Annals of Clinical Case Reports

Case Report
Published: 27 Aug, 2024

Paraneoplastic Neurological Syndrome as an Initial Indicator of Advanced Ovarian Cancer: A Case Report and Literature Review

*Aparna K[1], Christopher V[2], Jessica P[2] and Anita A[2]**

[1]School of Medicine, Queen's University, Kingston, Canada

[2]Department of Obstetrics and Gynecology, Queen's University, Kingston, Canada

Abstract

Paraneoplastic Neurological Syndromes (PNS) are a rare group of heterogenous disorders that occur in the context of malignancy. Paraneoplastic Cerebellar Degeneration (PCD) is a debilitating immune-mediated neurological syndrome characterized by the onset of acute or subacute cerebellar ataxia. There are no standard treatment guidelines for paraneoplastic syndromes, and thus, treatment is generally unsatisfactory. We present a case of a 68-year-old female with a 4-month onset of progressive neurological deficits characterized by cerebellar dysfunction. The patient also had a significant familial history of cancer and alcohol consumption. Antineuronal antibody testing showed the presence of anti-Yo antibodies, suggestive of a PNS. A CT abdomen, pelvis, and chest scan revealed a suspicious cystic ovarian epithelial neoplasm that was later confirmed as stage IIIC High-Grade Serous Ovarian Cancer (HGSOC). After intravenous immunoglobulin and corticosteroids, supportive therapy, and treatment of ovarian cancer with chemotherapy and surgical debulking, the oncological therapeutic response was excellent, indicated by the decrease of CA-125 tumor marker. Slight neurological improvement occurred for several months, followed by a period of stable symptoms and then slow neurological deterioration. This case report illustrates the unfavorable outcome of PCD despite early diagnosis and multimodal treatment. Further research is required to understand if the patient's alcohol consumption had any role in the onset and overall course of PNS.

Keywords: Paraneoplastic neurological syndrome (PNS); Paraneoplastic cerebellar degeneration (PCD); Ovarian cancer; Anti-Yo antibodies

OPEN ACCESS

Correspondence:
Anita Agrawal, Department of Obstetrics and Gynecology, Queen's University, 76 Stuart St, Kingston, ON K7L 2V7, Canada, Tel: 613-549-6666 (ext:4423);

Received Date: *24 Jul 2024*
Accepted Date: *22 Aug 2024*
Published Date: *27 Aug 2024*

Citation:
Aparna K, Christopher V, Jessica P, Anita A. Paraneoplastic Neurological Syndrome as an Initial Indicator of Advanced Ovarian Cancer: A Case Report and Literature Review. Ann Clin Case Rep. 2024; 9: 2665.
ISSN: 2474-1655.

Introduction

Paraneoplastic Neurological Syndromes (PNS) are a group of rare heterogeneous autoimmune disorders occurring in the setting of cancer [1]. The rates of PNS have increased over time, with recent epidemiological studies estimating an incidence rate of 0.4 to 1 per 100,000 person years [1]. Specifically, ovarian tumors represent about 10% of malignancies associated with PNS [2]. Although these conditions are associated with cancer, they do not arise from metastasis, direct tumor invasion, or treatment consequences [3]. Instead, they may clinically manifest from a previously undiagnosed cancer, during treatment of a recently diagnosed cancer, or cancer relapse [1]. PNS commonly precedes or follows the cancer diagnosis and targets any region of the nervous system.

These syndromes occur due to a generated immune response against antigens on tumor cells that are also normally almost exclusively present in the host nervous system [1]. Following tumor cell apoptosis, antigens are released and presented to helper T cells in peripheral lymph nodes *via* antigen-presenting cells [1]. CD4+ helper T cells then activate antigen-specific B cells to antibody-producing plasma cells [1]. The disease mechanism may vary depending on whether antibodies target cell-surface antigens or intracellular antigens [1]. Antibody-intracellular antigen interactions represent biomarkers of cytotoxic T cell-mediated cellular injury [1]. Conversely, antibody attacking cell-surface antigens bind *in vivo* and represents a pathological process [1]. For example, antibody attacks against Gamma Amino Butyric Acid (GABA)-R, N-Methyl-D-Aspartate (NMDA)-R, and AMPA-R result in neuronal dysfunction *via* internalization and receptor-cross linking [1].

To prevent the progression of irreversible neurological damage, early diagnosis and subsequent treatment are essential [3]. A combination of clinical and laboratory investigations, past or family

history of cancer, onconeural antibodies, and systemic symptoms (anorexia, weight loss, fatigue, fever) are all important for diagnosis [3]. Clinical manifestations of PNS are characterized by encephalitis, autonomic failure, cerebellar ataxia, peripheral neuropathy, and visual complains in addition to several others [3].

We describe below the case of a 68-year-old woman who developed new onset of primary cerebellar dysfunction, resulting in a diagnosis of paraneoplastic syndrome secondary to stage IIIC High-Grade Serous Ovarian Cancer (HGSOC).

Case Presentation

A 68-year-old female was admitted to the hospital following progressive neurological deficits for 4 months since May 2022, primarily characterized by cerebellar dysfunction. Symptoms included dysarthria, ataxia, reduced mobility, increased falls, and postural instability. The most recent fall resulted in a right styloid fracture. She consumed 16 to 20 alcohol beverages per week. A strong maternal and paternal family history of cancer was present. Physical exam initially showed bilateral nystagmus on end gaze laterally, mild saccadic extraocular movements, mildly impaired finger-to-nose with past-pointing, intention tremor bilaterally, poor rapid alternating movements, and mildly widened gait. Cranial nerves, strength, tone, reflexes, and sensory exam were unremarkable.

Antineuronal antibody testing (anti-Yo, anti-Ri, anti-Hu, anti-CV2, anti-amphiphysin, and anti-Ma2/TA) was only positive for anti-Yo. A CT abdomen, pelvis, chest scan showed a right ovarian 5.6 cm cystic lesion possibly indicating an incidental cystic ovarian epithelial neoplasm (Figure 1A).

A 4.5 cm right external iliac pathologic lymph node biopsy indicated a high-grade serous carcinoma of possible gynecological origin. A follow-up pelvic and transvaginal ultrasound confirmed a complex right ovarian cystic anechoic lesion with mural nodularity measuring 4.8 cm × 4.7 cm × 4.4 cm (Figure 1B).

Significant retroperitoneal lymphadenopathy, omental nodularity, and small-moderate volume of abdominal ascites was present. CA-125 (1790 kU/L, normal 0-35 kU/L) was elevated. A diagnosis of Paraneoplastic Neurological Syndrome (PNS) secondary to stage IIIC HGSOC was confirmed. She was transferred to the Gynecology Oncology service for the management of advanced

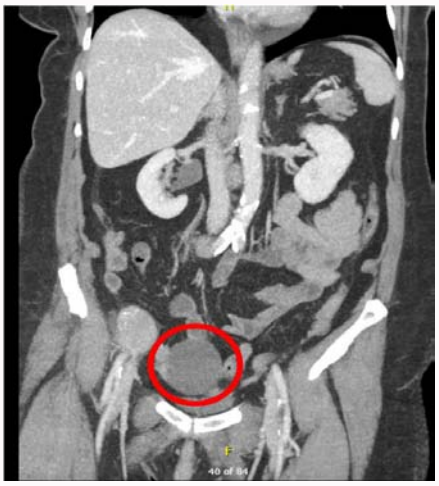

Figure 1A: CT abdomen/pelvis demonstrating right 5.6 cm ovarian cystic lesion (circled).

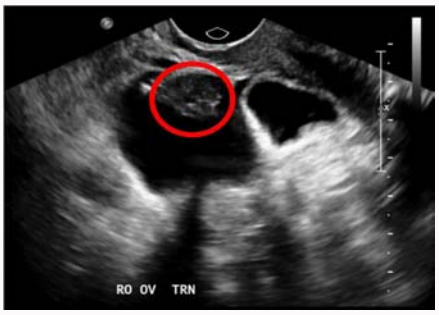

Figure 1B: Pelvic and transvaginal ultrasound demonstrating right ovarian cystic anechoic lesion with mural nodularity measuring 4.8 cm × 4.7 cm × 4.4 cm (circled).

HGSOC and PNS.

She was treated with 3 cycles of neoadjuvant carboplatin at AUC of 5 and paclitaxel 135 mg/m^2. Neurology service was consulted, and she received Intravenous Immunoglobulin (IVIG) (1g/kg over 24 h) and solumedrol, and improvements in speech and coordination were noted. Four weeks following the first IVIG dose, the neurologist recommended an additional dose of IVIG and solumedrol. With no improvement in speech and gait, the neurologist recommended continuing IVIG (1g/kg over 24 h) and solumedrol (1 g/day) for three additional months. Speech and language pathology advised a soft food diet with thickened fluids. Occupational and physical therapy were involved to improve mobility. A CT head revealed frontal and cerebellar atrophy in keeping with the diagnosis of PNS and not age related.

In December 2022, the patient underwent an interval debulking procedure which included laparoscopic extensive lysis of adhesions, omentectomy, and bilateral salpingo-oophorectomy. The pathology report indicated a 0.4 cm sized tumor located in the bilateral fallopian tubes. The tumor cells showed aberrant p53 overexpression and strong positivity for WTI and PAX8. The tumor specimens within the adnexa and omentum indicated an excellent chemotherapy response score of 3. CA-125 decreased to 62 kU/L (normal 0-35 kU/L) one-month post-operatively. Continuous speech and mobilization improvement were noted afterwards.

Adjuvant chemotherapy with carboplatin and paclitaxel was initially planned for three cycles. The patient experienced worsening dysarthria and limited gait three weeks later. Although the patient maintained her dexterity, it became increasingly difficult to understand her speech. Her PNS did not show any further improvement despite chemotherapy, surgical interventions, and normalization of CA-125 (21 kU/L, normal 0-35 kU/L). She was offered single-agent carboplatin chemotherapy for cycle 6, but the patient and her sister (power of attorney) decided to discontinue treatment after cycle 5. Her family was keen on a long-term care facility for 24-h supervision and one-on-one care. Currently, she resides in a long-term care facility where she continues to receive monthly IVIG treatment, except for a gap of two months. Although her mind is alert, she is unable to feed herself, balance, or ambulate due to severe ataxia and tremors for the past six months. The patient still participates in ongoing physiotherapy, enabling her to stand and hold onto her stationary bicycle. Notably, she can lift her legs to walk up the stairs. She does not have any urinary or fecal incontinence, remains aware of her surroundings, and occasionally becomes very emotional.

Discussion and Literature Review

Paraneoplastic Cerebellar Degeneration (PCD) is a rare immune-mediated neurological condition occurring in less than 1% of all cancer patients [4]. PCD is characterized by acute or subacute pancerebellar dysfunction, often with dizziness, nausea, and gait unsteadiness progressing to ataxia, dysarthria, dysphagia, diplopia, and nystagmus [4]. Multiple antibodies are associated with PCD such as anti-Yo, anti-Hu, anti-Tr, anti-Ri, anti-CV2, anti P/Q type voltage-gated calcium channel, amphiphysin, anti-Ma2, and anti-GluR1 [5]. These antibodies provide significant diagnostic value in addition to some prognostic value [5]. Specifically, anti-Hu, anti-Yo, or anti-Tr positive antibodies in addition to subacute cerebellar ataxia forms a definite case for PCD, even in the absence of malignancy [5]. The anti-Yo antibody (the most common antibody in PCD) occurs almost exclusively in female patients and is mostly associated with ovarian, breast, and other gynecologic malignancies [6]. These patients are often severely incapacitated, however the cause of death is rarely neurological disability. Notably, these patients only have restrictive cerebellar dysfunction [5]. It is thought that anti-Yo antibodies target cytoplasmic antigen cerebellar degeneration-related protein 2 found in the central nervous system and tumor tissue [7]. The calcium homeostasis dysregulation *via* anti-Yo antibodies might be the initial means of attack on Purkinje cells [7]. In contrast, the anti-Hu antibody is associated with small-cell lung cancer in over 85% of cases [5]. These patients present with more widespread neurological deficit known as paraneoplastic encephalomyelopathy and sensory neuronopathy [5]. The neurological disorders can result in the death of patients. Some anti-Hu-positive patients with isolated cerebellar disorders can develop Lambert-Eaton myasthenic syndrome [5]. It is thought that anti-Hu antibodies binding to nucleosomes in addition to inflammatory infiltration and neuronal degeneration may contribute to PCD [5].

Due to the limited number of published cases on PCD associated with onconeural antibodies in solid tumors, there are no established protocols or guidelines for treatment [4]. However, if PCD is suspected, a serum analysis to determine antineuronal antibodies is important [5]. Patients who are positive for anti-Yo antibodies must be assessed for occult ovarian or breast cancer [5]. A multimodal treatment strategy of clinical evaluation including neurological examination, imaging studies, and genetic screenings should be considered to address PCD symptoms and the underlying malignancy [8]. A few cases have demonstrated partial response to IVIG and treatment of primary tumor in addition to supportive therapy [4]. There are no evidence-based recommendations regarding immunosuppressive therapy, but it includes IVIG, steroids, plasmapheresis, cyclophosphamide, azathioprine, and rituximab [4]. Although there are improvements with these therapies, the impact is generally minimal [7]. This is because the antibodies are intrathecal, and thus, unaffected by IVIG and plasmapheresis [7]. Early PCD therapy in addition to speech therapy, psychological support, and intensive rehabilitation are essential for optimizing recovery [7].

In the case we presented, the positive anti-Yo antibody resulted in an extensive diagnostic workup, and HGSOC was recognized as the cause of PCD. After IVIG and corticosteroids, supportive therapy, and treatment of ovarian cancer with chemotherapy, and surgical debulking, the anti-tumor therapeutic response was excellent, demonstrated by the decrease of CA-125 tumor marker. Despite excellent oncological response, only a slight neurological improvement was noted which lasted for several months, followed by progressive neurological decline. No clinically significant variants or variants of uncertain significance were identified from next generation sequencing including the BRCA gene. Compared to other case reports of PCD in the literature, we consider our case to be unique due to the patient's significant history of alcohol consumption. Cerebral atrophy is a known result of alcohol-related cerebellar degeneration, whereby the cerebellar vermis is preferentially affected [9]. Involvement of the vermis is common in immune-mediated ataxias such as PCD [9]. Thus, although we cannot definitively determine that alcohol contributed to PCD in this case, it is a notable feature of the patient's history that must be considered.

References

1. Gilligan M, McGuigan C, McKeon A. Paraneoplastic neurologic disorders. Curr Neurol Neurosci Rep. 2023;23(3):67-82.
2. Zaborowski MP, Spaczynski M, Nowak-Markwitz E, Michalak S. Paraneoplastic neurological syndromes associated with ovarian tumors. J Cancer Res Clin Oncol. 2015;141(1):99-108.
3. Kannoth S. Paraneoplastic neurologic syndrome: A practical approach. Ann Indian Acad Neurol. 2012;15(1):6-12.
4. Deac S, Stana MM, Havasi AD, Cainap C, Popita AR, Bordeianu AM, et al. Paraneoplastic cerebellar degeneration associated with anti-Yo antibodies in an ovarian cancer case: A case report. Gynecol Oncol Rep. 2021;35:100695.
5. Renjen PN, Chaudhari DM, Shilpi US, Zutshi D, Ahmad K. Paraneoplastic cerebellar degeneration associated with ovarian adenocarcinoma: A case report and review of literature. Ann Indian Acad Neurol. 2018;21(4):311-4.
6. Cui D, Xu L, Li WY, Qian WD. Anti-Yo positive and late-onset paraneoplastic cerebellar degeneration associated with ovarian carcinoma: A case report. Medicine (Baltimore). 2017;96(32):e7362.
7. Russo AE, Scalone S, Leonardi GC, Scalisi A, Giorda G, Sorio R. Paraneoplastic cerebellar degeneration associated with ovarian cancer. Oncol Lett. 2013;5(2):681-3.
8. Fidahussain AA, Abid A, Paracha AA, Jeevan VE, Rueve J, Engelhardt M, et al. An etiological investigation of paraneoplastic cerebellar degeneration in ovarian cancer patients: A systematic review. Cureus. 2022;14(11):e31154.
9. Shanmugarajah PD, Hoggard N, Currie S, Aeschlimann DP, Aeschlimann PC, Gleeson DC, et al. Alcohol-related cerebellar degeneration: Not all down to toxicity? Cerebellum Ataxias. 2016;3:17.