

Case Report

Paraneoplastic cerebellar degeneration with fallopian tube adenocarcinoma

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Abstract

Background. Paraneoplastic cerebellar degeneration (PCD) is rarely caused by fallopian tube adenocarcinoma.

Case. We present a patient with PCD and fallopian tube cancer. Anti-Yo antibody, one of an anti-neuronal antibody, was positive in serum and cerebrospinal fluid. She was also positive for HLA A24, which is common in patients with PCD. Radical surgery did not significantly ameliorate her neurological impairment, although the dysarthria improved slightly.

Conclusion. This case highlights the importance of detecting the underlying malignancy in patients with subacute neurological impairment and shows that fallopian tube cancer can potentially cause PCD.

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Keywords: Anti-Yo antibody; Fallopian tube carcinoma; Paraneoplastic cerebellar degeneration

Introduction

Paraneoplastic cerebellar degeneration (PCD) is a rare neurological disorder that is characterized by the subacute onset of cerebellar dysfunction and is associated with an underlying malignancy. Many types of anti-neuronal antibodies have been identified in patients with PCD. Tumors such as ovarian cancer and breast cancer are commonly reported to be associated with PCD. Here, we present a rare case of PCD that occurred in a patient with occult fallopian tube cancer.

Case report

A 63-year-old woman (G2, P2) began to experience occasional episodes of dizziness in May 2003. The symptom

gradually became more severe and then she complained of dropping a teacup involuntarily. In June, she developed gait disturbance and occasional numbness of the extremities. Slurring of her speech occurred at the same time and subsequently became worse. She also lost about 8 kg of weight over 3 months. At the end of June, she was referred to the Neurology outpatient clinic of our hospital. At the first visit, she was alert and well oriented. Neurological examination showed vertical nystagmus, severe dysarthria, truncal ataxia, and dysdiadochokinesis. Her coordination was significantly impaired, but there were no sensory deficits. Her past medical history was unremarkable, except for trigeminal neuralgia 6 years earlier.

Brain MRI and CT did not reveal any abnormalities. Abdominal CT and pelvic MRI were also performed, and detected a 5 × 5 cm solid mass in her right pelvic cavity with para-aortic lymph node swelling, suggesting a gynecological malignancy (Figs. 1A, B). The serum CA125 and CA546 levels were 36 U/ml (normal <35) and 49 U/ml (normal <12), respectively, while other tumor markers (including CA19-9, CEA, and CA602) were within normal limits. Because PCD

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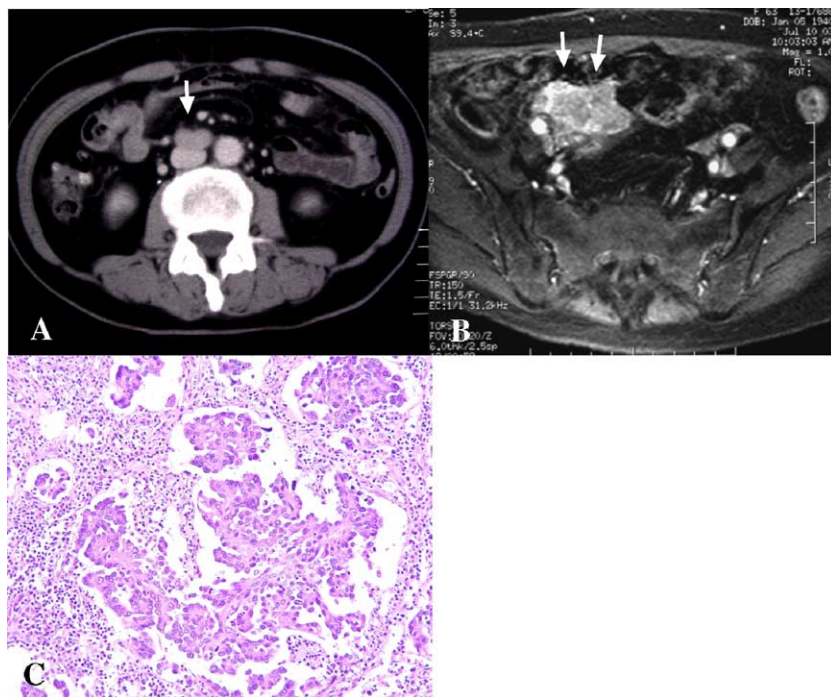


Fig. 1. Pelvic MRI, abdominal CT, and histopathological findings. (A) Pelvic MRI. A solid mass (5 × 5 cm in diameter) is seen on the right side (arrow). (B) Abdominal CT. Enlargement of para-aortic lymph nodes is seen (arrow). (C) Histopathological findings. Atypical cells are arranged in a papillary configuration, suggesting serous adenocarcinoma.

was suspected, anti-neuronal antibodies were examined, including anti-Yo antibody, anti-Ri antibody, anti-Hu antibody. Among these, only anti-Yo antibody was positive. This antibody was also detected in the cerebrospinal fluid, confirming a diagnosis of PCD associated with assumed gynecological cancer. After detailed discussion, radical surgery was scheduled. Before the operation could be done, her dysarthria became so bad that she could hardly communicate with the medical staff or her family and she eventually became completely bedridden.

At operation, a right adnexal mass about 6 cm in diameter was detected to which the appendix was firmly adherent. There was also massive para-aortic lymph node enlargement. Both ovaries appeared to be normal. Total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, and pelvic and para-aortic lymphandectomy were

performed. Intraoperative and postoperative pathology confirmed a diagnosis of serous adenocarcinoma originating from the right fallopian tube (Fig. 1C). Both ovaries were clear of tumor invasion, but the appendix was macroscopically involved. Tumor invasion was also positive in the para-aortic lymph nodes and right common iliac lymph nodes. Thus, the surgical stage of this fallopian tube adenocarcinoma was FIGO stage IIIc (pT3aN1M0).

The postoperative course was unremarkable with no major complications. Her neurological manifestations showed little change from the preoperative status, except that dysarthria improved slightly. Because of the high recurrence rate of tubal carcinoma, postoperative chemotherapy (paclitaxel: 180 mg/m², and carboplatin: AUC 6) was scheduled. After the first course, however, she refused additional treatment because of side effects such as emesis

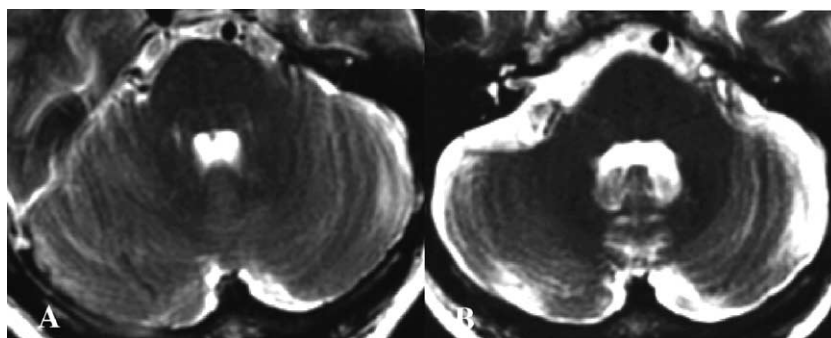


Fig. 2. Brain MRI findings. (A) MRI just before surgery. (B) MRI at 3 months after surgery. Note that the fourth ventricle is dilated and the gyrus is more prominent, indicating cerebellar atrophy.

and nausea. She was then given methylprednisolone pulse therapy, but there was no neurological improvement. At 2 months after surgery, brain MRI showed mild cerebellar atrophy (Fig. 2), while serum anti-Yo antibody was negative. At present, 22 months since operation, her neurological impairment is unchanged.

Discussion

PCD is one of the disorders categorized among paraneoplastic syndromes, and is a unique form of neurological dysfunction due to the remote effect of malignancy on the nervous system. The neurological features include ataxia, gait disturbance, dysarthria, vertigo, diplopia, and nystagmus. These symptoms sometimes precede discovery of the underlying neoplasm by more than a year, and may lead to severe disability while the tumor remains asymptomatic [1]. Ovarian cancer, lung cancer, breast cancer, and Hodgkin's lymphoma are the neoplasm most commonly associated with PCD. Review of the world literature showed that only four cases of PCD associated with fallopian tube adenocarcinoma have been reported previously (Table 1) [1–3].

The current hypothesis about the mechanism of PCD is that expression of neuronal proteins by the patient's tumor provokes an immune response that eventually causes neurological disorders [4]. So far, nine associated autoantibodies have been identified. Anti-Yo antibody is the most frequently detected (38%), followed by anti-Hu (32%), anti-Tr (14%), and then anti-Ri (12%) [5]. Anti-Yo antibody is a polyclonal IgG antibody that reacts with a cytoplasmic component of cerebellar Purkinje cells.

The precise role of anti-Yo antibody in the pathogenesis of PCD is unclear and there is no direct evidence that the presence of this antibody causes the loss of cerebellar Purkinje cells in PCD patients. The observation that anti-Yo antibodies activate T cells which can lyse target cells presenting the Yo antigen (also called cdr2) in vitro indicates that T cell responses have an important role in PCD [6]. In our patient, cerebellar degeneration was not arrested even after anti-Yo antibody became negative, suggesting that the assault of anti-Yo antibody-mediated immune complexes against Purkinje cells leads to ongoing

inflammation and degeneration even in the absence of the initial stimulus. Immunohistochemistry of the Yo antigen was performed on the tumor tissue but no positive staining was noted. However, serum antibodies to anti-Yo were detected. We could not conclude the significance of the anti-Yo antibody as we could not demonstrate direct lysis of tumor cells with the anti-Yo antibody.

The genetic background seems to be involved in the development of PCD. Tanaka et al. performed HLA typing of nine PCD patients with anti-Yo antibody, and all of them possessed HLA A24, which is found in approximately 35% of the Japanese population. Our patient was also positive for HLA 24A. Thus, HLA typing may be useful to assist in the diagnosis of PCD because anti-neuronal antibody tests can take several weeks.

There is no established treatment for the neurological deficits of patients with PCD [7]. Resection of the underlying malignancy may lead to some improvement or at least stop progression. The interval between the onset of neurological symptoms and treatment of the underlying malignancy seems to have no impact on the functional prognosis. We performed surgery within about 1 month of the onset of neurological symptoms, but failed to achieve functional improvement. Intravenous immunoglobulin-G and steroids are sometimes tried, but the effects seem to be limited. Rituximab was reported to dramatically improve neurological symptoms in a bedridden patient who regained the ability to walk and remained stable for more than a year [8].

The impact of PCD can be devastating. Shams'ili et al. reported that the 5-year survival rate of 19 PCD patients with anti-Yo antibody was less than 25%, with the median survival time from diagnosis being 13 months [5]. Rojas et al. reported that about half of PCD patients die from their cancer, while the rest die because of neurological progression [7]. As the poor prognosis of PCD patients is concerned, it can be difficult to decide whether or not to perform radical surgery, since the chance of neurological recovery is rather low and the risk of complications related to cerebellar ataxia is very high. Thus, decisions regarding treatment must be made after detailed discussion between the physician and patient. Rehabilitation might be a treatment option, as Pelmutter et al. reported a PCD patient who

Table 1
Previous case reports of PCD associated with fallopian tube adenocarcinoma

Author (year)	Age	First symptoms	Time interval until diagnosis	Positive antibody	Pathology (FIGO stage)	Treatment	Neurological improvement
Tanaka et al. (1995)	70	Diplopia, dizziness	4 months	Anti-Yo	Poorly differentiated adenocarcinoma (II)	Surgery, chemotherapy	(+)
Matsushita et al. (1998)	57	Dysarthria, diplopia	13 months	Anti-Yo	Poorly differentiated adenocarcinoma (Ic)	Surgery, chemotherapy	(++)
Matsushita et al. (1998)	70	Diplopia	3 months	Anti-Yo	Poorly differentiated adenocarcinoma (Ic)	Surgery, chemotherapy	(+)
Levite et al. (2001)	81	Diplopia, tinnitus	1–2 months	Anti-Yo	Serous adenocarcinoma	Surgery	(–)
Presented case (2003)	63	Gait, disturbance, dysarthria	1 month	Anti-Yo	Serous adenocarcinoma (IIIc)	Surgery, chemotherapy	(+/-)

showed functional improvement after 3 weeks of comprehensive inpatient rehabilitation [9].

In summary, we presented a rare case of PCD associated with fallopian tube adenocarcinoma. Anti-Yo antibody was positive in the serum and cerebrospinal fluid and the neurological symptoms stabilized after complete surgical resection. In patients with subacute onset of neurological impairment suggesting PCD, investigation of the underlying malignancy and anti-neuronal antibodies may help to make a definitive diagnosis.

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