Autoimmune encephalitis (NMDAR antibody) in a patient receiving chronic post-transplant immunosuppression

Anna Randall, Saif Huda, Anu Jacob, Andrew J Larner

Walton Centre for Neurology and Neurosurgery, Liverpool, UK

Correspondence to
Dr Andrew J Larner, Walton Centre for Neurology and Neurosurgery, Liverpool L9 7LJ, UK; a.larner@thewaltoncentre.nhs.uk

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ABSTRACT

Autoimmune encephalitis associated with antibodies (Abs) directed against the synaptic ligand-gated ion channel NMDA receptor (NMDAR) was first described as a paraneoplastic disorder in association with ovarian teratoma. Other forms of neoplasia have subsequently been reported although many patients do not have a tumour. Tumour removal, where applicable, and immunotherapy form the mainstays of treatment. We present a patient who developed NMDAR-Ab encephalitis despite being chronically immunosuppressed following organ transplantation, and who was eventually found to have an occult malignancy in the form of non-Hodgkin's lymphoma.

CASE REPORT

A 54-year-old woman presented with episodic vertigo over a 2-month period. She had double vision on horizontal gaze, with left directional preponderance, and had become unsteady when walking. Her family had noticed a change in her personality, with anxiety and low mood. There were no clear periods of improvement during this time. These symptoms occurred on the background of renal transplantation performed 7 years earlier for chronic pyelonephritis and hydronephrosis, with stable renal function on long-term immunosuppression (prednisolone 5 mg alternate days, mycophenolate mofetil 750 mg twice daily). There were no constitutional symptoms such as fever or weight loss. She was a non-smoker and rarely drank alcohol.

Initial examination showed gait ataxia, left-side intention tremor and dysdiadochokinesis. She had convergence–retraction nystagmus but no clear ophthalmoplegia. Tone was increased in the legs with sustained ankle clonus bilaterally. There was left-sided limb hyper-reflexia and an ipsilateral extensor plantar response. There was no consistent sensory deficit. Cognition was not formally examined but appeared intact.

We diagnosed a subacute brainstem syndrome. Non-contrast MR brain imaging showed high T2 signal affecting the right hemipons with rostral and caudal extension. In view of her chronically immunosuppressed state, our provisional diagnosis was central nervous system malignancy, possibly lymphoma.

Over the next few days, she made no clinical improvement and then developed auditory hallucinations, progressing to a fluctuating conscious level with orofacial dyskinesia and autonomic fluctuation. Cerebrospinal fluid (CSF) showed a normal opening pressure, mildly elevated protein at 0.54 g/L (0.15–0.45), elevated white cell count at 10×10^9/L (≤5) (100% lymphocytes) but CSF cytology showed no abnormal cells on three separate occasions. Oligoclonal IgG was present in the CSF but not serum. CT scan of chest, abdomen and pelvis was normal. Following empirical treatment with intravenous methylprednisolone the MR scan changes in the brainstem changes resolved but without clinical improvement.

A diagnosis of autoimmune encephalitis, initially thought less likely because of her immunosuppressed state, was supported by detecting serum and CSF NMDA receptor antibodies (NMDAR-Abs) on direct immunofluorescence live cell-based assay (NR1 and NR2b subunits expressed on human embryonic kidney cells).

There was no clinical improvement with first-line immunotherapy consisting of intravenous corticosteroids and intravenous

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immunoglobulin. Two cyclophosphamide infusions were then administered but subsequent infusions were precluded by the patient developing an acute abdomen due to caecal perforation requiring surgical management. Histology from the resected colonic segment showed a high-grade non-Hodgkin's B cell lymphoma. Shortly thereafter she died from sepsis and multiorgan failure. Permission for autopsy was not granted.

DISCUSSION

This case raises several issues: the pathogenic relevance of NMDAR-Abs; the development of NMDAR-Abs in a patient on chronic immunosuppression for renal transplantation; and the association of NMDAR-Abs with non-Hodgkin's lymphoma.

Even though the evolving symptom complex was consistent with suggested diagnostic criteria for 'possible autoimmune encephalitis',[1] an Ab-mediated cause seemed counterintuitive due to the cytostatic/inhibitory actions of mycophenolate mofetil on B and T lymphocytes.[2] Although the emergence of a new autoimmune disorder during immunosuppressive therapy may seem paradoxical, there are well-described examples such as the development of thyroid autoimmunity during alemtuzumab treatment of multiple sclerosis in association with immune reconstitution.[3] Secondary autoimmune diseases as a complication of autologous haematopoietic stem cell transplantations are also reported,[4] and we found one reported case of LGI1 Ab encephalitis occurring 15 months after bone marrow transplantation for aplastic anaemia in a 7-year-old boy.[5] It is unclear if NMDARs are expressed in the human kidney but NMDARs, including the NR1 subunit (the predominant target epitope of NMDAR-Abs), are expressed in rat podocytes.[6] Importantly, in this case there were no features of renal transplant rejection.

Recently, patients with NMDAR-Ab encephalitis have been shown to have ongoing NMDAR-Ab production from active germinal centres[7]; such reactions might possibly overwhelm the action of immunosuppressive drugs.

The detection of CSF NMDAR-Abs using a cell-based assay is highly specific for NMDAR-Ab encephalitis.[8] Furthermore, when NMDARs are expressed in live cells, the patient Abs must bind to the extracellular domains of the receptor, lending further weight to their pathogenic relevance. In hindsight, the patient's clinical course was fairly typical, progressing from behavioural abnormalities to a reduced conscious level with orofacial dyskinesia and autonomic fluctuation. However, the response to immunotherapy, although first line, was poor. Her initial presentation was of a subacute brainstem syndrome, with an anatomically appropriate corticosteroid-responsive lesion. Although brainstem white matter lesions are recognised in NMDAR-Ab encephalitis,[9] the patient had histological evidence of non-Hodgkin's lymphoma on a colonic biopsy.

Key points

- Chronic immunosuppression for organ transplantation does not preclude the development of another autoimmune disorder.
- Non-Hodgkin's lymphoma may be a rare cause of paraneoplastic autoimmune encephalitis.

The association of non-Hodgkin's lymphoma with limbic encephalitis is rare. This contrasts with the well-recognised association of Hodgkin's lymphoma with limbic encephalitis (Ophelia syndrome). This may occur in association with various paraneoplastic Abs, although to our knowledge there are only two published reports with NMDAR-Abs.[10 11] There have been a few reports of paraneoplastic limbic encephalitis associated with non-Hodgkin's lymphoma,[12 13] but to our knowledge this is the first report in association with NMDAR-Abs. It is unclear if NMDARs are expressed by lymphomas, as occurs with ovarian teratomas.[14]

The pathogenic mechanisms in this case remain uncertain. It may reflect the chance co-occurrence of immunosuppression, lymphoma and NMDAR-Ab encephalitis, or represent a paraneoplastic NMDAR-Ab encephalitis in association with a lymphoma related to chronic immunosuppression. Lymphoma is a well-recognised complication of renal transplantation.[15]

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