Redeemable “Progressive Supranuclear Palsy” Like Paraneoplastic Presentation in Carcinoma Breast

Sir,
Parkinsonism, typical or atypical, is a rare entity among paraneoplastic neurological syndromes (PNS).\[1\] Though they often antedate, PNS can also occur any time during the course of a malignancy or subsequent therapy. We report a case of rapidly worsening progressive supranuclear palsy (PSP) like PNS presentation in a patient with ductal breast carcinoma, who showed excellent response to immunomodulatory therapy.

A 62-year-old woman diagnosed with biopsy-proven ductal breast carcinoma, stage 4 (with skin and bone metastasis) was initiated on palliative chemotherapy with docetaxel and trastuzumab. Twelve months later, she developed a progressively slow gait along with generalized stiffness over the ensuing 4 months followed by hypophonia and tremulousness. She became dependent for all her activities of daily living and after an unprovoked fall was admitted. On examination, she had hypomimia, hypophonia, slow saccades with vertical restriction (downgaze > upgaze), axial and appendicular rigidity (grade 3), bradykinesia, normal power, with preserved normal deep tendon reflexes. She had marked gait initiation difficulty, festinant steps, and significant postural instability suggestive of secondary atypical parkinsonism, PSP like phenotype [Video 1 segment 1].

Her routine blood investigations were normal. Magnetic resonance imaging (MRI) brain showed no midbrain atrophy or signal changes in basal ganglia and there was no evidence of brain metastasis on contrast [Figure 1a-d]. Cerebrospinal fluid (CSF) analysis was normal with negative malignant cytology. Serum and CSF paraneoplastic antibody profile (including antibodies to amphiphysin, PNMA2, CV2, Ri, Yo, Hu, SOX1, recoverin, titin, Zic 4, GAD 65, Tr, IgLON, CRMP-5 antigens) and anti-thyroid peroxidase antibodies were negative. 18F-DOPAPET (18 fluoro-3,4-dihydroxyphenylalanine positron emission tomography) scan was normal ensuring the presynaptic dopaminergic integrity.

She was started on levodopa with dosage up to 600 mg/day to which there was hardly a response. Subsequently, she was given intravenous methylprednisolone (IVMP) pulses 1 g for 5 days. After the first dose of IVMP itself, there was an improvement in the velocity of vertical saccades and parkinsonism, and with further doses, she made a remarkable improvement [Video 1 segment 2 and 3]. She was later continued on monthly pulses of IVMP, and she became ambulant independently giving a meaningful survival extension with a good quality of life. On her last follow-up 18 months later, she had developed spinal metastasis and is on palliative care.
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Table 1: PSP phenotype like PNS

| Phenotype                                                                 | Number of patients | Malignancy                  | Antibody | Response to immunomodulatory treatment                | Response to Levodopa | Imaging (MRI/CT brain)                      | Functional brain imaging | Reference |
|---------------------------------------------------------------------------|--------------------|-----------------------------|----------|------------------------------------------------------|----------------------|---------------------------------------------|--------------------------|-----------|
| Marked bradykinesia, axial rigidity, rest and action tremors of upper limbs, downward gaze palsy, postural instability, dysarthria | 1                  | Breast carcinoma            | Anti-Ri   | No response to IVMP, tumorectomy, chemotherapy      | NA                   | MRI-nonspecific T2 white matter hyperintensities in caudate, putamen without midbrain atrophy | NA                       | 3         |
| PSP-rapidly progressive (vertical supranuclear gaze palsy, truncal predominant generalized rigidity, saccadic initiation delay, facial hypomimia, dysarthria) | 1                  | B-cell lymphoma             | None     | NA                                                   | +                    | MRI - Symmetric white matter small vessel ischemic changes | NA                       | 4         |
| PSP-rapidly progressive (dysarthria, vertical supranuclear gaze palsy, bradykinesia, axial rigidity, postural instability) | 1                  | Bronchial adenocarcinoma    | None     | NA                                                   | NA                   | CT-mild cerebral atrophy                    | NA                       | 5         |
| PSP-rapidly progressive (vertical supranuclear gaze palsy, bradykinesia, axial rigidity, postural instability, frontal lobe dysfunction) | 1                  | small cell lung carcinoma   | CRMP-5   | Responded to steroids, IVIG, chemotherapy            | Nil                  | MRI - Symmetric T2 hyperintensities in bilateral basal ganglia | NA                       | 8         |
| PSP-rapidly progressive (hypomimia, frozen eyes, axial rigidity, symmetric bradykinesia, severe postural instability) | 1                  | Breast carcinoma            | None     | ++++                                                 | Nil                  | MRI - Normal (F-DOPA PET)                   | Current report           |           |

IVMP - intravenous methylprednisolone; IVIG - intravenous immunoglobulin; NA - not available; PLX - plasmapheresis; += modest benefit; ++++ = remarkable benefit

The fact that our patient developed new parkinsonian symptoms favoring PSP within few months of the cancer diagnosis favored PNS. The rapid pace of progression of symptoms, within a span of 4 months, with significant postural instability and gait difficulty were red herrings even for prototype PSP. The F-DOPA PET being normal further clinched the possibility of a PNS by ruling out a degenerative cause for parkinsonism as it is a good tool for assessing presynaptic dopaminergic integrity. Her structural imaging of the brain was negative and clinicoimaging discordance frequently occurs in PNS. All these features and the lack of evidence of an alternative etiology argued in favor of an immune-mediated PNS. However as no onconeural antibodies were detected, she fulfilled the criteria for possible PNS.[1] Though CSF analysis demonstrated no inflammatory process, her clinical condition readily responded to immunomodulatory therapy again favoring an underlying immune-mediated mechanism.

Figure 1: MRI showing no midbrain atrophy or signal changes in the basal ganglia on axial T2 (a, b) and sagittal FLAIR (c) images. There was no evidence of brain metastasis on contrast imaging (d)
PSP like PNS occurs due to aberrant expression of tumoral antigens which are recognized by the host immune system as foreign, leading to humoral and T-cell immune-mediated attack on either cell surface or synaptic antigens.[3] The differential diagnosis is chemotherapeutic drug-induced atypical parkinsonism. The drugs which have been implicated are cytotoxic arabinoside, cyclophosphamide, etoposide, methotrexate, mitoxantrone, 5-fluorouracil, adriamycin, vincristine, gemcitabine, carboplatin, paclitaxel, and busulfan by a presynaptic nigrostriatal insult. However, the majority of these reported cases had a brisk improvement on withdrawal of the offending drugs and initiation of L-dopa therapy.[3] The appearance of symptoms after a year of chemotherapy and the absence of improvement on the initiation of levodopa therapy suggests that the etiology here was not a drug-induced adverse effect. The most remarkable response in our patient was noticed with IVMP therapy.

Previously only four reports of a PSP like PNS have been described [Table 1]. Rapidly worsening PSP have been reported in association with breast carcinoma and positive anti-Ri antibodies.[3] This patient had no functional imaging, did not respond to tumorectomy, immunotherapy, or levodopa, ultimately succumbing to her illness 8 months later.[3] B-cell lymphoma[4] and bronchial carcinoma[5] are the malignancies other than breast carcinoma though neither had any paraneoplastic antibody. Anti-Ri antibodies have been described in 2 patients with parkinsonism and breast cancer among 28 patients with paraneoplastic syndromes[6] making it the most commonly detected antibody in such a scenario and it has been associated with more severe neurological impairment. A review of anti-CRMP5 mediated PNS of 116 patients showed 3 patients to have parkinsonism.[7] A case of anti-CRMP5 mediated PSP like PNS associated with small cell lung carcinoma which responded to immunomodulatory therapy, like our patient has been documented.[8] However, this patient showed symmetric T2 hyperintensities in bilateral basal ganglia which cleared after 6 months of immunomodulation,[9] while our MRI was normal. A normal CSF study is not against a paraneoplastic etiology though an elevated CSF protein is occasionally seen.[4,5] Though CRMP-5, Ri, Ma2, and IgLON antibodies are most often associated with typical and atypical parkinsonian PNS manifestations, negative markers as in our case do not exclude it. Antibodies against intracellular cytoplasmic/nuclear antigens (Ri, CRMP5/CV2, Ma2) are often not considered pathogenic, as their target is inaccessible in vivo. Existing evidence suggests that autoreactive T cells are mediating the disease process, characterized by lymphocytic infiltration and damage of neuronal structures.[9] The PNS mediated by these antibodies have a variable response to immunomodulatory therapy which may not be as robust as when compared to antibodies against neuronal surface antigen (like Caspr2, DPPX, D2R, GABAAR, GABABR, GlyR, LGI1, and NMDAR) where the chief carnage is caused by the antibody.

Our case highlights the fact that rapidly worsening PSP in the background of ductal breast carcinoma may suggest a PNS. Functional imaging helps to rule out neurodegenerative etiology in the elderly. A therapeutic challenge with immunomodulatory treatment along with cancer management augurs best and gives meaningful survival extension with a good quality of life for such patients as confirmatory serological markers are often negative.

### Compliance with ethical standards

Ethical approval from the institutional review board was not required for this study.

### Informed consent

Formal consent was taken from the patient.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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