Expanding the Concept of Paraneoplastic Neuromyelitis Optica: A Cohort Description with Histological Staining

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Background

- Neuromyelitis optica (NMO) is an autoimmune Central Nervous System (CNS) syndrome distinct from MS [1]
- NMO is frequently associated with aquaporin-4 (AQP4) antibodies, found in 60 to 70% of patients [2]
- Paraneoplastic neurological syndromes are remote effects of cancer caused by an autoimmune response initiated by self-antigens expressed on cancer cells [3]
- Based on the potential relationship between cancer and a neurologic syndrome, definition exists for definitive or possible PNS [3]
- Paraneoplastic NMO has been previously described [4-8]
- The link between NMO and cancer needs further investigation

Objectives

- To describe a large case series of paraneoplastic NMO
- To confirm AQP4 expression by cancer cells can trigger NMO

Methods

- 10 patients were identified from a database of 155 NMO patients followed at the UBC NMO Clinic
- A retrospective chart review was done looking at demographics, NMO history, AQP4 serostatus and cancer histology
- Serum AQP4 status was done by a cell-based assay (CBA)*
- Pathological samples of cancer, when available, were stained with AQP4 (Courtesy Dr. Raffaele Iorio)

* CBA done at Mitogen Advanced Diagnostics Laboratory

Results (Clinical)

Table 1: Paraneoplastic NMO cohort description

Case	Sex	Age at NMO diagnosis	AQP4 status	Initial symptoms	Tumor type	Timing of cancer relative to NMO
1	F	54	+	Intractable nausea and bulbar weakness	Bilateral ovarian serous carcinoma†	+ 18 months
2	F	41	+	Right severe ON	Teratoma	- 4 months
3	M	61	-	LETM	Prostate adenocarcinoma	+ 3 months
4	F	49	-	LETM	Melanoma	+ 6 years
5	F	54	-	LETM	Rectal adenocarcinoma ‖ Endometrial adenocarcinoma Urothelial papillary carcinoma	- 14 years - 10 years - 1 year
6	F	62	+	Bilateral ON	Non-Hodgkin Lymphoma Lung adenocarcinoma	- 4 years + 6 years
7	F	59	-	Simultaneous LETM and bilateral ON	Breast cancer	+ 8 years
8	F	68	-	LETM	Breast cancer	+ 9 years
9	M	52	+	Right severe ON	Multiple Myeloma, IgG kappa	+ 15 years
10	F	65	+	LETM	Adrenocortical carcinoma	+ 6 months

Figure legend: An overview of the patients' demographics, NMO history, AQP4 serostatus and cancer subtype. † BRCA1 mutation ‖ Lynch syndrome. ON: Optic Neuritis. LETM: longitudinally extensive transverse myelitis; AQP4: aquaporine-4

- 10 patients (6.5%) were identified with paraneoplastic NMO
- The mean age is 57 years old (range 41-68)
- 80% of the cohort are women
- Longitudinally extensive transverse myelitis (LETM) is the most common presentation (50%)
- AQP4 serum antibodies were found in 50% of the cohort
- Cancer histological sub-types are heterogeneous, but breast cancer (30%) is the most prevalent type
- A mutation for BRCA1 was found for 1 patient (Case 1) and 2 patients (Case 5 and 6) had multiple cancers, 1 of them in association with Lynch syndrome (Case 5)
- Positive immunostaining for AQP4 was found on the ovarian serous carcinoma sample (Case 1- Figure 1)
- In 7 patients, the cancer was diagnosed after NMO

Results (Pathology)

Figure 1: AQP4 tumoral cells staining

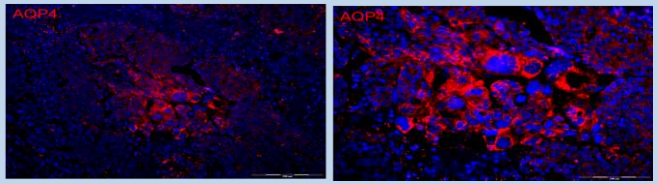

Figure legend: Indirect immunofluorescence using AQP4-IgG on a specimen of an ovarian serous carcinoma showing a positive reactivity in the cancer cells.

Discussion

- The prevalence of paraneoplastic NMO in our cohort is consistent with a prevalence of 5-12% found in other series [5-6]
- Ovarian serous carcinoma and adrenocortical carcinoma are cancer subtypes not previously described in association with NMO [4]
- Expression of AQP4 on cancer cells provides a possible pathological link between cancer and NMO
- As found in most of our patients, a subsequent occurrence of cancer is common in paraneoplastic syndromes [3]
- Higher average age is a possible confounder, but is described in previous paraneoplastic NMO cohort [5]
- Clinicians should have a higher level of suspicion for cancer screening in elderly patients presenting with NMO

Conclusion

- We described 10 new cases of paraneoplastic NMO and 2 new cancer histological subtypes
- We showed in a case of ovarian cancer that cancer cells express AQP4, suggesting AQP4 antibodies could be produced as part of an antineoplastic immune response leading clinically to NMO

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