EJCRIM
European Journal
of Case Reports
in Internal Medicine

GUILLAIN-BARRÉ SYNDROME AS THE INITIAL CLINICAL MANIFESTATION OF HODGKIN'S LYMPHOMA

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Received: 11/08/2025
Accepted: 26/08/2025
Published: 03/09/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The patient has provided his written informed consent to use his personal data for publication of this case report and any accompanying images.
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How to cite this article: Petrakis V, Tartanis G, Tsakaldimi S, Dragoumani I, Danadaki A, Roubakis C, Aggelopoulou C. Guillain-Barré syndrome as the initial clinical manifestation of Hodgkin's lymphoma. *EJCRIM* 2025;**12**:doi:10.12890/2025_005764

ABSTRACT

Background: There are a considerable number of published cases reporting the clinical development of neurological symptoms in people diagnosed with Hodgkin's lymphoma (HL). However, Guillain-Barré syndrome (GBS) as the initial clinical manifestation of HL is extremely rare. We describe a complex case of GBS with the subsequent diagnosis approach leading to the diagnosis of HL.

Case report: A 32-year-old male presented to the emergency department due to paraesthesia of the upper and lower extremities and muscle weakness of the lower extremities that began 1 week earlier, and diplopia observed during last 24 hours. The neurological examination revealed paresis of the left abductor nerve, moderate paraparesis, stocking-glove hypoesthesia, absence of tendon reflexes in the lower extremities, disturbance of deep sensory, sensory ataxia, dysesthesias and neuropathic pain of extremities. The lumbar puncture revealed albuminocytologic dissociation in cerebrospinal fluid. In the electrophysiological examination mainly motor demyelinating polyradiculoneuritis was reported. These findings supported the diagnosis of GBS and intravenous immunoglobulin (2 g/kg) was administered over 5 days. However, the patient deteriorated and developed more severe neurological symptoms including paresis of left peripheral facial nerve, right abductor nerve, oculomotor nerve bilaterally and severe tetraparesis. The patient had seven sessions of plasmapheresis with partial resolution of the neurological symptoms. A full body computed tomography scan was performed revealing enlarged mediastinal and mesenteric lymph nodes and multiple lesions in the splenic and hepatic parenchyma indicative of HL. Although a bone marrow biopsy was negative, a liver biopsy was performed, and the diagnosis of HL was confirmed. The patient was treated with chemotherapy and the neurological symptoms resolved completely

Conclusion: This case report highlights the need to include HL in the differential diagnosis in cases of GBS, although it is a rare phenomenon with a possible immunological basis. Early diagnosis and initiation of the appropriate treatment are vital in order to achieve the remission of neurological symptoms and signs.

KEYWORDS

Guillain-Barré syndrome (GBS), Hodgkin's lymphoma, neuropathy, lymphoma, paraneoplastic syndrome

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Neurological manifestations associated with lymphomas are not common and are mainly associated with severe forms and advanced stages of hematologic malignancies.
- Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy. GBS as a paraneoplastic syndrome is rare in both types of lymphomas, but it is more common in non-Hodgkin's lymphomas.
- Hodgkin's lymphoma should be included in the differential diagnosis of GBS, while it could be an initial clinical manifestation of Hodgkin's lymphoma in rare cases.

INTRODUCTION

Lymphomas develop due to abnormal growth of lymphoid tissue and are divided into Hodgkin's and non-Hodgkin's variants based on the presence of Reed-Sternberg cells[1]. Hodgkin's lymphomas (HL) represent approximately 11% of all lymphomas typically presenting with lymphadenopathy, pruritus and constitutional symptoms[2]. Extranodal sites, such as the nervous system can also be involved[2]. Neurological manifestations associated with lymphomas are not common and are mainly present in severe forms and advanced stages of hematologic malignancies[1,2]. There are many possible causes of these clinical conditions including invasion of the nerves, side effects of chemotherapy or radiation treatment, infectious diseases, pressure on surrounding tissues by a mass, or as a presentation of paraneoplastic syndrome (PNS)[3-5]. Sensory and motor neuropathy are predominately observed in non-Hodgkin lymphoma (NHL), while in HL cerebellar syndrome and limbic encephalitis are more frequently documented[5]. Peripheral nervous system abnormalities in HL and direct damage of peripheral nerves by lymphomatous infiltration or through lymphoma-induced immune complications are rare[6].

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy[4]. Demyelination and axonal loss of peripheral nerves lead to progressive, acute, and ascending weakness, acute muscle flaccid paralysis and abnormal sensation secondary to the inflammatory process[4]. GBS is diagnosed based on the findings of neurological examination, laboratory tests of blood and cerebrospinal fluid (CSF), and neurophysiological exams[4]. The clinical progress varies including life-threatening paralysis in the most severe forms[5]. GBS as a paraneoplastic syndrome is rare in both types of lymphomas, but it is more common in NHLs and in advanced stages of the disease[5].

We report a rare case of a patient who presented with neurological symptoms indicating the diagnosis of GBS in combination with CSF findings. Our diagnostic approach led to a diagnosis of HL. GBS was the initial clinical manifestation without other symptoms reported highlighting the need to include HL in the differential diagnosis.

CASE DESCRIPTION

A 32-year-old male presented to the emergency department due to a 1-week history of paraesthesia of the upper and lower extremities and muscle weakness of the lower extremities and diplopia observed during last 24 hours. The patient had no past medical history and was not a current or former smoker. There was no evidence of an infectious disease during the previous month. On admission, his vitals were normal, and no fever was documented. The neurological examination revealed paresis of the left abductor nerve, moderate paraparesis, stocking-glove hypoesthesia, absence of tendon reflexes in the lower extremities, disturbance of deep sensory, sensory ataxia, dysesthesias and neuropathic pain of extremities. The rest of the physical examination was normal with no abnormal findings during cardiopulmonary and lymph node assessment. The liver and spleen were not palpable. Initial laboratory tests revealed a normal white blood cell count (leukocytes 5.650 cells/µl), red blood cells (haematocrit 41%) and platelets (257.000 cells/µl), normal liver function tests (alkaline phosphatase 32 U/l, gamma-glutamyl transferase 13 U/l, aspartate aminotransferase 24 U/l, and alanine aminotransferase 22 U/l) and a normal creatinine level (0.72 mg/dl). Inflammatory markers were also assessed. C-reactive protein (6.5 mg/dl) and erythrocyte sedimentation rate (56 mm/hour) were elevated, while procalcitonin was within normal range (0.1 ng/ml).

A computed tomography (CT) scan of the brain showed no abnormal findings. In order to exclude the diagnosis of central nervous system infection and for further diagnostic purposes a lumbar puncture was performed which showed absence of cells (0 cells/µl), CSF glucose 52 mg/dl (normal CSF: serum glucose ratio) and elevated protein levels (445 mg/dl). Thus, albumincytologic dissociation in the CSF was revealed. Polymerase chain reaction analysis and CSF culture were negative. Screening for human immunodeficiency virus, hepatitis B virus and hepatitis C virus were negative. Tuberculin skin testing, Wright test for Brucella and serological tests for herpes simplex virus-1, herpes simplex virus-2, varicella-zoster virus, Cryptococcus, Toxoplasma, West Nile virus, syphilis, cytomegalovirus and Epstein-Barr virus were all negative. Immunological studies including antinuclear antibodies (ANA), rheumatoid factor (Rf) and serum complement components C3 and C4 and tumour markers (carcinoembryonic antigen, prostate-specific antigen, CA 125, CA 19-9, CA 15-3, human chorionic gonadotropin and alpha fetoprotein) were normal. In the electrophysiological examination mainly motor demyelinating polyradiculoneuritis was reported. The combination of clinical findings and results of laboratory

Case reports	Clinical presentation	Diagnostic approach and clinical outcome
Al-Attas et al.[3]	19-year-old male; Sudden facial weakness and difficulty with speech; A few days later, gradual symmetrical bilateral lower limb weakness followed by symmetrical bilateral upper limb weakness and bulbar symptoms; **CSF studies:** Albuminocytologic dissociation, protein elevation (232 mg/dl).	**CT scan:** Showed multiple enlarged mediastinal and hilar lymph nodes; **Biopsy:** Confirmation of HL; **Chemotherapy and IVIG:** Significant clinical improvement;
Polo-Romero et al.[6]	74-year-old woman; Paraesthesia, weakness in the lower limbs extending proximally, and lumbar pain that had progressed over 48 hours; Ascending progressive bilateral paralysis that extended to the sites of attachment of both thigh muscles, with tendon reflex suppression in the lower limbs and loss of control over the bladder sphincter within 24 hours; **CSF studies:** 20 leucocytes, glucose 55 mg/dl and protein 76 mg/dl; Persistent leucocytosis with no fever and no focal infectious in blood tests.	**Intravenous gamma globulin** (400 mg/kg/day during 5 days), without improvement of neurological symptoms. **Bone marrow aspiration and biopsy:** NHL diagnosis, diffuse infiltration by a B-cell lymphoproliferative process; **Chemotherapy:** with CHOP-rituximab (6 cycles)- no improvement; Abnormalities in the cranial vault, left tenth rib, D10 vertebral body, and left iliac blade with soft tissue masses-**neoplastic process**; Intrathecal cytarabine (6 more cycles of **systematic chemotherapy**); Death due to septic shock
Cros et al.[9]	66-year-old male; 2-day history of progressive muscle weakness and paraesthesia; **CSF studies:** Albuminocytologic dissociation, protein elevation (103 mg/dl).	**Plasmapheresis:** 6 sessions, clinical deterioration; **CT scan:** 7 mm precarinal lymph node of the thorax, triangular mass in the anterior mediastinal fat; **Biopsy:** Confirmation of HL; **Chemotherapy and IVIG:** Minimal clinical improvement.
Anderson et al.[10]	34-year-old male; 3-week history of ascending lower-limb weakness and 1 month ago right-sided facial weakness (acute inflammatory demyelinating polyneuropathy); **CSF studies:** Albuminocytologic dissociation, protein elevation (250 mg/dl).	**IVIG:** Clinical deterioration; **PET-CT:** Scan anterior mediastinal mass; **Biopsy:** Confirmation of HL; **Chemotherapy:** Early clinical Improvement.
This case	32-year-old male; 1-week history of paraesthesia of the upper and lower extremities and muscle weakness of the lower extremities and diplopia observed during last 24 hours; **CSF studies:** Albuminocytologic dissociation, protein elevation (445 mg/dl)	**IVIG:** Clinical deterioration; **Plasmapheresis:** 6 sessions, partial recovery; **CT scan:** Enlarged mediastinal and mesenteric lymph nodes and multiple lesions in splenic and hepatic parenchyma; **Biopsy:** Confirmation of HL; **Chemotherapy:** Fully recovered.

Table 1. Case reports of HL-induced GBS as initial clinical manifestation of HL.

tests supported the diagnosis of GBS and intravenous immunoglobulin (IVIG, 2 g/kg) was administered over 5 days. During the third day of immunoglobulin administration, the patient deteriorated and developed more severe neurological symptoms including paresis of left peripheral facial nerve, right abductor nerve, oculomotor nerve bilaterally and severe tetraparesis. The patient had seven sessions of plasmapheresis with partial resolution of the neurological symptoms. Full-body computed tomography (CT) scan was performed revealing enlarged mediastinal and mesenteric lymph nodes and multiple lesions in splenic and hepatic parenchyma indicative of HL *(Fig. 1 and 2)*. Although bone marrow biopsy was negative, a liver biopsy was performed and the diagnosis of HL was confirmed. The patient received two chemotherapy regimens based on haematologists consultations, BEACOPP (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone) and ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). One year after treatment completion there was no evidence of residual disease in full-body positron emission tomography (PET)-CT scan, and the neurological symptoms had completely resolved with a partial improvement in the findings of electrophysiological examination.

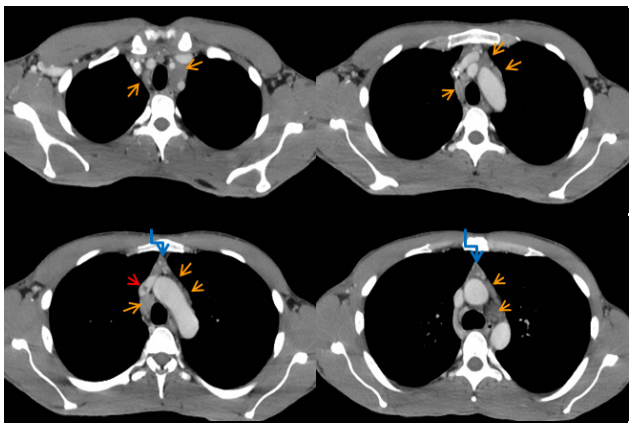


Figure 1. Computed tomography scan of the chest showing: multiple marginal and enlarged mediastinal lymph nodes (orange arrows), a central thrombus in the superior vena cava (red arrow), and are residual thymus gland (blue arrow).

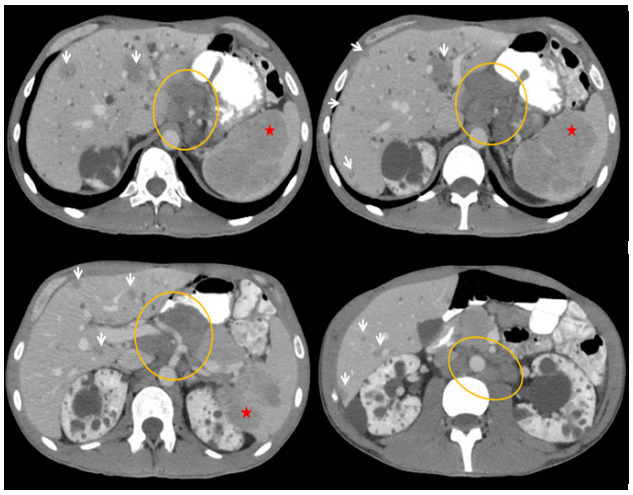


Figure 2. Computed tomography scan of the abdomen showing: multiple enlarged - en bloc paraaortic lymph nodes and around the Allerion tripod (orange circle), a large focal lesion in the spleen (red star) and scattered focal lesions in the liver (white arrow heads).

DISCUSSION

PNS with neurological clinical manifestations can develop in patients with malignancies and is a diagnosis which cannot be explained by the effects of the underlying tumour, metastasis, opportunistic infections or complications of chemotherapy[1,6]. The aetiology of these cases is based on possible autoimmune mechanisms, and the presence of neuronal autoantibodies confirms the diagnosis, although their absence does not exclude it[6]. The pathogenesis involves an analogous antigenic property among the underlying neoplastic disease via the central or peripheral nervous system[3]. The incidence of PNS in patients with lymphomas is quite rare and differs between HL and NHL[5,6]. Cerebellar syndromes and limbic encephalitis are more often associated with HL, while sensory neuropathy and motor system involvement more frequently occur in NHL[5,6]. Previous case reports have described the incidence of GBS in HL, but the majority of HL lymphomas[6-10].

Reduced cell-mediated immunity due to viral infections such as cytomegalovirus, Influenza virus and Epstein-Barr virus, diabetes mellitus, systemic lupus erythematosus, pregnancy and other clinical conditions can lead to GBS[4-6]. This pathogenic mechanism may also be involved in lymphomas. Studies in HL patients with GBS have proven findings of cell-mediated myelin damage[6]. In HL-mediated PNSs of the central nervous system, anti-Tr antibodies directed against Delta/notch-like epidermal growth factor-related receptor in Purkinje cell cytoplasm have been detected[4-6].

The diagnosis of GBS as an initial clinical manifestation of HL was documented in a young male patient who was presented with a manifestation and investigation suggestive of GBS, heralding an unconfirmed diagnosis of HL[3]. However, in this case the patient already had symptoms associated with a possible diagnosis of lymphoma such as productive cough and fever with fatigue and night sweats unresponsive to antipyretics[3]. In our case the patient did not develop these symptoms. Similarly to our case, Anderson et al. and Cros et al. described cases of GBS in otherwise healthy patients who presented with rapidly progressive muscle weakness and were found to have HL during a prolonged hospitalization and diagnostic process[9,10]. In addition to these case reports, Polo-Romero et al described a 74-year-old woman who presented with paraesthesia, weakness in the lower limbs extending proximally, and lumbar pain that had progressed over 48 hours and deteriorated with ascending progressive bilateral paralysis extended to the sites of attachment of both thigh muscles, with tendon reflex suppression in the lower limbs and loss of control over the bladder sphincter within 24 hours after admission[6]. GBS was confirmed and treatment with intravenous gamma globulin (400 mg/kg/day over 5 days) was initiated without improvement of neurological symptoms[6]. Due to persistent leucocytosis with no fever and no focal infection shown by blood tests further investigations were performed and after bone marrow aspiration and biopsy the patient was diagnosed with NHL. This patient did not respond to chemotherapy and died after 2 months due to septic shock[6]. Lisak et al. reported a case study series in which the patients developed GBS while undergoing chemotherapy or during a relapse of the underlying disease[7]. Julien et al., in a clinicopathological study of GBS and HL, reported a case of GBS in a man with relapsed HL[8]. *Table 1* lists case reports of GBS as first clinical manifestation of HL in the published literature so far.

GBS is usually treated with a 5-day course of IVIG in order to limit the progression of the disease[3]. In our case after the initiation of IVIG administration the patient deteriorated and developed more severe neurological deficits, although active and substantial progression of GBS after starting IVIG therapy is not common in the literature. He improved and his symptoms fully resolved after the completion of the chemotherapy treatment targeting HL. The reason for no response to IVIG monotherapy like in other published cases is not clear[2,3]. However, treatment of the underlying HL in cases of HL-induced GBS is vital in order to achieve the resolution of GBS symptoms.

One significant finding in our case was the extremely high

level of CSF protein (445 mg/dl). Similar protein levels in cases of HL-induced GBS have been reported in other studies with a range from 92 to 560 mg/dl[6-10]. Marked elevations in CSF protein, neurological deterioration after IVIG initiation, and constitutional symptoms with elevated inflammatory biomarkers may be evidence supporting the diagnosis of HL-induced GBS[10].

Whether GBS is a marker of occult cancer remains unclear[11]. A population-based cohort study of patients diagnosed with GBS between 1978 and 2017 using Danish registry-data was conducted and the results showed that GBS patients had a three-fold increased risk of cancer diagnosis in the first year of follow-up, decreasing over time[11]. The absolute cancer risk was almost 3% and GBS was found as an adverse prognostic marker for survival following cancer diagnosis[11]. Although PNSs occur in less than 1% of patients with malignancies, further investigation during the first year after hospitalization for GBS could lead to the diagnosis of neoplastic disease, particularly in patients without a clear infectious trigger[11].

In conclusion, GBS cases induced by lymphomas are rare, especially in HL. Limited case reports describe GBS as the initial clinical manifestation of HL like in our case. Potential autoimmune mechanisms may be involved in the pathogenesis of HL-induced GBS, but further studies are needed in order to clarify the pathophysiology of this disease. HL should be included in the differential diagnosis of GBS in previously healthy individuals with atypical clinical symptoms, significantly increased CSF protein levels, elevated inflammatory markers and failure of IVIG treatment to suppress the progress of neurological symptoms.

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