A 54-year-old Woman with Progressive Ataxia
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**About the Authors**
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**Summary**
Paraneoplastic cerebellar degeneration (PCD) is a rare but devastating syndrome associated with autoantibodies targeting cerebellar antigens expressed by tumours outside of nervous system. PCD is most often associated with breast and gynecological cancers and can precede clinical manifestations of the cancer. Of the dozen autoantibodies associated with PCD, anti-Yo is the most commonly identified. In this report, we present a case of a woman with progressive cerebellar ataxia and anti-Yo antibody, who has microscopic high-grade serous carcinoma found with empiric total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH-BSO). This case highlights the challenges in diagnosis, difficulty in identifying the occult malignancy, and the need for multidisciplinary collaboration between Internal Medicine, Neurology, Gynecology and Pathology. The literature relating to diagnosis, prognosis and treatment of PCD is also reviewed.

**Résumé**
L’ataxie cérébelleuse paranéoplasique (ou PCD pour paraneoplastic cerebellar degeneration) est un syndrome rare mais foudroyant, associé à la présence d’autoanticorps qui ciblent les antigènes cérébelleux et qui ont pour origine des tumeurs localisées à l’extérieur du système nerveux. Le PCD est la plupart du temps associé à des cancers du sein ou gynécologiques et peut précéder les manifestations cliniques du cancer. Parmi la dizaine d’autoanticorps associés au PCD, l’anti-Yo est le plus fréquent. Dans ce rapport, nous décrivons le cas d’une femme présentant une ataxie cérébelleuse et des autoanticorps anti-Yo. Celle-ci est atteinte d’un carcinome séreux microscopique de haut grade, découvert à la suite d’une hystérectomie abdominale complète et d’une salpingo-ovariectomie bilatérale (ou TAH-BSO pour Total abdominal hysterectomy bilateral salpingo-oophorectomy). Ce cas fait ressortir les problèmes d’établissement de diagnostic et de détection de tumeur maligne occulte, ainsi que la nécessité d’une collaboration multidisciplinaire entre professionnels de médecine interne, neurologie, gynécologie et pathologie. Nous faisons également le point sur la documentation relative au diagnostique, au pronostic et au traitement du PCD.
Case Presentation
A previously healthy 54-year-old Caucasian female presented with a six-week history of progressively worsening ataxia, dysarthria and involuntary movement of her limbs. She denied other neurological symptoms including vertigo, diplopia, or motor or sensory changes. Memory and comprehension were unaffected. She denied constitutional symptoms and had no personal history of malignancy. Her only medication was escitalopram for anxiety. Family history was unremarkable. She was a non-smoker and drank alcohol only occasionally.

Physical examination was remarkable for truncal ataxia, bilateral dysmetria, dysdiadochokinesia, ataxic dysarthria, saccades, diplopia and tibulation. She did not have nystagmus. Cranial nerves, motor exam, reflexes, proprioception and sensation were intact. Initial blood work including complete blood counts, electrolytes, renal function, liver enzymes, Hemoglobin A1c, serum Venereal Disease Research Laboratory test (VDRL), rapid plasma regain (RPR), vitamin B12 and thyroid stimulating hormone (TSH) were all normal.

Her presentation supported subacute cerebellar ataxia. Extensive work up was performed. Initial magnetic resonance imaging (MRI) of the head was unremarkable. cerebrospinal fluid (CSF) fluid revealed normal white blood, elevated total protein at 685 mg/L, and IgG at 138 mg/L. With oligoclonal pattern consistent with an inflammatory or immune process. CSF was negative for syphilis, bacteria, fungus or viruses. A repeat MRI head to specifically look for signs of Creutzfeldt-Jakob disease was also negative. Rheumatologic work up including anti-nuclear antibody (ANA), extracted nuclear antibody (ENA), rheumatoid factor (RF), anti-neutrophil cytoplasmic antibody (ANCA) were negative.

Further search in malignancy was carried out. Computed tomography (CT) chest, abdomen and pelvis showed two small left breast nodules and a left adrenal nodule measuring less than 0.8cm. The ovaries and uterus were normal. Designated adrenal CT confirmed that the left adrenal gland nodule was in keeping with an adenoma breast ultrasound and mammogram were unremarkable. Fecal occult blood testing, cancer antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), CA125, Alpha fetal protein (AFP), serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) were all within normal limits. Whole-body positron emission tomography (PET) revealed normal 18F-fluorodeoxyglucose (FDG) uptake.

The CSF was sent to Dr. Marvin Fritzler’s Mitogen lab in Calgary for analysis of PCD antibody panel. PCD panel results came back positive for high titre of anti-Yo antibody and all other antibodies were negative.

Since anti-Yo antibody primarily occurs in patients with PCD who have cancers of the breast, ovary, endometrium or fallopian tubes, upon discussion with gynecology and the patient and her family, the decision was made to empirically perform total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH-BSO). While the surgical specimen was grossly normal, histologic examination revealed microscopic foci of high-grade serous carcinoma in both ovaries, and intraepithelial (in situ) and invasive serous carcinoma of the left fallopian tube. (Figure 1) The final diagnosis was PCD secondary to bilateral ovarian serous carcinoma.

During the investigations, the patient was treated with two cycles of IVIG for suspected PCD with no neurological improvement. Despite of tumour removal and ongoing physical rehabilitation, patient continued to deteriorate neurologically. At the time of submission of this case report, the patient was completely bed bound. She was unable to speak, write or carry on activity of daily living due to severe truncal and appendicular ataxia.

Figure 1. Histology revealed occult foci of serous carcinoma (hematoxylin-eosin, 200x). (A) Surface ovarian involvement by high-grade serous carcinoma (arrows). (B) Serous tubal intraepithelial carcinoma.
Discussion
Pathophysiology
It is believed that PNS are immune-mediated processes in which autoantibodies against tumour antigen cross the blood brain barrier and mediate neuronal degeneration. Ovarian tumors have high potential to mount an immune response since anti-ovarian autoantibodies are frequently found in patients affected with these neoplasms.1 Table 1 summarizes the common paraneoplastic autoantibodies identified in PCD. Among these, anti-Yo and anti-Tr antibodies are predominantly associated with cerebellar dysfunction whereas other autoantibodies involve other areas of the central nervous system.

The target antigen of anti-Yo antibody (also called Purkinje cell antibody type 1 or PCA-1) is the cdr protein that is expressed by ovarian and breast cancers as well as the cerebellar Purkinje cells. As a result, anti-Yo antibody cross-reacts with Purkinje cells and causes degeneration. It is identified in the serum of up to 70% of the patients with PCD and carries a specificity of nearly 100% for the diagnosis of an underlying breast or gynaecological malignancy.2 It can be rarely associated with small cell lung cancer.3 Most patients (60 to 70%) with PCD do not have a cancer diagnosis at the onset of their neurologic symptoms.1,2

Clinical Presentation
Patients with PCD typically present with subacute cerebellar findings including downbeat nystagmus, saccades, limb and truncal ataxia, dysarthria, and dysphagia. As the diagnosis is often very challenging and delayed, symptoms typically continue to worsen for weeks or months to the point of severe disability. At the time of PCD diagnosis, more than 50% of patients with anti-Yo antibodies are unable to walk and have more functional disability than patients with other autoantibodies. Our patient was bed-bound and unable to care for herself or communicate by 12 weeks of presentation.

Diagnosis
The PNS Euro network has recommended a set of diagnostic criteria to distinguish “definite” from “possible” PNS depending on the presence of classical or non-classical neurological syndromes, presence of distinct antibodies, presence of a tumour, and improvement of symptoms after cancer therapy.4 To apply the diagnostic criteria to clinical practice, steps in the diagnosis of PCD include: 1) ruling out other causes of cerebellar ataxia; 2) confirming paraneoplastic phenomenon with CSF autoantibody analysis; and 3) searching for the underlying malignancy.

Mitogen laboratory in Calgary, founded by Dr. Marvin Fitzler, is the only Canadian facility to specialize in novel autoantibodies and biomarkers for autoimmune diseases. In addition to systemic autoimmune rheumatic diseases, Mitogen also researches and identifies autoantibodies associated with idiopathic ataxia and chronic inflammatory demyelinating neuropathy. Detailed panels of diagnostic tests can be found on website (http://mitogen.ca).

Whole-body CT scan in conjunction with pelvic ultrasound and mammogram are the first line investigations to search for the primary tumour. If no positive findings are seen, whole-body FDG-PET can identify a lesion as small as 1cm and is reported to have improved the diagnostic rate. Tumour markers including CA19-9, CEA, CA125 and AFP are often ordered although the yield is limited.

Occult malignancy in PCD is not uncommon. In a small case series, Hetzel et al found seven of the 19 patients with both ovarian cancer and PCD had no tumour symptoms or abnormal imaging prior to surgery.7 The decision for surgical resection was made exclusively based on the detection of autoantibodies. All these patients had high-grade ovarian adenocarcinoma on histology. We took a similar approach with our patient.

Treatment
Removal of the tumour is the first line of treatment to prevent disease progression. Unfortunately, eradication of the cancer cells does not usually reverse the neurological damage that is already present. There are no randomized controlled trials or large case studies in the treatment of

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<tr>
<th>Autoantibodies</th>
<th>Associated malignancies</th>
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<tr>
<td>Anti-Yo</td>
<td>Breast, Uterus, Ovaries</td>
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<tr>
<td>Anti-Hu</td>
<td>small cell lung carcinoma (SCLC)</td>
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<tr>
<td>Anti-Tr</td>
<td>Hodgkin’s disease</td>
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<td>Anti-CV2</td>
<td>SCLC, thymoma</td>
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<tr>
<td>Anti-Ri</td>
<td>Breast, gynaecologic cancers, and SCLC</td>
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<td>Anti-Ma2</td>
<td>Testicle, Lung</td>
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<td>Anti-VGCC (P/Q type)</td>
<td>SCLC</td>
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<td>Anti-SOX1</td>
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<td>Anti-ZIC4</td>
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this disease entity. Anecdotally, there has been neurological improvement in patients tried on various immunological therapies such as IVIG (attempted in our patient without improvement), corticosteroids, plasma exchange, azathioprine, cyclophosphamide and rituximab. However, in a large case series with 50 PCD patients, immunotherapy was not significantly associated with recovery. Counseling and rehabilitation are cornerstones of therapy in these patients.

**Prognosis**

In most patients suffering from PCD, prognosis is determined by the type of antibody rather than the underlying malignancy. The aforementioned retrospective analysis with 50 PCD patients demonstrated poor neurological outcome and dismal overall survival, especially for those with detectable anti-Yo and anti-Hu antibodies. In this analysis, the five-year survival rate of PCD patients with anti-Yo antibody was less than 25%. Similarly, in the largest case series review from the PNS Euronetwork database with 979 patients, the clinical course of PCD patients with anti-Yo and anti-Hu was found to be more severe than those with other antibodies. The median survival for patients with anti-Yo was 13 months and anti-Hu was seven months. In contrast, median survival for patients with anti-Tr was more than 113 months and anti-Ri more than 69 months. Mortality was caused by cancer itself in half of the patients with neurological progression being the cause of death in the other half.

**Conclusion**

Our case has several practical implications. First, progressive cerebellar ataxia has a broad differential diagnoses and a broad work up should be undertaken. Second, screening of neural autoantibodies is important in order to establish the diagnosis of PCD and to evaluate prognosis. The most common autoantibodies associated with PCD and their respective cancers include anti-Yo (gynecological cancers), anti-Hu (small cell lung carcinoma), and anti-Tr (Hodgkin lymphoma). The presence of one of these antibodies in CSF or serum should prompt a search for malignancy. Third, this case report is an example that neurological symptoms may develop long before any tumour-related symptoms or radiographic findings. If clinical suspicion of a specific type malignancy is high as in our case, preemptive surgical resection may be warranted. Last but not least, treatment of PNS emphasizes on medical therapy or surgical resection of the underlying malignancy. Immunological therapies have not been shown to have neurological benefits in large case series of PCD patients.

**Reference:**


