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Paraneoplastic Peripheral Neuropathy in a Case with an Anti-Yo Positive Ovarian Carcinoma

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ABSTRACT

Paraneoplastic neurological syndromes (PNS) are defined as distant effects of tumors on the nervous system other than metastasis, direct invasion, and metabolic and vascular effects. Despite being rarely encountered diseases of neurology, they are important as early indicators of systemic cancer. There are rare cases reported in the literature of paraneoplastic peripheral neuropathy associated with the development of ovarian malignancy. Our case exhibited positive anti-Yo, ovarian adenocarcinoma, and peripheral neuropathy.

Keywords: Paraneoplastic, Neuropathy, Ovarian carcinoma

ÖZET

Paraneoplastik Periferik Nöropatisi Olan Anti Yo Pozitif Over Karsinomu Olgusu

Tümörlerin metastaz, direkt yayılım, metabolic ve vasküler etkilerinin dışında sinir sistemi üzerindeki uzak etkileri paraneoplastik nörolojik sendromlar olarak tanımlanır. Nörolojinin oldukça nadir karşılaşılan hastalıkları olmalarına karşın, sistemik bir kanserin erken habercisi olmaları nedeniyle önem taşırlar. Literatürde ovaryan maligniteye bağlı gelişmiş paraneoplastik periferal nöropati olguları nadirdir. Olgumuzda anti Yo pozitifliği, over karsinomu ve periferik nöropati birlikteliği vardır.

Anahtar Kelimeler: Paraneoplastik, Nöropati, Over karsinomu

INTRODUCTION

Paraneoplastic syndromes (PNS) are defined as distant effects of tumors on the nervous system, other than metastasis, direct invasion, metabolic and vascular effects.[1] Despite being rarely encountered diseases of neurology, they are important since they are early signs of a systemic cancer. Neurological conditions generally are initiated subacutely and develop in weeks to months, and stabilize after reaching a certain level.[2] Thus, the diagnosis of a neurological condition may be indicative that a cancer is developing and consequently present the opportunity to initiate treatment of that cancer at an early stage. Clinical conditions involving the "paraneoplastic syndromes" (subacute development of sensorimotor polyneuropahty, cerebellar syndrome, dermatomyositis and Lambert-Eaton syndrome) in middle aged patients should trigger the investigation of systemic malignancy.[3]

There are rare cases reported in the literature of paraneoplastic peripheral neuropathy associated with ovarian malignancy. We present a case with positive anti-Yo, ovarian adenocarcinoma, and peripheral neuropathy.

CASE REPORT

A 65-year-old female patient presented at clinic complaining of numbness in her feet, balance problems and difficulty in walking. The numbness had developed 8 months previously, and her condition progressed over time. For the last 6 months before she presented at the clinic, she had balance problems when walking, and even fell down on occasions. She had lost 6 kg in the last month. Any reason was not known to explain the weight loss for the patient. Her neurological examination, mental evaluation and cranial nerve examination were within normal limits. Her muscle capacity was 5/5 in the four extremities and her muscular tonus was normal. Deep tendon reflexes were absent in all extremities and there were no pathological reflexes. There was glove and sock type hypoesthesia. Joint position sense in the lower extremities, and vibration sense in the distal parts of the upper and lower extremities were reduced. There was also truncal ataxia.

In laboratory examinations, liver and renal function tests, electrolyte levels, blood sugar levels, lipid profile, Hgb, Htc, MCV, Vitamin B_{12} level and thyroid function tests were all within normal limits. The erythrocyte sedimentation rate (ESR) was 50 mm/h. She was HIV negative in serum tests, and TORCH negative both in serum and cerebrospinal fluid (CSF) samples. Her IgG level in CSF was 3 times higher than normal and was accompanied by elevated levels of CA-125 and CA 15-3. CA- 125 levels was 1261 U/ml (Normal range: 0- 35 U/ml) and CA 15- 3 levels was 76.2 U/ml (Normal range 0- 31.3 U/ml). Serum immunoelectrophoresis displayed a gammopathy characterised by both IgG heavy chain and kappa light chain increase. The CSF immunoelectrophoresis result was normal.

Her mammography and thorax computed tomography (CT) images were within normal limits. Pelvic ultrasonography (USG) revealed a septated cystic neoplastic lesion 10 x 8.4 x 9.7 cm in dimensions and, with a solid component in the left ovarian region. A semisolid neoplastic lesion with a maximum dimension of 15 cm, containing large cystic components and heterogenous solid components was located above the bladder and left of the mid line in abdominal CT imaging of the pelvis. Fluid or acid had no view in pelvic visualization. Brain magnetic resonance imaging (MRI) was within normal range.

In her electroneuromyographic (ENMG) evaluation, compound muscle action potential (CMAP) amplitudes of ulnar nerve and posterior tibial nerve were low, but CMAP amplitudes of the peroneal nerve were at the lower range of the normal limits for laboratory testing. Sural nerve response was absent on the left side, and there was low CMAP amplitude and a long latency period on the right side. P1 cortical latency was delayed in the bilateral posterior tibial somatosensory evoked potential (SEP). EMG evaluation of muscles of the lower extremities revealed extensive, acute and chronic denervation symptoms which indicated the presence of sensorimotor axonal neuropathy dominance.

The patient was suspected of being anti-Yo positive, and anti-Hu negative in paraneoplastic syndrome related tests. Anti-Yo antibodies were studied by indirect immonufloresence, using anti–Yo kits (EURIMMUN, Germany). Immunohistochemical reactions were seen only within the cytoplasm of Purkinje cells where the antibodies were in the range of 34 kD and 62 kD proteins in Western blot analysis.

Bilateral salpingo-oophorectomy and total hysterectomy were subsequently performed in another center and the pathology report indicated ovarian mucinous adenocarcinoma. The patient rejected chemotherapy. Neurological findings were continued in the postoperative first year of the patient. Patient was followed with symptomatic treatment and physiotherapy program within annual, clinical progression wasn't observed.

DISCUSSION

The neurological effects of systemic cancers, other than tumors of primarily central nervous system origin, can be mainly classified into metastatic and non-metastatic effects. PNS, which are known as distant effects, are neurological conditions that may appear during any period of systemic cancer progress.[2] Since they can appear up to two years before clinical symptoms or signs of systemic cancer appearance, it is very important to diagnose them correctly.[2]

The most common characteristic of PNS is that their symptoms generally appear before tumor diagnosis. Thus, in most cases, the patient first presents to the neurology department for diagnosis. The second characteristic is that the underlying tumors are generally in a limited extent and progress more slowly than their related PNS. Thus, they are often treatable. When PNS appear, the tumor is generally non-metastatic, except for local lymph nodes.[3] However, neurological conditions are still frequently severe, leading to serious, often irreversible disabilities. Consequently, they were the most important findings in our patient.

PNS are more commonly detected in women than men.[4] Although the incidence is not exactly known, PNS with clinical symptoms were reported in less than 5% of cancer patients.[5] Although some authors claim that subclinical cases can reach up to 50%, neuroradiological tests for PNS of the central nervous system are frequently negative[4], as was the case in our patient. Although there are often no symptoms apart from atrophy of muscles, there are still some exceptions. Although the patient has lost six kilograms in the last month, weight loss is not typical for the over cancer.[2] Cerebrospinal fluid frequently shows mild or moderate pleocytosis, protein increase, IgG increase and oligoclonal bands, which can be indicative of inflammation of neural tissues.[6]

ENMG is diagnostic for paraneoplastic syndromes of the peripheral nervous system and muscles[7], and paraneoplastic subacute sensory neuropathy (SSN) is almost always related to the presence of anti-Hu antibodies. More than 70% of cases are observed in conjunction with small cell lung cancer (SCLC).[8, 9] SSN can also be seen with other cancers, including adrenal cancer, prostate cancer, neuroblastoma and different types of lung cancer. The pathology of SSN reflects common lymphocytic infiltration together with neuron loss; these characteristics do not depend on the clinical features.[4,10] Anti-Hu antibodies react immunohistochemically with the nuclei of all peripheral and central neurons and all SCLCs.[6] In paraneoplastic SSN paresthesia and dysesthesia start from the lower extremities and progress rapidly. All sensory modalities are affected, and there is loss of reflexes but motor weakness does not occur. In ENMG, sensory action potentials cannot be elicited but motor conduction studies are within normal limits, indicating a sensory axonal polyneuropathy.[7] Very rarely, in gynecological cancers, SSN related to anti-Yo may also be seen.[1,6] Our patient was diagnosed with paraneoplastic peripheral sensory and motor neuropathy associated with an anti-Yo positive ovarian carcinoma. Anti-YO which is also positive in our patient, particularly is an auto-antibody specific to ovarian cancer. Even if these antibody is positive, neurologic symptoms may not be seen in patients.[11] Subacute sensory-motor neuropathy rarely has a paraneoplastic cause. It is generally linked to lung cancer.[6] Fast developing distal symmetrical polyneuropathy, and in rare cases CIDP-like progress can be observed.[6] Axonal polyneuropathy is generally observed in the ENMG.[6] Our patient's clinical, laboratory and electroneuromyographic findings accorded with adenocarcinoma and sensory-motor axonal neuropathy affecting the lower extremities predominantly. The patient was anti-Yo positive and anti-Hu negative in paraneoplastic syndrome related tests.

Although the genesis of PNS are not clearly understood, many theories about their pathogenesis have been developed in recent years.[2,3] Autoimmune theory is the most widely accepted. However, the exact role of the autoantibodies in pathogenesis is unknown.[10]

In conclusion, the most important approach in the treatment of PNS is the diagnosis and treatment of the underlying cancer.[6] The neurological condition, if not totally cured, can at least be stabilized through the use of immunosuppressive or immunomodulator treatments like steroids, intravenous immunoglobin-IVIg, and plasmapheresis. Nevertheless, their cost-effectiveness should always be considered.

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