

# Response to abdominal hysterectomy with bilateral salpingo-oophorectomy in postmenopausal woman with anti-yo antibody mediated paraneoplastic cerebellar degeneration

Amita Bhargava<sup>1</sup>, Bharat Bhushan<sup>1</sup>, Gaurav M Kasundra<sup>1</sup>, Khichar Shubhakaran<sup>1</sup>, Guruprasad S Pujar<sup>1</sup>, Basavaraj Banakar<sup>1</sup>

<sup>1</sup>Department of Neurology, Dr. Sampurnanand Medical College, Jodhpur, Rajasthan, India

## Abstract

Paraneoplastic cerebellar degeneration (PCD) is a rare neurological disorder characterized by a widespread loss of Purkinje cells associated with a progressive pancerebellar dysfunction. PCD often precedes the cancer diagnosis by months to years. Here, we report a case of 44-year old postmenopausal woman who presented with PCD symptoms and high levels of anti-Yo antibodies titer since 8 months. We failed to conclude any neoplastic focus after thorough laboratory and imaging study. She minimally responded to methylprednisolone and immunoglobulin therapies. Despite therapy she was severely disabled. Planned abdominal hysterectomy with bilateral salpingo-oophorectomy (AHBSO) was done, histology revealed grade IIA borderline serous papillary carcinoma of ovary. Her neurological deficit responded dramatically to AHBSO. It is first case report who emphasize the response of AHBSO with presentation of anti-Yo antibody-mediated PCD and hidden nidus in post menopausal women.

## Key Words

Anti-Yo, abdominal hysterectomy with bilateral salpingo-oophorectomy, paraneoplastic cerebellar degeneration, postmenopausal

## For correspondence:

Dr. Bharat Bhushan, H. No. 21/267 Chopasani Housing Board, Jodhpur - 340 008, Rajasthan, India.  
E-mail: drbhushan90@yahoo.com

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## Introduction

Paraneoplastic neurological disorders may affect any part of the nervous system.<sup>[1]</sup> Paraneoplastic cerebellar syndrome is a rare neurological disorder that primarily emerges before the detection of malignancy.<sup>[2]</sup> Paraneoplastic cerebellar degeneration (PCD) is characterized by cerebellar atrophy with a diffuse loss of Purkinje cells, mediated by a cross-reaction of antibodies with tumor antigens and cerebellar tissue.<sup>[3]</sup> PCD can present with acute or sub-acute onset. The onset of symptoms and detection of antibodies precede diagnosis of the tumor more than 60% of the time, and in approximately 40% patients, antibodies were

not identified. However, this does not exclude the likelihood of occult malignancy.<sup>[4]</sup> We are reporting a case that showed dramatically response to PCD symptoms after abdominal hysterectomy with bilateral salpingo-oophorectomy (AHBSO).

## Case Report

A 44-year-old female presented with sub-acute onset progressive vertigo, nausea, and daily vomiting since 8 months. Since 7 months, she also developed dysarthria and gait and limb (right followed by left side over 2 weeks) ataxia. Her ataxia progressed over a period of 2 months, followed by a more gradual progression making her dependent for activity of daily living (ADL) within 6 months.

During the 8<sup>th</sup> month of her illness, she presented to us with Modified Rankin Scale (mRS) four. On examination, she was conscious, oriented with normal memory and intelligence. She had staccato speech, gaze evoked nystagmus in all directions, oculomotor dysmetria, slow saccades, broken pursuit, intention tremor, appendicular, and gait ataxia. Rest of the neurological examination was normal.

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She was investigated to consider differentials of vasculitis, inflammatory, demyelinating, infective, and immune-mediated cerebellar dysfunction. Investigations revealed bilateral cerebellar atrophy, positive anti-Yo antibody (titer - 1/603 by immunofluorescence; normal <1/500) and high normal CA-125 (29 U/ml; normal range: 0-35 U/ml). Other investigations including complete blood count, blood sugar, electrolytes, urea, creatinine, liver functions test, electrocardiography, chest X-ray, positron emission tomography (PET) scan [Figure 1] cerebral spinal fluid examination, and other specific investigations were normal [Table 1].

We kept diagnosis as anti-Yo antibody-mediated PCD. Intravenous methylprednisolone 1 g/d for 5 days was given but due to lack of response, one month later intravenous immunoglobulin (IVIG) 2 g/kg (over 5 days) was administered. After 2 weeks of immunotherapy, her vomiting and tremors subsided but vertigo and ataxia persisted. After 1 month follow up, her general condition improved but she remained almost bed bound.

We advised a repeat IVIG infusion and other second line chemotherapy for further expected improvement, but due to financial constraint and adverse effects, the patient refused. She opted for the alternative offer of AHBSO as a treatment of PCD by anecdotal reports in post-menopausal women. One and a half month after IVIG therapy, she underwent an uneventful AHBSO under general anesthesia. Intraoperatively, no evidence of malignancy was found. Histology revealed grade II-A borderline serous papillary carcinoma of the ovary [Figure 2]. Post surgery, by 2<sup>nd</sup> week, her dysarthria and vertigo

improved and by 1 month, she was ambulatory with support. By 2 months, she had minimal residual appendicular ataxia and ocular findings, and was independent for ADL with mRS grade 2. Post surgery her anti-Yo titer was 1/214.

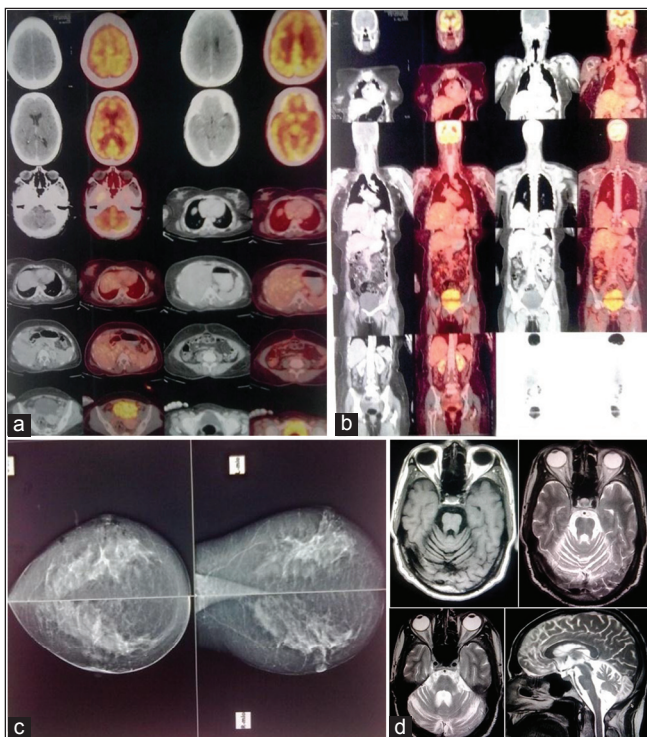
## Discussion

PCD is a rare non-metastatic complication of malignancies, and it is believed to be immune mediated. The autoantibodies are considered the result of an immunologic response to tumor and may cross-react with cells of the nervous system, causing neuronal damage. Anti-Yo-related PCD is most commonly found in women with gynecological and breast cancers, but it is also reported in other malignancies. Other PCD-related autoantibodies are anti-Hu and anti-Ri with small cell lung and breast cancer, respectively.<sup>[4]</sup> The anti-Yo antibodies that specifically damage the Purkinje cells of the cerebellum, also

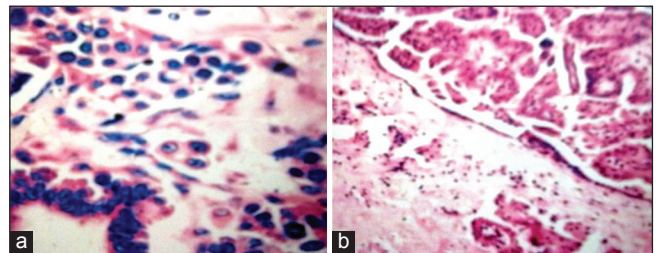
**Table 1: Laboratory test and imaging data**

Test	Value
CA 125	29 U/ml
CA 15-3	7.50 U/ML
Anti tissue transglutaminase	Negative
Paraneoplastic neuronal profile	Only Yo positive (Titer was 603 by Immunofluorescence, Normal <500/1 dilution), rest were negative (Hu, Ri, Amphiphysin, Ma2/Ta)
Post surgery Yo titer	1/214
MRI Brain	Bilateral cerebellar atrophy
MRA brain including neck vessels	Normal
CT Chest	Normal
PET- CT of whole body	Absence of obvious FDG-avid lesion involving the region of body scanned to favor primary malignant etiology
Mammography	Normal
Contrast MRI abdomen & pelvis	Normal
CSF analysis	Protein-36 mg/dl, sugar-84, total cell-3, ADA -2 U/L, Fungal, Gram and Z-N stain were negative
Varicella zoster & Herpes PCR	Negative

ADA = Adenosindeaminase, CSF = Cerebral spinal fluid, MRI = Magnetic resonance imaging, MRA = Magnetic resonance angiography, CT = Computerized tomography, PET = Positron emission tomography, PCR = Polymerase chain reaction



**Figure 1: (a and b) PET-CT Brain and whole body showing absence of obvious FDG –avid lesion, (c) Mammography – Normal, D; T1W axial, T2W axial and sagittal section brain showing cerebellar atrophy**



**Figure 2: Serous borderline tumor with microinvasion: Eosinophilic cell pattern of microinvasion, characterized by individual cells or small, irregular clusters of cells with abundant eosinophilic cytoplasm within the stromal stalks of serous papillae. The surrounding stroma exhibits no reaction, and the tumor cells are surrounded by clefts (A, H&E, x200; B, H&E, x100)**

called Purkinje cell cytoplasmic antibody type 1 (PCA-1). The Yo antigen is a cytoplasmic protein (CDR2) that interacts with c-Myc. CDR2 is expressed mostly on the Purkinje cells of the cerebellum and may also be present in neurons of the brain stem. Studies suggest that CDR2 sequesters c-Myc in the neuronal cytoplasm and down regulates its activity. Disruption of this interaction by anti-Yo antibodies may increase c-Myc activity, leading to apoptosis of the Purkinje cells. Antibodies could therefore play an initial pathogenic role in PCD, although the T-cell immune response is believed to be the major effect of neuronal degeneration.<sup>[5]</sup>

There are no established protocols for the treatment of most paraneoplastic syndromes (PNS).<sup>[6]</sup> Most investigators have initiated treatment with corticosteroids, plasma exchange, or IVIG.<sup>[7]</sup> Cyclophosphamide, tacrolimus, rituximab, or possibly mycophenolate mofetil may warrant consideration in patients who fail to stabilize or improve on less aggressive therapies.<sup>[8]</sup> Radiation therapy has been used as an adjuvant to chemotherapy for Hodgkin's lymphoma with PCD. Although few reports showed improvement with these therapies, generally, there is a minimal effect since the antibodies are intrathecal and unaffected by plasmapheresis or IVIG.<sup>[7,8]</sup> However, it has been demonstrated that early therapy of PCD may improve neurological status, accordingly we started immunomodulatory treatment regimes with corticosteroids followed by IVIG 4 weeks later. By immunotherapy, she showed improvement in vomiting and tremor but remarkably responded to AHBSO and achieved independence. Due to the borderline nature and early stage of the disease, we could not find tumor on imaging study. The only clue to opt AHBSO was a high normal level of CA 125. Tumor occurrence is preceded months or even years by cerebellar signs,<sup>[7,8]</sup> likewise we observed that PCD emerged without appearance of a primary tumor till AHBSO and was revealed at histology. Yo antibodies were not correlated with specific histological subgroups of ovarian cancer but are related to the staging of ovarian cancer.<sup>[9]</sup> Borderline tumors, as with other ovarian tumors, are difficult to detect clinically until they are advanced in size or stage. In patients with PNS, the sensitivity (83.33%) and specificity (25%) of PET scanning to detect tumors has been estimated to be low.<sup>[10]</sup>

In conclusion, post-menopausal and younger women who have completed their family and are diagnosed with anti-Yo antibody-mediated PCD without any substantiate features of other malignancies on non-invasive testing, AHBSO may be assumed to stabilize symptoms of PCD. Further investigations on the pathogenesis of PCD are required to identify more

effective therapies, which can stabilize or reverse the neurological symptoms.

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Dr. Isha Sood, Senior Resident, Department of Medicine, Dr. Sampurnanand Medical College, Jodhpur, Rajasthan, India

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