

# Paraneoplastic Cerebellar Degeneration (PCD) Associated with PCA-1 Antibodies in Established Cancer Patients

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## Research Article

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# Abstract

Paraneoplastic cerebellar degeneration (PCD) is a rare set of neurological disorders arising from tumor-associated autoimmunity against antigens within the cerebellum. Anti-Purkinje cell cytoplasmic antibody 1 (PCA-1), or anti-Yo, is the most commonly linked antibody and is classically associated with breast and ovarian cancers. Here we report case series of PCA-1 associated PCD in patients with known breast or ovarian cancer diagnosis not receiving immunotherapy. These cases highlight recognizing PCA-1 paraneoplastic syndrome triggered by cytotoxic chemotherapy, surgery, tumor recurrence and associated with development of second cancer. Diagnosis of the syndrome requires neurological workup with lumbar puncture (LP) with cerebrospinal fluids (CSF) studies, serum and CSF paraneoplastic antibody panel, and neuroimaging. Inpatient admission for prompt workup and initiation of treatment is recommended. Treatment most commonly includes immunosuppression with corticosteroids, plasmapheresis, and/or intravenous immune globulin (IVIG); however, we postulate that other immune modulating treatments may warrant consideration. In established cancer patients developing this syndrome, workup and treatment of tumor recurrence or development of second malignancy is recommended. These cases highlight the need for early recognition of the syndrome in patients receiving non immune based chemotherapy, for prompt workup and treatment.

## Introduction

Paraneoplastic cerebellar degeneration (PCD) is a rare set of neurological disorders arising from autoantibodies against host antigens within the cerebellum in the setting of cancer. More than 30 antibodies have been identified that target antigens in the brain; PCD has been associated with 12 of these antibodies.<sup>1</sup> Of these antibodies, anti-Purkinje cell cytoplasmic antibody 1 (PCA-1), also known as anti-Yo, is the most common and estimated to account for half of PCD cases.<sup>2,3</sup> Various tumor types are associated with this disease, including small cell lung cancer (SCLC), Hodgkin's lymphoma and, rarely, germ cell tumors and adenocarcinomas of varying organ origin. Breast and ovarian cancers, the focus of this case series, are the prevailing cancers found in PCA-1 associated PCD.<sup>4</sup> Even in these common variants, the overall incidence of the disease is exceedingly low. One retrospective analysis examined 557 breast and 253 ovarian cancer patients screened for PCA-1 and found the rate of positivity to be 1.6% and 2.3%, respectively. And of those with positive anti-PCA-1 antibodies, only 12% of patients actually had the clinical syndrome.<sup>5</sup>

The PCA-1 antibody is most frequently observed in the cerebral spinal fluid (CSF). Prior series have estimated that 93% of patients with PCD and other neurological disease will have abnormal CSF findings.<sup>6</sup> This antibody binds to Purkinje cell cytoplasm while sparing the nucleus and axons. Animal studies have demonstrated that intracellular antigen binding accumulation alone results in rapid loss of Purkinje cells.<sup>7</sup> Histopathologic findings at autopsy include perivascular cuffing and infiltration of the cerebellar Purkinje layer with both B cells and CD8 T cells.<sup>8</sup> These findings are most predominant in the cerebellum, but have also been shown in the cortex and brainstem.<sup>7</sup>

Though PCD can present with a wide variety of symptoms, patients most frequently present with subacute development of cerebellar deficits over the course of weeks to months. Severe ataxia is a hallmark of PCD. As our case series highlights, there are no characteristic symptoms that differentiate the disease from other forms of subacute cerebellar ataxia. Furthermore, symptoms suggestive of brainstem and cortex involvement are not uncommon but typically present later in the disease course.<sup>9</sup>

Due to the rarity of this disease, there are no gold standard diagnostic criteria. The diagnosis of PCD includes characterizing the paraneoplastic symptoms and confirmation via biomarker studies of both the serum and CSF, while ruling out other diagnoses with a similar clinical presentation.<sup>10</sup> Brain imaging, in the form of magnetic resonance imaging (MRI), is typically normal. Even when MRI changes are demonstrated, there is considerable overlap with findings observed in other cerebellar ataxias. In clinical practice, nearly all patients undergo MRI imaging during the evaluation of their disease as it helps to rule out other more common pathologies.<sup>11</sup>

The clinical syndrome of PCD usually precedes a cancer diagnosis, with one study estimating that 63% of patients are diagnosed with a malignancy during the evaluation of their neurological symptoms.<sup>10,12,13</sup> In fact, some tumors are not detectable when the syndrome is diagnosed, and expert clinicians have recommend thorough cancer surveillance with routine age-appropriate screening plus whole-body imaging every 3 to 6 months for 2 to 3 years following PCD diagnosis.<sup>12,13</sup> Conversely, some patients will have a prolonged subclinical course, with one study where patients who screened positive on serum antibody tests shortly after the diagnosis of cancer developing symptoms of up to 5 years later.<sup>12</sup> In 30% of PCD cases, ataxia develops during a period of cancer remission.<sup>12,14</sup> Given the variable timing of presentation, providers should maintain clinical suspicion for PCD regardless of the neoplastic disease course. Unfortunately, 52% of patients with PCD die of their malignancy, suggesting an association with advanced stage cancer and/or aggressive tumor biology. On the other hand, 29% of patients are estimated to die as a result of a debilitating neurological condition typically associated with the paraneoplastic disorder.<sup>12</sup> Taken together, PCD portends a poor prognosis for patients. Treatment for PCD is largely based on expert clinical opinion due to the rarity of the disease but most commonly includes immunosuppression with calcineurin inhibitors, corticosteroids, plasmapheresis, and/or intravenous immune globulin (IVIG) and, importantly, treating the underlying cancer.<sup>11</sup> The goal of this immunosuppression is to not only deplete pathogenic autoantibodies, but also to target lymphocytes that may be causing the autoimmune response.

Here we report a case series of PCA-1 associated PCD in patients with a known cancer diagnosis. These cases highlight the importance of early recognition and treatment of PCA-1 paraneoplastic syndrome and its possible indication of a new or recurrent cancer diagnosis.

## Methods

This study was conducted under IRB-approved protocol 2021 – 0192 covering retrospective chart reviews under the classification of not human research. Medical records of patients at our institution who developed PCA-1 associated PCD were reviewed. Clinical information, including cancer history, cancer-directed treatment, and serum and CSF titers of PCA-1 antibody were extracted. Case reports, case series, and literature reviews were identified with a PubMed search using the keywords “PCD” and “PCA-1” without any search limitations. From the references in articles identified through PubMed and found to be relevant, a search was performed using the Web of Science to locate additional case reports, case series or literature reviews cited by the original group of reports derived from PubMed.

## Results

Six patients with paraneoplastic cerebellar degeneration associated with PCA-1 antibody were identified (Table 1).

**Table 1**

Summary table of CSF and Serum Results in Patients with Paraneoplastic Cerebellar Degeneration (PCD) Associated with PCA-1 Antibody.

<u>Patient</u>	<u>Case #1</u>	<u>Case #2</u>	<u>Case #3</u>	<u>Case #4</u>	<u>Case #5</u>	<u>Case #6</u>
<i>CSF Results</i>						
WBC (cells/ $\mu$ L)	14	19	n/a	0	18	0
Protein (mg/dL)	71	n/a	n/a	72	n/a	161
Oligo	7	n/a	n/a	n/a	n/a	n/a
PCA-1 Ab CSF Titer	1:2048	1:4096	n/a	n/a	n/a	1:2048
<i>Serum Results</i>						
PCA-1 Ab Serum Titer	1:61400	1:122880	1:61400	1:122280	n/a	n/a

## Case #1

A 61-year-old woman with ovarian carcinoma undergoing treatment with an ERK inhibitor developed lower extremity weakness, ataxia, and difficulty with ambulation. These symptoms were initially right sided but eventually progressed to the left side. After two weeks, she presented to the emergency department (ED) as she could no longer stand. MRI of the brain and pelvis revealed no abnormalities. Inflammatory neuritis was considered as the most likely diagnosis, and she was initiated on methylprednisolone. She was discharged with planned outpatient lumbar puncture (LP) but returned to the hospital within 11 days for persistent symptoms. LP was performed, and a PCA-1 Ab titer of 1:2048 in the CSF was found. Her serum PCA-1 Ab titer was 1:61400. The patient was initiated on corticosteroids,

IVIg, and tacrolimus. Despite treatment, her symptoms did not remit and required a month-long hospital course and extensive rehabilitation. Unfortunately, she expired as a result of her ovarian cancer.

## **Case #2**

A 59-year-old woman with recently relapsed ovarian serous carcinoma developed double vision, dizziness and difficulty with ambulation approximately two weeks after her first cycle of carboplatin and doxorubicin. Examination revealed binocular vertical diplopia with partial left ptosis, leading to initial concern for third nerve involvement. She was admitted to the hospital. MRI of the brain and orbits, as well as CT venogram were all found to be normal. LP obtained two days later revealed a CSF PCA-1 Ab titer of 1:4096, with a serum PCA-1 Ab titer of 1:122880. The patient was treated for PCD with corticosteroids and tacrolimus with rapid resolution of symptoms. Steroids were tapered after 4 weeks. Her malignancy remitted and did not require further treatment; however, she developed progressive cerebellar atrophy over the next 18 months (Fig. 1).

## **Case #3**

A 57-year-old woman with ovarian cancer who had recently completed her second cycle of adjuvant carboplatin, paclitaxel, and bevacizumab developed right hand tremor that eventually progressed bilaterally. This was accompanied by ataxia and speech difficulties. She was seen at two other large academic institutions for workup and was diagnosed with PCD by LP at the second institution. Her CSF PCA-1 Ab titers were 1:61400. She was treated with corticosteroids, IVIg, and tacrolimus prior to transferring to our institution. She had residual speech deficits, truncal ataxia, and limb dysmetria initially. After her malignancy was cured, the patient transferred care locally and was lost to follow-up; therefore, the progression of neurological sequelae has not been evaluated. On the last telephone conversation, she was left with significant cerebellar symptoms.

## **Case #4**

A 63-year-old woman with newly diagnosed localized breast cancer underwent mastectomy. In the immediate post-operative period, she developed diplopia and blurred vision. She was discharged home after her symptoms remitted, but then developed ataxia and weakness in her legs. She presented back to the hospital and was admitted for stroke workup. A brain MRI demonstrated significant diffuse meningeal enhancement of the right occipital lobe suggestive of meningeal carcinomatosis. She was found to have positive PCA-1 Ab titers in the serum (1:122280) and diagnosed with PCD. She was treated with corticosteroids, IVIg, therapeutic plasma exchange, and cyclophosphamide. Neither the patient's paraneoplastic symptoms or cancer remitted, and she expired from her breast malignancy.

## **Case #5**

A 45-year-old woman developed worsening vision and associated-headache three months after completion of six cycles of carboplatin and paclitaxel for ovarian carcinoma. Her symptoms progressed

to dysarthria, vertigo and ataxia. MRI of the brain demonstrated right superior cerebellar FLAIR signal changes suggestive of leptomeningeal disease with CSF cytology being negative. She had positive CSF antibody. She was treated with corticosteroids and therapeutic plasma exchange. In this case, the paraneoplastic syndrome heralded tumor recurrence with retroperitoneal disease discovered on workup. She succumbed to her aggressive disease in less than 6 months.

## Case #6

A 59-year-old woman with past medical history of invasive ductal carcinoma of the breast developed facial palsy, diplopia, lower extremity weakness, and ataxia. She had electromyography (EMG) that showed peripheral demyelination with an autoimmune process high on the differential. She had positive PCA-1 Ab titers in the CSF of 1:2048, was diagnosed with PCD and treated with corticosteroids, IVIG, and therapeutic plasma exchange. At that time, the patient had also developed abdominal pain and fullness, which prompted investigation into the presence of a second malignancy. Contrast tomography (CT) scan revealed ovarian cancer. After her cancer-directed treatment, she had complete resolution of the paraneoplastic syndrome and eight years after diagnosis of the paraneoplastic syndrome, she has no evidence of cerebellar degeneration on MRI (Fig. 2). She was the only patient with clinical resolution of her cerebellar symptoms and remains cancer free 8 years after the diagnosis of her second cancer.

## Discussion

This single-institution case series of six patients highlights several scenarios in which PCD developed in established cancer patients, either in remission, undergoing treatment, or prior to the diagnosis with recurrent malignancy. These findings offer several insights when approaching patients with suspected PCD, most importantly that early recognition and treatment is critical. Patients who were diagnosed and treated aggressively early appeared to have better outcomes than those with delays in diagnosis. Additionally, PCD may herald a new or recurrent cancer, and treatment of the underlying malignancy remains a critical component of therapy.

Diagnosing subacute ataxia and, later, identifying its specific cause can prove challenging. First, subacute ataxias must be differentiated from other neurologic disease categories, such as peripheral neuropathies, which is quite difficult given the overlap in exam findings. Case #1, for example, was suspected to be secondary to inflammatory neuritis, and case #6 had findings of peripheral demyelination on testing, despite their eventual diagnosis of PCD. Even when symptoms are suspected to be secondary to a cerebellar process, 58% of ataxic adult patients go without a definitive diagnosis.<sup>15</sup> Case #3 exemplifies this circumstance, where the patient was diagnosed after repeating workup at a second academic institution. The challenge of diagnosis can be exacerbated by delays inherent in outpatient care. 3 of our 6 patients received their diagnosis of PCD from studies obtained while in the inpatient setting. It is possible that overlapping clinical entities caused by PCA-1 exist.

The primary means by which PCD is diagnosed is testing for antibodies in the CSF or serum.<sup>10</sup> CSF antibody tests are preferred, but serum tests are more convenient to obtain. The variability of presentation of PCD may account for delayed work up. For example, case #2 had visual changes with suspicion for cranial nerve III involvement and case #1 was originally diagnosed with inflammatory neuritis. Rare but positive brain imaging findings that needs further work up are sometimes noted, like in patient 5. Irrespective of imaging, which can be normal at initial work up CSF cytology, assessment for leptomeningeal disease is recommended. Cerebellar atrophy can be present in subsequent brain MRI. CSF analysis is highly recommended and initial CSF indices showing inflammation (increased WBC, increased protein, increased oligoclonal bands) with negative infection and negative malignancy while pending antibody results could suggest paraneoplastic syndrome.<sup>16</sup>

These cases may provide insight into factors that may precipitate the development of PCD in established cancer patients. Intriguingly, the development of PCD after chemotherapy or surgery are very rare and may be due to *de novo* antigen exposure, triggering a rapid inflammation. It is unclear if underlying autoimmune disorders are a precipitating factor for PCD; but these were not observed in our case series, favoring *de novo* antigen exposure as likely mechanism.

Future advances in this rare disease will be challenging, with too few patients to conduct prospective clinical trials. However, biological insight from small numbers of patients can be informative and help guide further research and clinical care. For example, as a pathognomonic feature of this disease is the presence of autoantibodies, a major therapeutic treatment strategy has been antibody-mitigating therapy with plasmapheresis and IVIG. There may be a role for therapy directed toward B cells, such as with rituximab. In one investigation, 3 of 9 patients had improvement with this therapy based on their neurologic symptoms measured by the Rankin Scale.<sup>17</sup> Additionally, the presence of infiltrating T and B cells in the brain raises questions of whether the lymphocytes are encountering antigen in the brain or in the periphery, clonally expanding, and then migrating into the brain.<sup>18,19</sup> This could potentially be studied by comparative T cell receptor (TCR) and B cell receptor (BCR) sequencing in blood and CSF or directly in brain parenchyma from autopsy specimens. These observations have potential therapeutic implications, as therapies in multiple sclerosis that target lymphocyte trafficking, such as fingolimod and natalizumab may be beneficial in this disease.<sup>20,21</sup> Finally, though immunosuppression has primarily focused on B cell-derived autoantibodies, perhaps the T cell component is equally important and stronger T cell directed immunosuppression may be considered as an adjunct (for example, the addition of tacrolimus, azathioprine or cyclophosphamide). Such immunosuppression must be considered concurrently with treatment of the underlying malignancy, which appears to be the most effective way to treat PCD.

Paraneoplastic cerebellar degeneration (PCD) associated with PCA-1 antibody is an important component in the differential diagnosis for new cerebellar findings in patients with cancer. This case series highlights the importance of prompt recognition, comprehensive neurologic work-up, and early immunosuppressive treatment. PCD may be a harbinger of a new or recurrent cancer diagnosis in patients and treatment of the underlying malignancy is essential. Breast cancer patients need work up for

ovarian cancer in addition to screening for recurrence and vice versa for ovarian cancer patients who develop this specific antibody mediated PCD. Further research should focus on the mechanisms of this autoimmune disease to better target immunosuppression and improve outcomes for patients.

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## **Availability of data and materials**

Not applicable.

## **Disclaimer/disclosures**

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## **Authors' contributions**

MJL and JSG drafted the initial manuscript. BAS and ST provided critical review of the manuscript. ST provided clinical data and supervised the effort. All authors read and approved the final manuscript.

## **Ethics approval**

The committee reviewed this submission and assigned a determination of Not Human Research. Internal code is 2021-0192.

## **Consent to participate**

The committee reviewed this submission and assigned a determination of Not Human Research.

## **Consent for publication**

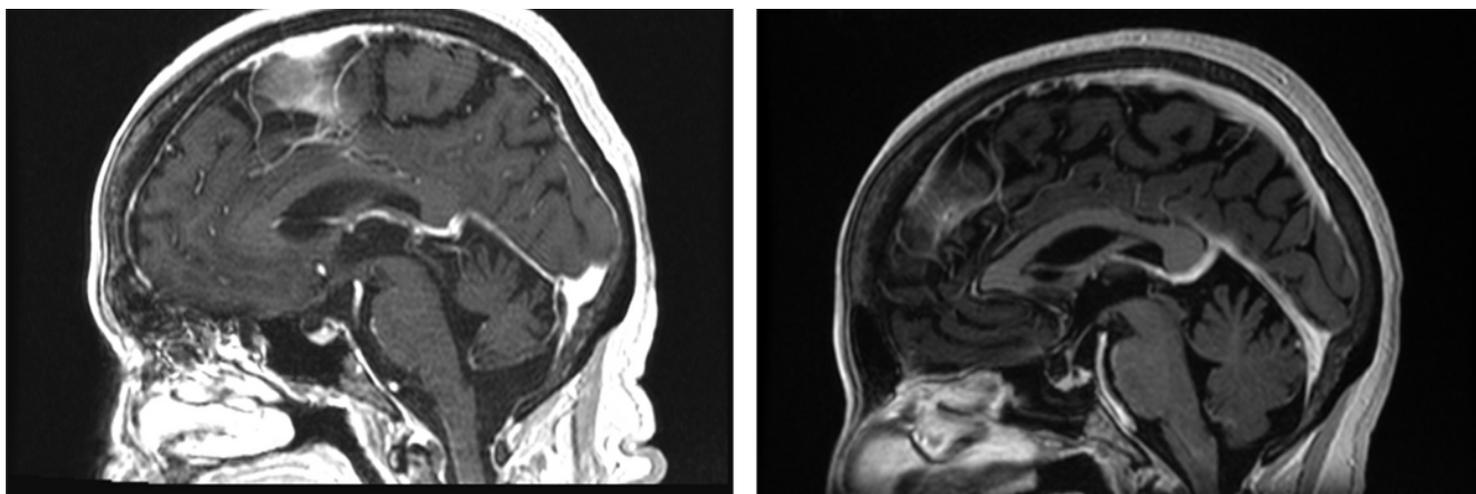
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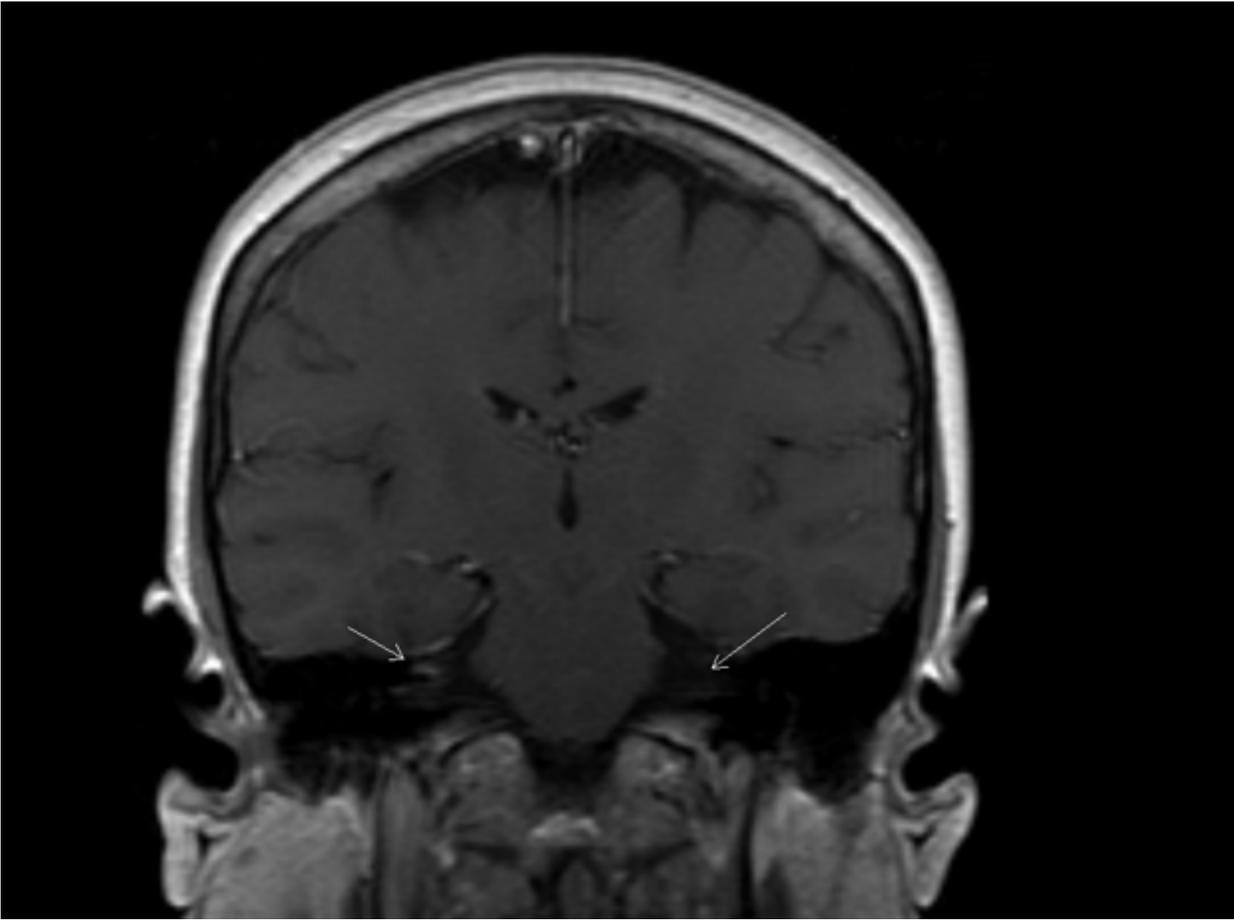
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## Figures



**Figure 1**

Case #2 demonstrating progressive cerebellar atrophy (left 18 months f/u).



**Figure 2**

MRI Brain of Case #6 following treatment. No evidence of cerebellar degeneration.