Case Reports

Alcohol-responsive Action Myoclonus of the Leg in Prostate Cancer: A Novel Paraneoplastic Syndrome?

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Abstract

Background: Paraneoplastic movement disorders in prostate cancer are rare, and to our knowledge paraneoplastic myoclonus has not previously been reported.

Case Report: We report two men with adenocarcinoma of the prostate who developed isolated alcohol-responsive action myoclonus of one leg. Myoclonus was absent at rest but triggered by movement, standing, or walking. Evaluations excluded malignant invasion of the nervous system, and testing for commercial paraneoplastic antibodies in serum and cerebrospinal fluid were unrevealing. Both patients experienced significant improvement with alcohol, and sodium oxybate was used in one patient with good initial benefit.

Discussion: Alcohol-responsive leg myoclonus might be a novel paraneoplastic syndrome associated with prostate cancer. The nature of the syndrome and the source of the myoclonus are currently unknown.

Keywords: Myoclonus, prostate cancer, paraneoplastic, movement disorders

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Introduction

Neurologic complications of prostate cancer may be related directly to the cancer, to metastatic disease, or to the side effects of treatment. Paraneoplastic syndromes associated with prostate cancer are quite rare, and include endocrinologic, hematologic, dermatologic, inflammatory, hepatobiliary, and neurologic syndromes. Neurologic paraneoplastic movement disorders (PMDs) associated with prostate cancer are even rarer, and these include ataxia secondary to paraneoplastic cerebellar degeneration, ataxia associated with limbic encephalitis, and myoclonus in limbic encephalitis and brainstem syndromes.

Here we describe two very unusual patients with prostate cancer, with remarkably similar alcohol-responsive unilateral leg action myoclonus. Alternative explanations for this unusual movement disorder (metastatic disease, known paraneoplastic syndrome) were excluded. We propose the possibility that these patients represent a novel paraneoplastic syndrome associated with prostate cancer.

Case reports

Patient 1

A 74-year-old man was diagnosed with prostate cancer in 2010 and underwent an uncomplicated laparoscopic prostatectomy. Histopathologic examination revealed adenocarcinoma, and abiraterone acetate in combination with prednisone was started for treatment. Three weeks after surgery, he became aware of jerking movements of the left foot and ankle triggered by movement or weight bearing. Two months after surgery he developed similar jerking of the right proximal leg, which then became much more prominent. Movements were triggered by moving the right leg against resistance and by walking, requiring use of a walker. On
examination, muscle tone, strength, sensation, and reflexes were normal, and there was no myoclonus at rest or with stimulus. On attempting to use the right leg to resist the examiner or to stand, he developed significant action myoclonus (Video 1, Segment 1), and he could walk only with assistance. We did not observe myoclonus of the left leg. An extensive evaluation including magnetic resonance imaging (MRI) of the brain and total spine, serum erythrocyte sedimentation rate (ESR), white blood cell and protein in cerebrospinal fluid (CSF; personal communication with his outside neuro-oncologist and neurologist), CSF studies for malignancy, and commercially available paraneoplastic antibody testing was unremarkable. An overnight ambulatory electroencephalography (EEG) was also normal. Intravenous steroids (methylprednisolone 1 g/day for a total of 5 days) produced a transient benefit in myoclonus, but intravenous immunoglobulin (IVIG; 2 g/kg/course) did not help at all. A combination of levetiracetam (2,000 mg/day) and clonazepam (0.5 mg/day; he developed sedation at higher doses) provided only modest benefit.

He discovered on his own that the movements were attenuated when drinking alcohol, and in fact reported that he was able to walk without using his walker when he ingested two stiff drinks of Scotch. This fact prompted us to start sodium oxybate as a symptomatic therapy (titrated up to 3 g/day), with moderate improvement noted in a dose-dependent fashion (Video 1, Segment 2). Four years after his original diagnosis he eventually succumbed to metastatic prostate cancer.

**Patient 2**

A 76-year-old male presented for evaluation of involuntary movements of the left leg. He had been diagnosed with metastatic
Alcohol-responsive Action Myoclonus of the Leg in Prostate Cancer

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We present two unusual patients with almost identical phenomenologies in the setting of prostate cancer. Common clinical features included unilateral action myoclonus of one leg triggered by movements such as standing or walking. Both patients experienced significant improvement with alcohol, and sodium oxybate was used in one patient (up to 3 g/day) with good initial benefit. Patient 1 also tried a combination of levetiracetam 2,000 mg/day and clonazepam 1.25 mg/day with only modest benefit, intravenous methylprednisolone 1 g/day for a total of 5 days with only transient benefit, and IVIG 2 g/kg/course without benefit. Extensive work up for neoplastic or known paraneoplastic syndromes was negative. No clear evidence of inflammation in serum or CSF was found in our patients.

We postulate that the myoclonus in our patients was likely spinal in origin. Although electrophysiologic testing was not available, their clinical features support this possibility. Myoclonus that is localized to only one limb, affects the leg, is proximal rather than distal, and is stimulus-insensitive supports a spinal rather than a cortical origin. In addition, there were no associated cortical findings on examination. The distribution of myoclonus did not follow a nerve root or peripheral nerve pattern, and the relatively widespread distribution of muscles involved argues against a peripheral generator in a root or plexus trunk.

An interesting clinical feature in our patients was their robust response to alcohol. While immunotherapies were disappointing, myoclonus in both patients markedly improved immediately after drinking alcohol. This may be attributed to alcohol’s enhancement of the effect of γ-aminobutyric acid, a major inhibitory neurotransmitter. Of note, alcohol responsivity is a feature of other forms of subcortical myoclonus, including myoclonus-dystonia syndrome (DYT11) and subcortical parkinsonism, as well as essential tremor and spasmodic dysphonia, among others. Administration of sodium oxybate, a derivative of γ-hydroxybutyric acid, as a symptomatic therapy in alcohol-responsive movement disorders has been studied.

Patient 1 had moderate improvement noted in a dose-dependent fashion.

While we cannot prove a paraneoplastic etiology, we believe that it is unlikely that the identical phenotypes and histories of prostate cancer in our patients are coincidental. The myoclonus in Patient 1 is not well explained as a surgical-related complication for several reasons: 1) the laparoscopic surgery was uncomplicated and the site of surgery was relatively distant from the lumbar plexus, nerve roots, or spinal cord; 2) the onset of myoclonus was subacute (3 weeks after the surgical procedure), rather than acute in the immediate postoperative period; 3) Patient 2 with identical phenotypes had not undergone any previous prostate surgery. Although focal neuropathies or neuropathies involving the ulnar, median, obturator, and femoral nerves, as well as the lumbosacral plexus have been reported after laparoscopic prostatectomy, the subacute presentation and distribution of myoclonus in Patient 1 argues against these causes.

Of note, a focal neurologic presentation does not exclude the possibility of paraneoplastic etiology as demonstrated in several reports, for example, in cases of paraneoplastic spinal segmental myoclonus or paraneoplastic stiff limb syndrome. To our knowledge, myoclonus has never been reported to be a side effect of abiraterone acetate or leuprolide. In addition, there was no clear temporal relationship between the initiation of these medications and the onset of myoclonus in our patients. The other medications in Patient 1 including levetiracetam and clonazepam are in fact anti-myoclonic agents, and unlikely to cause myoclonus.

Lack of evidence of inflammation in the CSF also does not exclude the possibility of paraneoplastic neurologic syndrome. Pimarasa et al. found no inflammatory CSF in 7% of 295 patients in their series. Malter et al. described 123 of 304 and 89 of 298 patients with selected autoimmune neurologic syndromes in their series. Although serum ESR is frequently checked in clinical practice in patients with suspected paraneoplastic syndromes, it may not be a sensitive marker for central nervous system (CNS) inflammation as the process may confine to the CNS. N-methyl-D-aspartate (NMDA) encephalitis is one example where evidence of the peripheral inflammatory process may be absent on clinical investigations.

Unfortunately, there is currently no true gold standard in the diagnosis of paraneoplastic neurologic syndrome. Clinicians typically confirm the diagnosis by the presence of previously described antibodies, classic neurologic syndromes, and cancers. This method, while it can be feasibly applied to clinical practice, may limit the diagnosis of novel paraneoplastic syndromes. Immunopathological identification of antigenic targets in a human brain or spinal cord may be absent on clinical investigations.
| Reference       | Phenomenology                          | Neurologic Syndrome          | Age (yrs) | T Dx–Syn (yrs) | Tumor Stage | Tumor Histopath | Antibody (Site of Sample) | Treatment (Response)                                                                 | Outcome                                                                 |
|-----------------|----------------------------------------|-----------------------------|----------|---------------|-------------|----------------|----------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Our case (Patient 1), 2015 | Myoclonus—action, rt leg | Alcohol-responsive action myoclonus of the leg | 74       | 0.1 (3 wks)   | Metastatic disease | Adeno          | Unknown (serum and CSF) | IVMP (only transient benefit), IVIG (no); combination of Aza, LEV, CLZ (modest); sod oxybicate (mod but less over time) | Initially stable but died 6 years after tumor diagnosis due to metastatic prostate cancer |
| Our case (Patient 2), 2015 | Myoclonus—action, lt leg | Alcohol-responsive action myoclonus of the leg | 76       | 1             | Diffuse bony metastasis | Adeno          | Unknown (serum and CSF) | IVIG (no)                                                                 | Stable neurologic sx                                                                 |
| Baloh et al., 17  | Myoclonus—face, masseter, pharyngeal and abdominal muscles | Brainstem syndrome—progressive loss of voluntary horizontal eye movements, dysphagia | 71       | 1             | Retroperitoneal pelvic mass contiguous with the prostate but no evidence of the tumor at other sites | Adeno          | Unknown                   | Rx of the cancer by bil orchiectomy; CLZ and VPA (mod); PLEX (no) | Died of aspiration 3 years after tumor diagnosis                               |
| Baloh et al., 17  | Continuous “muscle spasms”—rt face — both sides of face — pharyngeal and laryngeal muscles; mild gait ataxia | Brainstem syndrome—progressive loss of voluntary horizontal eye movements with relatively preserved vertical eye movements | 66       | 5             | Multiple pelvic lymphadenopathies but negative bone scan | Adeno          | Unknown                   | DZP, VPA, baclofen L2Z (modest with all); BoNT (“some relief”) | Ventilator-dependent; committed suicide 2 yrs after the onset                   |
| Modrego et al., 18 | Myoclonus—generalized, developed later | Limbic encephalitis—disorientation, incoherent, non-fluent speech, unstable gait | 74       | –0.1 (1 mo)   | Tumor invaded the prostatic capsule and spread to the rectal wall | Adeno          | Unknown                   | Rx of the 1st tumor only | Died within 2–3 mo after the onset of limbic encephalitis, thought to be due to pneumonia |
| McLoughlin et al., 19 | Ataxia—trunk | Cerebellar syndrome—rapidly progressive; pseudoobulbar palsy, diplopia, transient migratory paresis of rt inferior rectus, rotatory nystagmus | 67       | 0.25 (3 mo)   | “Poorly differentiated” | Unknown | Anti-VGCC (serum) | Recurrent cancer was treated with bil orchiectomy; corticosteroids, PLEX and guanidine HCl (all no) | Stable cerebellar syndrome; progression of eye movements, thought to be “opsoclonus myoclonus” |
| Clouston et al., 20  | Ataxia—trunk and gait | Cerebellar syndrome—subacute, cerebellar atrophy on neuroimaging LEMS | 68       | 5             | Bone metastasis of the pelvis 2 years after the original tumor diagnosis, and later to L2 and L3 vertebral bodies | Originally adeno; small-cell ca on repeat biopsy 5 yrs later | Anti-VGCC (serum) | Recurrent cancer was treated with bil orchiectomy; corticosteroids, PLEX and guanidine HCl (all no) | Stable neurologic sx → rapid deterioration after hepatic metastasis 6 mo after the recurrence |

Table 1. Paraneoplastic Movement Disorders (PMD) in Prostate Cancer
Table 1. Continued

| Reference          | Phenomenology             | Neurologic Syndrome | Age (yrs) | T Dx→Syn (yrs) | Tumor Stage | Tumor Histopath | Antibody (Site of Sample) | Treatment (Response) | Outcome                     |
|--------------------|---------------------------|---------------------|-----------|----------------|-------------|-----------------|--------------------------|----------------------|---------------------------|
| Matschke et al.21  | Ataxia—limbs and gait    | Cerebellar syndrome—unsteadiness, scanning dysarthria, nystagmus, saccadic dysmetria | 79        | −0.3 (6 mo)    | T4N1M1      | Adeno with local neuroendocrine differentiation | Anti-Yo (or anti-PCA1; serum and CSF) | None                | Deteriorated rapidly and died of heart failure within one week after admission |
| Iorio et al.22     | Ataxia—gait              | Cerebellar syndrome—cerebellar speech, nystagmus | 65        | 1.5            | T3aN0Mx     | Adeno           | Anti-mGluR1 (serum and CSF) | A course of IVIG (good) followed by oral prednisone (1 mg/kg/day) and monthly IVIG | Continued to improve on 9-mo follow up |
| Aliprandi et al.23 | Ataxia—limbs and gait    | Cerebellar syndrome—progressive dysarthria | 80        | −0.8 (10 mo)   | No evidence of extracapsular dissemination | Adeno           | Anti-CV2/CRMP5 (serum) | IVIG (2 courses; on Dx [modest] and 3 mo later [no]; Rx of the 1st tumor with bevacizumab and tamoxifen) | Remained markedly impaired despite the 2nd course of IVIG and no progression of underlying malignancy |
| Stern and Hulette24 | Ataxia—trunk             | Limbic encephalitis—Cerebellar syndrome | 76        | −0.1 (1 mo)    | N/A         | Small cell ca with a minor component of adeno | Unknown (negative anti-Hu, anti-Ri and anti-Yo) | None                | Died 12 days after admission |
| Jakobsen et al.25  | Ataxia                    | Limbic encephalitis—marked short-term memory impairment, personality changes, seizures, diplopia | 64        | −0.1 (1 mo)    | T3bN0M0     | Adeno           | Anti-Hu (ANNA-1; CSF) | IVMP (500 mg/day) for unknown duration, IVIG and PLEEx; Rx of the 1st tumor incl palliative external beam XRT | Died 6 mo after the onset of limbic encephalitis |
| Berger et al.26    | Ataxia—gait              | Recurrent brainstem syndrome—ophthalmoplegia, dysarthria, dysphagia, facial palsy, facial numbness; leg stiffness | 59        | −0.7 (8 mo)    | N/A but no evidence of metastasis | N/A            | Intraneuronal Abs (serum and CSF) but unknown exact Ag | IVIG and IVMP (good initially, but no after the last recurrence; rituximab, IV CTX [no], PLEEx [no]) | Rituximab led to respiratory arrest; leukopenia from CTX |

Abbreviations: 1o, Primary; Abs, Antibodies; Adeno, Adenocarcinoma; Ag, Antigen; ANNA-1, Anti-neuronal Nuclear Antibody Type 1; Aza, Azathioprine; bil, Bilateral; BoNT, Botulinum Toxin Injections; ca, Carcinoma; CLZ, Clonazepam; CSF, Cerebrospinal Fluid; CTX, xox; CV2/CRMP5, Collapsing Response Mediator Protein S; DZP, Diazepam; HCl, Hydrochloride; incl, Including; IVIG, Intravenous Immunoglobulin; IVMP, Intravenous Methylprednisolone; LEMS, Lambert–Eaton Myasthenic Syndrome; LEV, Levetiracetam; lt, Left; LZP, Lorazepam; mGluR1, Metabotropic Glutamate Receptor 1; mo, Month(s); mod, Moderate; mvmt(s), Movement(s); N/A, Not Applicable or Information Not Available; PCA1, Purkinje Cell Cytoplasmic Antibody Type 1; PLEEx, Plasma Exchange; rt, Right; Rx, Treatment; sod, Sodium; sx, Symptoms; T Dx→Syn, Time from Tumor Diagnosis to the Onset of the Neurologic Syndromes; VGCC, Voltage-gated Calcium Channel; VPA, Valproic Acid; wks, Weeks; XRT, Radiation; yr(s), Year(s).
be performed on a research basis, but not in routine clinical practice. With no proven gold standard or more immunological techniques to confirm the paraneoplastic etiology in our cases, we would not prematurely exclude the possibility of paraneoplastic neurologic syndrome based on the lack of inflammatory evidence in the CSF since this will limit the opportunity of further discovery of novel antibodies related to this potential paraneoplastic syndrome.

PMDs associated with prostate cancer are reviewed in Table 1. The most common neurologic complications of prostate cancer, 19% in one large series, are due to metastasis to the vertebrae and their neighboring structures through venous drainage of the lower paravertebral plexus (Batson’s plexus) leading to spinal cord or nerve root compression. Brain metastases are rare in prostate cancer. Paraneoplastic syndromes related to prostate cancer can involve neurologic, endocrinologic, hematologic, inflammatory, and hepatobiliary systems. Among the paraneoplastic neurologic syndromes reported are limbic encephalitis, neuropathy (anti-Hu reported in one case), brainstem syndromes, cerebellar degeneration, and Lambert–Eaton myasthenic syndrome (LEMS) with or without cerebellar degeneration (anti-voltage-gated calcium channel [anti-VGCC] reported in LEMS with cerebellar degeneration). Antibodies to exact targets were discovered in only some cases.

Two phenomenologies reported in the literature included ataxia (with a greater number of reports) and myoclonus. Ataxia has been reported in cerebellar syndromes, limbic encephalitis, and brainstem syndromes. Myoclonus has been reported in one case with a brainstem syndrome (another case in the same report with “continuous muscle spasms”) and one with limbic encephalitis. Of note, myoclonus is very rare in paraneoplastic syndromes with the exception of opsoclonus–myoclonus syndrome and NMDA encephalitis.

PMDs may be harbingers of prostate cancer. The neurologic syndrome associated with the PMDs occurred up to 10 months before the diagnosis of prostate cancer, and the most common tumor histopathology was adenocarcinoma. Small cell carcinoma was reported in one PMD case with paraneoplastic cerebellar degeneration. While it has been stated that paraneoplastic syndromes are more common in small cell-type carcinoma, our review showed that most PMDs were associated with adenocarcinoma. A VGCC antibody was found in a case with LEMS and cerebellar degeneration. Yo or Purkinje cell cytoplasmic antibody type 1 and metabotropic glutamate receptor 1 (mGluR1) and collapsing response mediator protein 5 (CV2/CRMP5) antibodies were found in three other patients with a pure cerebellar syndrome. One patient with ataxia in the setting of limbic encephalitis had positive anti-Hu antibody (or anti-neuronal nuclear antibody 1, ANNA 1). An intraneuronal antibody was identified in one patient with gait ataxia and a recurrent brainstem syndrome; however, the exact antigen is unclear. Other patients did not have antibodies that were identified. The failure to identify the exact antigen in our cases does not exclude the possibility of a paraneoplastic syndrome.

While treatment of the primary tumor is crucial, immunomodulatory therapies including IVIG, intravenous steroids, and plasma exchange have also been used with variable success: poor responses in cases with anti-Hu and anti-Yo (and our cases); initially good but non-sustained responses in cases with anti-CV2/CRMP5 and unidentified intraneuronal antibodies, and sustained responses in cases with anti-mGluR1. These findings may indicate a poor response for cell-mediated processes to intraneuronal/onconeural antigens (such as Hu, Yo, and CV2/CRMP5), and a better response to antibody-mediated processes to cell surface receptor antigens (such as mGluR1).

For symptomatic treatment of myoclonus, diazepam and valproic acid were employed in one brainstem syndrome case with moderate benefit. Our patient (Patient 1) had modest benefit from a combination of azathioprine, levetiracetam, and clonazepam. To our knowledge, alcohol responsivity has never been reported in PMD associated with prostate cancer. It is our hope that this paper will engender future reports of similar phenomena.

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