

# Guillain-barre Syndrome and Hemophagocytic Syndrome heralding the Diagnosis of Diffuse Large B Cell Lymphoma: A Case Report and Literature Review

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## Case report

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# Abstract

## Background

Central nervous system (CNS) lesions and peripheral neuropathy are rare among non-Hodgkin's lymphoma (NHL) patients. Usually, lymphoma infiltration or local oppression account for CNS or peripheral nerve lesions. The incidence of peripheral neuropathy was reported to be 5%. Guillain-Barre Syndrome (GBS) is rarer and may occur in less than 0.3% of NHL patients. Hemophagocytic syndrome (HPS) is another rare complication of NHL. It was reported that 1% of patients with hematological malignancies suffer from HPS. Diffuse large B cell lymphoma (DLBCL) combined with GBS has been reported in 10 cases to date.

## Case presentation

Herein, we reported the case of a 53-year-old man, who was initially hospitalized for abnormal feeling in lower limbs and urinary incontinence. He was finally diagnosed as DLBCL combined with GBS and HPS after 16 days, which is earlier than previously reported. Immunoglobulin pulse therapy, dexamethasone and etoposide were immediately administered. The neurological symptoms did not improve obviously, but cytopenia was relieved. However, GBS-related clinical manifestations partially recovered after one cycle of R-CHOP (Rituximab-Cyclophosphamide, Hydroxydaunorubicin, vincristine, Prednisone) chemotherapy, and disappeared after six cycles of R-CHOP.

## Conclusions

Literature review indicated that DLBCL patients combined with GBS were usually elderly, more than 80% of patients were male and over 60 years old. GBS could occur before lymphoma is diagnosed or occur after lymphoma is diagnosed or treated. Pathogenesis of GBS remains unclear. Molecular simulation is considered as the main mechanism. For such patients, tumor-related immune activation may be the main pathogenesis, and chemotherapy for lymphoma may be crucial. GBS and HPS heralding the diagnosis of EBV DLBCL is clinically rare. Herein, we reported a rare case and shared our clinical experience. If GBS occurs before lymphoma diagnosis, traditional therapies may be effective. Rapid diagnosis and timely treatment of DLBCL are crucial.

## Background

Central nervous system (CNS) lesions and peripheral neuropathy are rare among non-Hodgkin's lymphoma (NHL) patients. Usually, lymphoma infiltration or local oppression accounts for CNS or peripheral nerve lesions. The reported incidence of peripheral neuropathy is 5% [1]. Guillain-Barre Syndrome (GBS) is rarer and may occur in less than 0.3% of NHL patients [2]. Hemophagocytic syndrome (HPS) is another rare complication of NHL. It was reported that 1% of patients with hematological malignancies suffer from HPS [3]. Herein, we reported a case of diffuse large B cell lymphoma (DLBCL) combined with GBS and HPS.

## Case Presentation

A 53-year-old man was first hospitalized with abnormal feeling in lower limbs and urinary incontinence. Physical examination showed medium enlargement of spleen, obvious reduction of muscle strength in lower limbs, mild hypoalgesia below the hips and especially below the knees, and almost complete disappearance of knee-jumping reflexes. Muscle strength of the lower extremities had decreased progressively, and the patient was unable to walk within several days. At admission, blood routine test revealed normal white blood cell (WBC) count, hemoglobin of 117 g/L and platelets of  $43 \times 10^9/L$ . However, the patient rapidly developed anemia and thrombocytopenia. Lactate dehydrogenase (LDH) was 730 U/L, which was higher than normal level. Coagulation functions showed major increase of D-dimer, which was 10.23 mg/L. EB virus DNA was at normal level. Electromyography showed peripheral nerve lesions in lower limbs, axonal lesions involving moving fibers, and conduction abnormalities in left and right SEP. Tests of peripheral neuropathy-related antibodies showed GD IgM, GD IgM3 and GT1a IgM were positive. Colored ultrasound examination of abdomen indicated non-uniform echo of both liver and spleen parenchyma, and medium enlargement of spleen. Triglyceride was 3.28 mmol/L. Ferritin was 799.4 ng/ml, 4% reticulocytes were found in bone marrow smear, and hemophagocytosis was obvious. Activity of NK cells was 0.2%. Soluble interleukin 2 receptors (sIL-2R/sCD25) was 7030 U/ml. So concomitant GBS and HPS were considered. Immunoglobulin pulse therapy, dexamethasone and etoposide were immediately administered. The neurological symptoms did not improve obviously, but cytopenia was relieved. Subsequently, PET-CT scan confirmed spleen enlargement and showed increased and diffuse intake of FDG, with maximum SUV value of 11.8, average SUV value of 8.3 in spleen. The bilateral adrenal glands were significantly enlarged, with abnormally high FDG intake. No other enlarged lymph nodes and areas with abnormal FDG intake were found by PET-CT. Thereafter, splenectomy was performed. EBV positive DLBCL was considered based on biopsy of spleen. Fluorescent in situ hybridization did not detect BCL-2, BCL-6 and C-MYC translocation. In situ hybridization for EBV-encoded small RNA (EBER) was positive. Biopsy did not show involvement of bone marrow. After one cycle of R-CHOP chemotherapy, blood cells and triglycerides recovered to normal level. NK cell activity was elevated to 3.7%. Soluble interleukin 2 receptors (sIL-2R/sCD25) increased to 1127 U/ml. Muscle strength of lower limbs recovered gradually and the patient could walk with support. The patient could feel pain sensation in the lower limbs and had normal bowel function. After six cycles of R-CHOP, urinary retention disappeared.

**Table 1. Literature review of DLBCL combined with GBS**

Case	Publication time	Country	Age (years)/Gender	Type of GBS	Immune performance	Nerve conduction studies	Onset of GBS	Treatment of GBS and lymphoma
1	2013	Pakistan	M/70	unknown	unknown	Undetectable H reflexes, prolonged distal motor latencies in the right tibial, right ulnar and bilateral median nerves with evidence of a conduction block in the right tibial nerve.  Electromyography (EMG) showed no evidence of denervation.	Before chemotherapy	GBS: IVIG1g/kg.  Lymphoma: R-CHOP
2	2013	Germany	M/75	unknown	GM2 IgM	Axonal-demyelinating sensorimotor polyneuropathy accentuated in the legs and the sensory system.	After chemotherapy	GBS: IVIG, 30g/day*3d plasmapheresis.  Lymphoma: R-CHOP
3	2015	China	M/65	Atypical the exact type is unknown.	unknown	unknown	Spinal cord compression	methyprednisolone,500mg
4	2012	Japan	F/83	unknown	unknown	unknown	After chemotherapy	GBS: IVIG , steroid pulse dosage is unknown  Lymphoma: CHOP, R-CHO
5	2019	Japan	M/67	unknown	unknown	Prolonged distal motor latencies in the median and ulnar nerves as well as decreased motor and sensory nerve conduction velocities in the median, ulnar, and tibial nerves.	Before chemotherapy	GBS: IVIG,400mg/Kg/d*5c  Lymphoma: CTX
6	2020	USA	M/67	unknown	Negative	unknown	After chemotherapy	GBS: IVIG,400mg/Kg/d*5c  Lymphoma: R-DA-EPOCH
7	2019	China	unknown	unknown	GM1 IgM GD1b IgM	Absent sensory action potentials  in the lower limbs	unknown	unknown
8	2012	USA	M/61	Miller Fisher syndnore (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,400mg/Kg/d*5c  Lymphoma: R-CHOP
9	2018	Japan	F/48	GBS-like	unknown	unknown	Neurolymphomatosis	GBS: IVIG ,steroid pulse dosage is unknown  Lymphoma: R-CHOP
10	2020	Japan	M/70	unknown	unknown	The amplitude of compound muscle action	After chemotherapy combined with	GBS: IVIG,400mg/Kg/d*5d Lym R-CHOP

						potentials was reduced and the incidence of the F wave was significantly reduced in the motor nerves (ulnar and median). In the sensory nerves (ulnar, median, and radial), the amplitude of sensory nerve potentials was in the lower limits of normal.	phlegmonous gastritis	
11	2006	Spain	M/57	unknown	unknown	A severe reduction in amplitude of motor evoked potentials in right peroneal and posterior tibial nerves, with moderate decrease in left median and cubital nerves.	After chemotherapy	GBS: IVIG,400mg/Kg/d*5d Lymphoma+splenectomy , radiotherapy+R maintena
12	2015	Australia	F/72	AMSAN	Negative	Absent sensory and motor responses as well as 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,400mg/Kg/d*5d Lymphoma+R-CHOP+radic

DLBCL= Diffuse large B cell lymphoma, GBS= Guillain-Barre Syndrome, IVIG = Intravenous immunoglobulin, R-CHOP = Rituximab-Cyclophosphamide, Hydroxydaunorubicin, vincristine, Prednisone

## Discussion

Diffuse large B cell lymphoma (DLBCL) is one of the commonest types of lymphoma. Occasionally, hemophagocytic syndrome (HPS) could be an initial manifestation due to tumor factors and Epstein-Barr virus (EBV) infection[4]. Comparatively, Guillain-Barre Syndrome (GBS) is rarely diagnosed before lymphoma[5]. The incidence of GBS in non-Hodgkin's lymphoma is very low. Almost all studies on lymphoma-related GBS are case reports. Non-Hodgkin's lymphoma combined with GBS is more common than Hodgkin's lymphoma. We reported a case in which GBS and HPS were simultaneously confirmed heralding the diagnosis of lymphoma. According to the case reports, lymphoma types of these cases combined with GBS included DLBCL, Burkitt lymphoma, splenic marginal zone lymphoma and peripheral T-cell lymphoma[1-2][6-7]. Only about 10 cases of DLBCL have been reported to date[1,8-18].

GBS is a type of immune-mediated acute inflammatory peripheral neuropathy, manifested as multiple nerve roots and peripheral nerve damages. The main pathological feature is extensive inflammatory demyelination of peripheral nerves. It is a type of motor neuropathy that could progress rapidly and typically recover. The two commonest types of GBS are acute inflammatory demyelinating polyneuropathies (AIDP) and acute motor axonal neuropathy (AMAN). Other types of GBS including acute motor-sensory axonal neuropathy (AMSAN), Miller-Fisher syndrome (MFS), acute pan-autonomic neuropathy and acute sensory neuropathy are relatively rare[17]. Although most cases are curable, some patients may progress rapidly with irreversible nerve damage. The case reported herein had typical peripheral neuropathy symptoms before DLBCL was diagnosed. GBS type was considered as AMSAN. GBS-related gangliosides were tested and GD IgM, GD IgM3, GT1a IgM were found to be positive, which seemed to be atypical ganglioside. Gangliosides were positive in two out of five cases of DLBCL, with GBS, GM2 IgM, GM1 IgM and GD1b IgM positive[9,14]. Pathogenesis of GBS remains unclear. Molecular simulation is considered as the main mechanism[19]. Most studies believe that infection, neurotoxicity caused by chemical agents, infiltration of the peripheral nervous system and nerve root cells by lymphoma, vasculitis involving nervous system caused by tumor, lymphoma cells blocking small blood vessels and leading to ischemia, tumor-related protein deposition, and tumor-related bioactive substances may affect their immune system[12,20-21]. Kiyat Atamer A. et al. explained that various factors lead to the activation of T cells, production of antibodies against protein antigens and finally result in damages to the peripheral nerves[22]. In GBS animal models, Th1 and Th17 cytokines are up-regulated 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[26]. Given that the 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 may be the main pathogenesis for this patient.

Literature review indicated that DLBCL patients combined with GBS were typically elderly, more than 80% of patients were male and over 60 years old (summarized in Table 1). Neurophysiological examinations showed that both upper and lower extremities could be involved, and both motor and sensory systems could be damaged. GBS could occur before lymphoma is diagnosed. Tumor factors are mainly responsible for this type of GBS. GBS could also occur after lymphoma is diagnosed or treated. Infections or neurotoxicity due to chemotherapeutic agents account for GBS. In these reports, immunoglobulin pulse therapy for GBS widely used glucocorticoids alone or in combination with plasmapheresis. Chemotherapy protocols of CHOP±R and R-DA-EPOCH were

most often chosen. Occasionally, radiation therapy was administered. Outcomes were usually unsatisfactory in patients who developed GBS before lymphoma diagnosis and only immunoglobulin pulse therapy was used. GBS could be cured in most patients who developed GBS after chemotherapy. Our patient was immediately treated with immunoglobulin pulse therapy, etoposide, and dexamethasone when GBS and HPS were confirmed. Neurological symptoms slowly recovered and disappeared after R-CHOP chemotherapy. Either GBS or HPS is an emergency event and needs rapid management. Our clinical experience suggests that it is critical to quickly identify the underlying disease and administer directed therapy. We reviewed 12 cases of DLBCL combined with GBS (Table 1), five out of 12 (42.7%) cases suffered from GBS before, and six out of 12 cases suffered from GBS after DLBCL diagnosis. Almost all patients were treated with immunoglobulin, and some were also treated with plasmapheresis or glucocorticoids. All (100%) patients who developed GBS after DLBCL diagnosis, recovered. Comparatively, among patients who were diagnosed with GBS after DLBCL, one out of five patients did not benefit from immunoglobulin therapy and three out of five patients relapsed after GBS treatments. Consistent with literature reports, our patient did not initially respond to immunoglobulin, and his neurological symptoms relieved slowly and finally disappeared after R-CHOP chemotherapy. Therefore, we hypothesized that lymphoma may be the primary cause of GBS, and chemotherapy for lymphoma may be the key to improvement of the patient's symptoms.

HPS is a rare clinical syndrome with high inflammatory state caused by abnormally activated macrophages and cytotoxic T-cells, resulting in cytokine storms and organ damages. HPS is divided into primary and secondary, and lymphoma is one of the most important secondary factors leading to HPS[23]. EB virus is an important driver of HPS pathogenesis. Lymphoma-associated hemophagocytic syndrome (LAHS), is a clinical process that progresses rapidly and is often life-threatening with poor prognosis[24]. Delayed diagnosis of the underlying diseases may delay life-saving treatments for LAHS. Consequently, it is not enough to only treat HPS without treating aggressive lymphoma. Initially, patients may respond to HPS treatments. However, without further managements, they may relapse more quickly if the underlying lymphoma is not found[23]. As reported, the mean time for lymphoma diagnosis is 22 days[25]. The long diagnosis time (>20 days) is a negative factor of poor prognosis for LAHS patients[25]. Our patient was finally diagnosed as EBV positive DLBCL combined with GBS and HPS in 16 days, which was lower than previously reported[25]. Timely treatments may be crucial to achieve good results.

GBS and HPS heralding the diagnosis EBV DLBCL is clinically rare. Herein, we reported a rare case and shared our clinical experience. Traditional therapies may be effective in patients who develop GBS before lymphoma diagnosis. Fast diagnosis and timely treatment of DLBCL are crucial.

## Abbreviations

CNS☐Central nervous system

NHL ☐non-Hodgkin's lymphoma

GBS☐Guillain-Barre Syndrome

HPS☐Hemophagocytic syndrome

DLBCL☐Diffuse large B cell lymphoma

WBC☐White blood cell

LDH☐Lactate dehydrogenase

sIL-2R/sCD25☐Soluble interleukin 2 receptors

EBER☐EBVencoded small RNA

EBV☐Epstein-Barr virus

AIDP☐Acute inflammatory demyelinating polyneuropathies

AMAN☐Acute motor axonal neuropathy

AMSAN☐Acute motor-sensory axonal neuropathy

MFS☐Miller-Fisher syndrome

LAHS☐Lymphoma-associated hemophagocytic syndrome

R-CHOP ☐ Rituximab-Cyclophosphamide, Hydroxydaunorubicin, vincristine, Prednisone

## Declarations

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**Competing interests:** The authors declare that they have no competing interests.

**Consent for publication:** Written informed consent to publish was obtained from study participants.

**Availability of data and materials:** The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

**Code availability:** Not applicable.

**Authors' contributions:**

Study design: QZ, ZL, FX

Data collection: QZ, XL

Data analysis: QZ, ZL, FX

Data interpretation: QZ, ZL, FX

Preparation of manuscript: QZ, ZL, FX

Literature search/analysis: XL, XW, JS, YT

Fund collection: FX

All authors have read and approved the final manuscript.

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