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## **Ibrutinib Monotherapy As Effective Treatment of Central Nervous System Involvement by Chronic Lymphocytic Leukaemia**

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Central Nervous System (CNS) involvement by chronic lymphocytic leukaemia (CLL) is a rare but devastating complication with few effective treatment options and short survival (Moazzam et al., 2012; Poplawska-Szczygłowska, 1999; Tonino et al., 2011). The Bruton Tyrosine Kinase (BTK) inhibitor, ibrutinib, has high systemic activity in CLL (Byrd et al., 2013), and was recently reported to be effective in the treatment of 3 patients with CNS involvement by mantle cell lymphoma, where the cerebrospinal fluid (CSF) concentration reached 1 – 7% **This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as [doi: 10.1111/bjh.14000](https://doi.org/10.1111/bjh.14000)**

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of simultaneous blood levels (Bernard et al., 2015). This important observation suggests that ibrutinib may be one of the few agents capable of penetrating the blood-brain barrier and treating tumour cells in neurological “sanctuary sites” otherwise not susceptible to most conventional chemotherapeutic agents (Cheah et al., 2013). In order to illustrate that this reported phenomenon is not restricted to MCL, and to demonstrate that clinical CNS responses can occur at the lower (CLL) ibrutinib dose of 420 mg/day, we present a case of CNS-infiltrating CLL that responded promptly to ibrutinib monotherapy.

A 66-year-old man with previously untreated, Rai stage III CLL presented with a 4-month history of progressive left-sided sensory symptoms affecting both the upper and lower limbs. His initial symptoms were tightness, paraesthesiae and neuropathic pain in the left hand and left arm, followed by similar sensations in the left leg. Neurological examination revealed evidence of bilateral lower limb spasticity, more marked on the left side, without weakness. Magnetic Resonance Imaging (MRI) of the spinal cord showed cervical myelopathy with extensive signal change and expansion of the spinal cord from C2 to C7 (Figure 1A). The disproportionate radiological changes coupled with the relatively minor clinical deficits were supportive of leukaemic infiltration rather than alternative diagnoses, such as inflammatory myelopathy, an impression reinforced by CSF examination which showed elevated protein (0.81 g/l; normal range 0.15-0.45), normal glucose, and the presence of CD5+ CD19+ CD23+ CLL cells on flow cytometry (10% of CSF white cell count of  $4 \times 10^6/l$ , normal range 0-5, without blood contamination). The absolute lymphocyte count in the peripheral blood was  $94 \times 10^9/l$ . The patient was offered cytotoxic anti-CLL therapy but declined. On this basis, a three-month trial of oral corticosteroid therapy (directed against inflammatory myelopathy) was prescribed, with no clinical response and a subsequent MRI showing worsening of cervical myelopathy (Figure 1B).

The patient was then commenced on ibrutinib monotherapy at 420 mg daily as frontline treatment of CLL, with rapid shrinkage of bulky lymphadenopathy and splenomegaly, and resolution of constitutional symptoms. Over the course of 2 months, his neurological symptoms and signs resolved. A repeat MRI, performed 5 months after the start of ibrutinib, showed complete resolution of previous extensive spinal cord changes (Figure 1C). Repeat CSF examination was not performed due to the lack of a clinical indication, and CSF ibrutinib levels were not assessed. Eighteen months after commencing ibrutinib, the patient remains neurologically normal with no recurrence of his previous deficits.

Collectively, our case and the 3 cases reported by Bernard *et al* (2015) indicate that ibrutinib may represent a new avenue of therapy for CNS involvement by BTK-inhibition sensitive diseases, such as CLL, MCL and Waldenström Macroglobulinaemia (Simon et al., 2015). These observations underscore the need for drug development of novel small molecules to include exploration of their penetration and activity in the CNS, a cogent area of under-

researched application due to CNS disease being a common exclusion criterion in therapeutic trials. The inclusion of ibrutinib in combination with chemotherapy may also reduce CNS recurrence rates in less BTK-sensitive diseases, such as diffuse large cell lymphoma (Davis et al., 2010), a question that requires specific examination in on-going clinical studies, such as the phase 3 PHOENIX study of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) +/- ibrutinib (NCT01855750).

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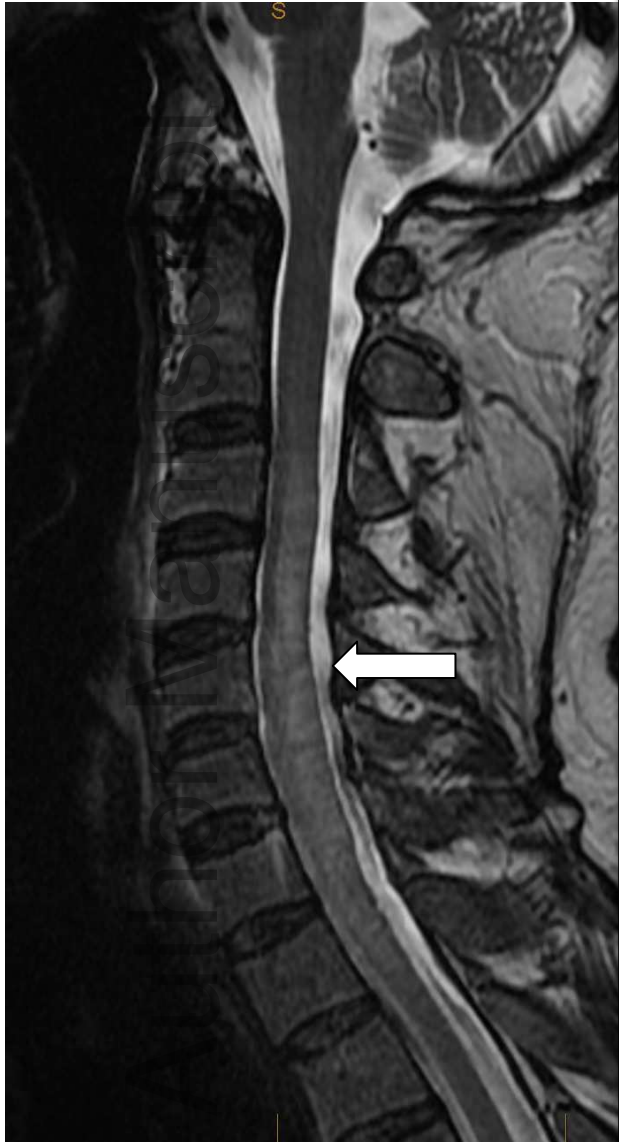
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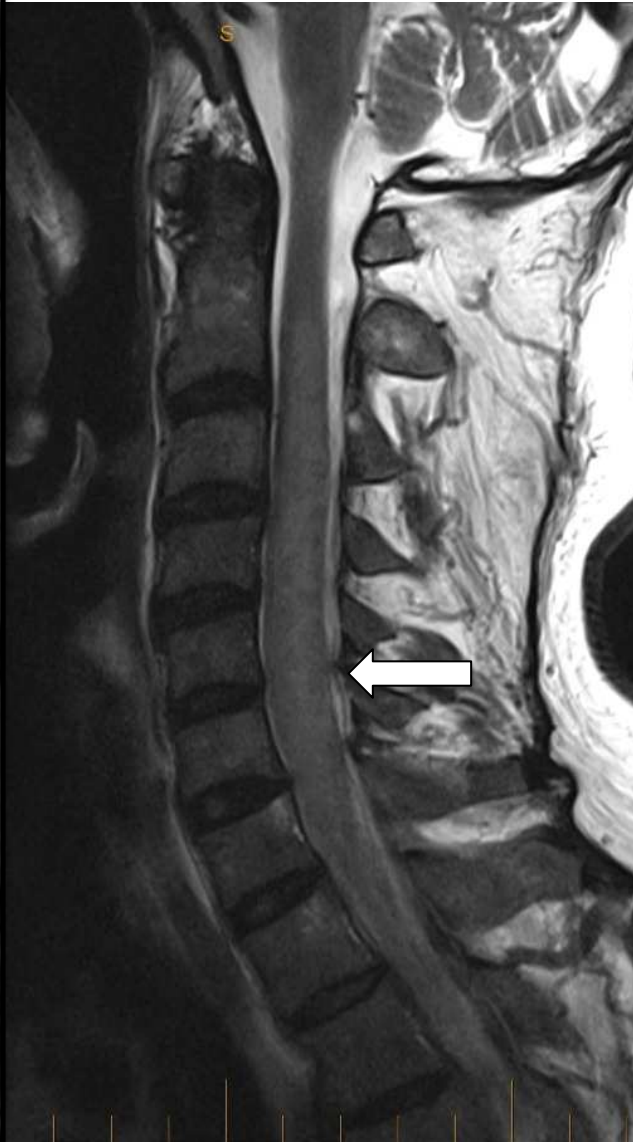
**Figure 1.** Magnetic Resonance Imaging of cervical spinal cord in a patient with chronic lymphocytic leukaemia (A) at the time of cervical myelopathy diagnosis; (B) after failed corticosteroid therapy; and (C) after 5 months of ibrutinib therapy.

**1A**



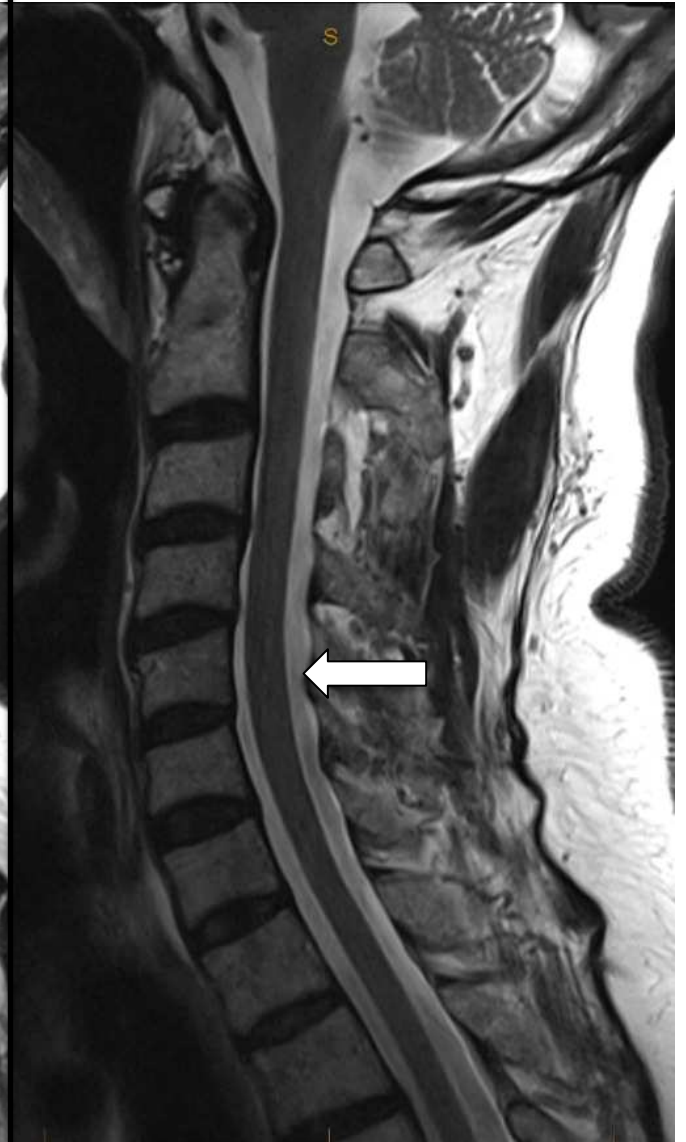
Initial presentation with cervical myelopathy

**1B**



Six months later; progressive myelopathy despite prednisolone therapy

**1C**



Twelve months later; complete resolution after ibrutinib monotherapy