An Unspecified Neurologic Paraneoplastic Syndrome Pointing out an Occult Relapse of Ovarian Cancer: A Case Report

Abdullah BÜYÜKÇELİK *, Ahmet DEMİRKAZIK *, Bülent YALÇIN*, Özden ŞENER, Güngör UTKAN*, Gökhan TULUNAY***, Fikri İÇLİ ***

* Department of Medical Oncology, Ankara University School of Medicine, Ibni Sina Hospital
** Department of Neurology, Ankara University School of Medicine, Ibni Sina Hospital
*** Department of Gynecology and Obstetric, Social Security Hospital, ANKARA

ABSTRACT

Neurologic paraneoplastic syndromes are rare in patients with ovarian cancer. These syndromes may point out an occult or relapsed disease. The management of the majority of neurologic paraneoplastic syndromes is difficult because no standard treatment is available but some type of them may subside with the treatment of underlying cancer. We present a case of neurologic paraneoplastic syndrome as a first symptom of relapsed ovarian cancer. However, we could not specify the syndrome with its clinical features and electrophysiological study. It subsided greatly following the cytotoxic chemotherapy for ovarian cancer and re-occured with the appearance of resistance to chemotherapy.

Key Words: Ovarian Cancer, Neurologic paraneoplastic syndrome, Chemotherapy

ÖZET

Non-Spesifik Nörolojik Paraneoplastik Sendromla Ortaya Çıkan Okkült Over Kanser Nüksü: Olgu Sunumu

Over kanserli hastalarda nörolojik paraneoplastik sendromlar seyrektir. Bu sendromlar, gizli veya nüks etmiş hastalığa işaret edebilir. Nörolojik paraneoplastik sendromların standart bir tedavi seçeneği olmadığı için tedavileri zordur. Ancak bazı tipleri, altta yatan kanserin tedavisiyle düzelebilir. Bu raporda, nüks etmiş over kanserinin ilk semptomu olarak beliren nörolojik paraneoplastik sendromlu bir olguyu sunmaktayız. Olgunun klinik özellikleri ve elektrofizyolojik çalışma ile sendromu tam olarak spesifiye edemedik. Over kanseri için uygulanan kemoterapi ile belirgin olarak düzeldi ve kemoterapi direncinin ortaya çıkmasıyla yeniden oluştu.

Anahtar Kelimeler: Over Kanseri, Nörolojik paraneoplastik sendrom, Kemoterapi

INTRODUCTION

The term of neurologic paraneoplastic syndrome refers to any kind of neurologic dysfunction occuring in patients with cancer, which is not caused by metastasis or direct invasion of nervous system by cancer, itself. Remote effects of cancer on nervous system mean that any neurologic disorder of unknown cause occurs exclusively or with increased frequency, in cancer patients. Both of these two terms are usually used interchangeably (1).

The best defined and symptomatic neurologic paraneoplastic syndromes are extremely rare. The frequency of recognized neurologic paraneoplastic syndromes is less than 1 percent in all of cancer patients. It is important to know the fact that not all patients with neurologic syndromes appearing to be paraneoplastic, have actually underlying cancer (2). Sensorimotor polyneuropathy is the most common type of the paraneoplastic syndromes involving the nervous system, followed by paraneoplastic cerebellar dejeneration in patients with ovarian epithelial cancer (3).

The cause and exact pathologic mechanisms of paraneoplastic syndromes are not known. There are five proposed mechanisms for the development of neurologic paraneoplastic syndrome in patients with cancer; (i) Nervous system is affected by substances secreted by tumor such as adrenocorticotropic hormone (ACTH), parathormone-related peptide and cytokines such as TNF and interleukins; (ii) Some opportunistic infections may be responsible for selected neurologic paraneoplastic syndromes, e.g. paraneoplastic cerebellar degeneration and limbic encephalitis; (iii) The competition by tumor for biochemical nutrients or substrates, e.g. tryptophan and niacin deficiency in large carcinoid tumors, is another possible mechanism; (iv) T-lymphocyte-mediated inflammatory response may be associated with tumor infiltrating or cytotoxic T-cells; (v) The most widely accepted mechanism is the autoimmun reaction against nervous system, e.g. subacute cerebellar degeneration, optic neuritis, opsoclonus-myoclonus, myastenia gravis, subacute sensory neuropathy and Lambert-Eaton myastenic syndrome (LEMS) (1, 2, 4, 5).

When a new neurologic syndrome develops in patients with known cancer, metastases to central nervous system should be ruled out first, because paraneoplastic neurologic syndromes are rare and metastases are common in cancer patients. A magnetic resonance imaging or computed tomography scan usually clarifies the metastases of central nervous system (1).

Majority of paraneoplastic syndromes are not effectively treated except LEMS and opsoclonus-myoclonus. While LEMS responds to plasmapheresis and 3,4-diaminopyridine treatment as well as treatment of primary malignancy, corticosteroid treatment is effective in opsoclonus-myoclonus (1, 6).

We present a case of unspecified neurologic paraneoplastic syndrome as an indicator for the relapse of ovarian epithelial cancer and discuss her clinico-electrophysiologic features.

CASE REPORT

A fourty-five years old woman was admitted to the hospital with the complaints of weakness, disphagia, hoarseness, regurgitation and neck pain in July 1995. Soft palate was paretic, deep tendon reflexes were globaly hypereactive and weakness in the distal extremity muscles was noted (muscle strenght was 3-4/5 according the Medical Research Council Criteria) on physical examination. Cranial nerves and sensorium were intact. Examination of other organ systems revealed no abnormality. Aspartate aminotransferase (AST) was mildly elevated, creatine phosphokinase (CPK) and lactat dehydrogenase (LDH) were normal. There was no abnormality in whole blood count, and the levels of glucose, alanin aminotransferase (ALT), total protein, blood urea nitrogen (BUN), creatine, sodium, potassium, calcium and phosphorus were also normal. CA 125 level was not elevated. Antibody against hepatitis C virus was positive but no evidence of hepatic disease was noted. Lumbar puncture was done to clarify the neurologic status of patient, and the appearance of cerebrospinal fluid was clear, colorless, and no clot formation was detected. The examination of cerebrospinal fluid showed that glucose level was 65 mg/dl (simultenous serum glucose level was 77 mg/dl), and albumin and chlorine levels were 15 mg/dl and 129 mmol/L, respectively. Cytologic examination revealed class II cytology and no microorganism including mycobacterium spp and fungi was isolated. Analysis of autoantibodies in the cerebrosipinal fluid and serum showed no

abnormalities, and screening for viral diseases was negative, except the antibody against hepatitis C virus. Antibodies against Toxoplasma gondii (IgM and G) were also negative.

MR of brain showed no abnormality. The magnetic resonance imaging of cervicothoracic vertebrae revealed degeneration and mild peripheral bulging of intervertebral discs in the levels of C5-C6, C6-C7 and Th6-Th7 with a minimal compression of subarachnoid space at the level of Th6-Th7.

There was an enlarged lymph node, 5 cm in diameter in the left para-aortic region on the CT of abdomen and pelvis. Also, the scan of CT of abdomen revealed a lesion of 5 cm in diameter in right lobe, postero-superior segment of liver. Lesion had a peripheral opacification following intravenous contrast injection, pointing out a hemangioma. There was no abnormality in esophagogastroscopy. Fine needle aspiration of enlarged left para-aortic lymph node revealed the recurrence of papillary adenocarcinoma of ovary.

In her medical history, she had a total abdominal hysterectomy and bilateral salpingo-ovariectomy for ovarian papillary cyst adenocarcinoma, with FIGO stage III in March 1995. Four cycles of CEP (cyclophosphamide, epirubicin and cisplatin) was applied as adjuvant basis. Shortly after fourth cycle of adjuvant chemotherapy patient was admitted to the hospital because of neurologic complaints mentioned above. Patient had only 5 months of disease free survival. She had a diagnosis of depression 4 years ago before admission. She had 4 healthy children. All 2 brothers and 4 sisters had diabetes mellitus.

Electrophysiologic study showed that the duration of motor unite action potentials was short and the incidence of polyphasic potential was high in proximal muscles studied. This finding was compatible with myopathy. The conduction velocity of motor and sensorial nerves, the amplitudes of sensorial nerve and of compound muscle action potentials were normal. Repetitive stimulation study of the biceps brachii muscle revealed a 25 percent increment in the compound muscle action potential and amplitude with a stimulation of tetanic frequency. The amplitude of compound muscle action potential dropped down to about a half of that of pretetanic stimulation level (from 5 mV to 2.7 mV), 4 minutes after tetanic stimulation. This was compatible with post-tetanic exhaustion. The findings of electrophysiologic study did not point out specifically to the disease of neuromuscular junction but there was an evidence of myopathy in studied muscles.

Since the disease relapsed shortly after fourth cycle of CEP, high dose ifosfamide (20 g/m2) was initiated for palliative treatment. Enlarged left paraaortic lymph node was stable but the complaints of patient related to nervous system were improved dramatically following two cycles of high dose ifosfamide regimen. Chemotherapy regimen was changed to ifosfamide and cisplatin combination because of the stable disease. No response to three cycles of ifosfamide and cisplatin combination was observed. Her neurologic complaints relapsed one month later after the last course of ifosfamide and cisplatin. Paclitaxel was considered for the third-line chemotherapy but the patient died of refractory disease with the deteriorating neurologic picture. Autopsy was not performed because of the refusal of the patient's relatives.

DISCUSSION

Neurologic paraneoplastic syndromes which are rare and indirect nervous system disturbance located distant from a neoplasm, have been reported in association with ovarian cancer. Majority of neurologic paraneoplastic syndromes were not treated effectively, while some of them may be subside following the effective chemotherapy, radiotherapy and surgery or any combination of them (1-4).

LEMS which is a disorder of the myoneural junction that results in proximal muscle weakness, is frequently associated with small cell lung cancer. Women are more affected than men in LEMS. Muscle weakness and fatigability that is usually worse in the proximal muscles are the clinical findings of LEMS. The bulbar musculature is not involved in LEMS, although one-third of patients suffer from dysphagia. Nerve conduction velocities have a characteristic pattern with normal conduction velocities and initially low amplitude compound muscle action potential (CMAP). The CMAPs increase to near normal levels following exercise. There is a decrement of the compound muscle action potentials at low stimulation rates

and an increase in the compound muscle in action potentials at high stimulation rates in repetitive nerve stimulation studies (1-4). It is unlikely that our patien had LEMS, since the absence of symptoms of autonomic nervous system and hyper-reactivity in deep tendon reflexes are not compatible with this syndrome. Dysphagia, weakness of limbs are compatible with myopathy, though the serum levels of CPK and LDH were normal. Likewise, electrophysiologic study did support the myopathy. Nevertheless, muscle biopsy could not be done to clarify myopathy in our patient. On the other hand, the increment of 25 percent in the amplitude of compound muscle action potantial was not enough for the diagnosis of LEMS, but considering the post-tetanic exhaustion these findings may point out to the disorder of neuromuscular junction.

Cerebellar degeneration is the frequently reported paraneoplastic neurologic syndrome in patients with ovarian cancer (1-3, 6). It is unlikely that our patient had paraneoplastic cerebellar degeneration because of absence of limb ataxia, dysarthria, nystagmus, vertigo and diplopia.

Dermatomyositis and polymyositis may be associated with cancer, especially breast and lung cancer. In these disorders, there is a subacute development of proximal muscle weakness, with or without pain and muscle tenderness and dermatomyositis has the classic heliotrope rash over the face, elbows, knees, and knuckles, in addition to the muscle weakness. CPK and LDH are elevated significantly in these diseases (1). There was no heliotrope rash, CPK and LDH elevation in our patient and electrophysiologic study was not compatible with myositis.

Sensorimotor polineuropathy is another paraneoplastic neurologic syndrome which may develope in patient with ovarian cancer (6). Sensorial loss was absent and deep tendon reflexes were hypereactive, in contrast to sensorimotor polineuropathy, although weakness in distal muscles was observed in our patient.

Our patient presented dysphagia, limb weakness and regurgitation without loss of deep tendon reflexes and with no sensory deficit. Metastases was ruled out by MRI and CT of central nervous system. The findings of electrophysiologic study were not specific to point out a definitive neurologic paraneoplastic syndromes. The relapsed ovarian cancer was documented by fine needle aspiration of enlarged para-aortic lymph node. Treatment with high dose ifosfamide resulted in dramatic improvement of neurologic status of our patient without any change in diameter of enlarged abdominal lymph node. It was likely that our patient had a neurologic paraneoplastic syndrome because; (i) it simultaneously occured with the relapse of ovarian cancer and (ii) it greatly subsided with the cytotoxic chemotherapy and re-occured with the development of chemotherapy resistance. It may also be possible that the neurologic paraneoplastic syndrome of this patient could not develop completely since the palliative chemotherapy was started early, and the course of the disease was very short after its recurrence.

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Correspondence:

Dr. Abdullah Büyükçelik

Ankara Üniversitesi Tıp Fakültesi,

Tıbbi Onkoloji Bilim Dalı

Cebeci Hastaneleri,

06590 Dikimevi ANKARA

Phone: +90 (312) 362 30 30 Dahili.7139

Fax: +90 (312) 319 22 83

e-mail: drabdullah@superposta.com