

# World Journal of *Clinical Cases*

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## Guillain-Barré syndrome and hemophagocytic syndrome heralding the diagnosis of diffuse large B cell lymphoma: A case report

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### Abstract

#### BACKGROUND

Central nervous system (CNS) lesions and peripheral neuropathy are rare among patients with non-Hodgkin's lymphoma (NHL). Lymphomatous infiltration or local oppression usually accounts for CNS or peripheral nerve lesions. The incidence of peripheral neuropathy was 5%. Guillain-Barré syndrome (GBS) is rare and may occur in less than 0.3% of patients with NHL. Hemophagocytic syndrome (HPS) is a rare complication of NHL. It has been reported that 1% of patients with hematological malignancies develop HPS. Diffuse large B-cell lymphoma (DLBCL) combined with GBS has been reported in 10 cases.

#### CASE SUMMARY

We report the case of a 53-year-old man who was initially hospitalized because of abnormal feelings in the lower limbs and urinary incontinence. He was finally diagnosed with DLBCL combined with GBS and HPS after 16 d, which was earlier than previously reported. Immunoglobulin pulse therapy, dexamethasone, and etoposide were immediately administered. The neurological symptoms did not improve, but cytopenia was relieved. However, GBS-related clinical symptoms were relieved partially after one cycle of rituximab - cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) chemotherapy and disappeared after six cycles of R-CHOP.



## CONCLUSION

GBS and HPS heralding the diagnosis of Epstein-Barr virus DLBCL are rare. Herein, we report a rare case of DLBCL combined with GBS and HPS, and share our clinical experience. Traditional therapies may be effective if GBS occurs before lymphoma is diagnosed. Rapid diagnosis and treatment of DLBCL are crucial.

**Key Words:** Diffuse large B cell lymphoma; Guillain-Barré syndrome; Hemophagocytic syndrome; Peripheral neuropathy; Case report

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**Core Tip:** Guillain-Barré syndrome (GBS) is uncommon in diffuse large B-cell lymphoma (DLBCL). GBS and hemophagocytic syndrome (HPS) heralding the diagnosis of Epstein-Barr virus DLBCL are clinically rare. Herein, we report a rare case of DLBCL complicated with GBS and HPS. We also analyze the reported cases extracted in PubMed in terms of all the possible etiologies of GBS. Traditional therapies may be ineffective in patients who develop GBS before lymphoma is diagnosed. Rapid diagnosis and treatment of DLBCL are crucial.

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## INTRODUCTION

Central nervous system (CNS) lesions and peripheral neuropathy are rare among patients with non-Hodgkin's lymphoma (NHL). Lymphomatous infiltration or local oppression usually accounts for CNS or peripheral nerve lesions. The reported incidence rate of peripheral neuropathy is 5%[1]. Guillain-Barré syndrome (GBS) occurs in less than 0.3% of the NHL patients[1]. Hemophagocytic syndrome (HPS) is a rare complication of NHL. It has been reported that 1% of patients with hematological malignancies develop HPS[2]. Herein, we report a case of diffuse large B-cell lymphoma (DLBCL) combined with GBS and HPS.

## CASE PRESENTATION

### Chief complaints

A 53-year-old man was hospitalized because of abnormal feelings in the lower limbs and urinary incontinence for more than 10 d.

### History of present illness

Symptoms started more than 10 d before presentation with recurrent abnormal feelings in the lower limbs and urinary incontinence.

### History of past illness

The patient denied any history of past illness.

### Personal and family history

The patient denied any family history of malignant tumors.

### Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.1 °C; blood pressure, 119/71 mmHg; heart rate, 96 beats per min; and respiratory rate, 20 breaths per min. Moderate enlargement of the spleen, obvious reduction in muscle strength of the lower limbs, mild hypoalgesia below the hips, especially below the knees, and almost complete disappearance of knee-jumping reflexes were observed. The muscle strength of the lower extremities progressively decreased, and the patient could not walk for several days.



### Laboratory examinations

Routine blood tests revealed a normal white blood cell count, hemoglobin level of 117 g/L (normal range 130-175 g/L), and platelet count of  $43 \times 10^9/L$  (normal range  $100-300 \times 10^9/L$ ). His lactate dehydrogenase level was 730 U/L (normal range 120-250 U/L). Coagulation function test showed a significant increase in D-dimer (10.23 mg/L, normal range 0.00-0.55 mg/L). The DNA of the Epstein-Barr virus (EBV) was normal. Electromyography showed peripheral nerve lesions in the lower limbs, axonal lesions involving motor fibers, and conduction abnormalities in the left and right somatosensory evoked potential. The tests for peripheral neuropathy-related antibodies were positive for GD IgM, GD IgM3, and GT1a IgM. The patient rapidly developed anemia and thrombocytopenia, and underwent further examinations. Triglyceride was 3.28 mmol/L (normal range  $< 1.7$  mmol/L). Ferritin was 799.4 ng/mL (normal range 21.81-274.66 ng/mL). 4% reticulocytes were found in the bone marrow smear, and hemophagocytosis was obvious. Natural killer (NK) cell activity was 0.2% (normal range  $\geq 4\%$ ). The soluble interleukin 2 receptor (sIL-2R/sCD25) level was 7030 U/mL (normal range 223-710 U/mL).

### Imaging examinations

Colored ultrasound examination of the abdomen indicated a non-uniform echo of the liver and spleen parenchyma and moderate enlargement of the spleen. Positron emission tomography-computed tomography (PET-CT) scan confirmed splenomegaly and showed increased and diffuse intake of fluorodeoxyglucose (FDG), with a maximum standard uptake value (SUV) of 11.8 and an average SUV of 8.3 in the spleen. The bilateral adrenal glands were significantly enlarged with abnormally high FDG intake. PET-CT revealed no enlarged lymph nodes or areas with abnormal FDG intake.

## MULTIDISCIPLINARY EXPERT CONSULTATION

The patient underwent splenectomy, and diagnosed with EBV-positive DLBCL based on spleen biopsy. Fluorescent in situ hybridization did not detect BCL-2, BCL-6, or C-MYC translocations. In situ hybridization was positive for EBV-encoded small RNA. The biopsy did not show bone marrow involvement.

## FINAL DIAGNOSIS

GBS, HPS, and EBV-positive DLBCL ([Table 1](#))[3,4].

## TREATMENT

Immediately after the GBS and HPS were diagnosed, the patient started on immunoglobulin pulse therapy (400 mg/kg daily for 5 d), dexamethasone (10 mg daily), and etoposide (100 mg weekly). For EBV-positive DLBCL, the patient received one cycle of R-CHOP chemotherapy (rituximab 375 mg/m<sup>2</sup> on day 0; prednisone 60 mg/kg on days 1-5; adriamycin liposomes on day 1; cyclophosphamide on day 1; vincristine on day 1). All the treatment protocols were determined by clinicians and patients together.

## OUTCOME AND FOLLOW-UP

The use of immunoglobulin pulse therapy, dexamethasone and etoposide did not improve his neurological symptoms, but cytopenia was relieved. However, after one cycle of rituximab - cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) chemotherapy, his blood cells and triglycerides returned to normal levels. The NK cell activity was increased by 3.7%. The soluble interleukin 2 receptor (sIL-2R/sCD25) decreased to 1127 U/mL. The lower limb muscle strength gradually improved, and the patient was able to walk with support. The patient experienced pain in his lower limbs and had normal bowel functions. After six cycles of R-CHOP treatment, urinary retention disappeared.

## DISCUSSION

DLBCL is one of the most common types of lymphomas. Occasionally, HPS can be an initial manifestation of tumor factors and EBV infection[5]. GBS is rarely diagnosed prior to lymphoma[6]. The incidence of GBS in NHL is low. Almost all studies of lymphoma-related GBS are case reports. NHL combined with GBS is more common than Hodgkin's lymphoma alone. In the present case, GBS and

**Table 1 Diagnostic criteria for diffuse large B cell lymphoma, Guillain-Barré syndrome and hemophagocytic syndrome**

	Diffuse large B cell lymphoma	Guillain-Barré syndrome[3]	Hemophagocytic syndrome[4]
Diagnostic criteria	Diagnosis is based on WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues	Bilateral and flaccid weakness of limbs Decreased or absent deep tendon reflexes in weak limbs; Monophasic course and time between onset-nadir 12 h to 28 d; CSF cell count < 50/μL <sup>1</sup> ; CSF protein concentration > normal value <sup>1</sup> ; NCS findings consistent with one of the subtypes of GBS; Absence of alternative diagnosis for weakness	The diagnosis HLH can be established if either 1 or 2 below is fulfilled: (1) A molecular diagnosis consistent with HLH; and (2) Diagnostic criteria for HLH fulfilled five out of the eight criteria below. (A) Initial diagnostic criteria (to be evaluated in all patients with HLH): Fever; Splenomegaly; Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin < 90 g/L (in infants < 4 wk: Hemoglobin < 100 g/L). Platelets < 100 × 10 <sup>9</sup> /L. Neutrophils < 1.0 × 10 <sup>9</sup> /L; Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides 3.0 mmol/L ( <i>i.e.</i> , 265 mg/dL); Fibrinogen < 1.5 g/L; Hemophagocytosis in bone marrow or spleen or lymph nodes; No evidence of malignancy. (B) New diagnostic criteria; Low or absent NK-cell activity (according to local laboratory reference); Ferritin 500 mg/L; Soluble CD25 ( <i>i.e.</i> , soluble IL-2 receptor) 2400 U/mL

<sup>1</sup>If colony-stimulating factor is not collected or results not available, nerve electrophysiology results must be consistent with the diagnosis Guillain-Barré syndrome.

NCS: Nerve conduction studies; GBS: Guillain-Barré syndrome; HLH: Hemophagocytic lymphohistiocytosis; CSF: Colony-stimulating factor.

HPS were simultaneously confirmed, heralding the diagnosis of lymphoma. According to the previous case reports, the lymphoma types in these cases combined with GBS include DLBCL, Burkitt lymphoma, splenic marginal zone lymphoma, and peripheral T-cell lymphoma[1,7,8]. Only approximately 10 cases of DLBCL have been reported to date[1,9-19].

GBS is an immune-mediated acute inflammatory peripheral neuropathy that manifests as damage to the multiple nerve roots and peripheral nerves. The main pathological feature is extensive inflammatory demyelination of the peripheral nerves. It is a motor neuropathy that progresses rapidly. The two most common types of GBS are acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy. Other types of GBS, including acute motor-sensory axonal neuropathy (AMSAN), Millen-Fisher syndrome, acute pan-autonomic neuropathy, and acute sensory neuropathy, are relatively rare [18]. Although most cases are curable, some patients may progress rapidly with irreversible nerve damage. Our patient had typical peripheral neuropathy symptoms prior to the diagnosis of DLBCL. GBS was considered to be AMSAN. GBS-related gangliosides were tested, and GD2 IgM, GD IgM3, and GT1a IgM, which appear to be atypical gangliosides, were positive. Gangliosides were positive in two out of five cases of DLBCL, with positive GBS, GM2 IgM, GM1 IgM, and GD1b IgM[10,15]. However, the pathogenesis of GBS remains elusive. Molecular simulations are considered the primary mechanism [20]. Most studies have suggested that infection, neurotoxicity caused by chemical agents, infiltration of the peripheral nervous system and nerve root cells by lymphoma, vasculitis involving the nervous system caused by tumors, lymphoma cells blocking tiny blood vessels leading to ischemia, tumor-related protein deposition, and tumor-related bioactive substances may affect the immune system[13, 21]. Atamer *et al*[22] explained that various factors led to the activation of T cells and the production of antibodies against protein antigens, finally resulting in damage to peripheral nerves. In GBS animal models, Th1 and Th17 cytokines are upregulated in the acute phase, and Th2 cytokines increase in the recovery phase, suggesting that T cell immune regulation disorders play a vital role in the pathogenesis of GBS[23]. Given that patients present with concomitant GBS and HPS, and HPS is also a clinical syndrome presenting with T cell activation, we hypothesized that tumor-related immune activation might be the primary pathogenesis for our patient.

A literature review indicated that DLBCL patients with GBS were typically elderly; more than 80% of patients were male and aged over 60 years (Table 2). Neurophysiological examinations showed that both the upper and lower extremities could be involved and both the motor and sensory systems could be damaged. GBS can occur prior to the diagnosis of lymphoma. Tumor factors are primarily responsible for this type of GBS. GBS can also occur after the diagnosis or treatment of lymphoma. Infection or neurotoxicity caused by chemotherapeutic agents can lead to GBS. In these reports, glucocorticoids alone or in combination with plasmapheresis were widely used in the immunoglobulin pulse therapy for GBS. Chemotherapy protocols for CHOP±R and R-DA-EPOCH were chosen most frequently. Occasionally, radiation therapy was administered. The outcomes were usually unsatisfactory in patients who developed GBS before lymphoma diagnosis, and used only immunoglobulin pulse therapy. GBS can be cured in most patients who develop it after chemotherapy. Our patient was immediately treated with immunoglobulin pulse therapy, etoposide, and dexamethasone after GBS and HPS were confirmed. Neurological symptoms slowly resolved and disappeared after R-CHOP chemotherapy. GBS and HPS are emergency conditions requiring rapid management. Our clinical experience suggests that it is critical to administer directed therapy, identify underlying conditions, and quickly initiate treatment. We reviewed 12 cases of DLBCL combined with GBS (Table 2). Among these cases, five (41.7%) had GBS before DLBCL diagnosis, and six had GBS after DLBCL diagnosis. Almost all patients were treated with immunoglobulins, and some were treated with plasmapheresis or

**Table 2** Reported cases of diffuse large B cell lymphoma combined with Guillain-Barré syndrome

Case	Publication year	Country	Age (yr)/gender	Type of GBS	Immune performance	Nerve conduction studies	Onset of GBS	Treatment of GBS and lymphoma	Response to treatment with IVIG/plasmapheresis	Ref.
1	2015	Australia	F/72	AMSAN	Negative	Absent sensory and motor responses and decreased amplitude in the upper and lower limbs, absent H reflexes, and reduced F waves in the upper and lower limbs	After chemotherapy	GBS: IVIG, 400 mg/kg/dx 5 d. Lymphoma: R-CHOP, radiotherapy	Progress is fast, dead	[1]
2	2013	Pakistan	M/70	Unknown	Unknown	Undetectable H reflexes, prolonged distal motor latencies in the right tibial, right ulnar, and bilateral median nerves, evidence of a conduction block in the right tibial nerve. Electromyography (EMG) showed no evidence of denervation	Before chemotherapy	GBS: IVIG 1 g/kg. Lymphoma: R-CHOP	Yes, recurrence of GBS, dead	[9]
3	2013	Germany	M/75	Unknown	GM2 IgM	Axonal-demyelinating sensorimotor polyneuropathy was accentuated in the legs and the sensory system	After chemotherapy	GBS: IVIG, 30 g/dx 3 d, plasmapheresis. Lymphoma: R-CHOP	No	[10]
4	2015	China	M/65	Atypical, the exact type is unknown	Unknown	Unknown	Spinal cord compression	Methylprednisolone, 500 mg	Unknown	[11]
5	2012	Japan	F/83	Unknown	Unknown	Unknown	After chemotherapy	GBS: IVIG, steroid pulse (the dosage is unknown). Lymphoma: CHOP, R-CHOP	Yes, CMV infection, dead	[12]
6	2019	Japan	M/67	Unknown	Unknown	Prolonged distal motor latencies in the median and ulnar nerves and decreased motor and sensory nerve conduction velocities in the median, ulnar, and tibial nerves	Before chemotherapy	GBS: IVIG, 400 mg/kg/dx 5 d. Lymphoma: High-dose CTX	No, dead	[13]
7	2020	USA	M/67	Unknown	Negative	Unknown	After chemotherapy	GBS: IVIG, 400 mg/kg/dx 5 d. Lymphoma: R-DA-EPOCH	Yes, Residual neurological deficits present	[14]
8	2019	China	unknown	Unknown	GM1 IgM, GD1b IgM	Absent sensory action potentials in the lower limbs	Unknown	Unknown	Unknown	[15]
9	2012	United States	M/61	Miller Fisher syndrome (MFS)	Negative	Prolonged distal motor latency (right median, ulnar, and tibial motor nerves), slowed motor nerve conduction velocity (right median and tibial motor nerves), prolonged minimum F-wave latencies (right median, ulnar, and tibial nerves), or absent F-waves (left fibular nerve)	Before chemotherapy	GBS: IVIG, 400 mg/kg/dx 5 d. Lymphoma: R-CHOP	Yes, recurrence of GBS, improved after chemotherapy, died of pulmonary embolism	[16]
10	2018	Japan	F/48	GBS-like	Unknown	Unknown	Neurolymphomatosis	GBS: IVIG, steroid pulse (dosage is unknown). Lymphoma: R-CHOP	Yes, recurrence of GBS, dead	[17]
11	2020	Japan	M/70	Unknown	Unknown	The amplitude of compound muscle action potentials was reduced, and the F wave's incidence was significantly reduced in the motor nerves	After chemotherapy (combined with phlegmonous gastritis)	GBS: IVIG, 400 mg/kg/dx 5 d. Lymphoma: R-CHOP	Yes	[18]

						(ulnar and median). In the sensory nerves (ulnar, median, and radial), the amplitude of sensory nerve potentials was in the lower limits of normal				
12	2006	Spain	M/57	Unknown	Unknown	A severe reduction in amplitude of motor evoked potentials in the right peroneal and posterior tibial nerves, with a moderate decrease in the left median and cubital nerves	After chemotherapy	GBS: IVIG, 400 mg/kg/dx 5 dLymphoma: Splenectomy, CHOP, radiotherapy, R maintenance	Yes	[19]

DLBCL: Diffuse large B cell lymphoma; GBS: Guillain-Barré syndrome; IVIG: Intravenous immunoglobulin; R-CHOP: Rituximab-cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; AMSAN: Acute motor-sensory axonal neuropathy.

glucocorticoids. All patients who developed GBS after DLBCL diagnosis recovered. Compared with patients diagnosed with GBS after DLBCL, one of the five patients with GBS before DLBCL diagnosis did not benefit from immunoglobulin therapy, and three patients relapsed after GBS treatment. Consistent with the literature, our patient did not initially respond to immunoglobulin, and his neurological symptoms were relieved slowly and finally disappeared after R-CHOP chemotherapy. Therefore, we hypothesized that lymphoma might be the primary cause of GBS and that chemotherapy for lymphoma may be the key to improving the patient's symptoms.

HPS is a rare clinical syndrome with a highly inflammatory state caused by abnormally activated macrophages and cytotoxic T-cells, resulting in cytokine storms and organ damage. HPS is divided into primary and secondary types, with lymphoma being one of the most important factors causing HPS [24]. EBV is an essential driver in the pathogenesis of HPS. Lymphoma-associated HPS (LAHS) is a clinical process that progresses rapidly, is often life-threatening, and has a poor prognosis[25]. Delayed diagnosis of underlying diseases may delay life-saving treatment of LAHS. Consequently, it is not sufficient to merely treat HPS without aggressive lymphomas. Patients with HPS may respond to the treatment initially, but have a quick relapse without further management if an underlying lymphoma is not found[25]. The mean time to lymphoma diagnosis was 22 d[26]. A long diagnosis time (> 20 d) is a negative factor for poor prognosis[26]. Our patient was finally diagnosed with EBV-positive DLBCL combined with GBS and HPS within 16 d, which is earlier than a previous report[26]. Timely treatment may be crucial to achieving good outcome.

## CONCLUSION

GBS and HPS heralding the diagnosis of EBV DLBCL are clinically rare. We report a rare case of DLBCL combined with GBS and HPS, and share our clinical experience. Traditional therapies may be ineffective in patients who develop GBS before lymphoma is diagnosed. Rapid diagnosis and treatment of DLBCL are crucial.

## FOOTNOTES

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