Case Report

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Paraneoplastic Cerebellar Degeneration with Anti-Yo Antibody in a Patient with Fallopian Tube Adenocarcinoma: A Case Report and Literature Review

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Abstract:

Paraneoplastic cerebellar degeneration (PCD) typically presents via acute to subacute cerebellar ataxia, dysarthria, and ocular dysmetria, resulting from tumor-induced autoimmunity against the cerebellum. In most cases, symptoms of PCD show months before a diagnosis of cancer. Therefore, it is important for clinicians to investigate the primary tumor in PCD cases in order to treat both conditions concurrently. Herein, we report a case of PCD associated with an anti-Yo antibody, leading to a diagnosis of left fallopian tube adenocarcinoma.

Keywords: anti-Yo antibody, gynecologic malignancy, paraneoplastic cerebellar degeneration, paraneoplastic neurological syndrome

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Introduction

Paraneoplastic cerebellar degeneration (PCD), a rare, devastating paraneoplastic neurological syndrome (PNS), is characterized by acute to subacute cerebellar ataxia, dysarthria, and ocular dysmetria caused by tumor-induced immune responses against cerebellar antigens[1].The essential diagnostic immunological marker of PCD is the presentation of highly specific anti-neuronal antibodies in the serum or cerebrospinal fluid (CSF). Anti-Yo antibody is the most frequently detected antibody in this syndrome, followed by anti-Hu, anti-Ri, and anti-Tr[2]. These specific antibodies can guide the investigation of the primary tumor; including small cell lung cancer, gynecologic malignancies, breast cancer, and Hodgkin lymphoma, which are common tumors in PCD[1]. Herein, we report on a case of PCD associated with an anti-Yo antibody, leading to the discovery of left fallopian tube adenocarcinoma. The patient was treated with bilateral salpingo-oophorectomy, chemotherapy, and immunosuppressive drugs.

Case report

A 73-year-old Thai female initially presented with a history of gait instability for 2 months. Three weeks prior to admission, she had developed progressive gait instability, scanning speech, and horizontal diplopia, which was worsened by the left lateral gaze, in which diplopia was resolved when she covered one eye. Also, she complained of fatigue, loss of appetite, and a significant weight loss of 5 kg within 2 months. She had no fever, headache, blurred vision, hearing loss, cough, hemoptysis, abdominal mass; abnormal vaginal bleeding, limb weakness, or loss of consciousness. She had a history of hypertension and dyslipidemia, and her current medications were propranolol, atorvastatin, and ezetimibe. There was no history of any tumors in her family.

Her neurological examination revealed normal pupillary size and both direct and consensual pupillary light reflex; partial ptosis of the right eye was observed. Although she had diplopia, her extraocular muscle (EOM) movement was not limited. Further eye examination by neuro-opticians demonstrated tiny left hypertropia by Hess test, and the three-step test was compatible with a skew deviation of the left eye. The abnormal cerebellar signs included broken eye pursuit, hypometric saccadic eye movement, bilateral horizontal gaze evoked nystagmus in all directions, scanning speech, limb dysmetria of all 4 extremities, truncal ataxia, and a wide-based gait. Other neurological examinations were within normal limits. The patient's physical examination showed a palpable, hard consistency and movable left breast mass, sized at 1x2 centimeters. No superficial lymph nodes were palpated and her other general systemic signs were within normal limits.

Magnetic resonance imaging (MRI) of the brain was within normal limits. The CSF revealed 6 mononuclear cells, with normal proteins and glucose levels. Her serum and CSF paraneoplastic antibody panels were revealed as strongly positive for anti-Yo antibody in both specimens. In order to search for the primary malignancy, several body neuroimaging was performed. The mammogram revealed two groups of Breast Imaging-Reporting and Data System (BI-RADS) and 3 coarse calcifications in the left upper central part of the left breast, which was consistent with possible fibroadenomas. A Computed tomography of whole abdomen demonstrated an enlarged left ovary; sized 2.3x3.5 centimeters, with heterogeneous contrast enhancement, multiple enlarged left paraaortic, and left common iliac lymph nodes. The ultrasound of the uterus and ovaries showed a small post-menopausal uterus, a thin endometrium and prominent hyperechoic combined with increased vascularity, without definite mass at the left ovary. Although, the imaging findings were not classically consistent with a malignant lesion, the strong association between anti-Yo antibody and gynecologic malignancy was essential warning data. Therefore, a laparoscopic bilateral salpingo-oophorectomy

was performed. The pathological findings of the left fallopian tube revealed a poorly differentiated adenocarcinoma, which was positive for CK7 and ER but negative for P53, WT1, PR, and CK20.

The final diagnosis was fallopian tube adenocarcinoma, associated with anti-Yo paraneoplastic cerebellar degeneration. Despite aggressive treatment consisting of adjuvant chemotherapy with carboplatin; including 5 consecutive doses of 1,000 mg methylprednisolone intravenously and 60 mg per day of oral prednisolone, the clinical benefits revealed neurologic stabilization without significant clinical improvement.

Discussion

This case was anti-Yo PCD secondary to left fallopian tube adenocarcinoma. This syndrome usually presents with the subacute development of severe cerebellar ataxia in both the trunk and limbs over a period of weeks to months[3]. It then reaches a plateau within 6 months of onset[3]. Symptoms of brainstem involvement are also often detected; such as dysarthria, nystagmus, diplopia, and dysphagia[3,4]. Neuro-ophthalmologic manifestation is unusual, with rare presentations including opsoclonus, progressive visual loss, upward gaze palsy with eyelid retraction, and skew deviation[5]. In pathologic studies of antibody-associated paraneoplastic brainstem encephalitis, two post-mortem examinations showed extensive gliosis, perivascular inflammation, and cell loss in the midbrain and pontine tegmentum, or selective neuronal loss within the third, fourth, and sixth nerve nuclei[6]. In our case, we suspected that the right eye partial ptosis might have resulted from selective neuronal damage of subunits of the right oculomotor nuclei. This innervates the levator muscles in the upper eyelid of the right eye, while her diplopia could be explained by skew deviation of the left eye. Any lesions along the pathway of prenuclear vestibular input to the oculomotor nuclei, which are mostly contained in the posterior fossa, have the potential to cause skew deviation. Unfortunately, there was no evidence by pathology or neuroradiology to confirm the lesions. We believe that in patients with PCD, antibodies do not only affest the cerebellum, but also could involve the brainstem selectively. From our perspective, her eye signs could be explained by selective brainstem damage similar to the involvement in the post-mortem study[6].

The brain MRI in the anti-Yo syndrome can be normal. Cerebellar atrophy tends to be worse in the midline and can only be seen at the time of irreversible damage.(7) This syndrome should be suspected when the patient has subacute severe cerebellar involvement with a normal MRI[8].

CSF abnormalities have been noted in 93% of patients with paraneoplastic neurological syndromes[9]. Pleocytosis and protein elevation are more common when study is performed early after symptom onset, and lymphocytes are often predominated when pleocytosis is detected[9]. However, these findings are neither sensitive nor specific, as early neural loss is followed by the non-inflammatory phase; when all neurons disappear, the inflammatory CSF findings also decrease over time. This temporal pattern of change suggested the non-inflammatory phase in our patient. Therefore, if clinical suspicion of PCD is high, despite a normal CSF study, serum or CSF-specific antibodies should be investigated.

PCD can be definitely diagnosed by the presenting of serum or CSF highly specific antibodies without other causes; such as metastases or infection. Essentially, antibody testing should be performed in both serum and CSF in order to avoid inconclusive results[10]. Anti-Yo is the most common antibody in this syndrome in nearly 50% of PCD, which can detect cancer between 90-98% of the time. It is frequently associated with gynecologic malignancies, and breast cancers, followed by Hodgkin lymphoma, small cell lung cancer, gastric cancer, esophageal cancer, prostate cancer and melanoma[2,3].

In more than 60% of cases, symptoms of PCD can present months before a diagnosis of cancer[4]; however, the cancer diagnosis can be either concomitant with or preceding syndrome's onset. In a few cases, a primary cancer cannot be detected even in an autopsy[2]. It is important for clinicians to search for the primary cancer in PCD cases in order to administer early treatment for both PCD and the primary cancer simultaneously.

The low prevalence of PCD has not allowed the conduction of randomized controlled trials, resulting in the current guidelines for the treatment of PCD being lacking. Some reports have demonstrated the benefits of early antitumor therapies; such as surgery, chemotherapy and immunosuppressive therapy in the first month, as being considered to be important in affecting the clinical course[11]. However, there are no current evidence-based recommendations for effective neurologic treatments on the various immunologic therapies; including plasma exchange, intravenous immunoglobulin (IVIG), corticosteroids, or other immunosuppressions. In this case, even though the treatment consisted of an early combination of tumor removal, chemotherapy, and corticosteroid therapy, the neurologic symptoms did not significantly improve, although there was some small benefit to stabilize the progression of her neurologic symptoms.

With regards to the mechanism, PCD patients show diffuse Purkinje cell degeneration throughout the cerebellar cortex, with CD8 lymphocytic infiltration and microglial activation in an autopsy[12]. The irreversible neuronal damage caused by the T-cell attack can explain their poor response to treatment and recovery. Early treatment of cytotoxic cell inhibition, including cyclophosphamide and IVIG seemed to benefit clinical responses on PCD, based on case reports[13,14]. Even though, the exact mechanism of IVIG, for PCD patients remains unclear, it is proposed as blocking T lymphocyte-antigen interactions by immunoglobulins[15]. Early intervention, with high-dose IVIG, with or without concomitant therapy, provides a better outcome. Patients with a good response were treated within one month of symptoms. Patients treated between one month and three months often had stable disease, while those treated after three months usually had a poor outcome[14]. Further studies are needed to identify the role of anti-Yo antibody and T cell–mediated neuronal destruction for developing targeted therapeutic treatment.

The median survival of PCD with anti-Yo is 13 months. Additionally, it is dependent on the types of primary cancer, which have worse survival in ovarian malignancies and better survival in breast cancer. The syndrome progresses from weeks to months leading to disability, with the majority of patients being left bedridden in addition to less than 10% of patients being able to ambulate without assistance over the long term[4].

Conclusion

PCD is a rare, devastating paraneoplastic neurological syndrome. It should be suspected in patients that have subacute severe cerebellar involvement, despite normal MRI and CSF studies. Detection of serum or CSF-specific antibodies is essential for the diagnosis. It is important for clinicians to rapidly investigate a primary cancer in order to provide early treatments for both the cancer and PCD simultaneously.

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Conflict of interest

The authors declare no conflicts of interest in this manuscript.

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