

CASE REPORT

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Favorable response to cyclophosphamide in a patient with refractory Guillain–Barre syndrome associated with chronic lymphocytic leukemia

Nicholas Lafferty, Tushar Sehgal, Andrew Duncombe, Haider Katifi, David Allen, Shoura Karar

ABSTRACT

Introduction: Neurological symptoms may occur in patients with chronic lymphocytic leukemia (CLL) through a variety of etiologies. However, autoimmune disorders involving the nervous system, such as Guillain–Barre syndrome (GBS), have only rarely been reported in patients with CLL, despite the well-established association between CLL and other autoimmune phenomena. Previous reports demonstrate no consistent approach to management of these cases.

Case Report: Here we report a case of severe GBS associated with newly diagnosed CLL. The patient did not respond to initial therapy with intravenous immunoglobulin, plasmapheresis, and corticosteroids, but demonstrated a rapid neurological and hematological improvement following cyclophosphamide infusion.

Conclusion: Here, for the first time, we describe the successful treatment of CLL-associated GBS using cyclophosphamide.

Keywords: B cell, Chronic, Cyclophosphamide, Guillain–Barre syndrome, Leukemia, Lymphocytic

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disorder characterized by the accumulation of monoclonal B-lymphocytes in peripheral blood, bone marrow, and lymphoid tissues [1]. A minority of patients with CLL develop neurological complications during the course of their disease, which may be accounted for by a variety of etiologies, including infections, leukemic infiltration of central nervous system (CNS) tissues, and CNS hemorrhage. However, autoimmune neurological syndromes have also been observed in this patient group [2, 3].

Guillain–Barre syndrome (GBS) is an acute, inflammatory polyneuropathy, caused by an aberrant autoimmune response that is typically precipitated by antecedent infection or other immune stimulus [4]. It has been observed in association with a number of malignancies, although a definite causative relationship, and any mechanism underlying this, has yet to be established [5].

Only a handful of reports have described GBS in association with CLL, and even fewer without a known infective trigger for the onset of GBS. These reports demonstrate no consistent approach to management of this rare clinical scenario.

Nicholas Lafferty¹, Tushar Sehgal¹, Andrew Duncombe¹, Haider Katifi², David Allen², Shoura Karar³

Affiliations: ¹Haematology Department, University Hospital Southampton, Southampton, UK; ²Neurology Department, University Hospital Southampton, Southampton, UK; ³Intensive Care Department, University Hospital Southampton, Southampton, UK.

Corresponding Author: Dr. Nicholas Lafferty, Haematology Department, Southampton General Hospital, Southampton, SO16 6YD, UK; Email: Nicholas.lafferty1@nhs.net

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Here, we present a case of CLL in a middle-aged man, complicated by the onset of GBS shortly after diagnosis. Our patient demonstrated swift resolution of GBS following administration of cyclophosphamide, after failing to demonstrate a response to first-line, GBS-directed therapies. To our knowledge, this is the first report describing successful treatment of CLL-associated GBS in this way.

CASE REPORT

A 60-year-old man with no significant past medical history was referred to Hematology clinic with a rising lymphocytosis and a 3-month history of weight loss, night sweats, and persistent cough. Examination revealed splenomegaly and generalized lymphadenopathy. Full blood count (FBC) showed a hemoglobin of 85 g/L, white cell count of $150 \times 10^9/L$, lymphocyte count of $140 \times 10^9/L$, and platelet count of $271 \times 10^9/L$. Blood film revealed an excess of mature lymphocytes and smear cells in keeping with a chronic lymphoproliferative disorder.

Within a month of his initial assessment, and prior to subsequent review in clinic for treatment planning, the patient was admitted to hospital with a two-week history of progressive, ascending numbness and weakness of his upper and lower limbs, associated with lower back pain. On examination, power was reduced proximally and distally in all four limbs, with the most significant weakness seen on movements involving the small muscles of the hand bilaterally, on hip flexion bilaterally, and on dorsiflexion of the left foot (all grade 2/5). Reflexes in the lower limbs were absent bilaterally. There was reduced temperature sensation to the mid-thighs and reduced proprioception to the ankles bilaterally. Glasgow Coma score was 15 and no cranial nerve deficits were observed.

Repeat FBC revealed a rise in the lymphocyte count to $163 \times 10^9/L$. Lactate dehydrogenase was raised at 413 IU/L. Creatinine clearance, blood electrolytes, folate, and vitamin B12 were within normal ranges. Immunoglobulin profile revealed a polyclonal rise in IgG (23.2 g/L) and IgM (3.2 g/L) but no paraprotein. Direct antiglobulin test was positive (IgG only). C-reactive protein was raised (88 mg/L), but there was no clinical evidence of infection, and a chest X-ray was clear. Human immunodeficiency virus and syphilis serology were negative. The case presented prior to the COVID-19 pandemic.

Bone marrow biopsy showed a hypercellular marrow with diffuse and nodular infiltration of small monomorphic lymphocytes. Immunophenotyping by flow cytometry showed a clonal B-cell population indicative of atypical CLL, with a Matutes score of 3/5 (CD19+, CD5+, CD20+, CD23+, surface immunoglobulin + [kappa; strong], CD79b+, CD10-, FMC7-, CD38-). Fluorescent in situ hybridization revealed del(13q14) as the sole abnormality. There was no IGH-CCND1 t(11;14) rearrangement to suggest an alternative diagnosis of mantle cell lymphoma. Staging computed tomography

(CT) scan revealed widespread lymphadenopathy in the neck, thorax, and abdomen (maximum diameter 1.9 cm) and splenomegaly (maximum diameter 19 cm).

Lumbar puncture was traumatic and cerebrospinal fluid (CSF) cell count revealed significant red cell contamination ($2080/\mu L$). Mononuclear cells were elevated ($202/\mu L$) and flow cytometry confirmed the presence of CLL cells within the sample. However, given the high peripheral blood lymphocyte count, it was thought that these could be accounted for by blood contamination. Cerebrospinal fluid protein was elevated (1928 mg/L). Polymerase chain reaction (PCR) screen on CSF for herpes viruses was negative.

Magnetic resonance imaging of the cervical spine and head (with gadolinium) showed no evidence of leptomeningeal enhancement or other significant abnormalities. Nerve conduction studies (NCS) showed dispersion of motor responses and delayed distal motor latencies, with present sural and radial sensory responses but absent hand digit sensory responses; in keeping with the acute inflammatory demyelinating polyneuropathy (AIDP) subtype of GBS.

The patient was initially treated with intravenous immunoglobulin (IVIg) at a standard dose of 0.4 g/kg/day for five days. Despite treatment, he developed progressive bulbar weakness and a decline in forced vital capacity (from 3.16 L on admission to 1.4 L four days later). On day +4 from his date of admission, he was admitted to the Neurological Intensive Care Unit (NICU), where he was intubated the following day.

A decision was made to start rituximab ($375 \text{ mg}/\text{m}^2$), which was started on day +10 as a split 2-day dose. He received the first 100 mg infusion without issues, but the following day, shortly after commencement of the infusion, it was terminated due to the patient suffering a severe hypotensive episode, requiring noradrenaline support. His blood pressure remained labile during his stay on NICU, reflecting GBS-associated dysautonomia. From day +12, he underwent four days of plasma exchanges (PE) using a standard protocol, and on day +14 he started prednisolone (1 mg/kg). No discernible improvement was observed, and thus on day +21 he was given a single dose of intravenous (IV) cyclophosphamide ($750 \text{ mg}/\text{m}^2$), together with a repeat 5-day course of IVIg (0.4 g/kg/day). Following this, he began to make a rapid clinical and hematological recovery. Three days after cyclophosphamide infusion, he was extubated, and his lymphocyte count had reduced to $71.6 \times 10^9/L$.

On day +29 he was discharged from NICU and begun inpatient rehabilitation. After discharge, he continued to demonstrate an excellent neurological recovery, with mild pedal hypoesthesia being his only persisting symptom. He received a further dose of cyclophosphamide and rituximab, achieving a partial remission of his CLL overall, but then was switched to second-line venetoclax and rituximab in view of a persistent lymphocytosis. On completion of two years of this regimen, he was fit and well and in complete remission.

DISCUSSION

Guillain–Barre syndrome is an acute immune-mediated polyneuropathy causing flaccid paralysis, with or without sensory and autonomic dysfunction [4]. The segmental demyelination seen in the AIDP subtype of GBS, as was seen in our case, is thought to arise from autoimmune attack involving both cellular and humoral mechanisms [6]. In most cases, the onset of GBS is preceded by an infective process, indicating that molecular mimicry between nerve and microbial antigens is involved in its pathogenesis [7]. In addition to supportive care, severely affected patients are treated with IVIg and/or PE [6].

Autoimmune phenomena are well-recognized as a complication of CLL, and are thought to occur as a result of quantitative and/or functional T-cell defects, or through the malignant B-cell producing an autoreactive antibody or exhibiting aberrant function as an antigen-presenting cell [8]. While autoimmunity most commonly manifests as autoimmune cytopenias, non-hematological autoimmune disorders have also been observed in CLL patients [9], including neurological syndromes [10]. Guillain–Barre syndrome, however, appears to be an exceedingly rare complication of CLL, with less than ten cases reported in the literature [11–18].

In our case, the diagnosis of GBS was made according to the classical clinical findings, coupled with the characteristic pattern of neuropathy seen on NCS and absence of any other cause for polyneuropathy. The presence of CLL cells in the CSF was thought to be due to blood contamination rather than true leptomeningeal infiltration of CLL. In any case, the clinical significance of positivity for CLL cells in the CSF is uncertain, given that evidence from autopsy studies has suggested that asymptomatic CNS involvement of CLL may be relatively common [19], and that CSF positivity for CLL cells has been shown to correlate poorly with final diagnosis in CLL patients being investigated for neurological symptoms [2].

In four of the published cases of CLL-associated GBS, a history of antecedent infection with herpes zoster virus (HZV) is present [11, 13, 17, 18], implicating this agent as an important trigger of GBS in this patient group. Our patient exhibited no clear clinical, radiological, or microbiological evidence of infection (including HZV), although his previous persistent cough may have been secondary to some form of respiratory tract infection, which could have been the precipitating event leading to GBS. However, the fact that initial GBS-directed interventions (IVIg and PE) failed to produce a response, yet a single infusion of cyclophosphamide resulted in rapid resolution of GBS, would suggest that the immune dysregulation associated with his CLL was, at least, the ongoing driver of his GBS.

A response in refractory CLL-associated GBS following CLL-directed therapy has been reported previously; using chlorambucil and prednisolone in one

case [14], and alemtuzumab in another [17]. Choosing an appropriate CLL-directed treatment for a patient with critical neuromuscular disease may provide a dilemma, given that, firstly, the oral route of administration may not be possible (as was the case in our patient); secondly, that highly immunosuppressive agents may be less desirable in view of the patient's susceptibility to hospital-acquired infections; and finally, that some anti-cancer agents have been implicated as a potential cause of GBS, including rituximab [17], bendamustine [17], and even cyclophosphamide [16]. Following the failure of GBS-directed therapies, we opted to give rituximab and prednisolone initially, before subsequently giving a dose of cyclophosphamide (in addition to further IVIg).

Rituximab is well-established as an agent used in the treatment of lymphoproliferative disorders, as well as a variety of autoimmune disorders [20]. Moreover, it has been used successfully in a case of GBS associated with cytomegalovirus in a post-allogeneic stem cell transplant patient [21]. However, our experience of using rituximab, in which our patient with GBS-associated dysautonomia developed life-threatening hypotension during infusion, suggests that some caution may be warranted regarding its use in GBS. In our case, it seems unlikely that rituximab played a major role in promoting his initial recovery, given that the patient received only a fraction of his intended initial dose. The role of corticosteroid treatment was also uncertain, given that he had received prednisolone for seven days (total dose 630 mg) without response before cyclophosphamide was given.

Cyclophosphamide is an alkylating agent widely used in anti-cancer therapies [22], including in CLL [1]. It also exerts an immunomodulatory effect on both B- and T-lymphocytes [23] and is used as an immunosuppressive agent in a variety of clinical settings [22]. A number of reports demonstrate the utility of cyclophosphamide, at varying doses, in the successful treatment of GBS associated with vasculitic disorders [23–25], but its use in GBS associated with CLL has not previously been reported. In our case, the prior failure of PE and IVIg would suggest that GBS did not arise purely as a result of humoral autoimmunity, and we would speculate that it was through modulation of aberrant T-cell function that cyclophosphamide may have provided resolution of his CLL-associated GBS.

The majority of patients who develop GBS survive and demonstrate a good neurological recovery, with 81% of patients being alive and able to walk at 12 months following diagnosis in one large multinational study [26]. Favorable outcomes have also been reported in the few cases of CLL-associated GBS described in the literature [11, 12, 14, 15–17], including in those who did not receive CLL-directed therapies. However, requirement for mechanical ventilation, as was seen in our case, has been established as a risk factor for death in GBS [27, 28]. Furthermore, longer duration of mechanical ventilation has been observed to correlate with a higher risk of acute complications [29] and inferior neurological outcome

[30]. This points to the potential importance of second-line therapies which may be able to expedite recovery in severe, refractory cases, such as ours.

CONCLUSION

Here, for the first time, we report the successful use of cyclophosphamide in the treatment of refractory GBS associated with CLL. Further reports of similar cases will help to clarify the optimal management strategy in this clinical context.

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Author Contributions

Nicholas Lafferty – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Tushar Sehgal – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Andrew Duncombe – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Haider Katifi – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

David Allen – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the

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Shoura Karar – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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