Aquaporin-4 IgG autoimmune syndrome and immunoreactivity associated with thyroid cancer

Soelberg, Kerstin; Larsen, Stine Rosenkilde; Mørch, Marlene; Thomassen, Mads; Brusgaard, Klaus; Paul, Friedemann; Smith, Terry J; Godballe, Christian; Grauslund, Jakob; Lillevang, Søren Thue; Asgari, Nasrin

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In 2006, recurrent dyspepsia occurred. A gastroscopy demonstrated an ulcerating jejunal tumor, which was surgically removed and diagnosed as adenocarcinoma. Serum AQP4-IgG, anti-Ma2/TA, antitransglutaminase, and antinuclear antibodies were detectable in 2010. Brain MRI was normal and whole-body MRI remained negative for metastatic disease. Three years later (2013), the patient died of disseminated adenocarcinoma in the retroperitoneum, lymph nodes, and gastrointestinal tract. No autopsy was performed. Potentially deleterious germline mutations such as RET, TP53, and the mismatch repair genes MLH1, MSH2, MSH2, and PMS2 were investigated, but none was identified. Immunohistochemical staining for AQP4 in the paraffin-embedded neoplastic thyroid tissue (3 μm) and the jejunum was performed after antigen retrieval, with primary rabbit anti-AQP4-4 antibody, dilution 1:400 (Alomone Labs, Jerusalem, Israel), and counterstaining with toluidine blue. Staining of the thyroid cancer revealed high-level expression of AQP4 in multifocal areas (figure). There was no AQP4 expression in the neoplastic tissue from the jejunum (not shown).

Discussion. We report the clinical and laboratory investigations of a patient with NMOSD who developed 2 apparently unrelated malignancies over a 6-year period. AQP4 was expressed in thyroid neoplastic tissue and later AQP4-IgG was detectable in serum. These findings suggest that autoimmunity against tumor-expressed AQP4 potentially elicited development of NMOSD, extending the spectrum of paraneoplastic AQP4 autoimmunity.4 Reportedly, 5% of patients with AQP4-IgG seropositive NMOSD had a history of neoplastic disease.5 Furthermore, 27% of individuals undergoing investigation for PNS were found to have detectable AQP4-IgG.4 Congruent with the current case, high AQP4 antigen expression in neoplastic tumor cells has been demonstrated in PNS.5 Outside the CNS, AQP4 is normally expressed at low levels in basalateral plasma membranes of epithelia in a number of tissues.6 It has been suggested that the differential expression of AQP4 may reflect the biological nature of neoplastic thyroid cells.6 In this case, the thyroid tumor was characterized as oncocytic carcinoma with high...
expression of AQP4, which appeared in a multifocal pattern (figure).

In addition to serum AQP4 IgG positivity, anti-Ma2/TA was also detected. This antibody is viewed as an indicator of limbic encephalitis, of which the patient did not manifest suggestive symptoms. However, onconeural antibodies may be detected in individuals without neurologic symptoms.7 Seropositivity for AQP4-IgG 8 years after onset of optic neuritis suggests that the patient’s blood–brain barrier remained intact, thus restricting entry of these antibodies into the CNS.

This case of NMOSD with AQP4-IgG seropositivity in the context of thyroid cancer expressing high-level AQP4 expands the spectrum of paraneoplastic autoimmunity targeting this antigen.

From Vejle Hospital (K.S., N.A.); Institute of Molecular Medicine (K.S., M.T.M., N.A.); University of Southern Denmark; Odense University Hospital (S.R.L., M.T., K.B., T.J.S., C.G., J.G., S.T.L.); Denmark; Clinical and Experimental Multiple Sclerosis Research Center and NeuroCare Clinical Research Center (F.P.); Charité-Universitätsmedizin Berlin; Experimental and Clinical Research Center (F.P.); Max Delbrueck Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, Germany; and University of Michigan Medical School (T.J.S.), Ann Arbor.

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Correspondence to Dr. Asgari: naagari@health.sdu.dk

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