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Case report

# Paraneoplastic cerebellar degeneration heralding recurrence of fallopian tube adenocarcinoma: A case report and literature review

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## 1. Introduction

Paraneoplastic neurologic syndromes (PNS) are a spectrum of rare immune-mediated disorders that occur in approximately 1 in 10,000 patients with cancer (Rosenfeld and Dalmau, 2018). Given the association between PNS and cancer, if PNS is suspected, screening for a malignant source should be initiated.

PCD has been associated with fewer than 1% of cancers – these include gynecologic malignancies, breast cancer, small-cell carcinoma and Hodgkin Lymphoma (Le May and Dent, 2018; Bataller and Dalmau, 2003). Paraneoplastic cerebellar degeneration is a diagnosis of exclusion. The absence of brain metastases must be confirmed when symptoms of PCD arise (Le May and Dent, 2018). A literature review of all known cases of PCD in patients with ovarian and fallopian tube carcinoma was performed and is summarized in Table 1. Symptoms of PCD include sub-acute but progressive gait disturbances, truncal and appendicular ataxia, dysarthria, dysphagia, vertigo, nystagmus, and dyplopia (Bataller and Dalmau, 2003). An estimated 20% of patients will develop mild memory and cognitive deficits with rare cases causing cerebellar cognitive affective syndrome (CAS) which can cause decrease in executive function, spatial cognition, visual-spatial memory and disinhibited or inappropriate behavior (Le May and Dent, 2018). These symptoms progress over the course of months, plateauing at 6 months, and often stabilize with treatment but generally are not reversible, often leaving the patient severely disabled.

PCD is mediated by a cross-reaction of antibodies with tumor antigens in cerebellar tissue causing loss of Purkinje cells, variable thinning of the granular layer, and inflammatory infiltrates and gliosis in the deep cerebellar nuclei (Bataller and Dalmau, 2003). There are over 30 different autoantibodies associated with PCD (Le May and Dent, 2018); the most common of which include anti-Hu, anti Ri/Nova, and anti-Yo. Anti-Yo antibodies, sometimes referred to as Purkinje cell cytoplasmic antibody (PCA1) are most associated with gynecological cancers (Negishi, 2014); however, their incidence is very low. In one study of 557 patients with ovarian cancer, only 2.3% of patients were positive for the antibody, and only 12% of those had clinical evidence of PCD (Le May and Dent, 2018).

In this report, we describe the case of a 64-year-old woman who developed PCD and was subsequently found to have recurrence of her cancer.

## 2. Case description

Patient MK presented with Stage IV B high-grade serous carcinoma of the fallopian tube and underwent primary R0 debulking and adjuvant chemotherapy and noted to have no evidence of disease on computed tomography (CT) scan in March 2019. Following primary therapy, the patient was enrolled on a phase III clinical trial of oral PARP inhibitor rucaparib versus placebo and IV nivolumab versus placebo and began treatment in March 2019.

The patient presented in early November 2019 reporting increasing dizziness and poor balance. Neurologic examination was without abnormalities. Patient was noted to have immunotherapy induced hypothyroidism with TSH 50.9 and free T4 0.29 and was started on levothyroxine.

Twice in the next two weeks the patient presented to the emergency department due to worsening dizziness, lightheadedness, and nausea. On the second presentation, in mid-November, she was admitted for

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**Table 1**
Summary of cases previously reported of paraneoplastic cerebellar degeneration in gynecologic cancers.

| Reference | Age | Time Interval | Initial Symptoms | Diagnosis of Malignancy | Timeline | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| O'Brien et al. (1995) | 62 | 2 months | Gait unsteadiness<br>Limb clumsiness<br>Transient diplopia | Metastatic Adenocarcinoma of the ovary | Recurrence | Plasmapheresis<br>Cyclophosphamide | Stable, until death |
| Matuchita (1998) | 70 | 3 months | Dizziness<br>Vertigo<br>Nausea | Stage 1c<br>Adenocarcinoma of the fallopian tube | Primary diagnosis | Cisplatin<br>Doxorubicin<br>Cyclophosphamide<br>5-fluorouracil | Stable |
| Matuchita (1998) | 57 | 13 months | Diplopia<br>Dysarthria | Stage 1c<br>Adenocarcinoma of the fallopian tube | Primary diagnosis | Cyclophosphamide<br>Pirarubicin<br>Cisplatin | Stable |
| Levite et al. (2001) | 81 | 2 months | Diplopia<br>Tinnitus | Serous adenocarcinoma | Primary diagnosis | – | – |
| Tanaka (2005) | 63 | 1 months | Dizziness<br>Gait disturbance<br>Dysarthria | Stage IIIc<br>Serous adenocarcinoma fallopian tube | Primary diagnosis | Methylprednisolone<br>Paclitaxel<br>Carboplatin | Stable |
| Selby (2011) | 61 | 3 months | Diplopia<br>Ataxia<br>Vertigo | Grade 3, serous carcinoma of the fimbria, with underlying invasion but no vascular invasion | Primary diagnosis | IVIG<br>Rituximab infusion<br>Carboplatin<br>Doxil | Stable |
| Russo et al. (2013) | 64 | – | Dysmetria<br>Truncal and limb ataxia Dysgraphia<br>Nystagmus | Stage IIIc<br>Serous papillary adenocarcinoma of the ovary | Late onset | IVIG<br>Corticosteroids<br>Paclitaxel<br>Carboplatin | Progressive decline |
| López et al. (2013) | 64 | 2 months | Gait disturbance<br>Dysarthria | Metastatic<br>Endometrioid adenocarcinoma of the fallopian tube | Primary diagnosis | IVIG<br>Chemotherapy* | Stable |
| Negishi (2014) | 62 | 1 month | Dysphasia<br>Vertigo<br>Gait disturbance | Stage IIIc<br>Clear cell carcinoma of the ovary | Primary diagnosis | IVIG<br>Methylprednisolone<br>Paclitaxel | Stable |
| Haggerty et al. (2015) | 59 | – | Dizziness<br>Ataxia | Stage IA<br>Adenocarcinoma of the fallopian tube | Primary diagnosis | IVIG<br>Methylprednisolone | Progressive decline |
| Elomrani (2014) | 80 | less than 1 month | Vertigo<br>Nausea/Vomiting<br>Nystagmus | Metastatic<br>Gynecological cancer not otherwise specified | Primary diagnosis | corticosteroids<br>Paclitaxel<br>Carboplatin | Progressive decline |
| Saeed and Gupta (2014) | 68 | 2 months | Ataxia<br>Dysarthria<br>Recurrent falls | Stage 3c<br>Serous adenocarcinoma of the ovary | Primary diagnosis | Chemotherapy* | Improvement, Moderate |
| Kumari (2014) | 65 | 3 months | Gait disturbance<br>Dizziness<br>Weakness | Stage IIC<br>Malignancy of the ovary | Primary diagnosis | Paclitaxel<br>Carboplatin | Stable |
| Li (2015) | 37 | 2 month | Dizziness<br>Vertigo<br>Nausea/Vomiting | Serous papillary cystadenocarcinoma of the ovary | Primary diagnosis | Paclitaxel<br>Carboplatin | Improvement, Moderate |
| Chien et al. (2015) | 44 | 3 months | Unsteady gait<br>Dysarthria | Stage IIIC<br>Serous carcinoma of the ovary | Primary diagnosis | Chemotherapy* | Not reported |
| Cui et al. (2017) | 65 | – | Imbalance<br>Vertigo<br>Gait disturbance | Stage III<br>Serous carcinoma of the ovary | Late onset, no definitive evidence of recurrence at 19 months | IVIG Methylprednisolone | Improvement, Significant |
| Renjen et al. (2018) | 65 | 2 months | Gait disturbance | Stage III A1<br>Serous adenocarcinoma of the ovary | Primary diagnosis | IVIG<br>Carboplatin<br>Paclitaxel | Improvement, Modest |

– Not documented.
* Type of chemotherapy not documented.

expedited evaluation. Her presentation was complicated by severe anxiety. Endocrinology was consulted during this admission and noted that her free T4 had normalized. Symptoms were felt to be not completely explained by hypothyroidism. As such, the pituitary and adrenal function were assessed and found to be normal. The Neurology team was then consulted, and proceeded with nerve conduction studies, needle electromyography, lumbar puncture, and MRI brain that showed no abnormalities. In this case given no focal defects and no abnormalities in testing the conclusion was that her lightheadedness and nausea were secondary to side effects from her trial medication and her gait instability was attributed to benign paroxysmal positional vertigo. The patient was discharged with plan for follow up with her oncologist in 1 week and instruction on canalith repositioning maneuvers.

At home, the patient experienced worsening gait disturbance resulting in several falls. She developed new dysarthria and had worsening emotional lability with increasing tearfulness. Paraneoplastic panel returned in December, she was noted to have + Anti-Yo Antibodies and diagnosed with Paraneoplastic cerebellar degeneration in December 2019. CT abdomen pelvis was obtained and showed mildly enlarged pelvic lymph nodes and her CA 125 had doubled from her baseline concerning for platinum-sensitive recurrence of her fallopian tube cancer.

The patient was admitted to the hospital for expedited treatment of PCD, both neurology and psychiatry teams were consulted. She received a 5-day course of pulse dose IV methylprednisolone and single agent carboplatin chemotherapy and underwent 2 cycles. Unfortunately, the patient experienced minimal improvement in her neurologic status and ultimately elected to discontinue cytotoxic therapy to pursue hospice care.

## 3. Discussion

In the present report, we describe the case of a patient who developed PCD 10 months after completion of initial treatment for fallopian tube carcinoma. She presented initially with vague neurological symptoms that progressively worsened over the course of a two-month period. During this period her symptoms were attributed to hypothyroidism, BPPV and medication side effect. This highlights the importance of considering PCD as a potential cause for symptoms such as vertigo and loss of balance in a patient with cancer remission. The clinical picture in this scenario was particularly clouded by concern for immune toxicity due to study medications, which may have ultimately delayed the appropriate diagnosis in her case.

Early detection of PCD is paramount as in most cases of PCD associated with fallopian tube cancer, only mild to moderate neurological improvement has been achieved following treatment. Reported therapies include plasmapheresis, intravenous immunoglobulin, and chemotherapy to treat the underlying neoplasm; however, there are no established protocols. In the majority of cases of PCD associated with fallopian tube cancer, there was minimal response to therapy, however treatment stopped progression of neurologic symptoms for some patients. The limited utility of reported treatments is thought likely due to intrathecal presence of Anti-Yo, making the antibodies unaffected by plasmapheresis or IVIG (Rosenfeld and Dalmau, 2018). From review of prior cases and our experience with this particular case we would recommend Anti-Yo antibodies to be evaluated for if patient presents with the complaint of ataxia, dysarthria, or diplopia given that in a few cases treatment with intravenous immunoglobulin, plasmapheresis, and chemotherapy were able to stop the progression of the neurologic symptoms. It appears that the key is early detection and treatment to avoid rapid progression of neurologic dysfunction.

As opposed to the present case, PCD usually pre-dates a cancer diagnosis, or rarely, heralds the diagnosis of a recurrence. PCD has been described prior to the appearance of primary tumor in fallopian tube carcinomas, however, there have been no reports of PCD heralding a recurrence in fallopian tube carcinomas. On average, time between a patient's initial symptoms and the diagnosis of PCD and subsequent cancer diagnosis is 2.7 months with a range of 2 weeks–13 months (Negishi, 2014; O'Brien et al., 1995; Matuchita, 1998; Levite et al., 2001; Tanaka, 2005; Selby, 2011; Russo et al., 2013; López et al., 2013; Haggerty et al., 2015; Elomrani, 2014; Saeed and Gupta, 2014; Kumari, 2014; Li, 2015; Chien et al., 2015; Cui et al., 2017; Renjen et al., 2018). In gynecological cancers, initial symptoms are most commonly vertigo, gait instability, and dysarthria. In general, symptoms worsen over time and patients are often diagnosed with BPPV or other neurologic disorders along their journey to diagnosis of PCD. As such, it is important to recognize the most common symptoms in PCD, including ataxia in both trunk and limbs, dysarthria, nystagmus, diplopia, and dysphagia.

Our patient with PCD exhibited significant alterations in mood, personality change, and disinhibition which have rarely been reported in cases of PCD. Patients with degenerative cerebellar disease can have increased rates of psychiatric disorders specifically mood disorders and personality changes (Key and Root, 2013). These are related to both neuropsychiatric syndromes as well as the reaction to new onset of disabilities. Physiologically there are anatomic connections between the cerebellum and the prefrontal cortex, parahippocampal areas, posterior parietal, temporal and occipital lobes (Key and Root, 2013). There are few reports of psychiatric symptoms associated with PCD even though there is a growing body of evidence for the role of the cerebellum in cognition, mood and affect regulation (Key and Root, 2013).

This patient's case highlights the importance of a wide differential including paraneoplastic syndromes in patients with gynecologic cancers in remission.

## Author contributions

Abigail Cain: Assisted in drafting and editing case report, performed literature review, provided oncologic care to patient.

Linsey Buckingham: Reviewed case report, provided oncologic care to patient.

Allision Staley: Reviewed case report, provided oncologic care to patient.

Leslie H. Clark: Edited and assisted in drafting case report, provided oncologic care to patient.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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