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A rare case of paraneoplastic cerebellar ataxia secondary to Gynaecological malignancy

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Abstract

We report on a rare case of paraneoplastic syndrome (PS) that was discovered on completion of diagnostic work up to be a fallopian tube carcinoma. A 65year old female, presented with 1 month history of imbalance, gait instability, incoordination of right upper limb, vertigo and vomiting. Cerebrovascular accident and drug intoxication was excluded. Indicative of further diagnosis of paraneoplastic syndrome was presence of adnexal mass in pelvis with identification of onconeural anti-Yo antibodies, detection of which leads to the confirmation of diagnosis. The anti- Yo (Anti-Purkinje cell) antibodies that specifically damage Purkinje cells of the cerebellum. Anti- Yo related paraneoplastic cerebellar degeneration is most commonly found in women with gynecological and breast cancers.

Keywords: Fallopian tube cancer, paraneoplastic syndrome, paraneoplastic neurological disease.

Introduction

Paraneoplastic neurologic syndromes (PNS) are rare disorders and they occur in 1-3% of all cancer patients [1]. These syndromes are a heterogenous group of cancer related neurologic diseases and it may affect any part of the nervous system, presenting with numerous neurological symptoms that mostly manifest prior (months to years) to the diagnosis of the tumor or in a patient with known malignancy [1]. These disorders are caused by mechanism other than metastasis, metabolic and nutritional deficits, infections, and coagulopathies or anti-cancer treatment related side effects [2]. The mechanism involved is thought to be due to onconeural antibodies expressed by malignant tumors are directed against neural antigen and thus lead to neurological symptoms [3]. Paraneoplastic neurological symptoms though rare, their clinical symptoms often severe, leading to correct diagnosis of a tumor disease that often responds well to treatment or is even curable [3].

Paraneoplastic cerebellar degeneration (PCD) is one of these neurologic disease and patients usually present with acute or subacute onset of ataxia, dysarthria and intention tremors. Although cognitive function usually preserved, mild cognitive or memory deficit can occur in approximately 20% of patient with PCD [1]. They will frequently have small cell carcinoma, Hodgkin's lymphoma or carcinoma of the breast or ovary and rarely found to be associated with other malignancies including esophagus, gastric and prostate adenocarcinomas in the literature. [1] On suspicion of a paraneoplastic syndrome with cerebral cerebellar involvement, antibodies against intracellular antigens, so called onconeural antibodies (Hu, Yo, Ri, CV2, amphiphysin) as well as antibodies against surface antigens (NMDA receptor, AMPA receptor, GABA receptor) should be determined.

The anti-HU antibodies (ANNA-1) have been reported in paraneoplastic neurological symptoms such as encephalomyelitis, limbic encephalitis and also in paraneoplastic cerebellar degeneration (PCD) and are triggered by small-cell lung cancer.

The anti-Ri (ANNA-2) antibodies causes symptoms of brain stem encephalitis and have also been observed in breast cancer as well as small-cell lung cancer. The Ma2 antibody is also found in limbic encephalitis and brain stem encephalitis.

Antibodies against surface antigens occur not only in autoimmune diseases but also within the framework of a paraneoplastic syndrome (e.g., limbic encephalitis) The anti-Yo antibodies detected in this case report are almost exclusively associated with gynecological tumors (breast cancer and ovarian cancer). In addition, these antibodies are sporadically described in women and men with adenocarcinomas, e.g., of the lungs or lymphomas [4].

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Anti-Yo syndrome usually presents as, acute to subacute (a few days to 4 months) cerebellar symptoms with stance and gait ataxia, nystagmus and dysarthria occur. Sometimes sensitivity disorders in patients have been described, due to damage to white columns^[5].

PCD is characterized pathologically by severe loss of Purkinje cells, with the presence of antibodies reacting with the cytoplasm of these cells associated with inflammatory infiltrates of the cerebellar cortex, deep cerebellar and inferior olivary nuclei leading to molecular atrophy^[6].

CSF diagnostics often lead to the detection of oligoclonal bands and thus to confirmation of an immune process. In cranial MRI, atrophy of the cerebellum is only seen in advanced stages^[3].

When onconeural antibodies have been detected, a search for a tumor likely causing these antibodies is mandatory; further disease progression can be arrested by removal of the tumor. An immunosuppressive therapy with corticoids, chemotherapy or immunomodulation to influence the autoimmune processes (to slow down the progression of cerebellar degeneration) is only rarely useful in cases of antibodies directed against intracellular antigens. The disease course as a whole is determined more by the neurological impairments than by the triggering tumor.

Incidence of primary fallopian tube carcinoma is 0.1%–1.8% of all genital malignancies and very few cases of its association to paraneoplastic neurological syndrome has been reported in the literature^[7]. Staging and therapy are similar to those for ovarian carcinomas. The majority of these carcinomas are diagnosed in an advanced stage. Both carcinomas have about the same age distribution, often occur in nulliparous women and frequently exhibit a serous-papillary histology^[8].

Case Report

A 65 years old female was admitted in Department of Medicine of Goa medical college and Hospital, Bambolim, Goa. Patient not a known case of hypertension or diabetes mellites, no history of addictions presented with one month history of imbalance, gait instability and incoordination of right upper limb, without weakness in any limbs. There was history of vertigo throughout the day with no postural association, non-projectile vomiting, 2-3 episodes per day for one week and slurring of speech for 3 days. There was no history suggestive of fever, headache, altered sensorium, seizure, sensory loss, bowel bladder

disturbances, diplopia, ptosis, dysphagia, syncope, regurgitation, chest pain. There was history of drug intoxication or toxin exposure. She was para one married for 35 years and postmenopausal for 10 years. There was no family history of breast, ovarian or endometrial cancer.

On examination patient was conscious, cooperative, oriented. Vitals were stable. Speech was slurred, comprehension was normal, lateral eye movement was weak, truncal ataxia was present, tongue fasciculations was present. Cerebellar signs were positive on right side. Both upper and lower limb tone was decreased however power was normal. There was no peripheral cause for vertigo. Systemic examination of respiratory and cardiovascular system was normal. No mass was palpable on per abdomen examination neither felt on per vaginal examination. Based on this clinical diagnosis of right cerebellar CVA was made and patient was further investigated.

Her hematological and biochemical profile was normal. 2D ECHO, MRI and CT B rain was normal, no infract or hemorrhage. CSF (cerebrospinal fluid) study showed increased protein – 110.8mg/dl (normal 15-45mg/dl), with cytoalbuminuric dissociation with culture sterile, no organisms were found. Nerve conduction study showed early sensory polyneuropathy.

Chest X-ray and mammography did not show any lesion, but pelvic ultrasound showed hypoechoic left adnexal mass 3.5 x 3.2 cm with no vascularity, uterus was normal and both ovaries were not well visualized. CA 125 was 102.6 U/ml (normal < 40 U/ml). CT whole abdomen revealed a 4 x 3.5 cm size lobulated heterogenous mass lesion not clearly separated from left ovary. With these investigations likely possible diagnosis was paraneoplastic cerebellar ataxia secondary to gynecological malignancy. Presence of Anti-Yo antibody in the body was checked, which came positive, confirming the diagnosis.

Patient was then planned for laparotomy and proceed. On opening, uterus, both ovaries and right fallopian tube was normal but left fallopian tube showed growth measuring around 5 x 5 cm with no pelvic lymphadenopathy, omental caking or deposits. Patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy with removal of left adnexal mass. Histo-pathological test showed high grade epithelial tumor with diffuse papillary pattern with areas of necrosis, hemorrhage and desmoplasia of left fallopian tube fimbrial end.

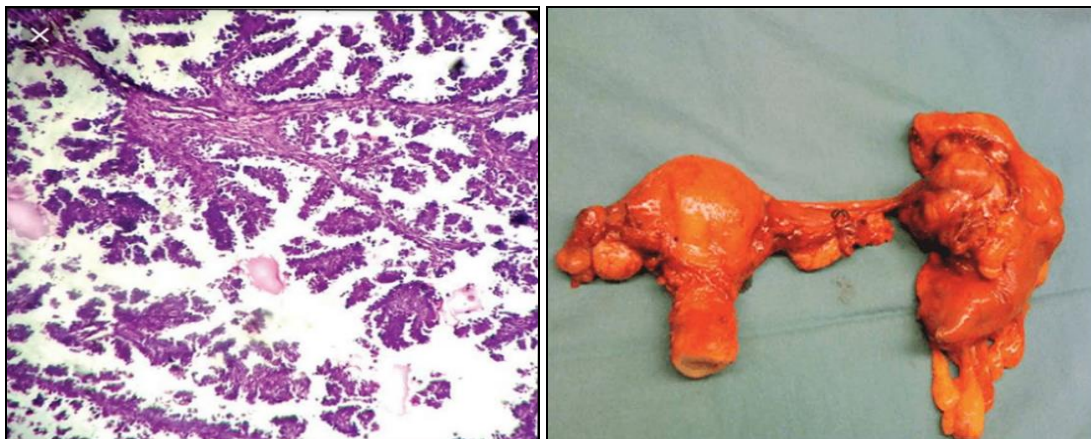


Fig 1: HPR of fallopian tube Ca (Right) and uterus, both ovaries and left adnexal mass (Left)

Post operatively patient was started on IVIG 0.4 mg/kg dose for 5 days with which clinical improvement was seen that was improvement in speech and decrease titubation. Patient was then planned for carboplatin and paclitaxel chemotherapy.

Discussion

Fallopian tube cancer is the least common gynecological cancer with incidence of 0.1-1.8%.⁷ its behavior is similar to ovarian cancer, most frequently seen between fourth and sixth decade of

life. It's been recently associated with mutation of BRACA 1 and BRACA 2 and should be considered as a part of hereditary breast ovarian cancer syndrome [9]. It has been stated that origin of high grade serous ovarian carcinomas are just precursor lesions of fallopian tubes as fimbria with its anatomic proximity as well as adhesions between tube and ovary favors the transmission of these invasive cells [10].

Paraneoplastic cerebellar degeneration is a rare neurological complication associated with different types of autoantibodies triggered by cancer. Anti-Yo represents the most frequent immune-mediated PCD, and its most frequently associated with gynecological cancers.

Nearly one-third of patients among large series of paraneoplastic syndromes presented with subacute cerebellar ataxia. Most common paraneoplastic antibody detected is Anti Hu, however only 18% present as a paraneoplastic cerebellar degeneration. Whereas patients with anti-Yo, Tr or mGluR1, express only as PCD in 100% of the cases. Most frequent association being anti-Yo (38%), anti-Tr (14%) and mGluR1 (4%) [6].

In our patient cerebellar symptoms appeared one month prior to diagnosis, just as described by Rojas *et al.* [11] in series of patients with anti-Yo antibodies and PCD. If patient had presented early and paraneoplastic syndrome was suspected earlier then early detection of adnexal mass was possible. Early diagnosis in initial stages before spread is needed for better cancer prognosis. Also since cerebellar degeneration once starts cannot be reverted back with removal of tumor or through immune modifying therapies including chemotherapy, as mechanism involves damage to Purkinje fibers by antibodies. [11] Median survival was months 22 for those with gynecologic cancer and 100 for breast cancer. Although paraneoplastic cerebellar degeneration leads to the diagnosis of cancer in 63% of the patients, cancer progression is the cause of death in 52% [11].

Neurological symptoms in our patient improved slowly post operatively with course of IV immunoglobulin, especially with regards to speech and titubation. Patient was then planned for chemotherapy. Complete rehabilitation is unlikely because cerebellar degeneration is triggered by the tumor associated antibodies.

In cases reported before of gynecological tumors with PCD, even after stage appropriate therapy for malignant tumor and with administration of immunoglobulins or immunosuppressive agents, most of these patients could only be partly relieved of their neurological symptoms. In some cases progress of the cerebellar degeneration was stopped while in other cases the symptoms deteriorated; cerebral metastases occurred additionally which led to an early mortality [12].

Conclusion

Paraneoplastic syndromes include a wide range of manifestations and can involve all systems. Clinicians should be aware of the existence of such syndromes, as they often precede the discovery of the underlying cancer. Rapid cancer-directed treatments are essential as they may improve the symptoms in some paraneoplastic syndromes.

Paraneoplastic cerebellar degeneration associated with anti-Yo (Purkinje cell) antibodies is almost invariably related to ovarian epithelial carcinoma. In this report, we present a case of a patient with fallopian tube carcinoma diagnosed almost month after PCD. Although rare, PCD and anti-Yo antibodies should raise the suspicion of a carcinoma of primary fallopian tube or ovarian origin.

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