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Case Report

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PARANEOPLASIC NEUROLOGICAL SYNDROMES IN BREAST CANCER: A CASE REPORT AND LITTERATURE REVIEW

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ABSTRACT

Background: Paraneoplastic neurological syndromes are rare. Their precise pathophysiologic mechanisms remain to be defined. They may develop at any point in the course of breast cancer, even preceding the formal diagnosis and can be quite debilitating when they occur. ***Case report:*** We present the case of a 38 year old woman with progressive worsening paresthesia in the upper limbs and walking difficulties. Extensive workup for etiology was negative. After 12 months of follow up and reevaluation, the identification of anti-amphisine antibodies led to the discovery of breast cancer. ***Conclusion:*** Patients with onconeural antibodies and neurological symptoms should be investigated for cancer thoroughly.

KEYWORDS: *Breast cancer, Paraneoplasic syndrome, Chemotherapie, Radiotherapy.*

ABREVIATIONS

PNS: Paraneoplastic neurological syndrome; MRI: Magnetic resonance imaging; EEG: Electroencephalogram.

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are defined as disorders of the nervous system that are due to a neoplasm but exclude tumor infiltration, compression, or metastasis.[1] These syndromes are rare accounting for less than 1% of patients with cancer.[2] The precise pathophysiologic mechanisms remain to be defined, although a proportion are thought to be immune mediated, involving the production of antibodies against neuronal surface antigens and antibodies against neuronal intracellular structures.[3, 4] Although PNS are well described in patients with breast cancer, the true incidence of these entities is largely unknown.[5] They may develop at any point in the course of breast cancer, even preceding the formal diagnosis in some cases. Various forms of neurological syndromes associated with breast cancer have been identified and they can be quite debilitating when they occur.[6] The presence of onconeural antibodies is very helpful to the diagnosis since some onconeural antibodies are usually associated with specific PNS and tumours.[7] We report the case of a 38-year-old woman with 12 months history of a walking disorder with positivity of anti-amphisine antibodies and eventual discovery of breast cancer. Relevant literature on PNS is also reviewed.

CASE REPORT

A 38-year-old woman with no family history suggestive of genital cancers or other malignancies experienced progressively worsening paresthesia in the upper limbs and walking difficulties and was admitted in the department of neurology. Magnetic resonance imaging (MRI) of the brain and electroencephalogram (EEG) were unremarkable and the patient was discharged.

Since the above investigations did not provide yield a diagnosis, she was readmitted again to be further evaluated after a follow up of 8 months. The patient was noted to have horizontal diplopia. Neurological examination found a pyramidal syndrome of the lower limbs, absent tendon reflexes in the four limbs, nystagmus and a posterior cordonal syndrome. Extensive workup for etiology was negative including lyme and syphilis and human immunodeficiency virus (HIV) serology. A specific determination of auto neuronal antibodies was made and came positive for anti – amphysine antibodies. The presence of these antibodies raised a high suspicion of a gynecologic cancer and the patient was referred to the gynecology department. Clinical gynecological examination found a left sided 3 cm axillary lymph node confirmed by breast imaging that revealed a lower outer quadrant mass of the left breast measuring 10 X 8 mm with axillary adenopathy compatible with malignancy and nodal metastasis classified as ACR 4. Immunohistochemistry was in favor of breast carcinoma: hormone receptors were strongly positive, Her2eu was negative and KI67 was 1% (Luminal A). A total body CT was than performed and was unremarkable. Lympectomy after preoperative

localization was decided and the the histopathological examination found that the resected specimen was exclusively formed by lymphatic nodal tissue. Out of 21 dissected lymph nodes, three were positive for carcinomatous metastatasis. The patient had post-operative mammary MRI that did not scho residual disease.

A couple of months later, the patient required a wheelchair for moving and a_spinal and cerebral MRI was performed and revealed a suspicious lesion in the right postero-lateral corner of the D10 vertebra but did not explain the clinical presentation according to neuro-surgury physicians. Scintigraphy was then performed and showed a focal hyperfixation in the humeral head and D10.

The patient subsequently received adjuvant chemotherapy including 4 cycles of FEC 100 and 4 cycles of docetaxel. She also received radiotherapy at the level of the D9 to D11 vertebra with a total dose of 30 Gy in 10 fractions (3 Gy/fraction) over 10 days. A locoregional radiotherapy mammary gland was also performed with a total dose of 66.6 Gy given in 37 fractions (1.8Gy/ fraction, 5 fractions /week). The patient have been under Zometa for two years, and have been receiving endocrine therapy (tamoxifene) for a year.

Up to the last follow up in december 2016, there were no signs of tumor progression. The patient was still tetraplegic and suffering from hyperesthesia in the four limps.

DISCUSSION

Paraneoplastic neurological syndromes are disorders of the nervous system, which are associated with cancer but are not caused by the growth of a tumor itself or by metastasis to the nervous system; nor are they a result of non-metastatic complications such as metabolic, secondary infectious, ischemic, or nutritional disorders or from side effects of antitumor therapy.[8] Paraneoplastic reactions can affect both peripheral and central nervous systems.[9]

These syndromes are hypothesized to be triggered by an abnormal autoimmune system response to an underlying malignancy or by humoral factors expressed by tumor cells and are often associated with onconeural antibodies, which are highly specific markers of underlying malignancy. The targets of the antibodies in PNS are tumor antigens that are normally expressed by neurones alone. Whereas the immune response elicited by the onconeural antigens may be beneficial by keeping the tumor in check, it may also gain access to the nervous system and cause severe neuronal damage.[10, 11]

PNSs are rare, affecting less than 1% of patients with cancer[2] although they are more frequent in association with specific malignancies. PNSs develop in about 3% to 5% of patients with small-cell lung cancer (SCLC), 15% to 20% of patients with thymoma, and 3% to 10% with B-cell lymphoma or plasmacytoma.[12] Gynecologic and breast carcinomas are, after small cell lung cancer, the group of solid tumors most frequently associated with PNSs.[13]

These syndromes have been reported in breast cancer as early as 1968.[6] While breast malignancy commonly presents as a breast lump or a suspicious radiological finding, 1–3% have non-metastatic-related paraneoplastic manifestations.[14] There are various forms of neurological syndromes associated with breast cancer, each distinguished by their symptom profile. Currently, breast cancer related neurologic paraneoplastic syndromes include sensory and motor-type neuropathies, paraneoplastic cerebellar degeneration, opsiclonus–myoclonus syndrome, stiff person syndrome, enchephalomyelitis (including limbic encephalopathy) and paraneoplastic retinopathy.[6] Other rare PNS associated with breast exist, including amylotrophic lateral sclerosis, rippling muscle disease, isolated myelopathy, Lambert–Eaton myasthenic syndrome and optic neuritis.[5] *Rojas-Marcos* et al[13] confirm that cerebral degeneration is the most frequent PNS in patients with breast or gynecologic tumors. Our patient presented with progressively worsening paresthesia in the upper limbs and walking difficulties and ended up in a wheelchair, she also developed horizontal diplopia. At neurological examination she had a pyramidal syndrome of the lower limbs, absent tendon reflexes in the for limbs, nystagmus and a posterior cordonal syndrome.

Neurological syndromes frequently precede the clinical manifestation of a tumor by months. Peterson[15] studied 55 cases of paraneoplastic cerebellar syndromes with antibody anti-Yo and found that neurological signs preceded the discovery of cancer in 65% of cases, with a delay of up to 15 months. In a series about 30 patients, Rojas[16] noted that the paraneoplastic cerebellar syndrome precedes the diagnosis of the tumor in 63% of cases, with an average delay of five months up to 13 months. Our patient had a similar course. Symptoms started 12 months before the diagnosis of the breast tumor.

Therefore, detection of onconeuronal antibodies may be helpful in diagnosing a potentially debilitating neurologic syndrome. Well-characterized onconeural antibodies that are associated with cancer and PNS include antibodies against the Hu, Yo, CRMP5, amphiphysin, Ri and Ma2 proteins. Some onconeural antibodies are usually associated with specific PNS and tumors and they may direct the search for an underlying neoplasm.[17]

Onconeural antibodies that are associated with breast cancer include cancer anti YO, anti Ri, and anti amphysine antibodies.[1] The presence of these anti amphysine antibodies raised a high suspicion of a

gynecologic cancer in our patient and led to the discovery of breast cancer.

Of the paraneoplastic syndromes, amphiphysin autoimmunity is one of the rarest[18] In 1997 Lennon et al.[19] described 11 patients with this autoantibody, seven of whom with carcinoma; amaong this seven, four were breast and three were lung tumors. Since then few additional cases have followed.[20,21] In patients with breast cancer, amphyphisin antibodies are specifically detected in patients with Paraneoplasic stiff person syndrome.[5]

In PNS, treatment of the underlying tumor is of vital importance. However, if a malignant neoplasm is identified, successful cancer treatment does not necessarly result in neurological improvement because the tumor cells do not produce the causative agents of PNS and onconeuronal antibodies and onconeuronal antigen-associated T lymphocytes may have already caused permanent damage to nervous system components. Improvement in neurologic deficits with concomitant cancer treatments is achieved in less than 30% of cases.[22] This is in agreement with our case report. Our patient was still tetraplegic and suffering from hyperesthesia even after appropriate cancer treatment. This is in contrast with other PNS, that are reported to improve with successful anticancer therapy.[5]

In conclusion, patients with onconeural antibodies and neurological symptoms should be investigated for cancer thoroughly. However, the diagnosis of PNS can be challenging given that not all patients will have a classical syndrome in association with well-characterized paraneoplastic antibodies or a demonstrable tumor. The next few years are likely to bring further insight into PNS and extend paraclinical diagnostic possibilities.

CONFLICTS OF INTEREST: The authors declare that they have no conflicts of interest.

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