A Case of Paraneoplastic Cerebellar Disorder in Ovarian Carcinoma with a Negative Serum Paraneoplastic Antibody Panel and a Positive CSF Anti-Yo Antibody Titer

Berger NF*, Kier MW*, Kim L† and Tiersten A‡

1Icahn School of Medicine at Mount Sinai, USA
2Department of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, USA
*Both the authors contributed equally to this work

Abstract
Paraneoplastic syndromes occur in less than 0.1% of gynecological cancers. Paraneoplastic cerebellar disorders are a subgroup of these syndromes and predominantly involve three antibodies, including anti-Yo or Purkinje cell cytoplasmic antibody type 1. In this case report, we present a 71-year-old woman with rapidly progressive cerebellar signs who was found to have metastatic serous ovarian carcinoma with anti-Yo antibody positive paraneoplastic cerebellar disorder and BRCA2 mutation on genetic testing. Interestingly, the patient’s serum paraneoplastic panel was negative; however, her CSF tested positive for anti-Yo antibody titers with a ratio of 1:512. The patient was started on carboplatin and nab-paclitaxel on a twenty-one day cycle. As the patient had no initial neurologic improvement to this treatment, she was also started on high-dose methylprednisolone for three days and then weekly for six weeks plus cyclophosphamide daily for three months. Her treatment course was complicated by periodic delays due to neutropenia that required holding and dose-reductions of cyclophosphamide as well as carboplatin/nab-paclitaxel. Interval measurements of CA-125 and CSF anti-Yo antibody titers showed treatment response with continuously down trending levels. Interval imaging demonstrated an excellent response with decreased adnexal mass size and resolution of lymphadenopathy and peritoneal/omental metastases. She underwent debulking surgery. She subsequently completed carboplatin and liposomal doxorubicin. She is currently on olaparib maintenance due to BRCA2 mutation. She has clinically improved, however, she continues to have issues with mobility, cerebellar head, and hand action tremors, which are managed by a movement disorder specialist.

Introduction
Paraneoplastic Neurological Syndromes (PNS) are a rare group of neurological conditions that occur in less than 1% of patients with cancer [1]. Although their pathogenesis is still unclear, PNS are believed to be immune mediated via CD8+ T cells that are directed against antigens expressed by tumors and normally found in the nervous system [2]. Antibodies implicated in these conditions involve those directed against intracellular neuronal proteins and those against neuronal cell surface or synaptic proteins.

Paraneoplastic Cerebellar Disorders (PCD) are a subgroup of PNS that predominantly involve three antibodies: Anti-Yo (also called Purkinje cell cytoplasmic antibody type 1), anti-Tr, and anti-metabotropic Glutamate Receptor 1 (mGluR1). Anti-Yo antibodies are almost exclusively associated with ovarian and breast cancers [3-5]. Anti-Tr and anti-mGluR1 antibodies are primarily associated with Hodgkin’s lymphoma [4]. PCD is defined by the loss of Purkinje cells and inflammatory infiltrates in the cerebral cortex, deep cerebellar nuclei, and inferior olivary nuclei [6]. Patients commonly present with acute and rapidly progressive cerebellar symptoms such as dizziness, nausea, vertigo, and vomiting. These advances to involve ataxia, nystagmus and dysphagia.

Here we present the case of a 71-year-old female who presented with anti-Yo positive PCD with metastatic serous ovarian carcinoma.

Case Presentation
A 71-year-old postmenopausal female presented to the emergency department after waking up with new slurred speech and loss of independent mobility. Her symptoms began three days prior with nausea and dizziness that progressed to weakness, mental fog, gait disturbance, and...
Berger NF, et al., Remedy Publications LLC.

was initiated on CNS penetrating chemotherapy with carboplatin. CSF studies for paraneoplastic process were still in process, patient followed by 8 mg of dexamethasone with prolonged course. While patient received an initial high dose of 12 mg of dexamethasone deterioration of her condition from her initial presentation. The emergency department. of PCD was made 17 days following initial presentation to the conjunction with the CT findings and lymph node biopsy, a diagnosis cells. Interestingly, the serum paraneoplastic panel was negative. In with a ratio of 1:512 and cytology remained negative for malignant Lumbar puncture found CSF positive for anti-Yo antibody titers mutation. CA-125 tumor marker was elevated at 181 U/ML. BRCA2 patient was started on dexamethasone. Genomic testing revealed immunophenotype was reported to be pax8+ and WT1+. The suggestive of high-grade pelvic-type serous carcinoma. The tumor ovarian cancer.

The report of her initial brain MRI performed at an outside institution described possible leptomeningeal enhancement in the cerebellar folia and vermis bilaterally and no appreciable enhancing lesions or T2/FLAIR changes in the brain parenchyma to suggest metastatic deposits. A repeat MRI at our institution confirmed that there was no evidence of leptomeningeal disease. A CT abdomen-pelvis revealed a large, heterogenous, enhancing cystic and solid pelvic mass that was inseparable from the posterior myometrium of the uterus and right adnexa with peritoneal carcinomatosis and liver capsule metastases (Figure 1). A small, right sided pulmonary embolism was also noted.

Right retroperitoneal lymph node biopsy was positive for metastatic carcinoma, compatible with Mullerian origin and highly suggestive of high-grade pelvic-type serous carcinoma. The tumor immunophenotype was reported to be pax8+ and WT1+. The patient was started on dexamethasone. Genomic testing revealed BRCA2 mutation. CA-125 tumor marker was elevated at 181 U/ML. Lumbar puncture found CSF positive for anti-Yo antibody titers with a ratio of 1:512 and cytology remained negative for malignant cells. Interestingly, the serum paraneoplastic panel was negative. In conjunction with the CT findings and lymph node biopsy, a diagnosis of PCD was made 17 days following initial presentation to the emergency department.

While the work up was in process, there was noted to be a rapid deterioration of her condition from her initial presentation. The patient received an initial high dose of 12 mg of dexamethasone followed by 8 mg of dexamethasone with prolonged course. While CSF studies for paraneoplastic process were still in process, patient was initiated on CNS penetrating chemotherapy with carboplatin target AUC 5 and nab-paclitaxel 260 mg/m² on a twenty-one day cycle to treat her ovarian cancer.

Given no significant neurological improvement after one cycle of carboplatin/nab-paclitaxel and the subsequent positive anti-Yo CSF results, additional therapy was initiated while carboplatin/nab-paclitaxel was continued: Methylprednisolone 1000 mg IV for three days and then weekly for six weeks; plus, cyclophosphamide 2 mg/kg daily, orally, for three months, which has been supported by other trials. Three weeks following this treatment, which included two additional cycles of carboplatin/nab-paclitaxel, a CSF anti-Yo antibody titer and serum CA-125 level were checked. As shown in Figure 2, her tumor demonstrated response to therapy both in the CSF through a reduction in the paraneoplastic anti-Yo antibody titer from 1:512 to 1:256 and in systemic disease with a reduction in CA-125 from 181 to 51. Her treatment course had periodic delays due to neutropenia that required holding and dose-reductions of cyclophosphamide as well as carboplatin/nab-paclitaxel.

Following six cycles of carboplatin and nab-paclitaxel, the anti-Yo antibody CSF titer was further decreased at a ratio of 1:64 and CT chest, abdomen, and pelvis demonstrated an excellent response to treatment response, she underwent debulking surgery with gynecology. Her neurologic symptoms showed some improvement, although she continues to have issues with mobility, cerebellar head, and hand action tremors. Patient also began to taper steroids at this point. The patient was then treated with a course of carboplatin AUC 4, dose reduced from AUC 5 due to thrombocytopenia and neutropenia, and liposomal doxorubicin. She is currently on olaparib maintenance due to presence of the BRCA2 mutation. Her cerebellar symptoms are medically managed by a movement disorder specialist. She was previously on trials of carbidopa/levodopa and primidone. She is currently taking gabapentin for residual movement symptoms.

Discussion

Paraneoplastic syndromes are a rare manifestation of ovarian
cancer. The onset of neurologic symptoms secondary to PNS is variable in occurring before or after a diagnosis. Interestingly, PNS has been diagnosed with no known malignancy in 3% to 13% of cases [3-5]. Signs of inflammation in the CSF are also typical, such as moderate lymphocytic pleocytosis, high IgG index, oligoclonal bands, and increased protein [6]. The initial MRI is often normal in most patients, however, transient diffuse cerebellar hemispheric enlargement or cortical-meningeal enhancement have been identified [7]. Fluorodeoxyglucose-PET can show cerebellar hyper metabolism [8].

The gold standard for diagnosis is serum paraneoplastic antibody panel. Yet, in our patient, the serum panel was negative. Fortuitously, a strong clinical suspicion led to CSF paraneoplastic panel being sent at the same time and the CSF manifested a strong positive titer for anti-Yo, despite the negative serum study.

Anti-Yo antibodies are directed against two cerebellar degeneration-related proteins that are present in the cytoplasm and proximal dendrites of Purkinje cells: CDR2 and CDRL2 [9]. Although prognosis is typically poor for all cases of PCD, survival for patients with anti-Yo antibodies has been shown to be significantly worse than for patients with other antibodies, with a median survival ranging from 13 to 22 months [3,4]. Shamsi’ili et al. [4] found the cause of death to be neurological in 67% of cases [4], while Rojas et al. found 29% of patients died from neurologic conditions, with tumor progression as the leading cause in 53% of patients [3]. Neurologic outcomes for patients with anti-Yo antibodies are also particularly poor, with 77% to 94% of patients becoming non-ambulatory [3-5].

Currently, there is no standard of care for the treatment of PCD, however targeting the underlying malignancy should always be pursued as it is shown to improve survival [4]. Thus, for our patient, she was initiated on the standard first line treatment for advanced stage ovarian cancer. Given lack of neurological improvement after a cycle, adjunct therapy with cyclophosphamide was started. Treatments directed at T-cell activation such as cyclophosphamide and rituximab have been recommended. Vernio et al. [12] found improvement or stabilization of neurological symptoms in 6 of 10 patients with PCD treated with cyclophosphamide [12]. Shamsi’ili et al. [13] reported some improvement in symptoms for 3 of 9 patients with anti-Yo or anti-Hu antibodies treated with four monthly infusions of rituximab [13].

Treatments targeting the removal of immunoglobulins such as plasma exchange and IVIg have had mixed results. Uchuya et al. [10] concluded that IVIg treatment was ineffective in improving neurological symptoms in PNS [10]; however, Keime-Guibert concluded that IVIg may help stabilize patients who are treated before the severe onset of symptoms [11]. Tacrolimus has also been shown to reduce the number of activated CDR2-specific T cells in CSF, which may also help treat anti-Yo PCD [14]. Future research in treatments that utilize autologous hematopoietic stem cell transplantation has also been suggested due to its use in other autoimmune disorders [3,4]. Monoclonal antibodies or pharmacologic compounds that block CXCR3 and IFN-gamma are also suggested as potential treatments due to the role these play in CD8+ T-cell activation [9].

Our patient has shown signs of a positive tumor response in the CNS through a decline in the paraneoplastic, anti-Yo antibody titer as well as signs of reduced systemic disease through a down trending CA-125 to 9 post-treatment and radiographic improvements. Clinically she has showed progress as well but has continued to have significant neurologic deficits requiring additional therapy.

**Conclusion**

Paraneoplastic cerebellar disorder is a rare and serious manifestation of ovarian cancer that requires strong clinical suspicion to diagnose. Our case highlights that a negative serum paraneoplastic antibody panel should not rule out further work up if there is a high concern. We recommend that if there is strong clinical suspicion, a lumbar puncture should be performed to check paraneoplastic syndrome markers and rule out paraneoplastic syndrome, even if serum markers are negative. Moreover, it is imperative to consider paraneoplastic syndromes as a potential etiology of neurologic...
symptoms which can present at any time point during one’s disease course. Future studies to improve our treatment decision making are needed.

Disclosure Statements

Authors Berger, Kier, Kim and Tiersten provided substantial contributions to the conception or design of the work, drafting the work and revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References


