CASE REPORT MANUSCRIPT

TITLE PAGE

Title of case report: Meningitis as a presenting feature of anti-NMDA receptor encephalitis

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PRESENTATION

A 33-year old, previously fit and well, Caucasian woman presented to a UK acute medical unit with two days gradual-onset pressure-like headache, fever, neck stiffness and vomiting. There was no travel history of note, or recent ill contacts.

On examination, she was pyrexial at 38.6°C and photophobia with nuchal rigidity, however with normal level of consciousness, and unremarkable systemic and neurological examination.

Initial tests included a normal white cell count, renal function and electrolyte levels, chest radiograph, CT brain and a C-reactive protein of < 1 mg/L. A cerebrospinal fluid (CSF) analysis revealed an elevated white cell count of 172×10^6/L, with complete lymphocytosis (Table 1). A working diagnosis of viral meningitis was made. Following LP, she was treated empirically with intravenous acyclovir. Three days later, her CSF virology polymerase chain reaction (PCR) screen returned negative. She was improving and discharged home.

She represented one week later with additional clinical features including confusion with impaired concentration, memory deficits and mild dysarthria. She remained febrile. She rapidly became increasingly agitated, and developed visual hallucinations and a generalised tonic-clonic seizure. Over five days, she developed a reduced conscious level alternating with agitation and mutism. She was intubated and ventilated, and treated empirically with high-dose intravenous cephalosporin and acyclovir for presumed infective meningoencephalitis. She was subsequently transferred to our hospital for further investigation and care. During this period, despite ongoing antimicrobial therapy she remained pyrexial and a persistently reduced GCS required critical care support. She later developed marked autonomic instability, along with new orofacial and upper limb dyskinetic movements.

INVESTIGATIONS

She underwent detailed investigation for infective and autoimmune causes of encephalitis and meningitis. Magnetic resonance imaging (MRI) of her brain with contrast was normal. A summary of her serum and CSF investigations are shown in Table 1. CSF repeatedly demonstrated marked lymphocytosis with elevated protein levels and an elevated opening pressure, as well as reduced CSF: serum glucose ratio on one occasion. Investigations for a number of infections were negative. Her electroencephalograms showed generalized slowing.

SERUM			CEREBROSPINAL FLUID (Three lumbar punctures performed on day 1, 13 and 23 of illness)			
Infective	**Autoimmune**	**Tumour marker** (reference range)	*Day of illness course*	*1*	*13*	*23*
Negative for: HIV antigen/antibody Hepatitis C antibody Anti-treponemal IgG CMV IgM and IgG EBV IgM Leptospirosis IgM Borrelia antibody Cryptococcal antigen Blood cultures	Negative for: Anti-VGKC MPO & PR3-ANCA C3 and C4 ANA Anti-CCP Anti-Ro Anti-La Anti-Smith Anti-RNP Anti-Scl-70 Anti-Jo-	LDH: 265 (125-220) CA-125: 8 (0-35) β-HCG: <1 (0-5) AFP: <2 (2-6) No paraproteins.	Opening pressure (cm H_20)	32	17	Not available
			White cell count ($\times 10^6$/L)	172 (100% lymphocytes)	85 (Differential not available)	143 (100% lymphocytes)
			Red cell count ($\times 10^6$/L)	35	6	0
			Protein (g/L)	0·77	1·07	0·32
			Glucose(serum glucose) (g/L)	2·3(no serum)	2·5 (10·5)	3·8 (6·1)
			Cryptococcal antigen	-	Negative	-
			ANCA	-	Negative	-
			Microscopy	No organisms seen (all three samples)		
			Virology PCRs	Negative for H. influenza, S. pneumoniae, N. meningitidis, enterovirus, HSV 1 & 2, VZV, parechovirus (all samples)		
			Culture and sensitivity	No growth, No mycobacteria (all samples)		
			Cytology	No malignant cells detected (all samples)		

HIV: Human Immunodeficiency Virus; CMV: Cytomegalovirus, EBV: Epstein - Barr virus; PCR: Polymerase Chain Reaction;
Anti-VGKC: Anti-voltage gated potassium channel; MPO & PR3 ANCA: Myeloperoxidase and proteinase-3 anti-neutrophil cytoplasmic antibody; C3 and C4: Complement component 3 and 4; ANA: Anti-nuclear antibody; Anti-CCP: Anti-cyclic citrullinated peptide; Anti-RNP: Anti-ribonucleoprotein; Anti-Scl 70: Anti-scleroderma, also known as anti-topoisomerase 1; Anti-Jo-1: Antibodies to histidyl tRNA synthetase; LDH: Lactate dehydrogenase; CA-125: Cancer antigen-125; β-HCG: Beta human chorionic gonadotropin; AFP: Alpha-fetoprotein; ANCA: Anti-neutrophil cytoplasmic antigen; H. influenzae: Haemophilus influenzae, S. pneumonia: Streptococcus pneumoniae; N. meningitidis: Neisseria meningitidis: HSV: Human simplex virus; VZV: Varicella zoster virus.

Table 1: Summary of serum and cerebrospinal fluid investigations

Serum live cell based assay for NMDA-receptor (NMDAR) antibodies from day 14 of illness was positive. Computed tomography (CT) of the pelvis demonstrated a left ovarian teratoma. Subsequent excision confirmed a stage 1A G1 immature ovarian teratoma. A diagnosis of anti-NMDAR encephalitis related to ovarian teratoma was made. Due to a sampling error, a CSF NMDAR antibody result was not available.

MANAGEMENT

The patient was treated with high-dose intravenous methylprednisolone followed by high-dose enteral steroid therapy and five cycles of plasma exchange. She underwent left salpingo-oophorectomy eight weeks following her initial presentation. Steroids were slowly reduced and stopped over three months. Further immunotherapy was not required. Because of the clear clinical diagnosis, supported by immunological assay and clinical improvement, repeat tests were not clinically indicated.

OUTCOME

Overall, she made an excellent recovery. After discharge from ITU, neuropsychiatric assessment documented features of executive dysfunction with concrete thinking and anxiety, however these rapidly improved. She was discharged from hospital after three months. She has remained well, and returned to work. Further assessments revealed only subclinical executive dysfunction. Serial gynaecological oncology reviews confirmed complete excision of teratoma, and absence of contralateral disease. Oncological prognosis is considered to be good. We consider that the likelihood of recurrence of encephalitis is low.

DISCUSSION

We made a definite diagnosis of anti-NMDAR encephalitis associated with ovarian teratoma, despite an initially atypical presentation with a clinical syndrome of meningitis.

Other diagnostic possibilities include infective and autoimmune causes of meningoencephalitis. Prior to NMDAR-antibody results becoming available, the clinical presentation was highly suggestive of this condition and met suggested criteria for "probable" anti-NMDAR encephalitis.[1] Following initial presentation with meningitis, the subsequent development of memory deficits, psychiatric disturbance, seizures and movement disorder is consistent with established clinical features of this condition.[2,and Dalmau et al 2008 as it is in Lancet neurol] Rapid clinical progression to reduced consciousness alternating with agitation, development of autonomic instability and movement disorder is well-described. Definite anti-NMDAR encephalitis was subsequently confirmed by the cell based assay.

I think everything above here is good – the thread gets lost below. I have tried to help but think this needs a bit more work.

Low-grade fever and non-specific headaches have frequently been reported in the prodromal phase of anti-NMDAR encephalitis. By contrast, signs of raised intracranial pressure including raised opening pressures and bilateral abducens palsies have infrequently been reported. Also, very rarely patients with nuchal rigidity have been described.[5] However, a prodrome with florid meningitis - nuchal rigidity, fever, lymphocytosis, raised protein and elevated opening pressures - observed in our patient Is very rare.[5]

One question is whether this could represent post-infectious antibody generation, as is well-recognised several weeks after HSV encephalitis.[3] But the very short time interval to emergence of fulminant encephalitis is against the possibility of *de novo* autoantibody generation. Alternatively, maybe the meningitis represents a mechanism to induce blood-brain barrier opening and CSF entry

of NMDAR-specific B cells..[2,and Dalmau et al 2008 as it is in Lancet neurol] If so, the patient should have pre-formed circulating NMDAR-specific B cells and perhaps this is reflected by the varied healthy and disease groups with serum NMDAR-antibodies. (Dahm et al 2014 Annals) Alternatively, the meningitis directly activated CNS-surveying NMDAR-reactive B cells which may necessitate loss of immunological tolerance to this molecule, and may account for the relative rarity of meningitis as a presenting complaint of anti-NMDAR encephlatis.

I THINK YOU CAN OMIT REF 4 – IT DOESN'T APPPEAR VERY RELEVANT

We carried out a literature search for articles pertaining to anti-NMDA receptor encephalitis presenting with meningitis (defined as the presence of nuchal rigidity and photophobia in association with a headache) using MEDLINE and EMBASE databases. A search for original articles published in English from January 1990 to September 2017, yielded 384 potential articles. We screened the titles and abstracts of these articles to look for relevant articles relating to clinical presentations. After excluding 307 articles, we sought the full-text articles of the remaining 77, none of which described meningitis as a presenting feature. A cited reference search (Google Scholar) however identified two reports describing meningitis as a presenting feature.[4,5] and was the Lim et al paper really consistent with meningitis?

CONCLUSION

This case highlights meningitis as an atypical presenting feature of anti-NMDA-receptor encephalitis. Clinicians should consider autoimmune encephalitides in individuals with meningitis, particularly where extensive investigations fail to identify a causative micro-organism and there is rapid development of an encephalitic phenotype. A multidisciplinary approach is required to address the neurological, gynaecological, oncological, and neuropsychiatric aspects of this challenging and incompletely understood disorder.

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