

# Anti-Yo Negative Paraneoplastic Cerebellar Degeneration Following Ovarian Carcinoma: A Case Report and Review of the Literature

## Over Kanseri Sonrası Gelişen Anti-Yo Negatif Paraneoplastik Serebellar Dejenerasyon: Olgu Sunumu ve Literatür Özeti

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### ABSTRACT

Paraneoplastic syndromes are disorders of organs or tissues that occur at a site distant from primary cancer or its metastases. Paraneoplastic cerebellar degeneration (PCD) is a rare and unusual non-metastatic neurologic complication as a remote effect of cancer. Clinically it is characterized by subacute onset by progressive pancerebellar dysfunction including truncal and gait ataxia, dysarthria and nystagmus. Although the role of these antibodies in the mechanisms of PCD remains unknown, the detection of these antibodies in serum of patients suspected of PCD often lead to a focused search for the underlying neoplasms. In this case report, it was aimed to increase our knowledge about this rare syndrome by investigating 55 years old female patient with PCD after ovarian cancer. (*JPMRS 2009;12:122-5*)

**Keywords:** PCD, ovarian carcinom, Anti-Yo, rehabilitation

### ÖZET

Paraneoplastik sendromlar primer kanserden veya metastazlarından uzak olan bir bölgede organları veya dokularda görülen hastalıklardır. Paraneoplastik serebellar dejenerasyon (PSD) ise kanserin uzak etkisi olarak nadir görülen non metastatik nörolojik komplikasyondur. Klinik olarak gövde ve yürüyüş ataksisi, dizartri ve nistagmusu içeren subakut fakat progresif panserebellar disfonksiyon ile karakterizedir. PSD'nin mekanizmasındaki rolü tam olarak bilinmese de bu antikorların serumda tespit edilmesi altta yatan kanserin araştırılmasında yol gösterici olmaktadır. Bu olgu sunumunda over kanseri sonrası PSD gelişen 55 yaşındaki bayan hastayı inceleyerek nadir görülen bu sendrom hakkında bilgilerimizi arttırmayı amaçladık. (*FTR Bil Der 2009;12:122-5*)

**Anahtar kelimeler:** PSD, over kanseri, Anti-Yo, rehabilitasyon

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### Introduction

Paraneoplastic syndromes may be defined as effects of cancer that occur at sites remote from both the primary tumor and its metastases. They are estimated to occur in less than 15% of malignancies and overall are most commonly associated with cancers of the lung, stomach, and breast. Although uncommon, their effects are often dramatic and sometimes more disabling than the tumor itself. They may precede, coexist or follow the primary tumor by months or years and often

follow an unpredictable course (1). Paraneoplastic syndromes affecting the nervous system, also called 'remote effects of cancer on the nervous system', can affect any portion of the nervous system, usually causing neuronal degeneration that cannot be ascribed to metastases or to destruction of vital systemic organs by the tumor or its treatment (2). Our current knowledge of these syndromes began around 50 years ago when Brouwer and Biemond (3) attributed a peculiar degeneration of the Purkinje cells of the cerebellum to cancers, often small, located elsewhere in the body. Since that time, a bewildering variety of nervous system disorders have been associated with cancer (4).

Paraneoplastic neurological diseases comprise a number of different clinicopathological entities such as Purkinje cell degeneration (paraneoplastic cerebellar degeneration), dorsal root ganglion degeneration (subacute sensory neuronopathy), failure of neuromuscular transmission (Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis), and more widespread damage to both central and peripheral nervous system (paraneoplastic encephalomyelitis) (5,6)

Paraneoplastic cerebellar degeneration (PCD) is a rare and unusual nonmetastatic neurologic complication as a remote effect of cancer (7). Clinically, it is characterized by subacute onset but progressive pancerebellar dysfunction, including truncal and gait ataxia, dysarthria, and nystagmus (8). The anti-onconeural antibodies (autoantibodies) associated with PCD include anti-Yo (anti-Purkinje cell antibody (anti-PCA1)) (9), usually associated with ovarian and other gynecologic cancers, anti-Hu (anti-neuronal nuclear antibody-1 (ANNA-1)) (10), found in patients with small-cell lung cancer, anti-Ri/Nova (ANNA-2) (10), detected in patients with breast cancer, and Anti-Tr, detected in patients with Hodgkin's disease (11). Although the role of these antibodies in the mechanisms of PCD remains unknown, the detection of these antibodies in serum of patients suspected of PCD often lead to a focused search for the underlying neoplasms. In this case report, it was aimed to increase our knowledge about this rare syndrome by investigating 55 years old female patient with PCD after 5 years from detection and treatment of an ovarian cancer.

## Case

In August 2007, a 55 year old woman presented to our hospital with sudden headache, dizziness, nausea and vomiting. In her history she was operated for ovarian carcinoma and subsequently exposed to 6 cure chemotherapy 5 years ago.

Speech and gait ataxia, dysphagia, dysmetri, dysdiadokokinesia, nystagmus, hypoesthesia, and areflexia in lower limb were detected in her examination. Examination of cranial nerves was normal. The muscle strength was well preserved. Pathological reflexes weren't detected. There weren't any significant pathology in cranial MRI and ear MRI, cranial BT. Electrophysiological tests were performed for hypoesthesia in lower limbs in order to evaluate polyneuropathy that's why she exposed to chemotherapy 5 years ago due to ovarian carcinoma. Electrophysiological evaluation was in the normal limits. Blood count, routine biochemical tests, spot urine tests, culture of blood and urine were also in normal limits. Cerebrospinal fluid (CSF) examination, protein and glucose level in CSF were in normal limits. Cytology and organisms of CSF were negative. But the index of immunoglobulin G was high compatible to paraneoplastic syndrome. Abdominal tomography and ultrasonography, and vaginal ultrasonography were normal. Both mammography and colonoscopy were unremarkable. Serum tumor markers (cancer antigen (CA) 19-9, CA 15-3, CA 125, carcinoembryonic antigen (CEA) and leukemia marker) were within normal limits. F-FDG whole

body and brain positron emission tomography scan were unremarkable. Pap smear examination was unremarkable.

The fact that any finding supporting meningeal involvement or cerebellar involvement in the cranial MRI of the patient who has such complaints as dizziness, dysarthria and ataxia has not been encountered supports that BOS researches are in a normal level except height of IgG and the patient has paraneoplastic syndrome because of experience of over ca. In evaluating the paraneoplastic antibody panel Anti-Hu, Anti-Yo, Anti-Ri, antibodies were within normal limits. Five cure plasmapheresis were administered to patient. Dizziness, nausea and vomiting complaints were regretted after the treatment of plasmapheresis. Physical therapy and rehabilitation program were started after plasmapheresis and continued 5 weeks. After the program of rehabilitation any improvement weren't gained in sitting balance and independent ambulation. The patient were discharged with home exercise program.

## Discussion

The paraneoplastic syndromes represent a diverse group of disorders that reflect the remote effects of cancer arising in any specific organ system. Although fewer than 15% of cancer patients experience these syndromes, recognition is important because clinical manifestations of paraneoplastic syndrome can precede those of the underlying malignancy by months, or even years (12). Paraneoplastic neurological syndromes are defined by the presence of cancer and exclusion of other known causes of neurological symptoms.

Several hypotheses have been advanced to explain the peculiar phenomenon of nervous system degeneration in patients with small (sometimes less than a centimeter in diameter), non-metastatic cancers. These hypotheses include, firstly, the secretion of a 'toxin' by the tumor (13). If one considers ectopic production of hormones, such as adrenocorticotrophic hormone (ACTH) or parathyroid hormone-related protein, by tumors as toxins, this mechanism certainly occurs in some instances. Secondly, the tumor and the nervous system may compete for an essential substrate, with the nervous system ending up the loser (14) Thirdly, opportunistic infections can affect the nervous system and so may cause neuronal degeneration. The best example is progressive multifocal leukoencephalopathy, a disorder caused by the papovavirus invading the brain. Opportunistic infections generally occur only in patients who are significantly immune suppressed, however, and most patients with paraneoplastic syndromes have small, solid tumors, such as lung or ovarian cancer, and show no evidence of immune suppression. Finally, the best current hypothesis is that most, if not all, paraneoplastic syndromes affecting the nervous system (as defined above) are immune-mediated (15).

Autoimmunity has been proposed for the pathogenesis of PCD since the identification of the anti-onconeural antibodies (9). However, it is now recognized that anti-Yo alone is not enough for the pathogenesis of PCD because some anti-Yo

(+) patients with ovarian cancer never develop PCD (16). Removal of the anti-Yo from patients by plasmapheresis usually does not ameliorate the neurological symptoms (17). In addition, animal models failed to reproduce PCD although the injected anti-Yo IgG was accumulated in cerebellar Purkinje cells (18,19). It was reported that about 50% of PCD patients aren't associated with anti-Yo (20,21).

In this case PCD was considered because of the presence of acute condition of cerebellar dysfunction and the absence of the risk factors (stroke, alcoholism, primer cerebellar and metastatic cerebellar carcinoma) for cerebellar dysfunction. Paraneoplastic syndromes can appear after years from primer carcinoma and about 50% of PCD patients aren't associated with anti-Yo (20,21) Thus existing of PCD 5 years after ovarian carcinoma and the absence of anti-Yo antibody in the serum didn't eliminate PCD in this case.

There have been various reports about treatment and prognosis of PCD. Various combinations of treatments for the underlying tumor with or without immunomodulation for the PCD in the form of steroids, plasma exchange and/or intravenous immunoglobulin (IVIg) and also rehabilitation endeavors were performed. Because PCD is considered to be an immunemediated syndrome, initial removal of the source of the antigen by treatment of the underlying tumor and suppression of the immune response should be attempted. Surgery is the cornerstone of management of epithelial ovarian cancer and has broad applications throughout the clinical course of disease, from initial diagnosis to palliative care. Comprehensive surgical staging is essential for precise prognostic determination and treatment planning for patients with apparent early-stage ovarian cancer. In conjunction with primary platinum-based chemotherapy, maximal cytoreduction at the time of primary surgery has been shown to be a powerful determinant of overall survival (13). Regression of cerebellar symptoms after complete tumor resection has only been reported in small-cell carcinomas of the lung and has not been reported in gynecological malignancies. Effective treatment of the cancer often correlates with stabilization of the neurological disorder.

Rojas et al. evaluated the long-term outcome of PCD and anti Yo antibodies in 2000. Of a total of 34 patients with PCD and anti-Yo antibodies, tumor progression was the cause of death in 52% of cases, whilst in 29% of patients it was the neurological condition. The failure to cure the cancer in 52% of patients was due to the fact that by the time the diagnosis had been made, most tumors had already metastasized to regional lymph nodes or distant organs (22). Attempts to treat the neurological symptoms on the whole, using chemotherapy, immunosuppression or immunoglobulins have not been reported to achieve any significant improvement (23). In addition, despite successful treatment of the primary tumour depending on its stage of development, there is usually no improvement in the patients' neurological symptoms. These generally have a greater negative impact on the patients' quality of life than the underlying malignancy.

Survival varied significantly between PCD patients according to antibodies. The median survival from time of diagnosis in the anti-Hu patients was 7 and in anti-Yo patients 13 months, confirming the grim prognosis (22,24,25). In contrast, the median survival in the anti-Tr (>117 months) and anti-Ri (>69 months) was not reached. Other factors predicting longer survival were administration of antitumor treatment and younger age.

It should be kept in mind that cases of cerebellar dysfunction seen often in rehabilitation practices can be depended on PCD, and it should be known that some PCD cases can be experienced before the diagnosis of carcinoma. Therefore, if etiological reasons cannot be diagnosed in the cases of cerebellar dysfunction, over and breast cancer, small-cell lung cancer and Hodgkin Disease should be eliminated.

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