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Case report

Paraneoplastic cerebellar degeneration in a patient with a primary fallopian tube adenocarcinoma. A case report and brief review

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ABSTRACT

We describe a 65-year-old woman with subacute cerebellar syndrome expressed as severe ataxia, and the presence of anti Purkinje cell antibodies (Anti-Yo). A small adnexal mass was only evident on PET CT with the pathological feature of fallopian tube adenocarcinoma. Anti-Yo antibodies have been strongly associated with paraneoplastic cerebellar degeneration, and nearly always associated to ovarian adenocarcinomas. Few cases have been reported in which this paraneoplastic syndrome has been related to fallopian tube adenocarcinoma. In this report, we discuss this association and its relation with fallopian tube and ovarian carcinoma.

1. Introduction

A cerebellar syndrome developing in days or weeks, without an identifiable intracranial occupying lesion, is most likely a remote consequence of cancer (Dalmau and Rosenfeld, 2008). The association between cancer and subacute cerebellar symptoms was first suspected by Guichard and Vignon in 1949 (cited in Dalmau and Rosenfeld, 2008) and confirmed only in 1976 (Trotter et al., 1976). Ovarian, lung, breast cancer and Hodgkin lymphomas, are most commonly associated with this paraneoplastic cerebellar degeneration (PCD). 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 (Shams'ili et al., 2003). Whereas different antibodies have been related with PCD, the presence of anti-Yo antibody predicts almost certainly the association with ovarian cancer (Shams'ili et al., 2003; Rojas et al., 2000). Here we report a woman with subacute cerebellar ataxia with anti-Yo antibodies, in whom a fallopian tube carcinoma was confirmed on laparoscopic exploration. Despite surgical removal, the neurological syndrome remained unaltered. Fallopian tube cancer has been rarely associated with PCD (Tanaka et al., 1992, 2005), even though it has been hypothesized that epithelial ovarian adenocarcinomas may actually arise from the fallopian tube (Erickson et al., 2013).

2. Case report

The patient is a 65-year-old woman, smoker of more than 20 cigarettes a day for 40 years and diagnosed with mild hypertension, treated with valsartan 50 mg daily. A right salpingo-oophorectomy was performed 30 years before to remove an ovarian cyst. Five months prior to diagnosis the patient was found dehydrated at her house, being admitted to a local hospital. After receiving primary care attention, the patient was transferred to our institution 4 months prior to diagnosis. Following a normal electroencephalogram and brain MRI, it was felt that her symptoms were all explained by a depressive state and a severe personality disorder, which she carried for many years. She was transferred to a Psychiatric Hospital where she stayed mainly bedridden. She could walk only with the aid of the hospital personnel. After 2 months, she developed a respiratory tract infection and was once again transferred to our institution. On admission, the patient had a severe dysarthria and asked not to be moved because she felt dizzy, with nausea and eventual vomiting. Besides dysarthria, there was horizontal nystagmus. Muscle strength was preserved despite a generalized weight loss. Tendon reflexes were present, except for ankle reflexes that were absent. Plantar responses were indifferent. Sensation to touch and pinprick was preserved. The most conspicuous finding was a marked dysmetria, being unable to perform a finger-to-nose test. The patient was unable to walk because of ataxia.

A brain CT scan was unrevealing except for periventricular white matter hypodensity, interpreted as small vessel pathology. A brain MRI confirmed T2 periventricular white matter hyperintensities attributed to small vessel disease. The brainstem was described as normal with mild cerebellar atrophy. Vitamin B12 level was normal and the

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patient was supplemented with intravenous thiamine without modifying her ataxia. Thoracic, abdominal and pelvic CT scans were unrevealing. A Cerebrospinal fluid (CSF), obtained through a lumbar puncture, was clear without cells and a protein content of 75 mg/dl. Two oligoclonal bands were present in CSF immunoelectrophoresis, which were not detected in serum. Anti-Yo antibodies were highly positive in blood, which prompted the search of a gynecological cancer by means of a PET-CT which showed abnormal hypermetabolic areas in the left adnexal and para-aortic regions (Fig. 1). Transvaginal ultrasound showed a 5-cm left adnexal mass and a 1.5 cm polypoid mass inside the uterus. A laparoscopic approach identified a left adnexal mass, which was compatible with a primary fallopian tube adenocarcinoma, as shown by biopsy specimen (Fig. 2). The patient underwent a total hysterectomy with left salpingo-oophorectomy and transperitoneal para-aortic lymphadenectomy. Final pathology specimen revealed a high-grade primary fallopian tube papillary serous carcinoma and desegregated fragments of high-grade papillary serous carcinoma inside the uterus (which probably fell from the fallopian tube carcinoma). There was no evidence of a second primary tumor in the endometrium (Fig. 2). One out of 17 para-aortic lymph nodes displayed metastatic involvement by fallopian tube adenocarcinoma.

The patient and her family decided not to pursue further chemotherapy given the precarious neurological condition. Neurological status did not change for the following 6 months, staying bedridden, with severe ataxia. No signs of pelvic or abdominal cancer spreading have become evident.

3. Discussion

Paraneoplastic cerebellar degeneration is a rare neurological complication associated with different types of autoantibodies triggered by cancer. Among them, anti-Hu (anti neuronal nuclear antibody 1, ANNA1), usually associated with small cell lung cancer (SCLC), combine different degrees of cerebellar degeneration, encephalomyelitis and sensory polyneuropathy (Dalmau and Rosenfeld, 2008; Rosenfeld and Dalmau, 2012). Anti-Ri (ANNA2) may express as PCD but also brainstem encephalitis, associated with breast and gynecological cancer. Anti-Yo (Purkinje cell antibody), just like other antibodies (anti-Tr, anti-Zic 4 and mGluR1) have a unique expression as subacute cerebellar degeneration. Anti-Yo represents the most frequent immune-mediated PCD, and is almost always associated to gynecological (ovarian) cancer (Shams'ili et al., 2003).

Shams'ili et al. (2003) in a large series of patients with paraneoplastic neurological syndromes describe nearly one-third presenting with subacute cerebellar ataxia. Although anti-Hu was the most frequent paraneoplastic antibody detected, only 18% presented as a paraneoplastic cerebellar degeneration. One-hundred percent of these patients having anti-Yo, Tr or mGluR1, expressed only as PCD, the most frequent association being anti-Yo (38%) followed by anti-Tr (14%) and mGluR1 (4%).

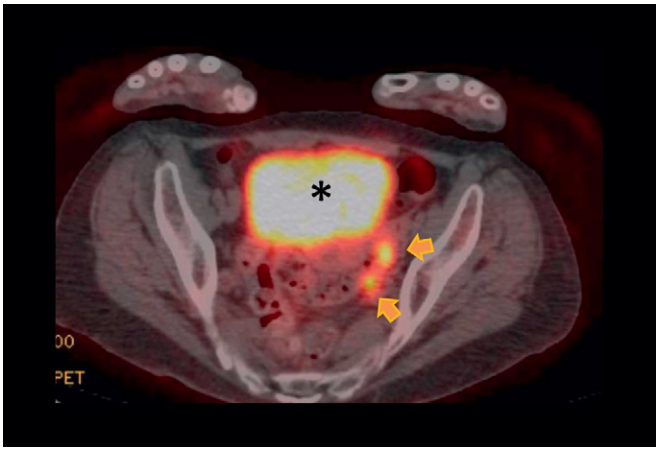

Fig. 1. PET CT showing a small area of hypermetabolism traced by fluorodeoxyglucose in the left adnexal region (arrows). A physiological accumulation of deoxyglucose within the bladder is also apparent (asterisks).

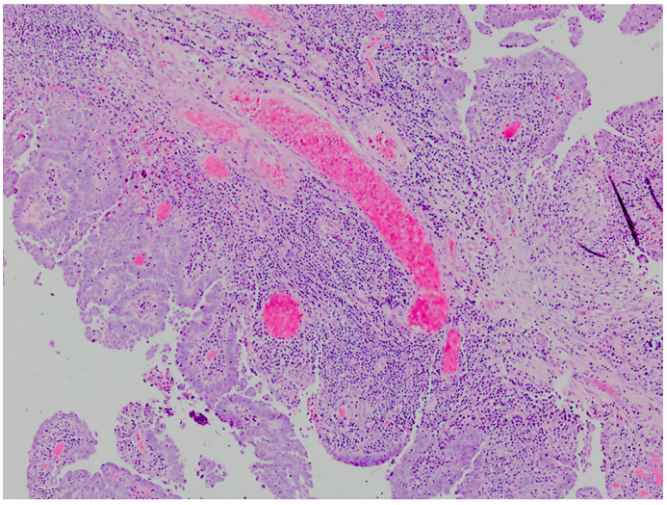

Fig. 2. Histology of an invasive serous-papillary adenocarcinoma of the fallopian tube. Magnification 200 fold (H&E).

In our patient cerebellar symptoms antedated the diagnosis of cancer by ~5 months, which is just the mean described by Rojas et al. (2000) in a large series of patients with anti-Yo antibodies and PCD. It is possible that in our patient an early detection of the adnexal mass would have been possible if the syndrome had been suspected. An early diagnosis is desirable because a better cancer prognosis is achieved if the tumor is detected in initial states without spread. Also, since cerebellar degeneration, once developed, does not seem to improve either by tumor removal or through immune-modifying therapies including chemotherapy (Rojas et al., 2000). The mechanism of damage to the Purkinje cells by the anti-Yo antibodies is not completely understood (Rojas et al., 2000). Recently, Greenlee et al. (2015) have demonstrated that anti-Yo IgG binds to a 62 kDa intracellular Purkinje cell protein. However, the mechanism of cell death is not simply due to intraneuronal antibodies accumulation.

Finally, it has been suggested that fallopian adenocarcinomas are indistinguishable from ovarian adenocarcinoma (Erickson et al., 2013). Indeed, the majority of the serous tumors appear to originate from dysplastic lesions in the distal fallopian tube, and what has been traditionally considered ovarian cancer may in fact be tubal in origin (Erickson et al., 2013), different from primary peritoneal adenocarcinoma (Sørensen et al., 2015). Despite this hypothesis, there are few reports of PCD in association with fallopian tube cancer (Tanaka et al., 1992, 2005; Matsushita et al., 1998; López et al., 2013). The association between ovarian adenocarcinoma and PCD has been estimated to affect a small proportion of women with this type of cancer (Darnell and Posner, 2003), but the numbers may vary significantly (see Dalmau and Rosenfeld, 2008). It is thus possible that a primary fallopian tube adenocarcinoma diagnosed at an early stage, would be considered an ovarian adenocarcinoma detected later, if a PCD had not been expressed.

4. Conclusion

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

ovarian adenocarcinoma, regardless of a primary ovarian or fallopian tube origin.

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