

Paraneoplastic cerebellar degeneration in patients with breast cancer: two case reports and literature review

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Abstract: Paraneoplastic neurological syndrome (PNS) is a rare immune-mediated syndrome occurring in less than 1-3% of patients with breast cancer. Two rare cases of paraneoplastic cerebellar degeneration with breast carcinoma were reported here with a brief review of the pertinent literature. The primary indications of these two female patients were progressive lower limb weakness and gait ataxia. Both from a clinical standpoint, as well as from the results of the performed staging examination. There was no reason to suspect breast cancer. The primary tumor previously reported was often occult. However, in our reports, autoimmune anti-Yo antibodies in the cerebrospinal fluid and serum were positive. The indication of anti-Yo antibodies led to the conclusion of the existence of paraneoplastic cerebellar degeneration. The awareness of detectable antibodies may help to enclude more common causes of neurological dysfunction.

Keywords: Paraneoplastic neurological syndrome; Paraneoplastic cerebellar degeneration; Breast cancer; Autoimmune antibodies

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1. Introduction

Paraneoplastic neurological syndrome (PNS) is a group of rare disorders that result from the non-metastatic, but remote neurological effects of cancer. Paraneoplastic cerebral degeneration (PCD) is classified as one of PNS[1]. It describes a rare neurological complication among tumor patients[2-4], who suffer from a non-metastatic tumor manifestation[5,6]. Only a small number of patients with breast cancer can be affected by PCD[7]. Their clinical presentation and course vary, and their pathogenesis is not well understood [8-10]. The neurological syndrome often precedes the diagnosis of cancer, interestingly PNS is invariably associated with the anti-Yo antibody[7]. However, awareness of the clinical condition is very important as therapy directed at the primary cancer, initiated early in the course, appears to be of benefit [11].

2. Case reports

2.1. Case 1

A 47-year-old menopausal woman without significant medical history presented with a 4-month neurological symptoms of bilateral tinnitus, dysarthria, reduced coordination and progressive weakness of bilateral legs. She developed increased difficulty in walking and bilateral lower limb weakness was sufficient severity to impair her independent movement. Antibody screening was strongly positive for anti-Yo antibodies. Physical examination showed a solid, mobile and tender mass (2×2cm) at the 12 o'clock position and 2cm from the nipple of her left breast, with an irregular border and without skin involvement. Axillary and cervical

lymph nodes were not palpable. Ultrasound examination of her breast revealed a solid mass in her left breast and classified as BI-RADS 4b. Then the patient received core needle biopsy of the mass, and the pathology showed ductal carcinoma in situ. Invasive ductal carcinoma of the left breast (2×1.4×1cm, grade II), partial high-grade ductal carcinoma in situ (maximum diameter: 0.5 cm) and negative sentinel lymph node were revealed on the pathological report. And immunohistochemistry report showed that the estrogen and progesterone receptor were negative, c-erbB-2 was +++, and Ki67 was 35% +. There were good changes in neurological symptoms at 2 days postmastectomy, while neurological symptoms persisted. The patient will receive 8 cycles of adjuvant chemotherapy (EC-TH, and 90mg/m² and 600mg/m² respectively, q3 weeks) and trastuzumab-based therapy which will continue for one year. The changes of the neurological symptoms need to be observed in the following days.

2.2. Case 2

A 29-year-old female patient without significant medical history developed dizziness, dysarthria, and reduced co-ordination when writing and walking in April 2015. No family history of neoplastic or neurological disease was reported in the past. The clinical syndrome worsened in the following 5 months with progressive lower limb weakness and gait ataxia.

Routine blood tests (including tumor markers CA19-9, CA125, CA15-3 and CEA) and autoimmune screening tests (AQP4, TORCH and ANCA) were within the standard range.

Electromyogram and brain MRI were normal which could not explain the neurological disorders. Based on these, her doctor proposed that the onset of a demyelinating disease was probable. A course of intravenous high dose steroids and immunoglobulin were then administered, without detectable response.

Interestingly, the mammography showed a solid mass in the left breast and classified as BI – RADS 2. And cerebrospinal fluid (CSF) analyses revealed oligoclonal bands. The subsequent examination of the serum revealed anti-Yo antibodies, and this finding was confirmed in the CSF. The indication of anti-Yo antibodies and the mammography led to the conclusion of the existence of PCD. To confirm the finding, the patient received core needle biopsy of her left breast on October 30, 2015. Then high-grade ductal carcinoma in situ, but not invasive breast carcinoma diagnosed by pathology. Modified radical mastectomy and axillary lymph node staging were performed on November 10, 2015. Invasive ductal carcinoma of the left breast (maximum diameter: 2.5cm, grade II, estrogen receptor positive, progesterone receptor negative, and c-erbB-2 +++, Ki67 60%+) and positive axillary lymph nodes (1/12) were diagnosed after post-operative pathology. There were no detectable changes.

Eight cycles of adjuvant chemotherapy (EC-TH) were then administered and trastuzumab-based therapy continued for one year. Unfortunately, after four cycles of adjuvant epirubicin and cyclophosphamide (90mg/m² and 600mg/m² respectively, q3 weeks), the neurological symptoms were still present. But, after 4 cycles of trastuzumab and docetaxel, the neurological symptoms grew better, like gait ataxia. Now, the patient is receiving continuous trastuzumab-based therapy.

3. Discussion

Paraneoplastic neurological syndromes (PNS) are rare neurological disorders that caused by a malignant tumor and not related to a metastatic or direct invasion of the nervous system[1].

The central or peripheral nervous system may be affected by these disorders which usually precede the diagnosis of primary cancer in 60% of cases[12-14]. They include cerebellar degeneration, sensory and motor neuropathy, limbic encephalitis, paraneoplastic opsoclonus-myoclonus-ataxia (POMA), Lambert-Eaton myasthenic syndrome (LEMS) and stiff person syndrome (SPS)[8]. Gynecological malignancies, small cell lung cancer (SCLC), breast cancer and malignant lymphoma are the most frequent primary tumors[20]. Paraneoplastic neurological syndrome (PNS) occurs in less than 1-3% of patients with breast cancer and these patients' prognosis remains poor [16,17].

An association between paraneoplastic cerebellar degeneration (PCD) and breast or gynecological malignancies was first identified in 1938, and the clinical syndrome first fully described by Brain in 1951[18]. Significantly, a link between breast cancer and PCD is being recognized[19].

PCD is characterized by subacute onset of cerebellar dysfunction, diffuse loss of Purkinje cells and heterogeneous immunopathology[15]. The pathogenesis of PNS is not completely understood, but it has been postulated that specific antibodies expressed in tumors may cross-react with nervous system cells[16]. Proteins expressed by tumors induce the production of antibodies that cross-react with similar proteins in the central nervous system, which cause neurological disorders[15]. A subset of patients presenting with PNS have no identifiable antibodies in their serum, but in some cases the anti-neuronal antibodies, such as anti-Hu, anti-Ri, anti-Yo and anti-Ma, have been detected in serum or CSF[16] (refer to Table 1). The key in this respect is that even the smallest carcinoma can be responsible for the associated symptoms.

When there is a clinical suspicion of paraneoplastic cerebral degeneration, the evidence of the specific antibodies in the serum may be useful in the search for the primary tumor, as specific antibodies are frequently associated with specific carcinoma[20,21]. The most prevalent antibody detected in the serum of patients with PCD is the anti-Yo (anti-Purkinje cell antibody). It reacts with several antigens in Purkinje cells and tumors. Furthermore, it is most commonly associated with breast, ovarian and other gynecological cancers. More significantly, its specificity is close to 100%[13]. Interestingly, anti-Yo antibodies are undetectable in normal people and it is therefore justified to screen women with anti-Yo for breast, ovarian and gynecological cancer. The detection of anti-Yo antibodies thus prompts a gynecological examination including tumor markers, ultrasound and mammography of breast, and computed tomography (CT) of chest, abdomen and pelvis[22,23]. In our two cases, the two patients' neurological syndromes were not detected early, although it seemed to have the typical clinical presentation. Because of both from a clinical standpoint, as well as from the results of the performed staging examinations, there were not reasons to suspect the tumor. But autoimmune anti-Yo antibodies in the CSF and serum were positive. The awareness of detectable anti-Yo antibodies helped to exclude more common causes of neurological dysfunction.

Table 1. Paraneoplastic antibodies in PCD

Antibody	Clinical syndromes	Immunohistochemistry	Western blot cerebellar extract	Gene	Associated cancer	Reference
Anti-Yo	Cerebellar ataxia	Cytoplasm of Purkinje cells and large brainstem neurons	34, 52 and 62 kDa	cdr34, cdr62-2	cdr62-1, Ovarian, breast	Fathallah-Shaykh et al. (1991); Peterson et al. (1992)
Anti-Hu	Cerebellar ataxia, PEM/SN	Nuclei of all neurons, nucleolar sparing	35 ±40 kDa	HuD, HuC, Hel-N1	SCLC	Szabo et al. (1991); Dalmau et al. (1992)
Anti-Ri	Cerebellar ataxia, OM	Nuclei of all central neurons, with nucleolar sparing	55 and 80 kDa	NOVA-1, NOVA-2	Breast, gynaecological, SCLC	Luque et al. (1991); Buckanovich et al. (1993)
Anti-Tr	Cerebellar ataxia	Cytoplasm and dendrites of Purkinje cells	±	Unknown	Hodgkin's lymphoma	Graus et al. (1997, 1998)
Anti-VGCC	Cerebellar ataxia, LEMS	±	±	CACNA1A	SCLC (60%)	Mason et al. (1997)
Anti-Ma	Cerebellar ataxia, brainstem dysfunction	Nuclei and cytoplasm of neurons	37 and 40 kDa	Ma1-5	Many	Dalmau et al. (1999)
Anti-Ta/Ma2	Limbic encephalopathy, cerebellar ataxia	Nuclei and cytoplasm of neurons	40 kDa	Ma2	Testis	Voltz et al. (1999)
Anti-CRMP5/CV2	PEM/SN, cerebellar ataxia	Cytoplasm of oligodendrocytes	66 kDa	CRMP5	SCLC, thymoma, gynaecological	Honnorat et al. (1996, 1999)
Anti-mGluR1	Cerebellar ataxia	Cytoplasm of Purkinje cells and brush cells, climbing @bres	±	MGluR1	Hodgkin's lymphoma	Sillevis Smitt et al. (2000)

OM = opsoclonus/myoclonus; VGCC = voltage-gated calcium channels; LEMS = Lambert-Eaton myasthenic syndrome.

The main clinical manifestations of PCD include subacute onset of dysarthria, diplopia, dizziness, nystagmus and gait ataxia. The clinical course is of rapid progression to severe functional disability[24] and its clinical progression is variable[25]. The onset of neurological symptoms precedes the identification of the tumor in 60% of cases and this case history highlights the challenge in making a diagnosis of PCD in such patients. Specific clinical signs differentiating paraneoplastic syndrome from other neurological pathology are lacking. This leads to delay in requesting antibody titers. However, the association between PCD and anti-Yo antibodies is the strongest in middle-aged women with breast cancer[18]. No antibodies are found in approximately 40% of patients with breast cancer, indeed, the absence of titers does not exclude the possibility of occult malignancy [19].

It is of note that up to 30% of patients with PCD become neurologically affected when the primary tumor is in remission, suggesting that the treatment of cancer alone is not enough. Like the second patient, despite the removal of the breast with cancer, there were no good changes in neurological symptoms. The treatment of the underlying malignancy improves survival, but does not affect the natural course of PCD. What remains frustrating is the fact that the paraneoplastic symptoms often continue to have a greater negative effect on the patients' quality of life than does the underlying malignancy[19]. PCD may occasionally present with the development of metastatic disease several years after treatment of primary breast cancer[14]. On a long-term follow-up in a specialized cancer center, 52% of patients with anti-Yo-positive PCD die of cancer and 29% of neurological malignancy[14]. One study stated median survival duration of 100 months for breast cancer patients, but 22 months for those with gynecological cancers[15]. But current studies report encouraging results, early therapeutic intervention may reverse or at the very least halt progression of neurological deficit[14].

Since only a small number of patients with breast cancer can be affected by PCD, results of immunotherapy are only based on case reports and small series[19]. Indeed, except in individual cases, the attempts to treat the neurological symptoms with immunoglobulins, chemotherapy, or with immunosuppression did not produce the desired effect[2]. Keime-Guibert were the first to examine the effect of a combination treatment employing immunoglobulin and cyclophosphamide and methylprednisolone in patients affected by cerebral degeneration combined with the presence of anti-Yo antibodies and in patients with symptoms of encephalomyelitis and anti-Hu antibodies. While the patients tolerated this combination treatment well, it was found that this treatment also failed to produce

the desired, significant and therapeutic improvement of the problems. Only in a few cases was a short-lived stabilization of the symptoms observed[14]. But current studies report encouraging results, it may be more effective when initiated early in the course of the disease, when cell loss is still minimal. If used within the first 3 months after diagnosis, initial treatment with IV immunoglobulin seems to occasionally stabilize neurological status. On the other hand, more recent studies report initial encouraging results with rituximab in patients with anti-Yo-positive or anti-Hu-positive PCD[16].

A study on a number of antibody specific paraneoplastic syndromes highlights the poor prognosis of anti-Yo-positive PCD, as well as the benefits of chemotherapy treatment. Only four out of 19 anti-Yo-positive patients remained ambulatory and the survival from time of diagnosis was poor in these patients. But anti-Yo-positive patients receiving antitumor treatment (with or without immunosuppressive therapy) lived significantly longer[14].

4. Conclusion

A small number of patients with breast cancer produce an antibody against the tumor and neuronal tissue, which causes paraneoplastic cerebellar degeneration. We have reported two rare cases of anti-Yo-positive PCD with breast cancer. In our cases, the histological characteristic precedes detection of the neoplastic disease and it is difficult to be diagnosed. Anti-Yo antibodies in the serum and CSF were positive. Anti-Yo antibodies is of importance in the detection of underlying malignancies. There is still no definite therapy for PCD, but an intensive diagnostic effect must be done in order to detect the underlying tumor as early as possible because it appears that early and prompts treatment against the cancer may offer hope to these patients.

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