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Case report

Paraneoplastic neuromyelitis optica and ovarian teratoma: A case series

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ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is a rare inflammatory disease of the central nervous system, characterized by the presence of auto-antibodies directed against aquaporin-4 (AQP4) expressed on astrocyte end-feet. Despite NMOSD does not primarily belong to the spectrum of paraneoplastic neurological syndromes, rare cases of association with neoplasia have been outlined. Here, we report the association of NMOSD with ovarian teratoma in 3 cases. Pathological analysis of teratomas revealed glial component strongly expressing AQP4 and closely localized to immune infiltrates. Our series highlight the rare association of teratoma with NMOSD and the possible paraneoplastic mechanism.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare inflammatory disease of the central nervous system (CNS) mainly characterized by attacks of transverse myelitis and optic neuritis. Aquaporin-4 (AQP4) antibodies are currently the serological and pathophysiological marker of the disease, binding to the AQP4 water channel mostly expressed on astrocyte end-feet (Wingerchuk et al., 2007). Although the predilection for the optic nerve and spinal cord in NMOSD is widely known, the involvement of other CNS locations has led to the description of an expanding spectrum of clinical syndromes. Medullary floor of the fourth ventricule and *area postrema* are enriched with AQP4 conferring these structures a high susceptibility to be affected. Thus, the involvement of such structures located within the brainstem results in isolated intractable hiccups, nausea and/or vomiting, (referred as *area postrema* syndrome) inaugural in up to 10% of NMOSD cases (Shosha et al., 2018). Although a rarity, an underlying cancer may be present in a small proportion of AQP4-antibody-positive patients, mainly affecting older ages with brainstem involvement (Pittock and Lennon 2008; Sepulveda et al., 2018). However, association of NMOSD with teratoma, as observed in anti-NMDA receptor encephalitis, remains anecdotal (Frasquet et al., 2013). Herein, we report three NMOSD cases with ovarian teratoma who displayed *area postrema* symptoms at disease onset.

2. Methods

Three patients were identified from the NOMADMUS database (French collaborative network on NMO and related disorders) who fulfilled NMOSD criteria and presented an underlying ovarian teratoma. Clinico-radiological data were retrospectively collected at three different centers in France: Toulouse, Pau and Bayonne. Embedded teratomas were collected from local pathology services, and analyzed at Toulouse University Hospital by seasoned neuropathologists. All

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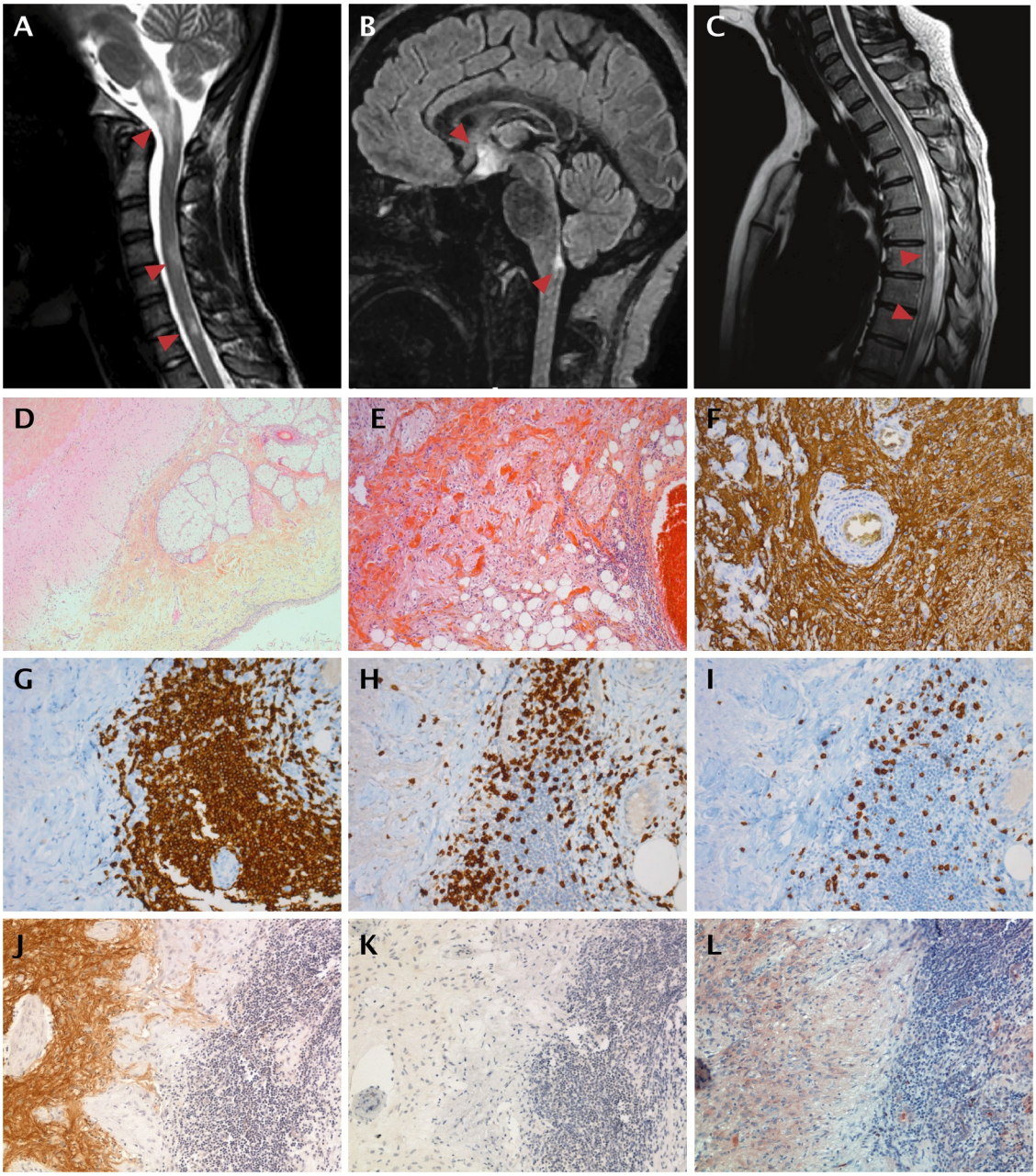

Fig. 1. MRI and pathological findings of paraneoplastic NMO patients. (A) Transversal T2 spinal cord MRI of case 1 (A) and 3 (C), Transversal T2 FLAIR Brain MRI of case 2 (B). Case 2 teratoma pathology stained with HE (D,E) and for GFAP (F), CD20 (G), CD3 (H), CD8 (I), AQP4 (J), MOG (K) and C9neo(L).

patients gave their written consent to be included into NOMADMUS study. AQP4-antibodies testing were performed by cell-based assay as previously described (Marignier et al., 2013), and glial fibrillar acidic protein (GFAP) antibodies testing according to Flanagan and colleagues' protocol (Flanagan et al., 2017).

3. Results

Case 1

Four months after teratoma ablation, a 15-year-old girl was admitted in internal medicine for a three weeks episode of intractable vomiting associated with severe asthenia, and weight loss. The patient was discharged after partial amelioration and no evidence of alterations in standard biological investigations. Two weeks later, the patient presented to the emergency room with a rapidly evolving tetraparesia and respiratory failure. She was admitted to intensive care unit requiringmechanical ventilation assistance. Brain and spinal cord magnetic resonance imaging (MRI) revealed two T2-weighted hyperintensities within the brainstem, and a cervical (C2, C4-C5, C6-C7) myelitis (Fig 1A). At diagnosis, serum and cerebrospinal fluid (CSF) onconeuronal and anti-NMDA-R antibodies were negative. Serum AQP4-antibodies were tested positive. The patient recovered under intravenous (i.v) steroids, and rituximab was subsequently initiated. Evolution was excellent and currently she is asymptomatic after 2 years on rituximab.

Case 2

A 21-year-old girl was admitted in the Gastroenterology Unit with nausea, vomiting, and headache associated with rapid loss of weight. Initial investigations including endoscopy and brain computed tomography (CT) scan showed no abnormalities. However, the patient progressively developed lower limb sensitive deficit, saddle anesthesia and urinary retention. Brain MRI revealed T2-white matter hyperintense

Table 1
Clinical, biological and pathological characteristics of reported cases.

	Case 1	Case 2	Case 3
Age, y / Sex	15/F	21/F	41/F
Clinical presentation	Nausea, Vomiting, Asthenia, Tetraparesia, Respiratory Failure	Nausea, Vomiting, Lower limbs sensory signs, Saddle anesthesia, Urinary retention	Nausea, vomiting, ataxia, lower limbs sensory signs
Symptoms onset	4 months after teratoma ablation	1 month before teratoma discovery	3 months before teratoma discovery
Auto-antibodies			
• Anti-AQP4	Pos	Pos	Serum Neg/ CSF Pos
• Anti-NMDA-R	Neg	Neg	Neg
• Anti-MOG	Neg	Neg	Neg
• Anti-GFAP	Neg	Neg	Serum Neg/ CSF Pos
• Onconeuronal*	Neg	Neg	Neg
CSF			
• Oligoclonal Bands	Pos	Pos	Pos
• Pleiocytosis (/mm^3)	65	87	130
• Dominant population	Lymphocytes	Lymphocytes	Lymphocytes
Treatment at the first episode	IV steroids (5 g)	IV steroids (5 g) Plasma exchange	IV steroids (3 g)
Teratoma pathology			
• Glial component	Yes	Yes	Yes
• AQP4 +	Yes	Yes	Yes
• Lymphoid structures	Yes	Yes	Yes
Evolution			
• Treatment	Rituximab, Tocilizumab	Rituximab	Mycophenolate mofetil
• Clinic	No relapse	2 optic neuritis episodes before teratoma ablation No relapse	No relapse
Follow-up			
• Anti-AQP4	Neg	Neg	Neg (CSF)

* Onconeuronal antibodies: anti-HU, anti Yo, anti RI, anti CV2, anti-amphyphisines and anti-EMA, anti-Ma1, Ma2, SOX1, neuropile.

lesions at multiple levels: hypothalamus, temporal lobes and *area postrema*. Spinal cord MRI displayed cervical (C3-C4), thoracic (T8) and *conus* T2-hyperintense lesions (Fig. 1B). Serum AQP4-antibodies were positive. The patient showed good recovery after plasma exchange, and i.v steroids. Two months later an abdominal and -pelvic CT scan revealed an ovary mass that proved to be a mature teratoma. Before removal, the patient developed two severe episodes of optic neuritis leading to important visual sequelae after 2 years. Nine months after onset of disease she was started on rituximab and experienced no further relapses.

Case 3

A 41-year-old woman was admitted to internal medicine department for asthenia within the previous month, bradycardia (40 bpm), associated with loss of weight and rare vomiting episodes. The investigation revealed a right ovarian teratoma that was removed two weeks later. She regained a normal heart rate. Few weeks before the admission, the patient progressively developed sensory symptoms (suspended radicular sensory level (T10-L1), proprioceptive ataxia of the lower limbs), pyramidal irritation and mild saddle anesthesia symptoms. Anti-AQP4-and anti-GFAP-antibodies were found in CSF but not in serum. Other autoantibodies including onconeuronal and anti-NMDA-R-antibodies were negative in both serum and CSF. Spinal cord MRI displayed a short cervical (C1-C3) and longitudinally extensive transverse myelitis (from T3 to *conus*). Brain MRI was normal. She recovered after i.v. steroids, and mycophenolate mofetil was further introduced. The patient did not relapse after 2 years of follow-up. Last neurological exam displayed only a mild sensory T10 level and last spinal cord MRI was normal. Oligoclonal bands persisted positive in CSF, but serum and CSF antibodies were again tested negative.

3.1. Pathological findings

All three teratomas revealed neuroglial tissue without immature component but including astrocytes revealed by a strong GFAP staining (Fig. 1D and F). This glial component highly expressed AQP4 but not myelin oligodendrocytes glycoprotein (MOG) (Fig. 1J and 1K). One histologic feature of these tumors was the presence of prominent lymphoid aggregates, mainly composed of CD20 B-cells which were localized close to the neuroglial tissue (Fig. 1D–G). CD3 staining revealed a more spread T cell infiltrate predominantly composed of CD4 T lymphocytes. Only few CD8 T cells were present. No staining for C9neo, a marker of complement activation, was found.

4. Discussion

Here we report three AQP4-antibody-positive NMOSD patients with lesions within the brainstem and spinal cord, in the context of ovarian teratoma.

The association of NMOSD with teratoma, expressing a neuroglial component and AQP4, raises the question of a paraneoplastic mechanism. Despite NMOSD is not thought to belong to paraneoplastic neurological disorders (PND), several NMOSD cases have been reported in association with AQP4 expressing tumors, preferentially lung and breast cancer (Pittock and Lennon 2008; Sepulveda et al., 2018). Even if, *area postrema syndrome* is a frequent initial symptom of NMOSD, it seems overrepresented in paraneoplastic presentations (Sepulveda et al., 2018; Shosha et al., 2018; Frasquet et al., 2013).

Although teratoma may be present in up to 50% of patients with NMDA-R-antibody encephalitis, the association of such neoplasm in the setting of NMOSD is a rarity (Frasquet et al., 2013). From a pathological standpoint, in our series teratomas shared a histological pattern with anti-NMDAR-associated tumors composed of prominent B-cell lymphoid aggregates close to neuroglial tissue. Marked intra-tumor lymphoid infiltrates is a characteristic of anti-NMDAR-associated tumors in contrast to those tumors without an underlying paraneoplastic manifestation (Dabner et al., 2012). Furthermore, the progressive disappearance of AQP4-antibodies (Table 1) and the absence of new relapses after tumor removal (under treatment) may suggest a paraneoplastic mechanism. This favorable disease course arise the question for immunosuppressive treatment maintenance.

One of our patients concomitantly developed AQP4and GFAP-antibodies which is a frequently feature associated with teratoma in anti-GFAP encephalomyelitis. Despite this patient did not develop typical anti-GFAP encephalomyelitis, myelitis and *area postrema syndrome* have been related to anti-GFAP autoimmunity (Ciron et al., 2019; Flanagan et al., 2017).

To conclude, these three cases highlight that NMOSD may be rarely related to a paraneoplastic mechanism in the context of ovarian teratoma, sharing important histological and clinical features with other antibody-mediated paraneoplastic neurological syndromes.

Disclosures

RBV, ACC, AS, RM, MB, GB, EE, JB, EUC have nothing to disclose.

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