CASE REPORT

Expanding the range of immunopathology in neuromyelitis optica spectrum disorder

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SUMMARY

Neuromyelitis optica (NMO) spectrum disorder typically associates with a pathognomonic antibody response directed against aquaporin 4 and a unique immunopathological signature characterised by loss of aquaporin 4 expression. We describe a tumefactive presentation of NMO in which a biopsy specimen demonstrated active demyelination and reactive astrocytes with preserved surface aquaporin 4 immunoreactivity and dystrophic processes. While the astrocytic pathology is more typical of classical multiple sclerosis, a positive NMO-IgG (1:80) and subsequent clinical presentation with an area postrema syndrome is consistent with a diagnosis of NMO spectrum disorder. This report expands the immunopathological features that have been reported in NMO spectrum disorder.

BACKGROUND

Neuro-myeilitis optica (NMO) is an inflammatory condition of the central nervous system that is associated with a unique immunopathological signature. In majority of cases an antibody that is reactive with aquaporin 4 (AQP4) (NMO-IgG) can be detected in the serum of the affected individuals. NMO-IgG has an extremely high sensitivity and specificity to the extent that NMO-IgG can be considered to be pathognomonic for the diagnosis of NMO.^{1 2} Moreover, immunopathological and in vitro studies are suggestive of a pathogenic role for NMO-IgG.^{3 4}

While initial reports suggested that a normal brain MRI was typical of NMO it subsequently became apparent that a wide range of MRI brain abnormalities could be observed in up to 60% of NMO cases and the term NMO-spectrum disorder (NMO-SD) evolved to encompass an expanded range of clinical presentations associated with NMO-IgG.⁵ Notably certain clinical syndromes, including intractable vomiting and hiccoughs, reflect dysfunction of cerebral regions with high levels of AQP4 expression. However, it is plausible that the broad spectrum of clinical and MRI presentations associated with NMO-IgG could reflect a wider range of immunopathogenic processes that act in concert with prototypical NMO-IgG-mediated complement-driven astrocytic injury.

In this report we describe a tumefactive presentation of NMO associated with NMO-IgG in which a biopsy identified preserved areas of AQP4 expression by dystrophic appearing astrocytes and discuss the immunopathological and diagnostic significance of this finding.

CASE PRESENTATION

A 29-year-old woman of Phillipino background was admitted in January 2015 with a 1 week history of progressive left-sided ataxic hemiparesis and sensory disturbance in the absence of features of systemic illness.

INVESTIGATIONS

MRI brain at presentation demonstrated a tumefactive-like T2/fluid-attenuated inversion recovery hyperintense lesion of the right thalamus and posterior limb of the internal capsule (figure 1A). There was diffusion restriction along the lateral aspect of the lesion (figure 1B) and two small nodules of contrast enhancement along its anterolateral margin abutting the posterior body of the right lateral ventricle (figure 1C).

The cerebrospinal fluid (CSF) contained $32 \times 10^6/L$ leucocytes (69% polymorphs, 29% lymphocytes, 2% monocytes); a protein of 404 mg/L; and CSF-specific oligoclonal bands. Flow cytometry demonstrated a predominantly T cell infiltrate with no malignant cells observed on cytology. Cryptococcal antigen, *Mycobacterium tuberculosis* complex and Epstein Barr Virus (EBV) PCR were negative.

Progressive weakness occurred despite administration of five doses of intravenous methylprednisolone and a brain biopsy of the thalamus was performed for diagnostic purposes. This showed an active inflammatory process with prominent perivascular and less pronounced interstitial lymphoplasmacytic inflammation (figure 2A). Almost all the lymphocytes were CD3 positive T cells, with moderate numbers of CD138 plasma cells, and very rare perivascular B cells. Occasional perivascular eosinophils and rare neutrophils were also present. There was near-total myelin loss on luxol-fast blue (LFB) staining (figure 2B), with relatively preserved axons on Garvey silver stain (figure 2B, inset). Large numbers of foamy macrophages were present, some of which contained LFB-positive material (figure 2B, arrows)—a finding consistent with active demyelination. Numerous reactive astrocytes were also found throughout the biopsy (figure 2B, arrowheads). Astrocytes were best visualised on glial fibrillary acidic protein (GFAP) immunohistochemistry (figure 2C) where they showed somewhat stunted and irregularly beaded processes resembling astrocytic clasmotodendrosis. They were strongly immunoreactive for AQP4 (figure 2D) in addition to GFAP (figure 2C). Immunohistochemistry for IgG showed widespread parenchymal staining. No viral inclusions were

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Figure 1 Axial T2/fluid-attenuated inversion recovery (FLAIR)-weighted MRI showing hyperintense lesion of right thalamus (A). Axial diffusion-weighted image showing restriction along lateral aspect of lesion (B). Axial T1 postcontrast MRI showing patchy enhancement of lesion (C). Sagittal T2/FLAIR-weighted image showing hyperintense area postrema (D).

seen, special stains for microorganisms (disastase Periodic acid-Schiff (dPAS), methenamine silver, Putt, auramine) were negative, and immunohistochemistry for SV40 (JC virus), toxoplasmosis, Herpes Simplex Virus (HSV) and Cytomegalovirus (CMV), as well as EBV Encoded RNA-1 (in situ hybridisation) (EBER 1 (ISH)) was negative.

Serological testing for NMO-IgG (Euroimmun) was positive with a titre of 1:80.

DIFFERENTIAL DIAGNOSIS

The biopsy findings of active demyelination and reactive astrocytosis with preserved AQP4 expression are consistent with a

diagnosis of tumefactive multiple sclerosis. However, the detection of NMO-IgG is considered to be diagnostic of NMO-SD. Although the CSF demonstrates a polymorphonuclear pleocytosis, typical of NMO-SD, the presence of CSF-specific oligoclonal bands favour a diagnosis of multiple sclerosis.

OUTCOME AND FOLLOW-UP

Nine weeks following the initial presentation the patient re-presented with intractable hiccoughs and vomiting. An MRI study at this time demonstrated a faintly enhancing hyperintense lesion in the area postrema and new T2 hyperintense signal change of the hypothalamus and proximal optic tracts

Figure 2 H&E stained section showing perivascular lymphoplasmacytic inflammation, numerous macrophages and some reactive astrocytes (arrowheads) (A). Combined H&E/luxol-fast blue (LFB) stain showing near-total loss of LFB staining of axons, and some LFB-positive debris in macrophages (arrows). In contrast, axons were relatively preserved (inset) with scattered axonal spheroids visualised on Garvey silver staining (B). Immunohistochemistry for GFAP confirmed the presence of numerous reactive astrocytes. Many had somewhat shortened, stubby (dystrophic) processes (C). Immunohistochemistry for aquaporin-4 showed strong immunoreactivity in the astrocytes (magnification $\times 400$ A–D) (D).

(Figure 1D). There was gliotic change of the previous tumefactive right thalamic lesion. Following a further course of intravenous methylprednisolone symptoms due to the area postrema syndrome resolved and the patient returned to the Philippines. NMO-IgG testing was repeated in April 2015 and remained positive. This finding coupled to the presentation with a classical area postrema syndrome favoured a diagnosis of NMO-SD and the patient was treated with 500 mg Rituximab in April 2015. NMO-IgG testing remained positive in April 2016 and a further 1000 mg dose of Rituximab was administered. The patient has remained in clinical remission following initiation of Rituximab therapy.

DISCUSSION

The immunopathological features of NMO were originally characterised on nine autopsy cases with unknown NMO-IgG status, but recently confirmed in a biopsy study of 14 NMO-IgG positive cases.^{3–6} Pathological studies of NMO-SD to date have emphasised the prominent loss of immunoreactivity for the astrocytic proteins GFAP and AQP4.³ The observation of perivascular deposition of immunoglobulin and complement has led to the hypothesis that NMO spectrum is primarily an NMO-IgG-mediated astrocytopathy with a discrete immunopathological signature. However, it is increasingly recognised that the pathogenesis of NMO and the occurrence of relapses must be at least in part related to factors other than AQP4 antibodies.

The detection of NMO-IgG is considered to be highly sensitive in distinguishing NMO-SD from multiple sclerosis. While NMO-IgG detection assays employ a variety of methodologies that vary in sensitivity and specificity, the Euroimmun cell-based assay (CBA) is observed to have 100% specificity for the diagnosis of NMO, in contrast to assays that use flow cytometry and live cells which return occasional false positive results.² While this case demonstrates some laboratory and pathological features of multiple sclerosis (CSF-specific oligoclonal bands and active demyelination), these observations could potentially challenge the notion that NMO-IgG testing with the CBA is 100% specific and it should be noted that it is unlikely that any biological assay has 100% specificity. Nevertheless in this instance the clinical, radiological and pathological findings coupled to positive NMO-IgG testing on serial assays are altogether consistent with a diagnosis of NMO-SD.

Despite the improved sensitivity of NMO-IgG assays ~30% of patients presenting with features of NMO-SD are NMO-IgG negative and it has recently emerged that some patients with NMO-IgG negative NMO-SD test positive for antibodies to myelin oligodendrocyte glycoprotein (MOG). Furthermore, a recent case of NMO-IgG negative/anti-MOG antibody positive NMO-SD had markedly elevated levels of CSF myelin basic protein (MBP) with undetectable levels of GFAP, indicating that the immune response in this subset of NMO primarily targets myelin rather than astrocytic antigen.^{7–8}

While we do not know the MOG antibody status or CSF MBP/GFAP levels of the patient reported in this study it is noteworthy that in this NMO-IgG positive patient lesional

pathology was characterised by active demyelination with axonal spheroids in the presence of reactive astrocytes with preserved surface expression of AQP4. Thus the findings described in this report coupled to the emerging literature suggests that NMO-SD can potentially have a heterogeneous immunopathology which targets astrocytic and myelin antigens and can result in varying degrees of active demyelination, axonal injury and astrocytopathy.

Learning points

- ▶ Neuromyelitis optica (NMO) is historically described as an astrocytopathy.
- ▶ This report represents a case of clinically definite NMO-spectrum disorder (NMO-SD) in which a biopsy early in the disease course demonstrated demyelination with preservation of astrocytes and aquaporin 4 expression.
- ▶ Heterogeneous immunopathology likely exists in NMOSD which can target astrocytic and myelin antigens.
- ▶ A variety of assays are available for the detection of NMOSD and the commercially available cell-based assay has the highest diagnostic specificity.²
- ▶ Individuals presenting with atypical demyelinating syndromes should be tested for NMO-IgG and myelin oligodendrocyte glycoprotein antibodies as part of the initial diagnostic work up.

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