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Case report

Myasthenia as a paraneoplastic manifestation of ovarian Cancer

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ABSTRACT

We describe the first case of myasthenia gravis as a possible paraneoplastic manifestation of ovarian cancer preceding its diagnosis.

1. Introduction

Gynecological tumors rarely present with neurological paraneoplastic symptoms, (Zaborowski et al., 2015) but ovarian tumors account for 10% of these conditions (Giometto et al., 2010). Most published cases describe paraneoplastic cerebellar degeneration, (Rojas-Marcos et al., 2003) peripheral polyneuropathy or neuronal antibody syndromes as neurological manifestations (NMDAR) in ovarian teratomas and tumors (Zaborowski et al., 2015).

Antigens expressed by tumor cells mimic antigens that are exclusive to the central nervous system (CNS), and the anti-tumor immune response causes neurological paraneoplastic manifestations. The coexistence of cdr2 and cdr2L antibodies is highly suggestive of para-neoplastic CNS syndrome, (Zaborowski et al., 2015) and the presence of anti-NMDAR antibodies is highly suggestive of teratoma (Zuliani et al., 2012). However, a substantial portion of the patients with neurological paraneoplastic syndrome do not present detectable antibodies (Zaborowski et al., 2015).

Myasthenia gravis (MG) is an immune-mediated neurological disease that affects neuro-muscular transmission. Approximately 10% of MG cases consist in paraneoplastic disorders (Dalmau & Rosenfeld, 2010; Toothaker & Rubin, 2009), mainly in patients with thymoma (Caliandro et al., 2010; Toothaker & Rubin, 2009) but rarely with other tumors (Dalmau & Rosenfeld, 2010). Antibodies active against acetylcholine receptors (AChR-Abs) are typically detected; however, 10–20% of the carriers do not exhibit this marker. Nerve stimulus tests, such as repetitive nerve stimulation (RNS) and single-fiber electromyography (SF-EMG), are important in the diagnostic confirmation of this entity (Caliandro et al., 2010).

1.1. Case report

A 61-year-old woman with no comorbidities had new onset bilateral ptosis. She was submitted to ENMG, where a progressive decline in compound muscle action potential (CMAP) amplitudes was observed after repetitive nerve stimulation, suggestive of neuromuscular junction blockade. She had an anti-acetylcholine receptor antibody dosage > 20 nmol/L (Reference Value < 0.45 nmol/L) and negative antibodies were noted: anti-GAD, anti-MUSK, anti-HU, and anti-YO. At this time, computed tomography (CT) of the chest did not reveal thymic alterations. The use of 60 mg pyridostigmine every 6 h was initiated without significant improvement of the symptom.

Thirty days after the diagnosis, the patient was hospitalized for dysphagia for solids and liquids. Esophagogastroduodenoscopy was performed, evidencing esophagitis, pangastritis and bulboduodenitis. Tomography of the abdomen revealed massive ascites and peritoneal thickening with a greater pelvic component. Magnetic resonance imaging confirmed the pelvic findings in association with 9561.8 U/mL CA-125 serum tumor marker levels. At admission, pulse therapy was initiated with 1 g/day methylprednisolone for 4 days. The condition evolved with respiratory worsening and the need of orotracheal intubation in an intensive care unit, and the patient remained under mechanical ventilation for 23 days. Throughout this period, CT-guided peritoneal biopsy was performed, revealing anatomopathological

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features compatible with neoplasm infiltration. Immunohistochemical studies corroborated papillary serous adenocarcinoma of ovarian origin.

In an attempt to reverse the myasthenic condition, the patient then started 6 plasmapheresis sessions, without clinical improvement and failure to perform ventilatory weaning. Then, 15 g of immunoglobulin EV D1-5 and 750 mg cyclophosphamide EV D1 was initiated every 21 days. One week after institution of these measures, the patient evolved with mechanical ventilation weaning and extubation. In addition, levels of the tumor marker CA-125 were reduced to 899 U/mL. After 20 days, abdominal CT revealed marked reduction of peritoneal thickening.

After a clinical meeting of the departments of Gynecology, Oncology and Neurology, the chemotherapy regimen was changed to carboplatin AUC5 D1 and 175 mg/m^2 paclitaxel D1 every 21 days. The first cycle occurred during hospitalization, and the patient was administered 40 mg/day prednisone and 60 mg pyridostigmine every 6 h. The patient was discharged and continued to receive treatment on an outpatient basis. A second cycle of chemotherapy was administered after 21 days, and she had no clinical symptoms related to myasthenia. Prior to the completion of the third cycle of chemotherapy, the patient was taking no medication for the treatment of myasthenia. At this time, after administering neoadjuvant therapy, the patient underwent a cytoreductive surgery with R0 resection. She received 3 additional cycles of chemotherapy and improved over the 6-month follow-up, with complete resolution of the myasthenic condition without the need for drugs to control the disease. Abdominal imaging revealed no evidence of disease with CA125 < 35 U/mL.

2. Discussion

We present the case of a middle-aged patient with standard treatment for ovarian cancer initiated during severe myasthenic crisis as a possible paraneoplastic manifestation. In 80% of ovarian neoplasms involving CNS paraneoplastic symptoms, the neurological syndrome precedes the detection of a pelvic mass (Toothaker & Rubin, 2009).

In most ovarian tumors, paraneoplastic neurological manifestations precede the detection of neoplasia by weeks or months (Zaborowski et al., 2015). In our patient, the symptoms of myasthenia preceded the diagnosis of ovarian cancer by only 5 weeks. Early investigation of paraneoplastic syndromes may allow earlier diagnosis of certain neoplasms, such as Hu syndrome associated with small cell lung cancer, but this possibility is debatable in ovarian cancer (Zaborowski et al., 2015). Our patient exclusively presented neurological symptoms when the tumor was FIGO stage IIIC.

Paraneoplastic neurological symptoms can greatly worsen patients' performance and, consequently, the cure rate (Zaborowski et al., 2015). In addition, these symptoms are the primary cause of death in approximately half of these patients (Zaborowski et al., 2015).

The anti-acetylcholine antibody presents an uncertain association with tumors such that its positivity does not help characterize the condition as a paraneoplastic syndrome. In the same manner, negativity of antibodies with strong associations with tumors, such as anti-HU and anti-Yo, was noted (Pelosof & Gerber, 2010).

Evidence that suggests causality is supported by the criteria of Graus (Graus et al., 2004) and Marcos (Rojas-Marcos et al., 2003): important temporal link and chemotherapy as a second-choice drug for myasthenia. Our patient's myasthenic condition improved in association with the reduction in CA-125, a possible predictor for the oncologic response. These findings were subsequently confirmed by imaging tests. Caliandro et al. (2010) was the first to describe the concomitance between myasthenia and ovarian tumors. However, establishing the causality of the conditions was more unlikely given that myasthenia only developed during the recurrence of ovarian cancer.

Resection of the primary tumor seems to be the best method to control CNS paraneoplastic syndromes (Toothaker & Rubin, 2009). Responses to plasmapheresis, corticosteroids and immunomodulators often vary depending on the type of predominant immune response. T lymphocyte cytotoxicity-mediated disorders appear to be less responsive to these measures compared with those disorders associated with antibodies against surface antigens (Toothaker & Rubin, 2009).

Cyclophosphamide is a chemotherapeutic agent of the alkylating class with cytotoxic action. The mechanism of cell death occurs by creation of cross-links DNA strands and thus prevention of their replication. Election of this drug was due to its benefical immunosuppressive properties in the treatment of myasthenic crisis and good anti-neoplastic activity in ovarian cancer (McGuire & Hoskins, 1996).

As the resolution of the myasthenic condition may be associated with the control of the baseline neoplasia, it was decided to optimize oncologic treatment by initiating a combined regimen of carboplatin and paclitaxel. At this point, literature data describing cases of neuromuscular junction involvement and development of myasthenic syndrome with cisplatin were evaluated by the entire team (Wright & Drouin, 1982).

To our knowledge, this is the first case of possible causality between an ovary tumor and myasthenia gravis as a paraneoplastic syndrome. Due to the anti-neoplastic and anti-myasthenic properties of the chemotherapeutic agent cyclophosphamide, we determined that it was an optimal time to initiate antineoplastic treatment with this medication.

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