

Anti-Yo positive and late-onset paraneoplastic cerebellar degeneration associated with ovarian carcinoma

A case report

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Abstract

Rationale: Paraneoplastic cerebellar degeneration (PCD) is a rare nonmetastatic neurological complication often associated with ovarian, breast, and other gynecologic cancers. Anti-Yo is one of the antionconeural antibodies found in patients with PCD. It primarily emerges before a malignancy is detected.

Patient concerns: In this report, we describe an unusual case involving a patient who exhibited anti-Yo-positive PCD 1 year after being diagnosed with ovarian cancer.

Diagnoses: Histopathology of the resected tissues and Antineuronal antibody testing.

Interventions: The patient was treated with intravenous immunoglobulin (IVIG, 1g/d) for 1 week and a large-dose of methylprednisolone (0.4 g/kg/d) for 5 days. At the same time, underlying complications were prevented actively, and the peripheral nerves were protected.

Outcomes: Although most patients with anti-Yo-positive PCD do not improve after treatment, our patient significantly improved after receiving active and effective treatment.

Abbreviations: CSF = cerebrospinal fluid, CT = computed tomography, MRI = magnetic resonance imaging, PCD = paraneoplastic cerebellar degeneration, PNS = paraneoplastic neurological syndromes.

Keywords: anti-Yo, neurological complication, ovarian carcinoma, paraneoplastic cerebellar degeneration

1. Introduction

Paraneoplastic neurological syndromes (PNS) are a rare group of syndromes that occur in patients with cancer and are not caused by the presence of metastases or the direct infiltration of tumors into the nervous system. Malignant tumors associated with PNS are mainly found in ovarian cancer, breast cancer,^[1] small cell lung cancer,^[2] and so on. Paraneoplastic cerebellar degeneration (PCD) is a rare and unusual nonmetastatic neurologic complication, which is a remote effect of cancer.^[3]

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According to previous findings, it is well known that a malignant disease can lead to antibody formation, causing secondary clinical effects. PCD with ovarian cancer is 1 example. Clinically, it is characterized by acute or subacute onset with progressive pancerebellar dysfunction, including asymmetry of truncal and limbs, gait ataxia, dysarthria, and nystagmus (mostly vertical).^[4] Several specific antionconeural antibodies have been found in serum and cerebrospinal fluid (CSF) in some patients with PCD, depending on the underlying tumor.^[5,6] Anti-Yo-associated PCD occurs almost exclusively in middle-aged women with ovarian cancer.^[7]

Several reports have shown that response to treatment in PCD is not satisfactory, especially in anti-Yo-positive PCD patients. In this report, we present an anti-Yo (+) ovarian cancer patient with subacute-onset PCD, whose symptoms significantly improved after treatment.

2. Case report

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The First Affiliated Hospital of Bengbu Medical College. Written informed consent was obtained from all participants.

A previously healthy 65-year-old married female farmer, mother of 5 children, was admitted to a local hospital for progressive abdominal distention for 3 months since September 2012. She had been menopausal for more than 10 years. As an ovarian tumor marker, her CA-125 level was 270 U/mL (normal range: 0–35 U/mL), while other serum tumor markers (CA19–9, CA15–3, CEA, and leukemia cell marker) were within normal limits. Pelvic color Doppler ultrasound examination revealed a

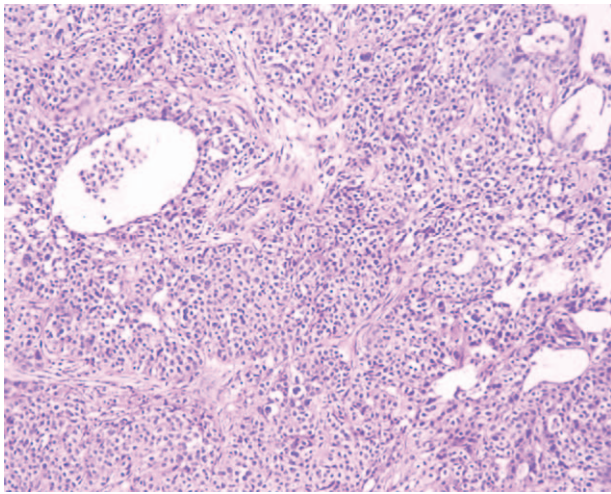


Figure 1. Histopathology of the resected tissues reveals stage III serous ovarian carcinoma. The papillary structure disappeared, and the tumor cells showed a large mass, the parenchyma adenocarcinoma. The cell atypia was large, the mitotic figures were few, and the interstitial was very few.



Figure 2. Antineuronal antibody testing (anti-Yo, anti-Ri, anti-Hu, anti-CV2, anti-amphiphysin, and anti-Ma2/TA). The testing was positive only for anti-Yo.

cystic solid and irregularly fixed mass in the left ovary. The patient underwent exploratory laparotomy, which revealed a 10×15 cm left ovarian tumor with an irregular surface. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy. Final histopathology of the resected tissues revealed stage III serous ovarian carcinoma (Fig. 1). The papillary structure disappeared, and the tumor cells showed a large mass, the parenchyma adenocarcinoma. The cell atypia was large, the mitotic figures were few, and the interstitial was very few. She was treated with paclitaxel and cisplatin for 7 cycles and exhibited a complete response to chemotherapy. She remained disease-free and had no recurrence.

In September 2013, the patient presented with imbalance, episodic vertigo, nausea, and vomiting without any apparent reason. Her brain computed tomography (CT), which was performed in a local hospital, was normal. Thus, the patient and her family ignored her symptoms. Nevertheless, these symptoms were progressively exacerbating. Slurred speech and vertical nystagmus gradually appeared. In February 2014, she was admitted to our department with severe ataxia of the trunk, limbs and gait, along with slurred speech, dysmetria, and pathological nystagmus, which had developed over the preceding month. Neurological examination: The patient suffered from ataxia, imbalance and gait disturbances, speech disorder (dysarthria), and vertical nystagmus. There were Romberg sign (+), finger–nose test (+), and heel–knee test (+). There was no obvious abnormality in sensory system. She had normal defecation and urination, but poor diet and sleep.

Mild neutrophilic granulocytosis was found (72.9%, normal: 50%–70%) in the blood analysis. Biochemical and urine analysis revealed no abnormalities. Furthermore, emission-CT, electroencephalogram, CT of the brain, and magnetic resonance imaging (MRI) of the brain with gadolinium enhancement examinations were unremarkable. The patient only received MRI of the brain, which could exclude cancerous metastasis of central nervous system. According to the follow-up of the patient, the possibility of cancer metastasis could be ruled out. Based on these results, stroke, infection, toxic cerebellar lesions, cerebellar tumors, and hereditary cerebellar degeneration were excluded from the possible

diagnoses. Her CA-125 level was 20 U/mL. CT scans of the abdomen and pelvis were normal. There were no definitive evidences for the recurrence of ovarian cancer. CSF examination did not reveal any abnormality. Antineuronal antibody testing (anti-Yo, anti-Ri, anti-Hu, anti-CV2, anti-amphiphysin, and anti-Ma2/TA) was positive only for anti-Yo (Fig. 2). These findings were consistent with the diagnosis of PCD.

The patient was treated with intravenous immunoglobulin (IVIg, 1 g/d) for 1 week and a large-dose of methylprednisolone (0.4 g/kg/d) for 5 days. At the same time, underlying complications were prevented actively, and the peripheral nerves were protected. Audiovestibular testing clearly indicated improvement after treatment. She was independently mobile in bed, and could sit and stand with supervision. Moreover, her speech was more intelligible. Besides, seeing to fast forward and side face, the patient had vertical nystagmus when she was admitted to our hospital, while the nystagmus disappeared after treatment. Audiovestibular testing included Romberg sign. The patient was not stable, no matter whether eyes open or closed, but she could stand steady after treatment. Finger–nose test and heel–knee test were negative after treatment. This empirical treatment with IVIg and methylprednisolone may be effective and worthy of being recommended. To date, she has been alive for 19 months without any evidence of recurrence.

3. Discussion

At present, the pathogenesis of PCD is not completely understood. However, it has been considered to be associated with antibody and T-cell responses against the expression of shared epitopes in the nervous system and the tumors.^[8] In recent years, 6 specific antineuronal antibodies have been found in serum and CSF of some patients with PNS such as anti-Hu [antineuronal nuclear antibodies (ANNA)-1], anti-Yo (purkinje cell antibody type 1), anti-Ri (ANNA-2), anti-CV2, anti-amphiphysin, and anti-Ma2/TA.^[1,9,10] Furthermore, it has been believed that anti-Yo-associated PCD occurs almost exclusively in women and is most likely associated with ovarian, breast, and other gynecologic cancers, although exceptions have been seen.

There were many previous studies correlating PCD and cancer.^[11–13] The fact that this patient responded to the treatment for ovarian cancer would strengthen the association between gynecological malignant tumors and paraneoplastic syndrome.

PCD occurs at any stage of the course of cancer. This case has proven that if acute or subacute cerebellar disease occurs in middle-aged woman with ovarian cancer and progresses without any signs of intracranial hypertension, we should consider the PCD; but only when cerebellar stroke, infection, toxic cerebellar lesion, cerebellar tumors, or hereditary cerebellar degeneration have been excluded based on careful physical examination and imaging findings. Early definite diagnosis is conducive to timely treatment.

A subset of patients with anti-Yo PCD shows improvement. The natural tendency of the disease to plateau around 6 months after onset makes it difficult to determine whether treatments were effective. Isolated cases of PCD related with anti-Yo only respond favorably to the immunomodulatory therapy. This is one of the interesting aspects that can offer this case. In general, PCD predates the cancer diagnosis. However, in approximately 30% of patients, the ataxic symptoms occur when the cancer is in remission.

However, the specific pathological mechanism of PCD was still not fully understood. Some research showed that dysregulation of calcium homeostasis by anti-Yo antibodies may be the initial mechanism of attack on purkinje's cells. The authors suggest a pathway where PCs are first silenced by interruption of calcium signaling by internalized anti-Yo antibodies, and then cleared by cytotoxic T cells and microglia. PKC α (the catalytic subunit of PKC), a calcium-dependent kinase, Cav2.1, a voltage-gated calcium channel, and the calcium-dependent protease calpain-2 were upregulated, which would increase intracellular calcium levels, potentially triggering cell death pathways, which need to be further explored.^[14]

For such patients, the removal of the primary tumor is the mainstay of treatment, along with plasma exchange, IVIG, as well as immunosuppressive agents (cyclophosphamide), antitumor drugs (rituximab), or corticosteroids, which can be administered after surgery. Based on the results of this case, a combination of IVIG and methylprednisolone can be recommended.

It has been known that approximately 50% of the damage to a patient's nervous system manifests before the cancer is diagnosed. Before the primary lesion is found, the detection of related antibodies could provide basis for early diagnosis and has significance for diagnosing the tumor type. However, no antibodies have been identified in approximately 40% of patients.^[15] Further studies are required to characterize mechanisms leading to neuronal death in PNS.

Therefore, it can be seen that on one hand, it is vital to investigate the mechanism of PCD in patients with ovarian cancer in the pathogenesis of immunology. On the other hand, female patients who present with symptoms of PCD should be thoroughly screened for gynecological malignancy. Therefore, female patients who present with symptoms of ovarian cancer should be provided timely and effective treatment to prevent PCD. Early awareness of PCD and timely treatment is important for patients to have a good prognosis.

The potential causal relationship between ovarian cancer and PCD needs to be investigated. Therefore, in addition to the need of neurologists for continuous learning, surgeons working in this field also need to study and gain an interdisciplinary understand-

ing of these so-called marginal diseases. Early treatment with maximal preservation of central nervous system function and improvements in antitumor immunity are the main treatment goals for the future. Further studies that would eventually enable physicians to prevent or cure this disease are therefore desirable.

4. Conclusion

PCD with anti-Yo (+) could exhibit after ovarian cancer, whose symptoms could be significantly improved after treatment by IVIG and a large-dose methylprednisolone. This would contribute to the early detection and treatment of PCD for ovarian cancer patients, which is important for patients to have a good prognosis.

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