

Paraneoplastic cerebellar degeneration associated with ovarian carcinoma: case report and review of literature

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ABSTRACT

Paraneoplastic cerebellar degeneration (PCD) is a rare complication of some malignant cancers caused by an autoimmune response against neuronal antigens expressed by tumor cells. It is most commonly described in women with gynecologic or breast cancer, however, there have been reports in other types of cancer. Symptoms include ataxia, dysarthria and tremors, which could be the first manifestations of an underlying malignancy. A 50-year-old woman had acute PCD with anti-Yo antibodies from an underlying invasive ovarian carcinoma. She developed speech dysfunction, asthenia and ataxia. Antineuronal antibody testing was positive only for anti-Yo. These findings were consistent with the diagnosis of pancerebellar degeneration. The patient was treated with intravenous immunoglobulin (0.4 g/kg/day) for 5 days and 6 sessions of plasma exchange. After this treatment, the neurological examination was partly improved.

Paraneoplastic clinical syndromes affect <1% of patients with cancer; however, the frequency of subclinical levels of paraneoplastic autoantibodies in asymptomatic patients with cancer is unknown. Numerous studies have reported that ovarian cancer patients show signs of paraneoplastic neurological syndromes before or after their cancers are diagnosed. This case underlines the importance of early diagnosis, which can allow appropriate treatment that may stabilize the neurological symptoms.

KEYWORDS

Ovarian cancer, paraneoplastic cerebellar degeneration, anti-Yo antibodies, pancerebellar degeneration, plasma exchange, antineuronal antibody, ataxia, speech dysfunction.

Introduction

The term paraneoplastic neurological syndrome (PNS) refers to a rare and unusual 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^[1].

The presence of malignant tumors associated with PNS is mainly found in ovarian cancer, breast cancer and small cell lung cancer. In gynecological cancers, the incidence of occurrence of PNS is approximately 1 per 1000 new cases. Clinically, it is characterized by acute or subacute onset with progressive pancerebellar dysfunction including ataxia, lack of balance, speech dysfunction, dysphagia and nystagmus.

Case report

A previously healthy, 58-year-old woman presented to the emergency department with abdominal distention and pain. Pelvic color Doppler ultrasound examination revealed a cystic solid and irregularly fixed mass and ascites. Evaluation of ovarian tumor markers revealed the following levels: CA-125: 1965 KU/L (normal range: up to 35.0), Ca 15.3: 36.4 KU/L (normal range: up to 25), Ca 19.9: 138 KU/L (normal range: up to 39), CEA 1.0 ug/L (normal range: up to 5.2), HE4 1945 pmol/l (nor-

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mal range: up to 140). A preoperative computed tomography (CT) scan revealed a solid ovarian mass adherent to the sigma, ascites, multiple enlarged lymph nodes and peritoneal carcinosis. After the preoperative evaluation, the patient was selected for primary surgery. In February 2018, she underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, colon resection extended up to the splenic flexure, resection of the caecum and terminal ileum, colon rectum anastomoses and ileum colon anastomosis, and removal of the bulky iliac lymph node.

Final histopathology of resected tissues revealed stage IIIc G3 serous ovarian cancer. In April 2018 she started treatment with taxol and carbo platinum. In the same period, she developed speech dysfunction, asthenia and ataxia. Her brain CT examination was normal. Neurological examination revealed ataxia, imbalance, slurred speech, gait disturbance, nystagmus, upper limb tremor, a positive finger-nose test and a positive

heel-knee test. Biochemical and urine analysis revealed no abnormalities. She underwent electromyography, which gave normal findings. Magnetic resonance imaging (MRI) of the brain excluded cancerous metastasis of the central nervous system. Cerebrospinal fluid (CSF) examination did not reveal any abnormality. Antineuronal antibody testing (anti-Yo, anti-Ri, anti-Hu, anti-CV2, anti-amphiphysin, anti-Ma2/TA) was positive only for anti-Yo (Table 1, Figure 1). These findings were consistent with the diagnosis of pancerebellar degeneration (PCD).

The patient was treated with intravenous immunoglobulin (IVIg, 0.4 g/kg/day) for 5 days [3] and 6 sessions of plasma exchange. After this treatment, the neurological examination was found to be partly improved: the slurred speech was improved, as were the nystagmus and upper limb tremor. The finger-nose test and heel-knee test were still positive. So she repeated a

complete cycle of therapy (plasma exchange and infusion of immunoglobulin).

After 6 months, the neurological examination was little improved. The patient was orientated, the slurred speech was still improved, but some alterations persisted: the positive finger-nose test, upper limb tremor and nystagmus. She completed seven cycles of chemotherapy and exhibited a complete response to chemotherapy, as shown by a negative CT scan (Table 2).

Discussion

Paraneoplastic cerebellar degeneration, one of the most common paraneoplastic presentations of cancer, is character-

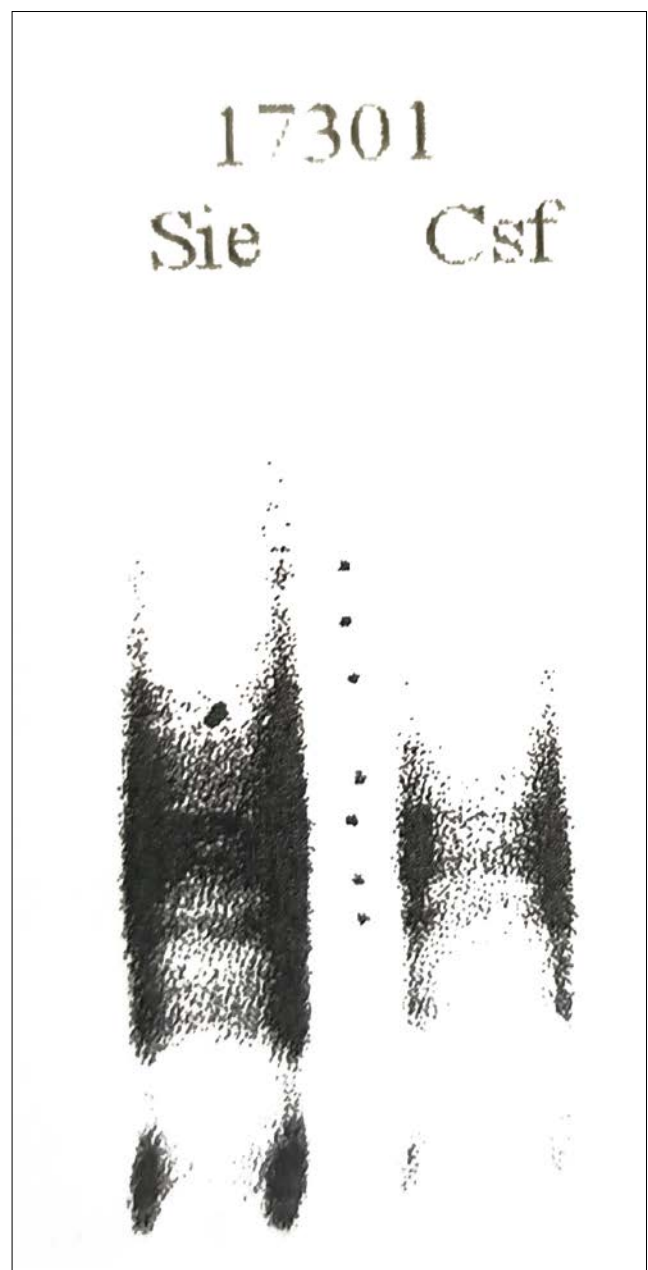
Table 1 Immunoblot test for anti-neuronal IgG antibodies in the serum. The test was positive only for anti-Yo.

| | | | |
|-----------------------|-----------------|-------------------|----------|
| Anti Hu ab | NEGATIVE | Anti-SOX1 ab | NEGATIVE |
| Anti-Yo ab | POSITIVE | Anti-titin ab | NEGATIVE |
| Anti-Ri ab | NEGATIVE | Anti-zic ab | NEGATIVE |
| Anti-amphiphysin ab | NEGATIVE | Anti-GAD65 ab | NEGATIVE |
| Anti-CV2 ab | NEGATIVE | Anti-Tr (DNER) ab | NEGATIVE |
| Anti-Ma2-Ta ab | NEGATIVE | Anti-recoverin ab | NEGATIVE |
| Filicori et al., 1991 | 63 | 105 | 91% |

Table 2 Main characteristics of the patient.

| | |
|--|--|
| Age (years) | 58 |
| Parity | 1001 |
| Surgery | Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, colon resection extended up to the splenic flexure, resection of the caecum and terminal ileum, colon rectum anastomoses and ileum colon anastomosis, removal of the bulky iliac lymph node. |
| Histopathology diagnosis | Stage IIIc G3 serous ovarian cancer |
| Chemotherapy | 7 cycles of taxol and carbo platinum |
| Neurological symptoms and neurological examination | Ataxia, imbalance, slurred speech, gait disturbance, nystagmus, upper limb tremor, positive finger-nose test, positive heel-knee test |
| Positive antineuronal antibodies | Anti-Yo |
| Treatment | Intravenous immunoglobulin (0.4 g/kg/day) and plasma exchange |

Figure 1 Western blot. Oligoclonal immunoglobulins in serum and liquor.



ized by severe pancerebellar dysfunction. The postmortem study shows extensive loss of Purkinje cells (PCs) with relative preservation of other cerebellar neurons. Inflammatory infiltrates in the deep cerebellar nuclei and brainstem are also identified in some patients [4].

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 tumors. 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. Furthermore, it has been suggested 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. PCD can occur at any stage in the course of cancer.

These antineuronal antibodies are preferentially investigated by serological analyses while CSF examination is performed only infrequently. Schwenkenbecher et al. retrospectively investigated 12 patients with antineuronal antibodies against PCs, focusing especially on the CSF.

While standard CSF parameters infrequently revealed pathological results, all the patients presented oligoclonal bands indicating intrathecal IgG synthesis. These findings suggest that patients with a cerebellar syndrome display a distinct immune reaction within the CSF including intrathecal synthesis of disease-specific antibodies [5].

The specific pathological mechanism of PCD is still not fully understood. Some research has shown that dysregulation of calcium homeostasis by anti-Yo antibodies may be the initial mechanism of the attack on PCs. The authors suggest a pathway in which PCs are first silenced by interruption of calcium signaling by internalized anti-Yo antibodies, and then cleared by cytotoxic T cells and microglia. PKC ϵ (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 [5].

Anti-Yo antibodies in PNS have, in most cases, been found in women, and there are very few reported cases in men [2]. In contrast to other antibodies, anti-Yo antibodies are almost always detected alone in serum without any other coexisting type of antineuronal antibody [3]. Malignancies commonly associated with PCD include gynecological cancer (20%), breast cancer (28%), and Hodgkin's disease (16%).

Owing to the T cell-mediated selective mechanism of destruction of PCs, cerebellar symptoms are usually present in isolation, and patients are often left with significant long-term disability resulting from irreversible and extensive PC destruction. Evidence that supports the involvement of T-cell mechanisms includes the difficulty of treating these disorders with strategies directed at the humoral immune response (e.g., plasmapheresis) and the presence of extensive infiltrates

of oligoclonal cytotoxic T cells in the central nervous system (specifically in the cerebellar cortex, deep cerebellar nuclei and inferior olivary nuclei) and tumors in affected patients [6-8]. In PCD, there is usually also evidence of inflammation in the CSF, consisting of moderate lymphocytic pleocytosis, increased protein concentration, high IgG index, and CSF-specific oligoclonal bands. Initial MRI of the brain is usually normal in most patients, and cerebellar atrophy can develop in late stages [9].

There is no standard of care for PCD because there are no studies above the class IV level of evidence. Removal of the primary tumor is the mainstay of treatment in these patients, along with plasma exchange and IVIG, as well as immunosuppressive agents (cyclophosphamide), antitumor drugs (rituximab) or corticosteroids, which can be administered after surgery. As described in a review by Venkatraman et al. [10]; immunotherapies, steroids, IVIG and plasma exchange, have been extensively used in managing this condition, with limited success. Although some reports indicate benefit from antitumor therapies such as surgery and chemotherapy, this has not been consistently observed. In this review, the authors reported a study by Candler in which only tumor therapy was described as effective in stabilizing or improving neurological outcomes in 63 patients with paraneoplastic neurological syndromes, including 11 who were positive for the anti-Yo antibody. In cases where a tumor is found at the time of PCD diagnosis, the use of immunosuppressive drugs and monoclonal antibodies is controversial, but is often attempted in conjunction with antitumor approaches.

It has been reported 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 the basis for early diagnosis and has significance for diagnosing the tumor type. However, no antibodies are identified in approximately 40% of patients. Further studies are required to characterize mechanisms leading to neuronal death in PNS [9].

In addition to a possible role in early detection, paraneoplastic autoantibodies can also indicate tumor recurrence and can be considered biomarkers for disease monitoring during patient follow up. It has been reported that the return of PNS symptoms after successful treatment of the tumor can indicate tumor recurrence [11].

Conclusion

PCD with anti-Yo (+) can appear after the onset of ovarian cancer, whose symptoms could be significantly improved after treatment with IVIG and plasmapheresis. Paraneoplastic neurological disorders that appear in ovarian cancer patients are considered to be remote effects of the cancer and may occur in association with onconeural antibodies.

Panels of paraneoplastic antigen targets of these onconeural antibodies may be useful in developing diagnostic immunoassays for early detection of ovarian cancer and its recurrence in the clinical setting.

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