Isolated ZIC4 Antibodies in Paraneoplastic Cerebellar Syndrome With an Underlying Ovarian Tumor

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Objective: To describe a patient with paraneoplastic cerebellar syndrome and the uncommon association of isolated ZIC4 antibodies and ovarian cancer.

Design: Case report and review of the literature.

Setting: Hospitalized care, follow-up in private practice.

Patient: A 60-year-old woman with severe paraneoplastic cerebellar syndrome and an underlying ovarian adenocarcinoma.

Interventions: Neurological examination, lumbar puncture, laboratory tests, radiological imaging, and histological examination.

Main Outcome Measures: Clinical course and titer of anti-ZIC4 antibodies in serum.

Results: Laboratory and cerebrospinal fluid tests revealed the isolated presence of ZIC4 antibodies. Screening results for small cell lung carcinoma were negative, while abdominal computed tomographic scan was suggestive of ovarian adenocarcinoma, which was confirmed by histological examination. Glucocorticosteroid administration and chemotherapy led to complete remission of paraneoplastic cerebellar degeneration.

Conclusion: To the best of our knowledge, this is the first case of paraneoplastic cerebellar degeneration in a patient with isolated ZIC4 antibodies associated with ovarian adenocarcinoma.

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The ZIC gene family includes 5 genes that are highly conserved across evolution. These genes encode zinc finger proteins that are expressed during development and maturation of the central nervous system and have critical roles in the development of the cerebellum. Some ZIC4 antibodies are usually associated with SCLC. Some patients with PCD expressing ZIC4 antibodies may also have other paraneoplastic antibodies like anti-Hu. So far, to our knowledge, no association between isolated ZIC4 antibodies and ovarian adenocarcinoma has been reported in a patient with PCD before.

**REPORT OF A CASE**

A 60-year-old woman was referred to our department with progressive gait ataxia and dysarthria. Routine laboratory test results were normal. Cranial magnetic resonance imaging showed no signs of atrophy or gado-linum uptake. Thus, a cerebellar tumor as well as underlying ischemia were excluded.

Serological tests for tumor markers showed pathological findings for cancer antigen 125 (1021.00 U/mL; normal, <35 U/mL), cancer antigen 15-3 (292.2 U/mL; normal, <25 U/mL), and cancer antigen 72-4 (30.75 U/mL; normal, <6.90 U/mL), pointing at a primary gynecological cancer.

Paraneoplastic antibody screening for anti-Yo, anti-Hu, anti-CV2, anti-Tr, and anti–metabotropic glutamate receptor type 1 was negative, while anti-ZIC4 antibodies were detected in serum (titer, 1:1 638 400) and in the cerebrospinal fluid of the patient. Thoracal and abdominal contrast-enhanced computed tomographic scans were performed, revealing a 6-cm inhomogeneous tumor with increased contrast uptake in the right ovary and a 5-cm tumor in the left ovary. Thoracal imaging was normal.

After initiation of a corticosteroid pulse therapy with 1 g of intravenous methylprednisolone per day for 3 days, dysarthria and gait ataxia improved slightly, but she still was not able to walk unassisted. Nystagmus was unresponsive to steroid treatment.

Since the clinical and paraclinical picture strongly suggested an ovarian carcinoma, the patient was referred for laparoscopic surgery at the Department of Gynecology. Histological examination confirmed an ovarian adenocarcinoma with lymph node metastases (staging PT2a pN1 MO L1 VO Pn 0; FIGO IIC, R0, G2). After oncological consultation, the patient was additionally treated with chemotherapy and surgery, the patient showed a clear and rapid amelioration. Nystagmus and atactic symptoms were fully reversible, and complete remission was achieved within 3 weeks. Six months after surgery and chemotherapy, the neurological status of the patient was stable, without signs of ataxia. The serological follow-up examination 6 months after surgery revealed that the follow-up titer of 1:25 600 was markedly decreased.

**COMMENT**

It has been postulated that in patients with cerebellar dysfunction of unknown etiology isolated detection of ZIC4 antibodies represents PCD associated with SCLC. In our case, screening for SCLC was negative, while an ovarian adenocarcinoma could be identified. Interestingly, antibodies typically associated with gynecological tumor (like anti-Yo) were not detected. Thus, to our knowledge, this is the first reported case of paraneoplastic cerebellar degeneration in a patient with isolated ZIC4 antibodies and ovarian adenocarcinoma. Because the paraneoplastic neurological disorder precedes the primary clinical manifestation of the underlying malignancy in more than 50% of cases, theoretically another tumor (SCLC) may develop later on, yet our patient had no history of smoking. The complete clinical remission as well as the more than 40-fold decreased antibody titer after successful treatment of the ovarian adenocarcinoma further underscore the pathophysiological scenario in our patient.

Our case highlights the importance of a comprehensive evaluation for onconeural antibodies in patients presenting with a complex, and likely paraneoplastic, clinical picture. Early identification and management of the underlying neoplasm may lead to stabilization and in some cases marked improvement of the neurological syndrome and thus quality of life.

**REFERENCES**