A Novel approach using O-CVP to treat paraneoplastic NMO spectrum disorder associated with follicular lymphoma

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SUMMARY
Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune neuroinflammatory disorder of the central nervous system that very rarely may be a paraneoplastic phenomenon. We describe the case of a woman with a longitudinally extensive transverse myelitis (LETM). We identified a previously undiagnosed, follicular lymphoma and she was treated with the immunotherapy regime (obinutuzumab, cyclophosphamide, vincristine and prednisolone; O-CVP) for paraneoplastic NMOSD. Following two cycles, there was almost complete radiological remission of the myelitis and the patient showed some improvement in her neurological function. This case illustrates the heterogeneous aetiology that LETM may have and that O-CVP may be used as therapeutic option in patients with NMOSD driven by follicular lymphoma.

BACKGROUND
Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated autoimmune disease of the central nervous system characterised by a combination of longitudinally extensive myelitis, optic neuritis and cerebral inflammation. Recurrent relapses result in increasing disability and, therefore, prompt and aggressive treatment is usually necessary. Pathogenic antibodies to aquaporin 4 (AQP4) are expressed in the majority of patients with NMOSD. Rarely, AQP4-positive NMOSD can be a paraneoplastic phenomenon, usually driven by a solid tumour, and the timing between diagnosis of the neoplasm and NMOSD is variable. We present a case of NMOSD, associated with an underlying follicular lymphoma.

CASE PRESENTATION
A woman in her late 60s reported a 6-week history of progressive bilateral lower limb weakness, paraesthesias and numbness spreading proximally. She also noted a month of abdominal bloating and 1 kg of unintentional weight loss. Examination showed that the cord lesion had regressed on age > 60 years old, greater than four nodal sites, international prognostic index (FLIPI) score of 4 (based on age >60-years old, greater than four nodal sites, haemoglobin of <120g/L and stage 3 disease).

INVESTIGATIONS
An MRI of the spine showed longitudinally extensive transverse myelitis extending from C2 to T5, with associated swelling and cord expansion at T2 level (figure 1A). MRI brain was normal. Serum analysis was positive for anti-AQP4 antibodies and hepatitis B core antigen and negative for anti-MOG (Myelin oligodendrocyte glycoprotein) antibodies, HIV and syphilis serology. Cerebrospinal fluid analysis showed normal range white blood cells, lactate, no oligoclonal bands and no elevated immunoglobulins. A diagnosis of NMOSD was made, and as part of her further work up, CT imaging identified extensive para-aortic and pelvic side wall lymphadenopathy, a bulky multifibroid uterus and an adjacent enhancing nodule raising concern of an ovarian lesion. MRI pelvis showed fibroids, with well-visualised and normal appearing ovaries. Positron emission tomography (PET)-CT scan showed an FDG (fluorodeoxyglucose)-avid conglomerate of lymph nodes in the left para-aortic, common iliac, internal iliac, external iliac, right supraclavicular and bilateral subsegmental regions. Subsequent histology of a CT-guided lymph node biopsy identified small to medium-sized lymphoid cells arranged in a vague nodular pattern. Immunohistochemistry showed lymphoid cells positive for CD20, CD79a, CD19, BCL-2, CD10 and BCL-6 and confirmed a low-grade follicular lymphoma. Cyclin-D1 was negative and Ki-67 stained less than 5% of all cells. The patient had a follicular lymphoma international prognostic index (FLIPI) score of 4 (based on age >60-years old, greater than four nodal sites, haemoglobin of <120g/L and stage 3 disease).

TREATMENT
The patient was initially treated with high-dose intravenous methylprednisolone at presentation, followed by oral prednisolone. She had a poor clinical response and was transferred to a tertiary neurology centre for a 5-day course of plasma exchange. A repeat MRI spine 3 weeks after plasma exchange showed that the cord lesion had regressed and was visible from C4/5 to T5 (figure 1B), but there was no significant clinical recovery. On discussion between the haematology and neurology teams, it was concluded that the NMOSD was a likely paraneoplastic phenomenon and it was decided to treat the lymphoma, rather than manage her with active observation. Obinutuzumab, cyclophosphamide,
Figure 1 (A–C) Sagittal MRI T2 weighted images of upper spine at different stages. Initial images were acquired on presentation and prior to any therapy (A) and show extensive intramedullary high signal from C2–T5 with some cord oedema; there was no pathological enhancement (not shown). Subsequent images taken 4 weeks and 3 weeks after intravenous Methylprednisolone and plasmapheresis, respectively, (B) show regression of the intramedullary high signal and improvement of the cord oedema and further imaging after the third chemotherapy cycle (C) shows further improvement and some subtle cord thinning at T3 level.

OUTCOME AND FOLLOW-UP
She tolerated two cycles of O-CVP well and repeat neurological assessment performed prior to her third cycle showed an improvement in power (3/5 in hip flexion bilaterally), recovery in hallux proprioception, brisk lower limb reflexes and up-going plantar reflexes. Repeat imaging performed following the patient’s second cycle showed further regression of the longitudinal spinal cord signal change, being barely perceptible on repeat imaging (figure 1C).

During her admission, she received active rehabilitation and following her first cycle of treatment was transferred to an inpatient neurorehabilitation unit for ongoing therapy. Following her third cycle of O-CVP the patient developed neutropenic sepsis requiring an intensive care unit admission, after which no further cycles of treatment were given. A PET-CT scan performed 3 months following cessation of treatment showed a complete metabolic response of her follicular lymphoma and she was subsequently managed with an active observation strategy. Following recovery from neutropenic sepsis, she underwent a further 10 weeks in an inpatient neurorehabilitation unit before being discharged home, with ongoing community rehabilitation.

DISCUSSION
Paraneoplastic neurological syndromes (PNS) are ‘neurological disorders that can affect any part of the nervous system, often presenting with stereotyped clinical manifestations, that occur in association with cancer and have an immune-mediated pathogenesis’. AQP4 antibodies are defined as a ‘lower risk’ antibody for association with cancer, and approximately 5% of patients with NMOSD are thought to have an underlying paraneoplastic cause.

Unlike some other types of PNS, existing reports of paraneoplastic NMOSD have identified no typical underlying malignancy. A wide range of malignancies have been reported, most commonly solid tumours, including breast and lung. Patients with paraneoplastic NMOSD tend to be older at presentation (median age of 55 compared with 40) and are more likely to be men than in non-paraneoplastic NMOSD, although the majority in both groups remain women (29.4% vs 6.6%).

Rarely, paraneoplastic NMOSD has been reported in association with B-cell lymphomas. Of these, there is one AQP-4 positive case described of suspected follicular lymphoma (where identification of the primary site was not possible). In this case, the patient was treated with pulsed methylprednisolone before being commenced on R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisolone) chemotherapy and, after two cycles, there was an improvement in cord inflammation, as shown via MRI, in serum AQP4 levels and in the patient’s symptoms.

Acute treatment of NMOSD involves high-dose steroids, with plasma exchange if required to achieve remission, followed by maintenance immunosuppression with oral immune modulatory agents such as azathioprine or rituximab. As with all paraneoplastic conditions, treatment is tailored to include treatment of the underlying malignancy. Follicular lymphoma treatment depends on the staging and whether the cancer is symptomatic and ranges from active observation to immunochemotherapy induction, followed by subsequent immunotherapy maintenance. Given that our patient had stage 3 follicular lymphoma, with neurological sequelae, treatment was warranted. The FLIPI score is used to guide treatment decisions. The GALLIUM trial, a phase III open-label randomised control trial has shown that in patients with a high risk of premature mortality (FLIPI ≥2), obinutuzumab increases progression-free survival, although with an unclear effect on long-term survival, and has subsequently been approved by the national institute of clinical excellence (NICE) for treatment in this group.

Our patient met the requirements for treatment with obinutuzumab with chemotherapy. While rituximab has a well-characterised role in NMOSD treatment, the decision was made to treat with O-CVP as we felt that the neurological sequelae would be better controlled with aggressive lymphoma control, and we were reassured by the common target of both monoclonal antibodies (CD20 inhibition). Furthermore, obinutuzumab is a type II CD20 antibody, which differs from rituximab, a type I CD20 antibody; resulting in enhanced antibody-dependent and complement-dependent cellular cytotoxicity.

An additional consideration was the site of B-cell activity in NMOSD and whether the drugs can cross the blood–brain barrier. PNS can be the result of epitope expression by the cancer, or by autoantibody production. Unfortunately, we did not have the facilities available to determine which was the mechanism driving anti-AQP4 in our patient. However, regardless of the underlying mechanism, the pathogenesis of NMO is well understood. AQP4 is a water channel highly abundant in the central nervous system, particularly in the end-feet of glial cells bordering the blood–brain barrier. Antibodies to this protein cause blood–brain barrier disruption, inflammation and often damage to the surrounding neurons. It is an ongoing question of research whether anti-AQP4 antibodies are produced intrathecally or within the blood, and studies indicate that blood production is more likely. This peripheral anti-AQP4
production, together with blood–brain barrier disruption in NMO, suggests that a requirement to cross an intact blood–brain barrier is not required for NMO therapies. Consistent with this, there is evidence that rituximab is not effective at crossing the blood–brain barrier. There are no studies to date on the ability of obinutuzumab to do so.

In summary, this case of follicular lymphoma associated with AQP-4-positive NMO reinforces the importance of looking for a neoplastic process in patients with NMOSD; particularly those who are older. While prior case reports have demonstrated the use of rituximab in treating patients with this association, we report the efficacy in this case of using an alternative treatment strategy with an obinutuzumab chemotherapy-based regime, in paraneoplastic NMOSD.

### Learning points

- Neuromyelitis optica spectrum disorder (NMOSD) can rarely be a paraneoplastic neurological syndrome.
- Although unusual, the underlying cancer responsible can include follicular lymphoma.
- A high index of suspicion is needed to identify patients with paraneoplastic NMOSD, which is more likely in elderly patients.
- Treatment of our patient’s NMOSD, by treating the underlying follicular lymphoma with obinutuzumab, cyclophosphamide, vincristine and prednisolone, resulted in a good radiological and neurological outcome.

### Contributors

All authors were involved in treating the patient in this case. DAP, HD and MP wrote the manuscript. PP and ES reviewed the final manuscript before submission.

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### Competing interests

HD, DAP, MP and ES have no competing interests. PP: the below are his competing interests. Specific funding: no specific funding regards this submission. HD and MP wrote the manuscript. PP and ES reviewed the final manuscript before submission.

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### Case report

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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