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# A RARE CASE OF ANTI-YO POSITIVE PARANEOPLASTIC CEREBELLAR DEGENERATION (PCD): CASE REPORT

**KEY WORDS:** Paraneoplastic cerebellar degeneration, Anti-Yo antibodies.

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**ABSTRACT**

Paraneoplastic cerebellar degeneration (PCD) is a rare entity and can precede the symptoms associated with malignancy by months or years. The most common cancers associated with PCD include Small Cell Lung Cancer, Gynecological, Breast cancers and Lymphomas. Paraneoplastic antibodies manifest as multifocal neurological disease except Anti Yo and Anti Tr antibodies which result in a pure cerebellar syndrome. The clinical presentation is typical of a pancerebellar disorder characterized by appendicular and limb ataxia with speech and gait impairment. Treatment is directed at the cause. A host of immunological therapies have been tried with uncertain efficacy. This report presents a case of paraneoplastic cerebellar degeneration secondary to an infiltrating carcinoma of both breasts diagnosed by FDG-PET scan with positive anti-Yo antibodies.

## INTRODUCTION:

Paraneoplastic cerebellar degeneration is a rare disorder that can be associated with almost any malignancy, commonest cancers include Small Cell Carcinoma of Lung, Gynecological, Breast cancers and Lymphomas (particularly Hodgkin's Disease). The cerebellum is a frequent site of paraneoplastic autoimmunity. However only two antibodies are known to cause pure cerebellar syndromes, while most others are associated with a variety of other neurological dysfunction including limbic encephalitis, opsoclonus-myoclonus, sensory neuronopathy, Lambert-Eaton Myasthenic Syndrome (LEMS), retinopathy and dermatomyositis. The neurological symptoms precede the diagnosis of cancer by months, even years.

## DESCRIPTION OF THE CASE:

Mrs SK, a 45 year old non-diabetic, non-hypertensive lady presented to the Neurology out-patients department with sudden onset vertigo, not associated with tinnitus, hearing loss, blurring of vision or change in posture or head position for 2 days. These symptoms were persistent and was followed a week later by unsteadiness on standing and during walking. She was swaying in all directions while keeping her feet together and had to stand with her feet widely spaced to maintain balance. The unsteadiness during walking worsened on attempting to climb stairs, particularly with her feet on different steps, but did not worsen when she entered a dark room or on closing her eyes. She had a tendency to fall and required support to walk. Two weeks later she developed a slurred speech where she was unable to pronounce every syllable clearly and distinctly and appeared to pause before uttering each syllable. This was followed another week later by tremulousness of the fingers of both hands, right more than left, on trying to reach for an object. The tremulousness was not present at rest. These symptoms were present for over two months before she came to our OPD and were non-progressive. There were no symptoms suggestive of cranial nerve involvement. She did not have memory impairment or behavioral disturbances, weakness of limbs, twitching of muscles, loss of sensation, diurnal variation of symptoms, bowel or bladder disturbances. There was no known exposure to drugs or toxins, no antecedent history of fever or rash, no known thyroid disorder, no history of shock-like jerky movements. She had a history of weight loss of 4 kgs in the last 3 months, but it was not associated with excessive menstrual bleeding, alteration in bowel habits, cough, blood-tinged expectoration of sputum or a breast swelling. She had no known comorbidities, was born out of a non-consanguineous marriage and did not have any family members similarly affected. She had normal appetite and sleep, was on a mixed diet and had no addictions.

## ON EXAMINATION:

Patient was conscious, oriented, had mild pallor and stable vitals. Higher mental and lobar functions were normal. Cranial nerve examination revealed bilateral horizontal gaze evoked nystagmus, with normal pursuit and saccades, normal fundus examination and normal bulbar cranial nerves. Her motor examination showed normal bulk, with mild hypotonia affecting all 4 limbs, but with normal power. Sensory examination was normal for pain, temperature and touch sensation over face, limbs and trunk, with a normal joint position, vibration and cortical sense. Cerebellar examination revealed a scanning speech, nystagmus as described above with dysmetria and intention tremor on the finger-nose, finger-finger-nose and heel-shin tests, bilateral dysdiadokokinesia, rebound phenomenon and truncal, stance and gait ataxia. Her superficial and deep tendon reflexes were preserved and plantar was bilateral flexor.

Her evaluation included a complete hemogram with ESR, which showed a Hb% of 8.4 g/dl, normal total and platelet counts with mildly raised ESR. Her fasting blood sugar, HbA1c, renal and liver functions tests, electrolytes, Vitamin B12, Vitamin B1, Vitamin E, Thyroid Function tests were all within normal limits. MRI Brain plain plus contrast was unremarkable, as was her Nerve Conduction Study. HIV serology and anti-GAD antibody tests were negative. Her CSF examination showed mild elevation in protein levels. In view of her history of weight loss, she was also evaluated for paraneoplastic causes and an extensive search was made to ascertain the etiology. She was subjected to a CT Thorax, which was normal. An ultrasound of the abdomen revealed a simple renal cyst, her peripheral blood film and CA-125 levels were normal and her PAP smear did not show any malignant cells. An ultrasound of the breast revealed multiple ill-defined hypo-echoic lesions in both breasts but was suspected to be benign in etiology. A whole body PET scan showed few irregular FDG avid solid nodular lesions in the both breasts.

She was referred to the general surgeon who carried out an USG guided tru-cut biopsy of the lesion in the right breast. Histopathological examination revealed Invasive mammary

carcinoma Nottingham histological grade 3. In view of her biopsy findings and because she had a pure cerebellar syndrome Anti Yo antibodies were sent for, which turned out to be strongly positive. A modified radical mastectomy was carried out on the right breast and a simple mastectomy was done on the left breast. She was also administered 6 cycles of chemotherapy with Adriamycin, Cyclophosphamide and 5-Fluorouracil. There was a mild improvement of her dysarthria and also her stance and gait ataxia though she still required support to walk. One month after completion of her chemotherapeutic regimen, she was given a course of Intravenous Immunoglobulin at 2g/kg body weight over a period of 5 days. She has shown further improvement of her dysarthria and can walk with the help of a walker.

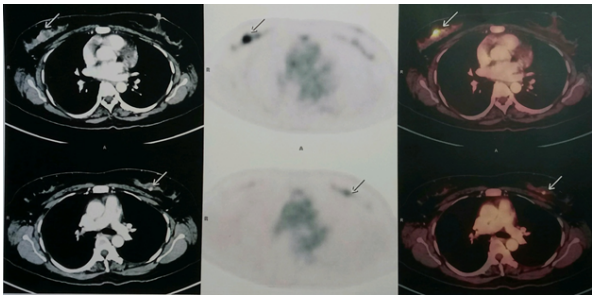

**Fig:** From (L) to (R): CT Thorax, FDG PET Scan showing FDG-avid solid nodular lesions in bilateral breasts in the retro-areolar region and Fusion PET CT images of the same. The lesions are marked by arrows.

## DISCUSSION:

The cerebellum is a common site for paraneoplastic autoimmunity. Most common among the antibodies is the Anti-Yo antibody seen in patients with breast, ovarian, endometrial or fallopian tube cancers.[1] They are directed against the cdr proteins expressed by the purkinje cells and are associated with a T cell mediated cytotoxic response against these cdr proteins.[2]

Small cell carcinomas of the lung are associated with Anti Hu antibodies which along with cerebellar dysfunction, is likely to cause multifocal neurological manifestations including limbic and brainstem encephalitis, myelitis and sensory neuronopathy. They can also express Anti P/Q type Calcium channel antibodies which with cerebellar degeneration, can cause LEMS.[3] Anti-Tr antibodies produced by Hodgkin's disease and rarely Non-Hodgkin's Lymphoma are directed against the Delta/Notch like Growth factor-related receptor (DNER) of purkinje cells.[4] These antibodies like Anti-Yo antibodies are responsible for a pure cerebellar syndrome.

Other antibodies include Anti-Ri antibodies secondary to breast, gynecological malignancies and SCLC which are responsible for opsoclonus-myoclonus and encephalitis in addition to cerebellar symptoms[5], Anti CV2/CRMP5 antibodies arising from SCLC and thymomas, cause in addition to PCD, limbic encephalitis, encephalomyelitis, chorea, peripheral neuropathy and optic neuritis and Anti Ma antibodies from germ cell tumours of the testis result in limbic, hypothalamic and brainstem encephalitis with occasional PCD.

They clinically manifest as acute onset of vertiginous symptoms, nausea, vomiting followed several days later by gait instability, truncal and appendicular ataxia, oscillopsia and dysarthria.[6] They may worsen for several weeks to months before stabilizing. Depending upon the underlying etiology, they may also have other neurological signs and symptoms, even cognitive impairment. In most patients neurological manifestations precede the cancer symptoms by weeks or months.[7]

Diagnostic testing should include a MRI of the brain which is usually normal, but may show contrast enhancement in the cerebellar folia in the acute phase and may show diffuse cerebellar atrophy later.[8] CSF shows mild pleocytosis with increase in protein count. Tests to rule out other causes including Vitamin levels, thyroid function tests, HIV and anti GAD antibodies must be carried out. A search for paraneoplastic biomarkers is not routinely done and must be carried out only if there is sufficient evidence of underlying malignancy.

Neurological outcome is usually poor, treatment should be directed at the underlying cancer.[3,7] Various immunotherapies including IV Immunoglobulins, Plasma Exchange, Corticosteroids, Azathioprine, Rituximab and Cyclophosphamide have all been tried in varying combinations.[9] One case series of 15 patients suggested an improvement in outcome if IVIG was administered within 3 months of symptom onset.[10] The type of antibodies also decide outcome, Anti Hu or Anti Yo antibodies are less likely to show improvement whereas those with Anti Tr, Anti CV2 and Anti Ri antibodies have a slightly better chance of neurological recovery.

## CONCLUSION:

Although paraneoplastic cerebellar degeneration is a known entity it is not often suspected particularly in the absence of clear-cut cancer manifestations. It is imperative that this entity is recognized early, so that appropriate efforts can be put in to ensure an early diagnosis of the underlying malignancy.

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