatment of HLH. However, its suppressive effect on immune system may also cause potential exacerbation of infection in autoimmune rheumatic disease-induced HLH patients complicated with severe infection. Therefore, the use of VP-16 in such cases was inconclusive.

CASE SUMMARY

In this case study, we propose a potentially effective strategy for managing a patient diagnosed with secondary HLH complicated with systemic lupus erythematosus (SLE) and chronic coronavirus disease 2019 infection. Our approach involves early administration of low-dose VP-16 (100 mg twice a week, 300 mg in

total), combined with methylprednisolone, cyclophosphamide, and cyclosporine A. The administration of etoposide effectively led to improvements in various indices of HLH.

CONCLUSION

Low dose etoposide proves to be an effective approach in alleviating HLH while mitigating the risk of infection.

Key Words: Macrophage activation syndrome; Hemophagocytic lymphohistiocytosis; Infection; Systemic lupus erythematosus; Etoposide; Case report

Core Tip: Etoposide has been utilized in severe and refractory cases of macrophage activation syndrome (MAS). However, in cases where severe infections and autoimmune disorders are present concurrently, the use of etoposide carries the risk of bone marrow suppression and exacerbation of infections. In this case report, we successfully avoided bone marrow suppression and controlled both MAS and severe infection in patients in such condition by using a modified etoposide regimen.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) encompasses a range of hematological conditions with potentially life-threatening conditions, characterized by hyperactivation of the immune system, especially macrophages, cytotoxic T-cells, and NK cells. There are two distinct types of HLH, the primary (genetic) HLH, which is commonly seen in the pediatric population[1], and the secondary (acquired) HLH, which is more frequently identified in the adult population. Secondary HLH can be provoked by malignancies, infectious diseases like epstein-barr virus (EBV), cytomegalovirus (CMV), and severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019 (COVID-19) infections, as well as rheumatological disorders, in particular sJIA, adult-onset Still disease, systemic lupus erythematosus (SLE), and Kawasaki diseases[2,3]. Macrophage activation syndrome (MAS) is referred to a condition when secondary (acquired) HLH occurs due to underlying auto-immune disorders (as SLE in our case)[4]. This condition manifests by an uncontrolled release of pro-inflammatory mediators mainly tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-1, and IL-18, along with increased expression of chemokines such as CCL2, CCL3, CCL5, and CXCL10 (especially notable in COVID-19)[3], which may in turn cause multi-organ failure and often lead to fatal outcomes.

The overall mortality rate of MAS is reported to be around 12%[5], and notably exceeds 42% in SLE patients[6]. Etoposide (VP-16), an antineoplastic agent that exerts its effects through the inhibition of topoisomerase II, has been approved by FDA for the treatment of small cell lung cancer. However, due to its excellent efficacy in managing MAS/HLH, it was recommended for the treatment of HLH in HLH-2004 guideline[7]. By inducing DNA damage and subsequent apoptosis, VP-16 can eliminate and quiescent activated T cells, with minimal impact on innate immune cells. As a result, it reduces the release of inflammatory cytokines including IFN-γ[8]. High-dose intravenous immunoglobulin (IVIG) or methylprednisolone, as the first-line treatment for HLH, may not consistently yield positive outcomes, especially in severe cases. In such instances, prompt administration of VP-16 has been proven to be beneficial. Nevertheless, it should be noted that VP-16 has an adverse effect of dose-dependent bone marrow suppression, potentially leading to prolonged neutropenia[9]. In the following case report, we present the instance of a 40-year-old Chinese female who developed HLH secondary to SLE and pulmonary infection in her hospital stay. Through early implementation of a combination therapy involving low-dose etoposide (100 mg twice a week, totaling 300 mg), methylprednisolone, cyclophosphamide, and cyclosporine A, we achieved a successful cure.

CASE PRESENTATION

Chief complaints

Her major complaint upon arriving at our hospital was an unremitting high fever of unknown origin that had lasted for over a week, peaking at 39.1 °C. The patient also reported proximal muscle weakness in the upper extremities and a dry mouth.

History of present illness

In February 2023, a 40-year-old Chinese female was referred to our hospital shortly after receiving diagnoses of SLE and pulmonary infection at a local medical facility. She provided a verbal informed consent for the documentation of her case. Other investigations were unremarkable. Prior to admission to Tongji Hospital, she had been taking oral prednisone 5 mg once daily.

History of past illness

Additionally, she was infected with COVID-19 two months prior to her admission and continued to experience intermittent episodes of coughing with white frothy sputum.

Personal and family history

Apart from a cesarean-section surgery in 2007, her medical history held no significant events.

Physical examination

During our examination, we observed a non-pruritic butterfly-shaped rash and facial swelling. On auscultation, bilateral moist rales were detected.

Laboratory examinations

Upon admission, we conducted a thorough investigation, affirming our diagnosis of MAS based on her prior medical history involving EBV, CMV, COVID-19 infection plus SLE. Notably, we observed significant elevations in ferritin, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamic transaminase (GGT), and IL-2R (sCD25), while fibrinogen levels were found to be diminished (Figure 1). The patient had fever over a week, peaking at 39.1 before admission to our hospital, hypertriglyceridemia (3.51 mmol/L), high ferritin (1959 μg/L), low number of NK cells [NK cells count: 75/μL (Reference range: 150-1100/μL)]; high sCD25 (IL-2R) level [1493 U/mL (reference range: 223-710 U/mL)], supporting the diagnosis of HLH according to the HLH 2004 criteria. However, hemophagocytosis was not evident in the bone marrow biopsy, and no hepatosplenomegaly was observed in the ultrasound. The rheumatological blood panel disclosed several abnormal markers consistent with an SLE diagnosis. Specifically, we detected elevations in ANA, anti-dsDNA, anti-Smith antibody, anti-u1-nRNP, anti-histone antibody, anti-nucleosome antibody, and anti-RO52, while complement 3 and complement 4 were low. Although both CMV and EBV nucleic acid tests were negative, serological markers indicated a pattern of past infection. Urinalysis showed a total urine protein of 84 mg/L, with a total trace protein of 14.4 mg/L. A 24-hour urine collection showed a total urine protein of 243.6 mg/24 hours, and a total trace protein of 41.8 mg/24 hours, indicating damage to kidney due to SLE.

Imaging examinations

Chest computed tomography (CT) revealed several key features: Multiple nodules in both lungs, notably a larger nodule at the right lung apex; thickening of interlobular septa in both lungs, indicative of interstitial pulmonary edema; a small volume of pericardial effusion; a slight bilateral pleural effusion; and a slight bilateral interlobular effusion.

FINAL DIAGNOSIS

The patient was diagnosed with MAS and SLE with pulmonary infection.

TREATMENT

The patient was given methylprednisolone succinate 40 mg IV (daily), cyclosporine A, cyclophosphamide, and a limited course of etoposide 100 mg twice weekly for 3 sessions upon admission. Prior to initiating etoposide treatment, the patient developed hypoxemia. A chest CT angiography ruled out embolism, prompting consideration of hypoxemia origins: Pulmonary inflammatory exudation or microthrombosis linked to hemophagocytic syndrome. As precautionary measure, prophylactic heparin was prescribed. Following the application of etoposide, various indicators exhibited significant improvement. Initial laboratory results before etoposide treatment revealed a hyper-inflammatory state, characterized by elevated levels of ferritin (1659.1 ug/L), lactate dehydrogenase (325 U/L), IL-2 receptor (1457 U/mL), IL-10 (49.3 pg/mL), and TNF-α (32.2 pg/mL). Despite several days of treatment with methylprednisolone succinate and cyclophosphamide, no favorable changes were observed. Due to diagnosis of hemophagocytic syndrome and pulmonary infection, a low-dose etoposide regimen (100mg IV) was administered on the 4th, 8th, and 11th days of hospitalization, totaling 300 mg. Interestingly, after the first etoposide administration, a remarkable decrease in ferritin level (from 1659.1 to 769.7 ug/L) was seen. Furthermore, a notable decrease of at least two-fold was observed in IL-2 receptor, IL-10, and TNF-α. Fibrinogen level dropped below 2 g/L and remained low for 10 days (Figure 1). Hence, a single dose of human fibrinogen 500 mg IV was infused, resulting in a gradual and sustained increase in fibrinogen levels, which was normalized by the 21st day of hospitalization. Fibrinogen infusion and the third dose of etoposide were administered on the 11th day of hospitalization. Because both treatments were given on the same day, it's possible that the improvement was a result of both primary and supportive treatments. In conjunction with etoposide, other treatments were introduced,

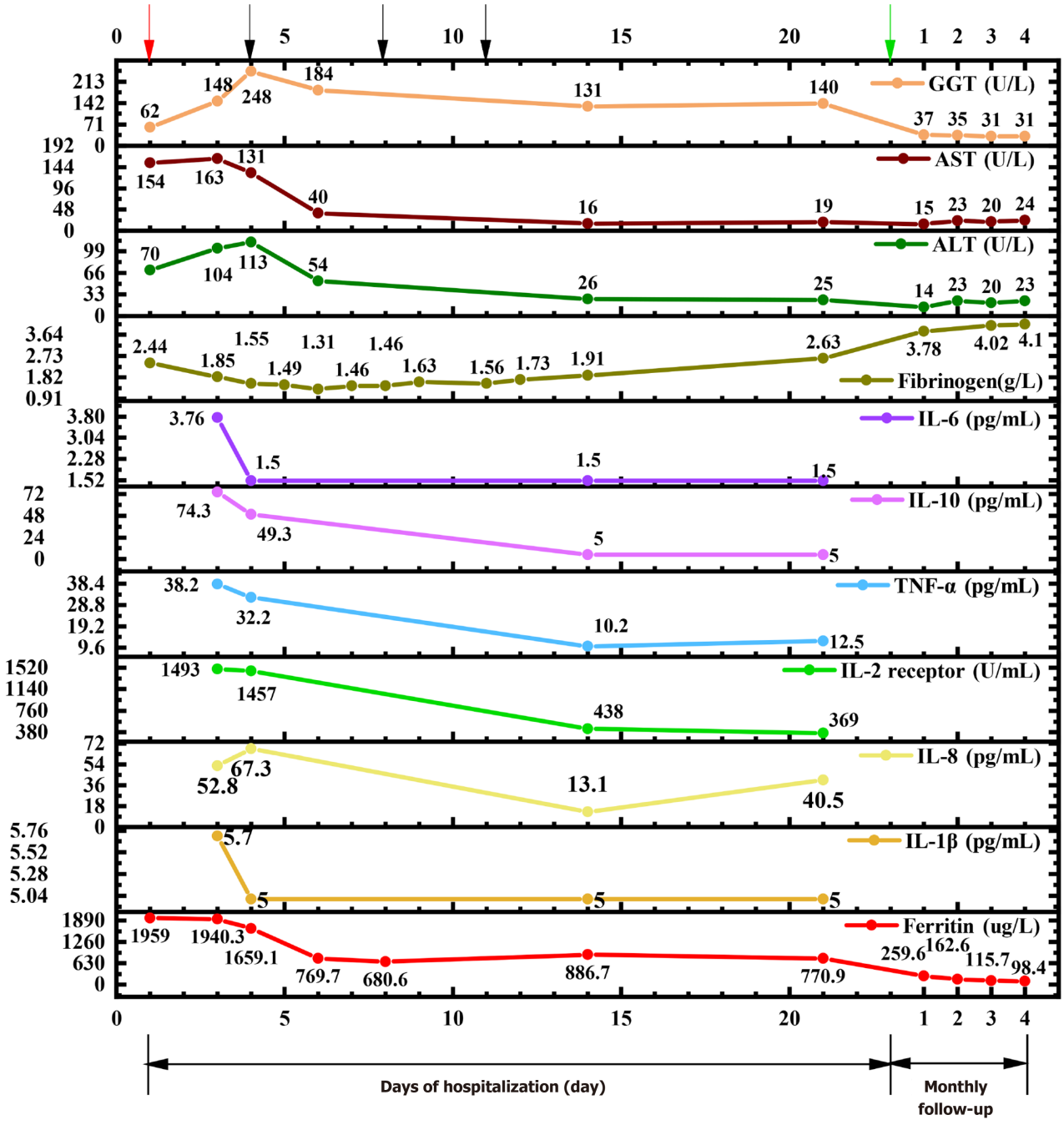

Figure 1 Key index trend before and after treatment with etoposide. Vertical coordinates: Levels of indexes; Horizontal ordinate: Days of hospitalization or monthly follow-up. Red arrow: Admission; Black arrow: Etoposide administration; Green arrow: Discharge.

including "IVIG" 5 g/day for five consecutive days (totaling 25 g), as well as cefoperazone + sulbactam 3 g IV daily, ganciclovir 250 mg IV daily, fluconazole 200mg PO daily to prevent further pulmonary complications. Cefoperazone and sulbactam were used on the second day of hospitalization. On the first day, white blood counts (WBC) count was 2.45 × 10^9/L (reference range: 3.5-9.5 × 10^9/L), neutrophils count was 1.61 × 10^9/L (reference range: 1.8-6.3 × 10^9/L), lymphocytes count was 0.6 × 10^9/L (reference range: 1.1-3.2 × 10^9/L). The patient was susceptible to severe infection, so cefoperazone and sulbactam were prescribed to prevent infection. A single session of therapeutic plasma exchange was performed. Plasma exchange was performed on the fourth day of hospitalization. As shown in Figure 1 before plasma exchange, the levels were as follows: Ferritin at 1659.1 μg/L, IL-8 at 67.3 pg/mL, sCD25 at 1457 U/mL, TNF-α at 49.3 pg/mL, ALT at 113 U/L, AST at 131 U/L, and GGT at 248 U/L. After plasma exchange, these levels significantly decreased: Ferritin dropped to 769.7 μg/L, IL-8 to 13.1 pg/mL, sCD25 to 438 U/mL, TNF-α to 10.2 pg/mL, ALT to 54 U/L, AST to 40 U/L, and GGT to 184 U/L. These reductions indicate that plasma exchange was effective. Two infusions of human granulocyte colony-stimulating factor (G-CSF) at a dose of 200 μg were administered. G-CSF is a common medication to increase the number of white blood cells and neutrophils. In our case due to low WBCs and neutrophils (WBC: 2.66 and 3.14 × 10^9/L; Neutrophils: 1.67 and 2.49 × 10^9/L on 4th and 22nd day respectively), G-CSF was infused on the 4th day and 23rd day of hospitalization (Supplementary Table 1). After 23 days of treatment, the patient was discharged from the

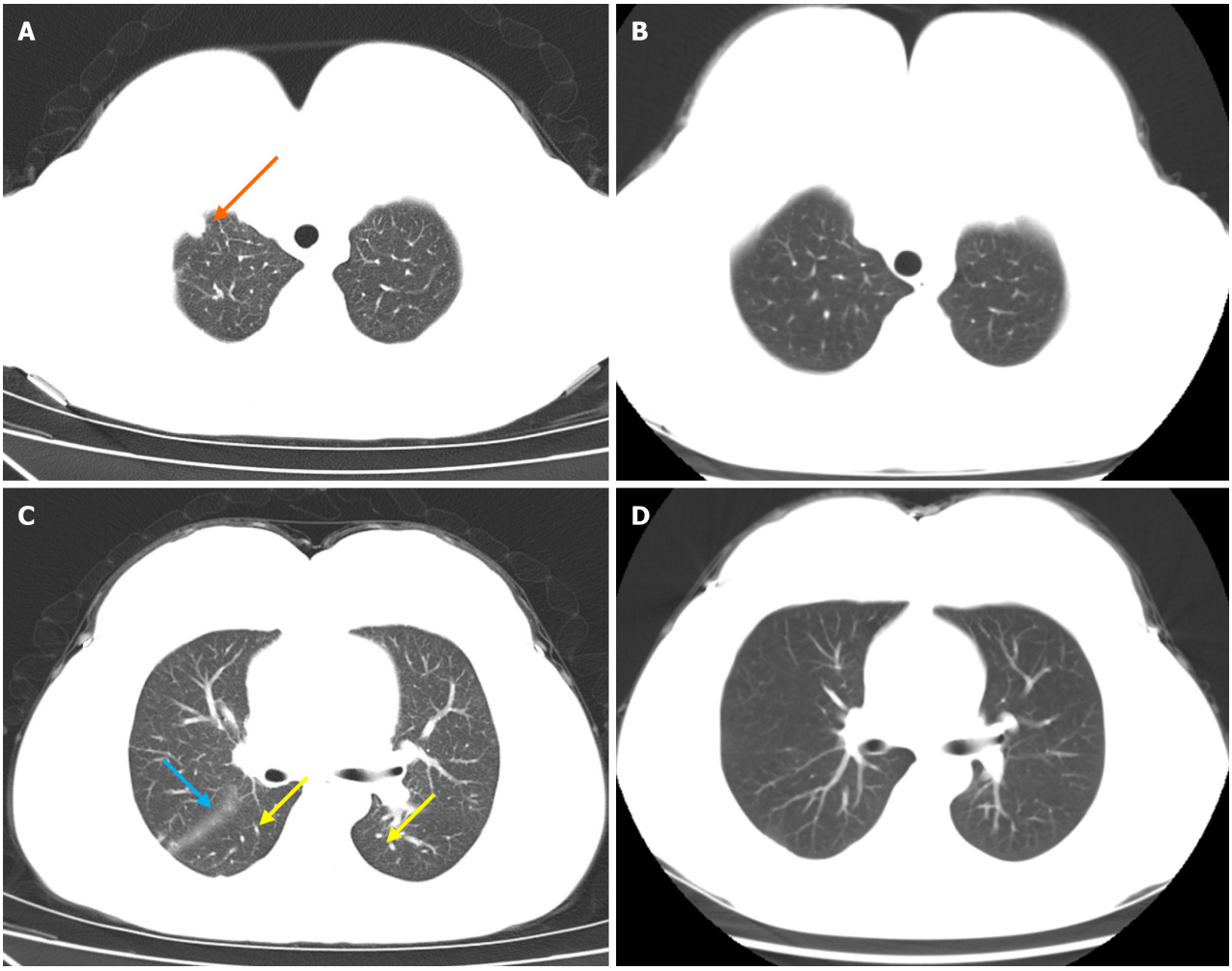

Figure 2 Chest computed tomography scan images before and after treatment. A and C: Chest computed tomography (CT) scan images before treatment; B and D: Chest CT scan images after treatment. Arrows: Nodes or interlobular septa before treatment

hospital.

OUTCOME AND FOLLOW-UP

Monthly appointments were arranged until 4 months after discharge, revealing evident improvement in lung lesions. Anti-dsDNA testing yielded negative results, indicating remission of SLE. No coagulopathy was present. Ferritin levels remained within the desirable range. Chest CT result showed the presence of micronodules in the upper lobe of the right lung and lower lobe of the left lung. A few cord-like foci were observed in the lingular segment of the upper lobe of the left lung and the lower lobe of the right lung. Some nodules had disappeared compared with the previous CT scan (Figure 2). There was no evidence of malignancy 4 months after discharge.

DISCUSSION

Etoposide is typically considered for refractory cases of HLH or when the first-line treatment (high-dose corticosteroid and cyclosporine) fails to yield desirable outcomes. In this case report, given the undesirable responses to treatments with methylprednisolone succinate and cyclophosphamide, we decided to introduce etoposide. However, administering high doses of etoposide may potentially lead to bone marrow suppression, which posed a concern given the patient's concurrent pulmonary infection. Standard dosage of etoposide as per the HLH-2004 guideline may exacerbate the existing infection. It has been reported that a lower dose of etoposide (50 mg/m^2 per dose) is effective in addressing macrophage activation and hypercytokinemia. Four patients experienced complete resolution of hemophagocytic signs and symptoms following a single infusion of etoposide, while the remaining patients required two infusions. No patients had experienced recurrent hemophagocytic phenomenon[9]. Although several reports have demonstrated early administration of low-dose etoposide was successful in treating HLH patients[6,10-14], the efficacy of this approach in MAS patients, especially in those in combined with severe infections was not reported. In this case, we adopted the low-dose etoposide

strategy to manage the MAS patient with SLE and pulmonary infection, resulting in a successful outcome. Subsequent to the treatment of low-dose etoposide, each inflammatory index was improved, with a crucial highlight being the absence of infection worsening. The post-discharge follow-up results of this patient showed favorable progress, including improvement of both MAS and pulmonary infections.

Cytotoxic T cells (CTLs), also known as killer T cells or $CD8^+$ T cells, are a type of T cells that are able to eliminate cancer cells, virus-infected cells, as well as damaged cells. Low-dose etoposide is believed to restore immune homeostasis by clearing activated immune cells including CTLs and macrophages, along with restraining their production of inflammatory cytokines. This action not only diminishes macrophage activity, but also prompts newly activated CTLs to clear macrophages and virus-infected cells[15].

CONCLUSION

In conclusion, employing a low dose and short course of etoposide proves to be an effective approach in alleviating MAS while mitigating the risk of infection. This approach is particularly suitable for MAS patients with concurrent infection. By reducing the cumulative etoposide dosage and optimizing the dosages of other medications to their minimal effective levels can minimize the risk of potential adverse effects. However, it's worth noting that the available data are limited, thus further research is necessary to fully explore the potential benefit of low dose etoposide.

FOOTNOTES

Author contributions: Gao SP, Luo XF and Kosari M contributed equally to this study (responsible for data collection and analysis); Zhong JX, Tu W, and Yang L contribute equally to the study design and data analysis; Gao SP, Li WJ, and Kosari M drew the data and drafted the manuscript; Zhong JX revised the manuscript. All authors have confirmed the final approval.

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