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A case of Carcinoma Breast with Cerebellar Dysfunction - Paraneoplastic Syndrome

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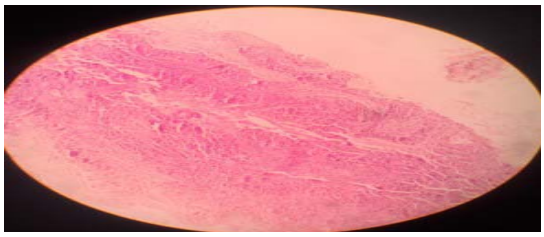
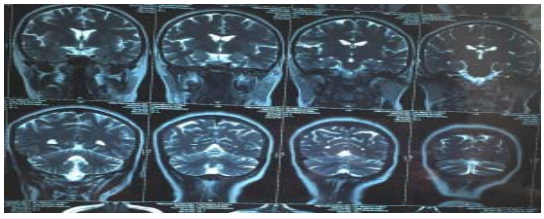
Abstract : Paraneoplastic Syndrome, as Paraneoplastic cerebellar degeneration (PCN), in carcinoma breast is a rare entity due to autoimmune response. We report a case report of 52 year female with carcinoma breast along with symptoms and signs of cerebellar dysfunction which on further evaluation is found to be anti-YO autoantibody positive paraneoplastic syndrome. Inspite of surgical and chemotherapy patients neurological condition worsened indicating the poor prognosis of the condition.

Keyword :PCN- Paraneoplastic Cerebellar Degeneration, IDC- Infiltrating Ductal Carcinoma, CSFCerebrospinal fluid, Anti YO- anti YO autoantibodies, ONA- Onconeural antibody



Histology



MRI brain

Introduction

Paraneoplastic syndrome which is a rare entity is believed to be initiated by an autoimmune system in response to the underlying malignancy (1). Carcinoma breast can be associated with paraneoplastic syndrome in 1-3% (2). Association between breast carcinoma and cerebellar dysfuntion as a paraneoplastic syndrome is a known entity yet a handful of cases have been reported. We present such an association.

Case Presentation

A 52 year female with no past medical history or prolonged drug intake came with complaints of lump in left breast for the past 8 months which is progressive sudden onset of difficulty in walking for the past week along with slurring of speech, giddiness, which was progressive. There was no disturbance in bowel or bladder habits or any symptoms of focal or profound neurological deficit. On examination patient, the breast lump was clinically consistent with carcinoma present in the upper outer and central quadrant and was clinically Stage IIIa(T3N1M0). had nystagmus, dysarthria, dysdiadokinesia, past pointing, pendullar knee jerk suggestive of cerebellar dysfunction. Biopsy of the breast revealed Infiltrating Ductal Carcinoma -Not Otherwise Specified- Grade II with ER Negative; PR weakly positive and Her-2neu Strongly positive (figure 3). Metastatic workup including, USG abdomen, CTabdomen & chest, Bone scan all turned out negative for metastasis. MRI brain was taken to rule out metastasis which showed cerebellar atrophy with no evidence of metastasis (figure 1) . CSF analysis was done which was normal with no abnormalities. Anti YO autoantibodies was sort which was strongly positive. As per our Tumor board policy patient received 4 cycles of Chemotherapy, as neoadjuvant therapy and the lump responded well to treatment and almost disappeared.

The chemo regimen being 5-FU,Adriamycin and cyclophosphamide. Patient was put on a course of steroids. But the neurological symptoms progressed. Later the patient was operated, modified radical mastectomy was done (figure 2). Post-op pathological report came as IDC-NOS in a small area. Yet the patient's neurological symptoms progressed and became wheel chair bound.

Review of Literature

Neurological manifestations of cancer are common, disabling, and often multifactorial. The concept that malignant disease can cause damage to the nervous system above and beyond that

caused by direct or metastatic infiltration is familiar to all clinicians looking after cancer patients. These ‘‘remote effects’’ or paraneoplastic manifestations of cancer include metabolic and endocrine syndromes such as hypercalcaemia, and the syndrome of inappropriate ADH (antidiuretic hormone) secretion. Paraneoplastic neurological disorders (PNDs) are remote effects of systemic malignancies that affect the nervous system. The term PND is reserved for those disorders that are caused by an autoimmune response directed against antigens common to the tumour and nerve cells.

Incidence

The incidence of PND depends on the stringency of the criteria used for the diagnosis. In the first systematic study of PND, Croft and Wilkinson coined the term ‘‘carcinomatous neuromyopathy’’ to describe patients with cancer who had neuromuscular abnormalities. They found that 4% of women with breast cancer, 16% of men with lung cancer, and 6.6% of patients with all cancers had evidence of a PND compared with 1–2% of age matched controls.

Pathogenesis

Several lines of evidence support the designation of PNDs as autoimmune disorders of the nervous system. The targets for most of the paraneoplastic antibodies are so-called ‘onconeuronal antigens’, proteins shared by both tumor cells and neural tissue constituents. Furthermore, pathological studies in PND cases (largely limbic encephalitis and cerebellar degeneration) have shown infiltration of the tumor as well as target nervous tissue by inflammatory cells [Rosenblum, 1993]. The inflammatory cells consist of perivascular accumulations of CD4+ T cells and B cells, as well as parenchymal CD8+ T cells and microglia [Bernal *et al.* 2002; Jean *et al.* 1994]. Both T cell and antibody-mediated processes have been implicated. **Albert and co-workers showed that activated T cells from the CSF of a patient with paraneoplastic cerebellar degeneration could lyse target cells presenting Yo antigen *in vitro* [Albert *et al.* 1998]**. Analysis of CSF frequently reveals mild lymphocytic pleocytosis, intrathecal synthesis of IgG and oligoclonal bands [Furneaux *et al.* 1990]. Paraneoplastic antibodies may be detected in the CSF, and in some cases, there is evidence of intrathecal synthesis of these antibodies. The relative contributions of cell-mediated and humoral mechanisms to neural damage in PNDs are not clear and probably differ among different syndromes. In general, antibodies are more likely to play an important pathophysiological role in syndromes associated with antibodies against cell surface antigens [Darnell and Posner, 2003].

Diagnosis, Management and Prognosis

As far as diagnosis of PCN in Carcinoma breast is concerned, it is essential to rule-out metastasis to the brain after confirming the diagnosis of carcinoma itself. Drug and other neurological or autoimmune diseases should be ruled-out too. MRI brain helps in ruling out the metastasis, even then CSF analysis is required to rule out micro-metastasis. MRI brain will be normal in most of the cases and will show evidence of atrophy or degeneration in advanced cases. Measurement of antibodies will be helpful in diagnosing PCD. Antibodies which are associated with PCD are Yo, Hu, Ri antibodies among which Yo is found to be commonly elevated. Though 40% of cases will be antibody negative. Antibody negative cases are found to be comparatively good in prognosis. Management of the breast cancer is as with the one’s without PCD. Various modalities have been tried to stop or improve the degeneration process including Plasmapheresis, steroids, chemotherapy, targeted antibody therapy. But none has so far given any promising results. Prognosis of patients with PCN who are antibody positive is poor compared to those with antibody negative patients.

Discussion

Association between breast malignancy and cerebellar degeneration, paraneoplastic syndrome, was first identified in 1938 and the syndrome was fully described by Brain in 1951 (3). It is because of the autoimmune response, with onco-neural antibodies (ONA) targeted against the onco-neural antigens shared by tumor cells and nervous tissue. Anti-Yo antibody is the most common ONA associated with PCD followed by anti-Hu, anti-Tr and anti-Ri (4, 5). Cdr2, also known as Purkinje neuronal protein, is expressed on cells within the cerebellum and is similar to the tumour antigen that is expressed in breast and ovarian tumours for anti-Yo antibody (6). Cross-reaction between the ONAs and normal proteins occur, resulting in abnormal immune- mediated responses that cause cerebellar injury and neuronal dysfunction. The feature of cerebellar ataxia due to PCD in carcinoma breast usually precedes the tumor lump in 60% of cases(7). But in our case the lump preceded the symptoms of cerebellar dysfunction. Confirmation of PCD requires ruling out metastasis by imaging and CSF analysis and antibody level evaluation. MRI brain in early stages will mostly be normal and in advanced stages may Show cerebellar atrophy.(8,9). This atrophic changes was seen in our patient. CSF analysis in majority of PCD patients shows lymphocytic pleocytosis and elevated protein level(10).

In our patient the CSF analysis showed no abnormality. As previously mentioned Anti YO levels will be detected in PCD which will be Absent in otherwise normal individual. It has been quoted that 40% of PCD Presents with negative antibody status(11). It appears negative antibody in PCN is a good prognostic feature. In our patient the antibody level was strongly positive and the patients status deteriorated inspite of measures. This was in accordance with some of the previous literature(12). Imaging modalities of brain usually MRI will be normal in patients with PCD though patients ith advanced disease may show features of cerebellar degeneration or atrophy but the main aim is rule out metastasis to the brain. Clinical progression is variable with median survival, as quoted in some studies, is about 100 months for carcinoma breast with PCD(13). The patient in our report is more in line with the literature. The patients neurological symptoms progressed inspite of chemotherapy, steroids and surgical removal of the initiating tumor and became wheelchair bound. Various lines of treatment including plasmapheresis, immunoglobulin, have been used. The roles of these treatments are yet questionable with poor outcomes in antibody positive PCD patients.

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