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A Case Report Of Paraneoplastic Cerebellar Degeneration Associated With Breast Cancer(Id- L3985)

Dr.Evangelin Blessy.G, Dr.N.V.Sundarachary, Dr.U.Veeramma, Dr.G.Rama Krishna

Abstract:
Paraneoplastic neurological syndrome encompasses several neurological disorders including paraneoplastic cerebellar degeneration (PCD) caused by an immune-mediated mechanism in patients with an underlying malignancy. We report a case of a 47 year old female paraneoplastic cerebellar degeneration with breast carcinoma. She presented with Symmetrical progressive chronic limb and gait ataxia of cerebellar type. Relevant investigations including genetic analysis to exclude primary cerebellar pathology were done which didnt give any clue. Systemic examination revealed hard right breast mass which was subsequently confirmed as breast carcinoma and paraneoplastic cerebellar dysfunction was confirmed by positive anti–yo antibodies in the serum. So its important to include to paraneoplastic cerebellar dysfuntion as an important differential diagnosis in subacute to chronic cerebellar dysfuntion as it may guide us to find underlying malignancies.

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I. Introduction:

Paraneoplastic cerebellar degeneration (PCD) is an uncommon disorder that can be associated with any cancer; the most commonly associated are lung cancer (particularly small cell lung cancer [SCLC]), gynecologic and breast cancer, and lymphoma (particularly Hodgkin disease [HD]) . There are nearly thirty different antibodies (Abs) associated with this condition.[1] Between 90% and 98% of patients with cerebellar ataxia and anti-Yo Abs have a cancer detected. The neurologic symptoms frequently precede or coincide with the diagnosis of cancer. Only about 1% of all persons thought to have a paraneoplastic syndrome turn out to have antibodies to neurons (Pittock et al, 2004).

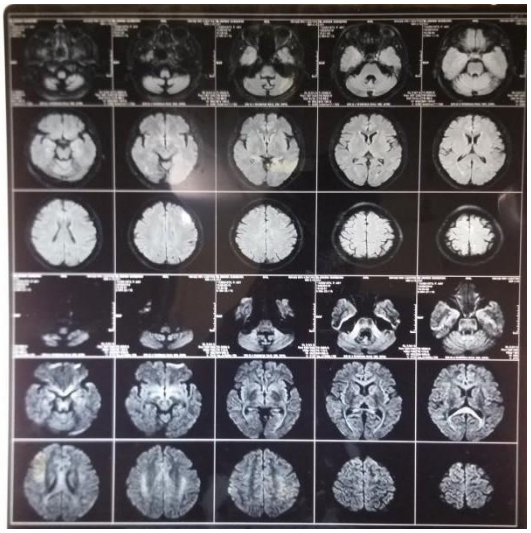
In this paper, we report a case of a 47-year-old woman who presented with symptoms of PCD and was subsequently diagnosed with a breast carcinoma.

II. Case Report:

A 47 year old female presented with speech disturbances and gait disturbances of 10 months duration. The first symptom was slurred speech noticed by her children and they were describing it as speech of an alcoholic. Very soon, she developed unsteadiness while walking with swaying to both sides. There was history of tremulousness of hands while reaching objects. No history of vertigo. These symptoms initially progressed for about 8 months, so she visited various hospitals. By the time she came to us, there was no swaying while walking, no tremulousness of hands but speech disturbances didn't improve. She was diagnosed as hypothyroid 6 months after onset of initial symptoms and is on 25 micrograms of levothyroxine. She is not an alcoholic and her family history is unremarkable. Nervous system examination revealed scanning explosive speech with impaired tandem walking, without limb and gait ataxia and without any motor, sensory, autonomic, cranial nerve abnormalities.

Our initial diagnosis was a hereditary ataxia of pure cerebellar type. Her routine blood tests were within normal limits. TSH was elevated with normal T3 and T4. There was mild cerebellar atrophy on MRI. Genetic analysis for SCA 1,2,3,6,7 showed no abnormal CAG repeats. With a negative genetic analysis, and with patient reporting improvement of symptoms, we have revised our diagnosis and considered paraneoplastic etiology. Systemic examination also showed hard right breast mass which we missed in our initial examination .There was evidence of hyperdense lesion in right breast on mammogram. FNAC and Biopsy were in favour invasive ductal carcinoma of histological grade 3.We have investigated for serum paraneoplastic profile which showed positive serum anti YO antibodies. U/S abdomen and CXR findings were unremarkable. Bone scan showed no evidence of any radiotracer uptake. So our final diagnosis is Paraneoplastic cerebellar dysfunction with stage 3 (T3N1M0) carcinoma right breast. We treated her with IV steroids but there was not much improvement in her symptoms.

Patient completed 4 cycles of chemotherapy and is currently awaiting breast surgery.



NAME: M.JNANA SUNDARI. AGE& SEX :46Y/F

REF.BY: DR. G.V.RAMANA RAO. MD, DPM. DATE: 13-May-19.

MRI: BRAIN (PLAIN)

MRI of Brain has been done by taking multiecho, multiplanar technique.

- Prominence of cerebellar folia.
- Rest of the posterior fossa structures and fourth ventricle are normal in signal intensities.
- Neuroparenchyma is normal in signal intensities.
- Brainstem and perimesencephalic cisterns are normal.
- Supratentorial ventricular system is normal.
- No evidence of ICSOL.
- No evidence of infarct / haemorrhage.
- No evidence of extra axial collections.

IMPRESSION: -

MILD CEREBELLAR ATROPHY.

HISTOPATHOLOGY REPORT

PATIENT NAME: N. Gnana Sundari AGE /SEX: 47yrs/ F LAB NUMBER: 291/19
REFERRING DOCTOR: Dr.Hemanth, Surgical Oncologist
RECEIVING DATE: 5.08.2019 REPORTING DATE: 7.08.2019

BIOPSY REPORT

NATURE OF SPECIMEN: Trucut biopsy from breast lump

GROSS EXAMINATION: Received multiple linear gray white tissue bits each measuring 0.4 cm in length (All embedded)

MICROSCOPIC EXAMINATION:

Sections studied show breast tissue with a tiny focus of an infiltrating malignant epithelial tumor in which the tumor cells are arranged in trabecular patterns and with tubules comprising to less than 10% of the tumor. The individual tumor cells exhibit moderate pleomorphism with increased N:C ratio, scant to moderate eosinophilic cytoplasm and hyperchromatic nuclei with inconspicuous nucleoli. The mitotic activity is not discernable. The stroma is desmoplastic with pockets of chronic inflammatory cell collections. The adjacent ducts show atypical ductal hyperplasia.

Opinion: Histological appearances are suggestive of

- An invasive carcinoma of breast (Invasive ductal carcinoma), no special type
- Histological Grade (Scarff-Bloom-Richardson System - Nottingham Modification) : G2 (3+2+1=6)

Medical Laboratory Report

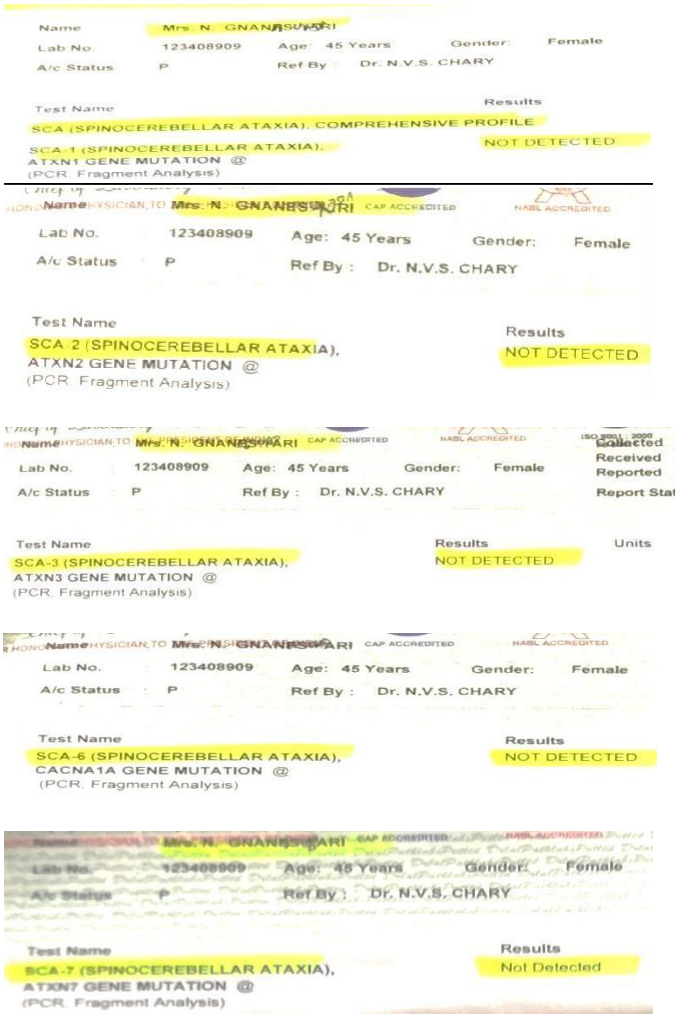
Mrs. JNANA SUNDARI N
PID NO: P21190018086
Age: 47 Year(s) Sex: Female

Reference: Dr.SUNDHARACHARY N V MD DM(NEU),,
Sample Collected At:
ARC-DJ SPECIALITY LAB
22-13-35, NEAR NUKALAMMA TEMPLE, LALAPETA, GUNTUR ,VIJAYAWADA,ANDHRA PRADESH,522003
522003

VID: 21190118457
Registered On: 24/07/2019 08:45 AM
Collected On: 24/07/2019 8:45AM
Reported On: 24/07/2019 06:56 PM

Investigation	Observed Value	Biological Reference Interval
Neuronal Antibody Profile-3 (Serum,Immunoblot)		
Anti - Amphiphysin	Negative	Negative
Anti - CV2/CRMP5	Negative	Negative
Anti - PNMA2 (Ma 2 / Ta)	Negative	Negative
Anti - Ri/ANNA - 2	Negative	Negative
Anti - Yo/PCA - 1	**Positive**	Negative
Anti - Hu/ ANNA - 1	Negative	Negative
Anti Recoverin	Negative	Negative
Anti SOX1	Negative	Negative
Anti Titin	Negative	Negative
Anti Zic4	Negative	Negative
Anti GAD65	Negative	Negative
Anti Tr(DNER)	Negative	Negative

Medical Remarks: Kindly correlate clinically



III. Discussion

Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system . They are caused by mechanisms other than metastasis or by any of the complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of patients the neurologic symptoms precede the cancer diagnosis. Clinically disabling PNDs occur in 0.5–1% of all cancer patients.

PNDs are mediated by immune responses triggered by neuronal proteins (onconeuronal antigens) expressed by tumors. In PNDs of the central nervous system (CNS), many antibody-associated immune responses have been identified. These antibodies react with the patient's tumor, and their detection in serum or cerebrospinal fluid (CSF) usually predicts the presence of cancer. When the antigens are intracellular, most syndromes are associated with extensive infiltrates of CD4+ and CD8+ T cells, microglial activation, gliosis, and variable neuronal loss. T cell—mediated cytotoxicity may contribute directly to cell death in these PNDs. Thus both humoral and cellular immune mechanisms participate in the pathogenesis of many PNDs. This complex immunopathogenesis may underlie the resistance of many of these conditions to therapy. In contrast to the disorders associated with immune responses against intracellular antigens, those associated with antibodies to antigens expressed on the neuronal cell surface of the CNS or at neuromuscular synapses are more responsive to immunotherapy . These disorders occur with and without a cancer association, and there is increasing evidence that they are mediated by the antibodies.

In Paraneoplastic cerebellar degeneration (PCD) , the cerebellar symptoms have a subacute onset and steady progression over a period of weeks to months; in more than half the cases, the cerebellar signs are recognized before those of the associated neoplasm. Symmetrical ataxia of gait and limbs—affecting arms and legs more or less equally—dysarthria, and nystagmus are the usual manifestations; some have vertigo. Striking in fully developed cases has been the severity of the ataxia, matched by few other diseases. Occasionally, myoclonus and opsoclonus or a fast-frequency myoclonic tremor may be associated ("dancing eyes– dancing feet," as noted below). In addition, there are quite often symptoms and signs not strictly cerebellar in nature,

notably diplopia, vertigo, Babinski signs (common in our cases), sensorineural hearing loss, disorders of ocular motility, and alteration of affect and mentation—findings that serve to distinguish paraneoplastic from alcoholic and other varieties of cerebellar degeneration. SCLC, cancer of the breast and ovary, and Hodgkin lymphoma are the most commonly associated tumors.

Anti-Yo is the most frequent and well-characterized antibody associated with PCD. The antibody is usually associated with breast or gynecologic tumors (Peterson et al., 1992). Anti- Yo antibodies have been identified in a few male patients with PCD and cancer of the salivary gland, lung, and esophagus. Some patients with predominant truncal ataxia, opsoclonus, and other ocular movement abnormalities may harbor an antibody called anti-Ri. In such cases, the tumor is usually a breast carcinoma or, less frequently, gynecological cancer, bladder cancer, or SCLC (Luque et al., 1991). These patients may also develop dementia, mixed peripheral neuropathy, axial rigidity, myoclonus, brainstem encephalitis, and laryngeal spasms (Pittock et al., 2010).

In patients with SCLC the development of PCD may be the presenting symptom of paraneoplastic encephalomyelitis (PEM), in which case other areas of the nervous system become involved and anti-Hu or anti-CV2/CRMP5 antibodies are usually identified . Patients with symptoms restricted to cerebellar dysfunction and negative anti-Hu antibodies often harbor voltage-gated calcium channel (VGCC) antibodies (Graus et al., 2002). Patients with PCD associated with Hodgkin disease develop Tr antibodies (Graus et al., 1997); these antibodies are directed against Delta/Notch-like epidermal growth factor-related receptor (DNER) (de Graaff et al., 2012). The neurological disorder may develop before or after the diagnosis of the lymphoma, sometimes heralding tumor recurrence. Sox1 antibodies are found in about 50% of patients with PCD and SCLC but are not found when PCD is associated with other cancers.

The CSF may show a mild pleocytosis (up to 60 cells/mm^3 in a few of our patients) and increased protein, or it may be entirely normal. Early in the course of the disease, CT scanning and MRI show no abnormality, but after a few months, atrophy of the brainstem and cerebellum may appear.

Pathologically, there are diffuse degenerative changes of the cerebellar cortex and deep cerebellar nuclei. Purkinje cells are affected prominently and all parts of the cerebellar cortex are involved. Degenerative changes in the spinal cord, involving the posterior columns and spinocerebellar tracts, have been found rarely. The cerebellar neuronal degeneration is frequently associated with perivascular and meningeal clusters of inflammatory cells

Little can be done to modify the cerebellar symptoms, although there are on record several cases in which there was a partial or complete remission of symptoms after removal of the primary tumor (Paone and Jeyasingham). Furthermore, in some cases associated with Hodgkin disease, there has been spontaneous improvement of the cerebellar symptoms.

Several single-case reports describe patients with PCD who improved after treatment of the tumor, plasma exchange, intravenous immunoglobulin (IVIg), rituximab, or

immunosuppression with cyclophosphamide or corticosteroids (Blaes et al., 1999; Shams'ili et al., 2006). However, because of early, irreversible neuronal loss most patients with PCD do not improve with any of these treatments (Vedeler et al., 2006).

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