identified an IgM kappa paraprotein of 21 g/L and free kappa component. The patient underwent a number of biochemical investigations that included a thorough assessment of his neurological status. These investigations revealed a postural tremor without any latency, upper limb dystonia, cranial nerve deficits, bilateral but predominantly right sided facial weakness, poor balance with frequent falls and bulbar signs necessitating permanent use of a wheelchair. Examination revealed no cranial nerve deficits, bilateral but predominantly right sided postural tremor without any latency, upper limb dystonia, holding hands partially flexed at the wrists. There was positional variability of tremor, being most prominent when arms abducted at the shoulders and partially flexed at the elbows. The tremor also involved directionally stereotyped repetitive movements, mainly involving wrist extension and pronation. He had an action tremor but no terminal worsening. Consequently, the patient underwent a number of biochemical investigations that included an IgM kappa paraprotein of 21 g/L and free kappa light chains of 199 mg/L with a kappa:lambda ratio of 10.94. At this point, the patient was referred to hematology for review. There was no significant family history and Eastern Cooperative Oncology Group performance status (ECOG) status was 3. He was a nonsmoker with minimal alcohol intake and his routine medications included primidone and clonazepam. Differential diagnoses included lymphoma (most likely lymphoplasmacytic lymphoma (LPL)/WM) with associated CNS involvement in the form of BNS, paraneoplastic manifestation of possible malignancy or an incidental finding unrelated to his neurological symptoms. Initial investigations included computed tomography (CT) of the neck, chest, abdomen, and pelvis, magnetic resonance imaging (MRI) of head, whole spine and pelvic bones, bone scan, and lumbar and brachial nerve roots as well as cauda equina nerve roots. The most common radiological manifestations of BNS are thought to be leptomeningeal/dural infiltration or parenchymal involvement of the brain or spinal cord. BM had shown normal trilineage hematopoiesis with an increased population of small, mature lymphocytes, some of which had a plasmacytoid appearance. Flow cytometry of the BM identified an infiltrate of CD19+ B cells that accounted for 90% of CD45+ events, as well as 2 distinct clonal populations. First, a monoclonal CD5+, CD10−, kappa (weak)+, CD23+, FMC7−, CD79b−, CD200+ B-cell population with a CLL score of 5/5. The second was a monoclonal CD5−, CD10−, kappa (strong)+, CD23−, FMC7−, CD38−, CD43−, CD200−, CD22+ B-cell population (Figure 1A–H). Peripheral blood (PB) morphology was unremarkable and flow cytometry confirmed the 2 distinct clonal populations in keeping with those identified in the BM. Flow cytometry on the CSF sample identified the CD5−/CD10−/kappa + population only (Figure II-L). BMT histology showed normal trilineage hematopoiesis, several nodules co-expressing CD23 and the lymphoid enhancer binding factor 1 (LEF1) in B cells, which appeared to also stain positively with CD5 by immunohistochemistry (IHC). In keeping with BM and PB samples, the BMT also identified a co-existing second nodule, which was negative for CD5, CD23, and LEF1. Examination of the LN showed a cellular sample with numerous small mature lymphocytes. A population of these cells appeared to be plasmacytoid in appearance, and flow cytometry again identified 2 distinct
clonal populations as detected in the BM, BMT, and PB samples. Molecular analyses to ascertain the mutational status of MYD88 L265P and the tumor suppressor gene TP53 were performed on both BM and CSF samples, with the MYD88 mutation present in both samples. However, both the BM and CSF were negative for TP53 mutation. Fluorescence in situ hybridization (FISH) analysis of 200 nuclei from CD19+ purified cells from PB showed no evidence of deletions of ATM or TP53.

The patient was discussed at regional lymphoma MDM and with a national expert at University College London. CLL was diagnosed concurrently with BNS at Binet stage B; however, did not meet criteria for treatment. An initial 2 cycles of modified MATRIX (methotrexate, cytarabine, rituximab but no thiopeta) chemotherapy regime were administered. More intensive treatment was chosen due to aggressive nature of initial presentation with plans for consolidation with autologous stem cell transplant in first remission. This was thought to be preferable with ibrutinib reserved for relapsed disease, especially in view of its CNS penetration.4,5 Following completion of 2 cycles of chemotherapy, BM recovery, and intensive in-patient physiotherapy, the patient underwent repeat biochemical and radiological evaluations. He had good neurological improvement and is now mobilizing independently with a walking aid. Examination revealed bilateral but predominantly right upper limb tremor, with dystonic features and action tremor with mild ataxia. There was full power proximally in the upper limbs, but mild weakness at wrist extension and finger abduction. There was full power in lower limbs. There was global areflexia, but no objective sensory deficit. From review of previous power grading, there felt to be significant improvement. Biochemically, the paraprotein in PB had fallen by 33%. CSF protein had decreased by more than 50% with flow cytometry demonstrating a persistent, but reduced, clonal population of abnormal cells. MRI images were reviewed and had shown partial improvement in intracranial disease. The patient was rediscussed with the national expert and 2 further cycles of modified MATRIX were administered (a total of 4 cycles). To date he has achieved a very good partial response (VGPR) and continues to improve neurologically6 (Table 1).

Cases of BNS present clinical, diagnostic, and management challenges. Our patient’s long history of neurological symptoms may have obscured initial diagnostic investigations. Extensive neurological follow-up, as well as immunoglobulin and light chain profiles raised a possibility of a lymphoproliferative disorder. The literature on the topic is limited but 2 relatively recent publications2,4 guided both the diagnostic and management approach of this very rare condition. Review of flow cytometry and IHC data performed on multiple sample types noted a dual population of cells: a distinct CLL clone and

Figure 1. Lymphocyte population of BM gated using low-side scatter properties and strong CD45 expression. (A), CD19 expression on lymphocytes demonstrating the presence of two populations, one which has weak expression of CD19 (blue population), and a second which has brighter expression of CD19 (purple population) (B). The purple population represents a monoclonal CD5+, CD10−, kappa (weak)+, CD23+, FMC7−, CD79b−, CD200+ B-cell population with CLL score of 5/5. The blue population correlates to a monoclonal CD5−, CD10−, kappa (strong)+ CD23−, FMC7−, CD38−, CD43−, CD200−, CD22+ B-cell population (C–H). The bottom panel represents the CSF and is suggestive of the presence of an isolated CD5−, CD10−, kappa+ B-cell population (I–L). BM = bone marrow; CSF = cerebrospinal fluid.
a co-existing WM clone. Analysis of CSF using flow cytometry identified an isolated population of CD5− CD10− B-cells. There was no evidence that the CLL clone had crossed the blood-brain-barrier. Although a very common adult leukemia, CLL very rarely affects the central nervous system. Only about 1%–2% of patients have been shown to have neurological symptoms related to CLL. The morphological presence of lymphoplasmacytoid lymphocytes in the CSF is currently gold standard for the diagnosis of BNS, with positivity for MYD88 by molecular testing providing diagnostic support. CLL and WM are closely related conditions, they both arise from B cells at the late differentiation stage of their life cycle. The co-existence of CLL in this patient’s case added to the complexity and rarity of his presentation. As cases of BNS are relatively rare, there is no consensus or national/international guidance for treatment options. Treatment of choice focused on presenting symptoms and disease area to maximize chances of entering long-term remission as well as minimizing both short- and

| Assessment | Baseline | Post 2 Cycles of Treatment | Post 4 Cycles of Treatment | Posttransplant |
|------------|----------|---------------------------|---------------------------|---------------|
| ECOG       | 3        | 0                         |                           |               |
| CSF        |          |                           |                           |               |
| Total protein (g/L) | >6.00 | 3.03 | 1.57 | |
| Glucose (mmol/L) | 4.3 | 3.8 | 3.7 | |
| Leucocytes (×10^9/L) | 239 | 11 | <1 | |
| Polymorphs (%) | 10 | 0 | 0 | |
| Lymphocytes (%) | 90 | 0 | 0 | |
| Cell cytology | No tumor cell population identified | Moderate number of small mature lymphocytes some with plasmacytoid features | Some small mature lymphocytes with plasmacytoid features | Not applicable |
| Morphology | Significant lymphoid cells with plasmacytoid appearance | Not applicable | Not applicable | |
| Flow cytometry | Monoclonal CD5− CD10− Kappa+ B-cell population identified | Not applicable | Persistence of MYD88 L265P positivity (UCL) | |
| Molecular | MYD88 L265P positive, negative for TP53 exons 4-10 mutations | MYD88 L265P undetectable (UCL) | | |
| Bone Marrow |          |                           |                           |               |
| Flow cytometry noted 2 distinct populations of cells | Monoclonal CD5+ CD10− Kappa (weak)+ CD23+ FMCM7+ CD79b− CD20+ B-cell population. CLL Score 5/5 | Monoclonal CD5− CD10− Kappa (strong)+ CD23− FMCM7− CD38− CD43− CD200− CD79b+ CD22+ B-cells | Persistence of CLL clone (UCL) | |
| Molecular | MYD88 L265P positive, negative for TP53 exons 4-10 mutations | MYD88 L265P undetectable (UCL) | | |
| Trephine | These features together with MYD88 positivity are in keeping with lymphoplasmacytic lymphoma, whilst the CD5+ clone has a CLL phenotype | | | |
| Pathology | CD5+ clone has a CLL phenotype | | | |
| Peripheral Blood |          |                           |                           |               |
| Flow cytometry noted 2 distinct populations of cells | CD5+ CD10− Kappa (weak)+ | CD5− CD10− Kappa (strong)+ | | |
| Pathology | CD5+ clone has a CLL phenotype | | | |
| Lymph Node Biopsy |          |                           |                           |               |
| Flow cytometry noted 2 distinct populations of cells | CD5+ CD10− Kappa (weak)+ | CD5− CD10− Kappa (strong)+ | | |
| Pathology | Lymph node core needle biopsy is dominated by the CD5−/CD10−clone which has demonstrated MYD88 positivity in previous samples, in keeping with lymphoplasmacytic lymphoma | | | |
| Immuno proteins |          |                           |                           |               |
| T protein (g/L) | 85 | 66 | 59 | 37 |
| IgM (g/L) | 37.4 | 24.24 | 7.59 | 0.43 |
| Monoclonal (IgM K) band size | 21 | 14 | 3 | <1 |
| Largest nodal size by CT (cm) | 3.1 | 1 | | Lymph node size reduced from previous study |
| MRI findings | Thickening of multiple nerves: cranial nerves (third and trigeminal), cranial nerve branches (infraorbital nerve), postganglionic nerve roots and brachial and lumbar plexi | Exiting nerve roots thickening noted in the lumbar and sacral region in the sagittal sequence | No significant cranial nerve thickening. Overall appearances show improvement compared with previous imaging. | |
long-term side effects. Ibrutinib was initially considered as a treatment option, as it crosses the blood-brain-barrier; however, following discussion with the national expert a more intensive treatment regime was advised due to symptoms related to disease burden. Following completion of 4 cycles of MATRIX chemotherapy, he has recently attended for an in-patient assessment by hematology and neurology teams at University College London where he underwent a BM biopsy and lumbar puncture. Results of these 2 tests have demonstrated a deeper response, with undetectable MYD88 L265P but persistence of CLL clone in BM by flow cytometry. Imaging showed no active disease. His ECOG has now been upgraded to 0. This patient is currently undergoing investigations and evaluations for carmustine and thiotepa (CARTH) chemotherapy with autologous stem cell transplant with the aim of obtaining long-term remission. This patient has continued to have significant improvement with mobility, requires less help with daily activities, and now mobilizes with only a rollator.

We have presented an unusual case of co-existing BNS/LPL and CLL or biclonal composite lymphoma, in a patient with a long history of an underlying neurological disorder. Although three cases of composite LPL and CLL have been published, this is the first where LPL presentation includes BNS. As such, it has presented a diagnostic, investigative, and management challenge requiring additional investigations and collaboration with national experts to formulate an appropriate and individualized treatment plan.

AUTHOR CONTRIBUTIONS
KC and AA are co-lead authors. KC, MC, MM, and DD contributed to manuscript review.

DISCLOSURES
The authors have no conflicts of interest to disclose.

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