Paraneoplastic Cerebellar Degeneration Associated with Gynecological Malignancy: Two Contrasting Case Reports

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Abstract: Paraneoplastic cerebellar degeneration is a rare neurologic disorder associated with several forms of cancer, including gynecological. It may present months or years prior to or after the diagnosis of cancer. Recognition of the condition is paramount for early diagnosis of the underlying malignancy and/or for mitigating the permanent effects of the cerebellar degeneration. We present two cases of paraneoplastic cerebellar degeneration associated with gynecological malignancies which illustrate the varied timings of presentation and outcomes of the disorder.

Keywords: Paraneoplastic cerebellar degeneration, diplopia, nystagmus, ovarian cancer, gynecological cancer.

INTRODUCTION

Paraneoplastic neurological syndromes are a heterogeneous group of neurologic disorders caused by an immune response to an underlying malignancy. The principle pathologic mechanism is onconeural immunity (a cancer-stimulated immune reaction that cross reacts with neural tissue) [1]. These syndromes include paraneoplastic sensory neuropathy, paraneoplastic encephalopathy, and paraneoplastic cerebellar degeneration. Paraneoplastic cerebellar degeneration (PCD) involves the cross reaction of antibodies toward tumor antigens and cerebellar tissue, specifically Purkinje cells. While PCD may be associated with any cancer, the most commonly identified are gynecological, small cell lung, breast, and lymphoma [1-9]. The ensuing immune reaction results in progressive inflammation and destruction of cerebellar tissue. Clinical presentation of PCD is typically subacute and gradual. Systemic neurologic manifestations include progressive ataxia, gait disturbance, vertigo, nausea, dysarthria, and dysphagia. Ophthalmic manifestations derived from the cerebellar dysfunction are typically diplopia and nystagmus. While the syndrome often precedes the diagnosis of cancer by months or even years, it may present years following the diagnosis of a malignancy [2,10]. We present two cases which contrast the onset and outcomes of PCD with respect to the underlying malignancy and survival: Case 1 describes a patient with symptoms of PCD for several months prior to being diagnosed with fallopian tube adenocarcinoma who has survived both conditions for over 10 years, and Case 2 involves a woman diagnosed with PCD over two years after the diagnosis of ovarian cancer who survived for only four months.

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CASE ONE

A 53 year old woman presented with a one month history of progressively worsening diplopia. Past medical history was significant for hypertension and smoking for over 20 years. She had undergone fallopian tubal ligation and a subsequent total hysterectomy approximately 30 years prior. Over the preceding two months, she had been experiencing worsening symptoms of light-headedness, dizziness, and difficulty with balance and gait. In addition, she had a 20 lb weight gain within the past year. A brain MRI was normal. Neurologic examination prior to the onset of visual symptoms was unrevealing and she was diagnosed with anxiety and depression. Ophthalmic examination revealed a fairly comitant 8-10 prism diopter esotropia and end gaze low amplitude high frequency horizontal jerk nystagmus. One month later, repeat examination by a neurologist demonstrated mild dysarthria, a wide based ataxic gait, and an intention tremor. A multitude of serum tests and a lumbar puncture for infectious, collagen vascular, and autoimmune etiologies were performed, including serum paraneoplastic autoantibodies. The only abnormality detected was an elevated serum Purkinje cell cytoplasmic (Yo) antibody titer (1:320). A repeat brain and cervical MRI, and CT of the chest, abdomen, and pelvis were all normal. A PET scan demonstrated a small area of focal activity just lateral to the bladder posteriorly on the right, prompting a bilateral salpingo-oophorectomy which revealed a high grade serous adenocarcinoma of one fallopian tube. No further treatment for the cancer was instituted. Ten years later, the patient has had no recurrence of cancer and her neurologic condition has essentially stabilized: diplopia, esotropia, and nystagmus persist, she has significant dysarthria, and requires significant assistance with activities of daily living because of severe ataxia.

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CASE TWO

A 49 year old woman presented with a 10 day history of worsening diplopia. She was diagnosed with stage 3 C papillary serous carcinoma of the ovary with abdominal metastases two and one half years prior, initially treated with chemotherapy. She had recurrences 8 and 20 months later, each treated with separate cycles of chemotherapy. Her last cycle was completed 4 months prior. Examination revealed a small angle esotropia which worsened in right gaze, and variable nystagmus. A brain MRI was normal. Over the next few weeks, she developed worsening symptoms of dizziness, headaches, dysarthria, and dysphagia. A serum paraneoplastic autoantibody panel was obtained, including neuronal nuclear antibody (Hu and Ri), Purkinje cell cytoplasmic antibody (Yo), and Parvovirus IgG and IgM titers, all of which were negative. A lumbar puncture was performed and the results were nondiagnostic; cerebral spinal fluid paraneoplastic autoantibody titers were not obtained. Despite the negative serum antibody tests, based on the clinical presentation and history of ovarian cancer, paraneoplastic cerebellar degeneration was diagnosed. She underwent two separate courses of plasmapheresis, intravenous immunoglobulin, and intravenous corticosteroid therapy, and another cycle of chemotherapy was begun. Despite this, two months after the onset of diplopia, her dysphagia progressed and she required gastrostomy tube placement. Four months after the onset of diplopia, her overall condition deteriorated, chemotherapy was discontinued, and she expired as a result of the persistent metastatic ovarian cancer as well as the cerebellar degeneration.

DISCUSSION

Paraneoplastic cerebellar degeneration is a neurologic syndrome that usually precedes the diagnosis of cancer by months or even years, but may present years after cancer diagnosis [2,10]. While paraneoplastic autoantibodies are valuable markers of disease, their precise role in the destructive pathologic process is uncertain [1]. Tumor proteins creating an immune response results in the production of IgG antibodies as well as activated cytotoxic T cells, which appear to be central in the cancerous and (in cases of paraneoplastic syndromes) non-cancerous tissue destruction [11]. Regarding PCD, Purkinje cell cytoplasmic (anti-Yo) antibodies are associated with gynecologic and breast malignancies, neuronal nuclear antibodies 1 (anti-Hu) are associated with small cell lung and neuroendocrine malignancies, neuronal nuclear antibodies 2 (anti-Ri) are associated with breast and small cell lung malignancies, and anti-Tr antibodies are associated with Hodgkin's disease [11]. Ensuing cerebellar cell inflammation and degeneration leads to the subacute onset of clinical disease. Neurologic symptoms may be preceded by prodromal symptoms of dizziness, nausea, and vomiting [1]. Symptoms of ataxia and unsteady gait typically progress over several months, with dysarthria and dysphagia being later findings. Ophthalmic findings vary in onset time and are reflective of ocular manifestations of cerebellar disease: nystagmus, saccadic pursuits, esotropia, and skew deviation. Such abnormalities may lead to symptoms ranging from generalized blurred vision to overt diplopia. A somewhat paradoxical finding in the setting of underlying malignancy is weight gain, as seen in Case 1 of the present report. Hyperphagia and weight gain associated with PCD have been previously reported, and are hypothesized to be related to an affect the disease process may have on the hypothalamus [10].

Diagnosis of PCD is often difficult in the early stages of the disease, particularly considering that the neurologic symptoms precede the diagnosis of cancer in the majority of cases. Brain MRI is typically normal, but rarely shows cerebellar edema or atrophy later in the disease course. Because of the lack of significant objective signs on examination despite multiple symptoms early in the course of disease, patients may be errantly diagnosed with psychiatric illnesses (akin to present Case 1) [8]. Serum and cerebral spinal fluid paraneoplastic autoantibody panels are the most useful diagnostic test, but still are not 100% sensitive for the disease or specific for underlying malignancy, and positive antibody testing is not mandatory for diagnosis of paraneoplastic syndromes [1]. Current and future research further elucidating the antibody response and uncovering new antibodies will likely improve the diagnostic utility of these tests [12].

The only known effective and reliable treatment of PCD is diagnosing and treating the underlying malignancy, which, when successful, typically stops the progression of neurological compromise but usually fails to reverse existing deficits. Apart from addressing the underlying malignancy, immunomodulating therapies such as plasma exchange, immunoglobulin infusion, and immunosuppression (including corticosteroids, rituximab, and tacrolimus) have been attempted [11,13]. Most reports regarding these therapies are limited, and, likely in large part because of the paucity of cases, controlled clinical trials are lacking [11].

Prognosis of PCD is poor, with a reported <25% survival rate at 5 years in patients with anti-Yo antibodies [14]. Cause of death has been reported to be approximately 50% from the underlying malignancy and 50% from the neurologic disease [15].

Patients with PCD often go undiagnosed for weeks to months after seeking medical care for their symptoms. During this elapsed time, permanent neurologic deterioration progresses, and malignancy goes unchecked. Normal brain imaging studies and routine serum tests greatly contributes to the delay in diagnosis. These patients often present to their primary care physician, oncologist, gynecologist, and/or consultant neurologist or ophthalmologist prior to definitive diagnosis. Patient demographics which should elevate suspicion for PCD are those with a known history of associated cancers and women at risk for gynecologic or breast malignancy. Any patient with classic cerebellar neurologic and/or ophthalmic symptoms with normal imaging studies warrants high consideration. When PCD is suspected, serum (and possibly cerebral spinal fluid) paraneoplastic autoantibody panels should be ordered. If positive or if suspicion is high despite negative antibody tests, exhaustive investigation for an underlying malignancy should be conducted. Early recognition of the process is critical to mitigate morbidity and mortality from both the underlying malignancy and PCD.

CONFLICTS OF INTERESTS

The authors have no conflicts of interests or financial interests regarding the material in this manuscript.

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