Opsoclonus as a suspected paraneoplastic syndrome of endometrial cancer

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Abstract

Paraneoplastic opsoclonus is well described in neuroblastoma. In the adult oncologic population, opsoclonus is seen usually within the context of opsoclonus–myoclonus ataxia and is associated most strongly with small-cell lung cancer. Patients with paraneoplastic opsoclonus are often seronegative. Patients with gynecologic malignancies are known to be predisposed to paraneoplastic syndromes; however, we describe the first case of paraneoplastic opsoclonus in association with endometrial cancer.

Introduction

Gynecologic malignancies are capable of causing neurologic changes through non-metastatic paraneoplastic effects. The development of cerebellar degeneration in patients with ovarian cancer, often associated with the measurable emergence of the PCA-1 (anti-Yo) antibody, perhaps is the most frequently cited example of this phenomenon. To the best of our knowledge, we report the first case of opsoclonus as a suspected paraneoplastic manifestation of endometrial cancer.

Opsoclonus refers to involuntary, conjugate, multivectorial, saccadic eye movements. It can occur as an isolated neurologic anomaly but, when it occurs with involuntary multifocal jerking movements of the skeletal musculature, the phenomenon is known as opsoclonus–myoclonus syndrome (OMS). The syndrome often includes features of ataxia, or incoordination with voluntary movements. In the setting of malignancy, opsoclonus is linked most clearly to neuroblastoma, occurring in 3% of childhood cases. Anti-neuronal antibodies, usually to nuclear antigens, are considered markers of immune system activation in this disorder, detected in 81% of pediatric patients. However, the relationship between the antibodies and the appearance of the syndrome is unclear as 25% of those children with neuroblastoma without neurological symptoms may be found with the same antibodies. As is frequently seen with other paraneoplastic neurological syndromes, opsoclonus–myoclonus in the setting of neuroblastoma most often occurs in the setting of limited-stage disease. In the adult oncologic population, opsoclonus–myoclonus ataxia is associated most strongly with small-cell lung cancer and breast cancer, often also associated with anti-neuronal nuclear antibodies, especially ANNA-2 (anti-R). Other adult tumor types linked to this syndrome include non-small-cell lung cancer; melanoma; sarcoma, and non-Hodgkin's lymphoma. A thorough search of the medical literature uncovered no reports of paraneoplastic opsoclonus, with or without detectable auto-antibodies, in endometrial cancer patients.

Case Report

A 65-year-old woman presented with several months of increasing abdominal girth. The clinical examination showed ascites, and abdominal imaging revealed omental caking. Cytology tests of paracentesis fluid were negative, but a biopsy of a peritoneal nodule revealed metastatic serous carcinoma of Mullerian origin. CA-125 was measured at 171 U/mL. She was referred to the Mayo Clinic, where she had an exploratory laparotomy with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy. The pathological examination of the uterus revealed an invasive FIGO grade III serous adenocarcinoma of mixed serous-endometrioid types, arising in an endometrial polyp (Figure 1). There was no invasion into the myometrium. Both ovaries and Fallopian tubes were pathologically normal. Intraoperatively, there was no evidence of carcinomatosis but the omentum appeared enlarged and inflamed; omental biopsies revealed high-grade papillary serous carcinoma. One pelvic lymph node, of 53 pelvic and seven para-aortic nodes sampled, was positive for metastatic disease. The clinical, imaging, and pathological features were consistent with stage IV endometrial cancer.

Two weeks prior to her surgical debulking, the patient experienced the acute onset of involuntary eye movements and oculispolis that quickly rendered her unable to walk. Within a week of her first symptoms, she was wheelchair-bound and keeping her eyes closed almost constantly even during wakefulness to avoid “bouncing vision”. Although she had initially reported a non-specific dizziness, this complaint also worsened after seven to ten days and she developed vertiginous sensations with a clear rotational component but no tinnitus or hearing loss. An otolith-repositioning maneuver on the right side did not produce any lasting improvement in her visual or gait disturbances. She could not identify any antecedent infectious symptoms. The only prior neurologic history was that of pseudo-claudication from lumbar spinal stenosis. On neurologic examination, low-amplitude high-frequency ocular flutter and square-wave jerks were evoked by vertical gaze, and similar but larger-amplitude and lower-frequency movements were seen in both directions with sustained lateral gaze. Pupillary light responses were preserved. Funduscoppy was normal. The remainder of the cranial nerve examination was normal. Gait was abnormal, in excess of her baseline difficulties with osteoarthritis of the knees and pseudo-claudication, primarily consistent with ataxia. Mild incoordination was also observed with hand movement.

Her work-up included magnetic resonance imaging of the brain, which showed no signal abnormality or abnormal enhancement in the cerebellum, brain stem, or elsewhere. A serum paraneoplastic autoantibody evaluation for muscle and neuronal AChR, P/Q and N-type voltage-gated calcium channels, neuronal voltage-gated K+ channels, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, amphiphysin, and CRMP-5 IgG was completely negative. CSF analysis was not performed. Within a week postoperatively, her neurologic symptoms began to recede with resolution of her upper extremity incoordination as well as dramatic improvement of her involuntary eye movements and vertiginous symptoms. Within three weeks postoperatively, during which time she had been transferred to a rehabilitation hospital, she could rise from a chair independently and her gait had improved to the point that she could proceed 16 steps with the use of a walker. After five weeks of postoperative recovery and...
two doses of carboplatin/paclitaxel chemotherapy, with a decline in her CA-125 to 10 U/mL, the patient had improved to the point that her opsinclonus was only barely visible during saccadic testing and she was able to rise from a wheelchair and climb on to an examination table under her own power. Five months later, she had complete resolution of her opsoclonus and ataxia, ambulating without a cane or walker.

Discussion

The primary goal in treating paraneoplastic autoimmunity is to remove the inciting antigen. While OMS often can be a monophasic process outside of the context of an associated malignancy, spontaneous remission of paraneoplastic neurologic disorders is uncommon; complete or partial neurologic recovery seems to occur only with treatment of the underlying tumor. Although the serum paraneoplastic autoantibody evaluation was negative for previously described markers of cancer-associated autoimmunity, as has been true in many documented reports, it nonetheless remains likely that this patient’s condition was immunologically mediated. It is postulated that opsoclonus is caused by interference with premotor omnipause neurons in the brainstem, but the precise pathophysiology, especially as it might relate to an autoimmune mechanism, is unclear. Rapid improvement in immunologically mediated nervous system disorders typically is associated with antibody-mediated phenomena, especially for neuromuscular disorders. For central nervous system disease, the mechanism for antibody-mediated pathology and its reversibility with therapy has not been clearly delineated.

To our knowledge, this is the first report of opsoclonus in association with endometrial cancer. There are no established markers to identify adult patients with paraneoplastic opsoclonus–myoclonus but the patient’s neurologic symptoms rapidly abated and ultimately resolved altogether following surgical and chemotherapeutic interventions for her stage IV disease. The temporal alignment between the improvement in her neurologic function and the treatment of her cancer strongly suggests a paraneoplastic phenomenon. A review of the English-language literature reveals three cases of OMS in association with ovarian neoplasms, and all three patients’ neurologic symptoms were ameliorated by anti-neoplastic therapy: a 15-year-old with a mature teratoma and a negative paraneoplastic panel, whose symptoms improved after surgery; a 45-year-old with epithelial ovarian carcinoma and negative PCA-1, ANNA-1, and ANNA-2 antibodies, whose neurologic status improved after surgery and chemotherapy; and a 58-year-old with anaplastic adenocarcinoma of the ovarian duct and negative anti-Ri: an antibody associated with paraneoplastic opsoclonus-myoclonus syndrome associated with malignant fibrous histiocytoma: neuropathological findings. Cesk Patol 2004;40:63-7.

References


Figure 1. High power view of grade III endometrial adenocarcinoma, mixed serous and endometrioid types, arising in an endometrial polyp. There was no myometrial invasion detected.