A 54-year-old man presented with a week of decreasing right vision and painful eye movements, his having a diagnosis of diffuse large B-cell lymphoma (DLBCL) of the ocular adnexa established 2.5 years earlier when presenting with right proptosis and diplopia. At that time, the tumour was debulked. He received six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) and 30 Gy fractionated orbital radiotherapy. Regular surveillance with ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET) demonstrated no residual disease or recurrence.

At presentation, left visual functions were normal. Right eye visual acuity was 6/60, with no colour perception and a right relative afferent pupillary defect (RAPD). Right downgaze was restricted, with diplopia on vertical gaze, and a pale optic disc.

Brain MRI demonstrated multiple periventricular and juxtacortical lesions, some enhancing, with enhancement and swelling of the intra-orbital right optic nerve (Fig. 1A and B). Criteria for dissemination in time and space were met. FDG-PET body scan showed multifocal uptake in deep white matter of the right frontal and parietal lobes, the left parietal lobe and the corpus callosum with hypometabolism in the right cerebral cortices and striatum. There was no pathological extracranial FDG uptake. CSF analysis demonstrated mild lymphocytosis but no atypical cells on cytological examination. There were oligoclonal bands in CSF and serum, with no unique bands in CSF. His condition was suggestive of atypical demyelination and was treated with intravenous methylprednisolone, followed by a tailing dosage of oral prednisolone. The clinical and radiological features improved over a month, with right acuity of 6/6, and resolution of the RAPD.

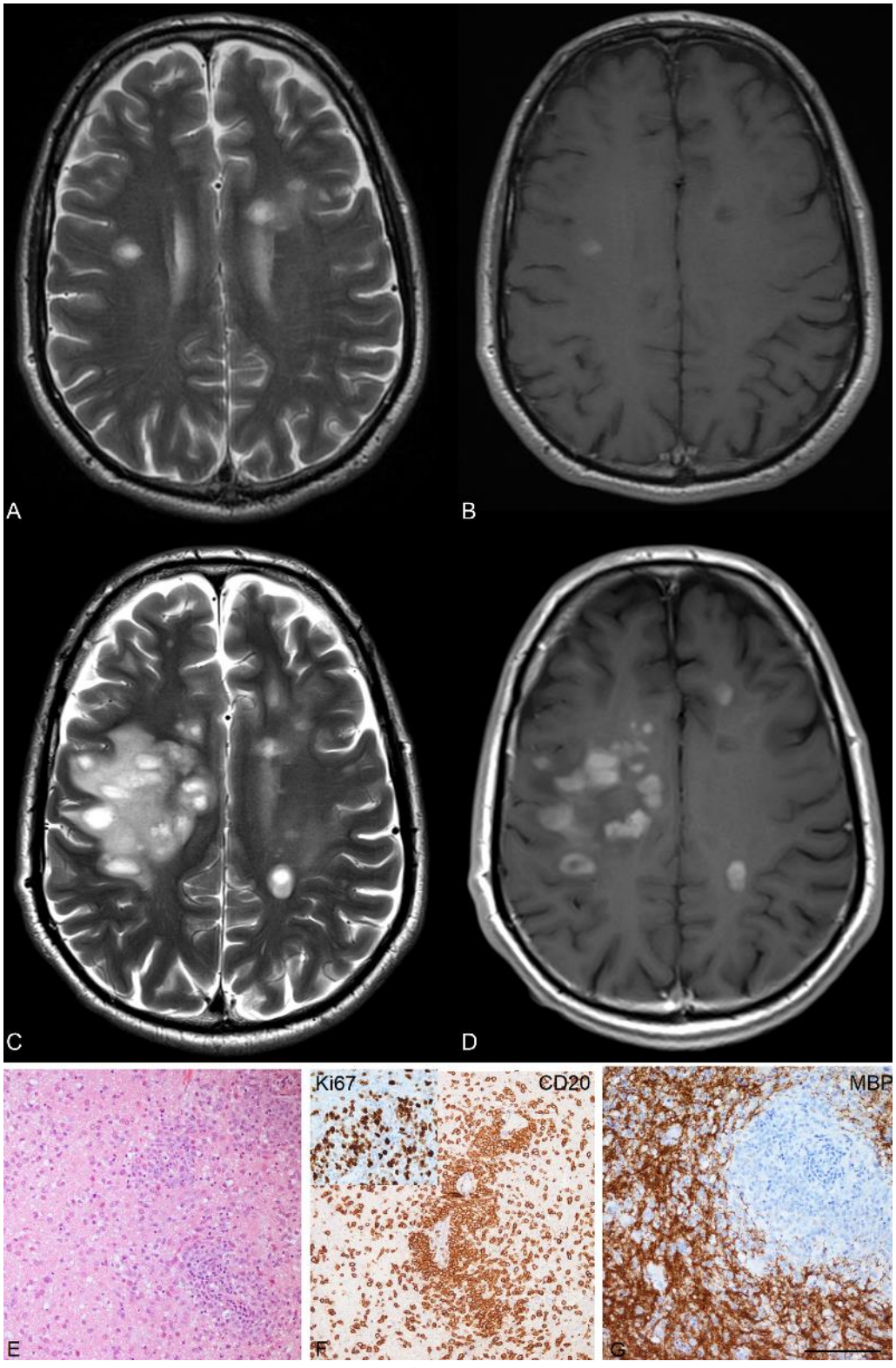

Figure 1

Three months after initial presentation, he developed left facial weakness and an unsteady gait, with right acuity still 6/6, without an RAPD, but with right visual-field restriction. He had a left upper-motor neurone facial weakness and reduced power in left sternocleidomastoid and trapezius muscles. There were left-sided pyramidal signs with

increased tone in left upper and lower limbs, left ankle clonus and mild strength reduction in left hip and knee flexion. Left upper-limb and bilateral lower-limb reflexes were brisk, both plantar responses were flexor, and he had bilateral heel-shin ataxia.

Repeat brain MRI showed multiple enhancing right fronto-parietal lesions (Fig. 1C and D). Repeat FDG-PET demonstrated heterogeneous multifocal areas of uptake, predominantly in deep white matter of the right frontal and parietal lobes, with involvement of the corpus callosum as well as deep white matter of the left parietal lobe. CSF analysis was unremarkable.

Biopsy of a lesion in the right frontal lobe was consistent with non-germinal centre DLBCL (Fig. 1E to G) but, unlike his original DLBCL which had focal CD10 positivity, this had no CD10 staining. All other major markers were identical. There was no evidence of demyelination. He was treated with four cycles of high-dose intravenous methotrexate and cytarabine, followed by 40 Gy whole-brain fractionated radiotherapy.

The patient remained disease-free for over three years, then developing intracranial recurrence, manifest as confusion with visual-field deficit. He died one year later despite treatment with an autologous haematopoietic stem-cell transplant, rituximab and temozolamide.

Although the initial optic neuropathy was broadly consistent with a typical presentation for optic neuritis, some features (such as older age, lymphoma history and absence of unique CSF oligoclonal bands) suggested an atypical cause. However, screening for atypical causes was clear, and he responded well to corticosteroids. A definitive diagnosis was

only established later with tissue biopsy, triggered by the unexpectedly aggressive clinical and radiological features.

It is widely reported that the sensitivity of CSF cytological analysis for CNS lymphoma is low [1], increasing with repeat CSF sampling. While there are no clear data on the difference in diagnostic yields in parenchymal versus leptomeningeal CNS lymphoma, it seems reasonable to assume that it is comparatively lower in parenchymal disease. Studies of non-lymphomatous CNS malignancies reached a similar conclusion. Conversely, while use of FDG-PET in diagnosis of CNS lymphoma is not yet routine, one meta-analysis of its accuracy reported sensitivity of 0.88 and specificity of 0.86 [2]. Furthermore, while demyelinating lesions tend to be hypometabolic on FDG-PET [3], some reports have demonstrated hypermetabolic lesions in tumefactive multiple sclerosis [4]. In our case, the initial FDG-PET findings were felt to be non-specific, as increased FDG uptake can be seen in both CNS lymphoma and tumefactive multiple sclerosis.

Although minimally-invasive testing was repeatedly reassuring, the recent history of orbital lymphoma warranted further investigation. Intracranial spread of ocular adnexal lymphoma is rare, although one extensive case series [5] reported that, at 11%, DLBCL was the most likely major histological type to present with intracranial disease (compared with 4% for the whole case series). In our case, his initial ocular adnexal lymphoma was highly aggressive, with the mass in tight contact with his optic nerve at the time of debulking. It is probable that he had microscopic systemic disease at the time, and though he received systemic chemotherapy, R-CHOP has poor penetration of the blood-brain barrier.

This case highlights the importance of extra vigilance in patients with apparent optic neuritis with atypical features. Most important here was the history of a higher-risk

extracranial lymphoma, where initial chemotherapy did not cross the blood-brain barrier. The presence of extensive oedema with a large number of enhancing lesions on the second MRI after a course of corticosteroids is also considered a red flag for an alternative diagnosis to demyelination. While not present here, clinicians should additionally be alert to severe or prolonged pain, severe visual loss (worse than 6/60), bilateral simultaneous presentations, prolonged deterioration over more than two weeks, and lack of recovery after six weeks.

It also serves as a reminder that, although non-invasive testing for CNS lymphoma is available, the most reliable investigation is biopsy of an identified lesion. Indeed, the utility of biopsy is not just limited to CNS lymphoma. It can confirm an uncertain diagnosis or revise a previous diagnosis, and allow initiation of appropriate management. We would advise clinicians to consider biopsy where the presentation is atypical, or when unexpected features later emerge.

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FIGURE LEGEND

Figure 1: Initial MR scan of brain (A, B) showing juxtacortical and periventricular enhancing lesions; repeat MR scan of brain (C, D) on neurological deterioration 3 months later showing multiple right fronto-parietal lesions with ring-enhancement; (E) H&E stain showing infiltrates of atypical lymphoid cells mainly in perivascular spaces in the white matter; the parenchyma shows marked gliosis but no necrosis; (F) CD20 immunostaining confirms a B cell lymphoma with a high proliferation rate on Ki67 labelling (inset), morphology in keeping with diffuse high grade B cell lymphoma; (G) Myelin basic protein immunohistochemistry showed rarefaction in the regions of lymphoma infiltration but no demyelination. Bar equivalent to approx. 240 microns