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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PARANEOPlastic neurologIcal disorders represent a group of heterogeneous neurological disorders in patients with an underlying neoplasm. Paraneoplastic neurological disorders are relatively rare, and their incidence is estimated as 0.01% of cancer patients.1 Their pathogenesis is attributed to immunological adverse effects of the immune defense directed against the tumor and not to metastases or direct invasion by the tumor.

Clinical features of paraneoplastic neurological disorders are pleiotropic. The paraneoplastic cerebellar degeneration (PCD) is the most characteristic syndrome. Paraneoplastic cerebellar degeneration usually exhibits a subacute onset of symptoms with subsequent steady progression. Symmetrical limb ataxia and cerebellar gait ataxia, dysarthria, and nystagmus are the cardinal features. In approximately one-third of the cases with PCD, the underlying neoplasm is a pulmonary malignoma, typically a small cell lung carcinoma (SCLC). Furthermore, there is also a frequent association of PCD with ovarian carcinoma as well as with Hodkin lymphoma, accounting for 25% and 15%, respectively.3

The Purkinje cells of the cerebellum are a frequent collateral target of the immune response, which is primarily raised against the underlying malignancy.2 In the great majority of patients with PCD, the most prevalent paraneoplastic antibody response detected in serum and cerebrospinal fluid is the anti–Purkinje cell antibody 1 (anti–PCA-1 or anti–Yo), usually indicating a gynecological malignancy like breast or ovarian cancer.3 Antibodies against a nuclear antigen ( termed ANNA-1 or anti-Hu) may be also present and they are most closely linked to paraneoplastic encephalomyelitis.2 Because the anti–Yo antibodies interact with cytoplasmic rather than cell surface membrane proteins of the Purkinje cells, the pathomechanisms causing Purkinje cell death have been questioned. In slice organotypic cultures of rat cerebellum, Greenlee et al4 described recently that anti–Yo antibodies were ingested by viable Purkinje cells, accumulated intracellularly, and finally led to cell death. These findings suggest that autoantibodies directed against intracellular Purkinje cell proteins can be endocytosed. Thus, they may cause cell death and may be directly involved in the pathogenesis of paraneoplastic cerebellar degeneration.5
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. Isolated 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-linium 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, 1:1638400) 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 3-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 (paclitaxel and carboplatin). Following surgery and chemotherapy, 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 onconeuronal 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.

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**REFERENCES**