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Tremor and Other Hyperkinetic Movements

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

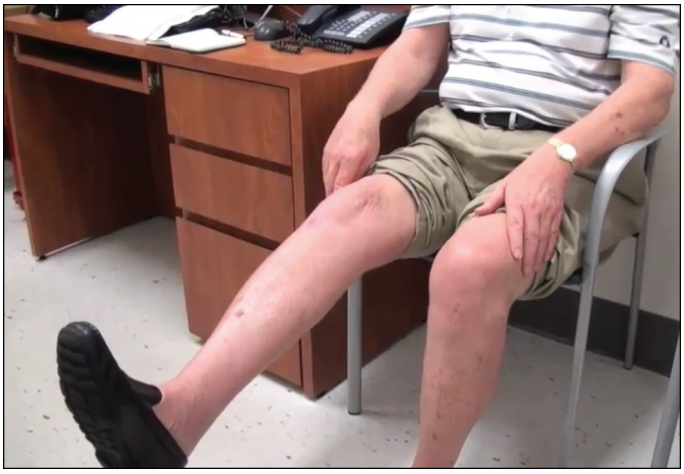
Neurologic complications of prostate cancer may be related directly to the cancer, to metastatic disease, or to the side effects of treatment. Paraneoplastic syndromes associated with prostate cancer are quite rare, and include endocrinologic, hematologic, dermatologic, inflammatory, hepatobiliary, and neurologic syndromes.[1] 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

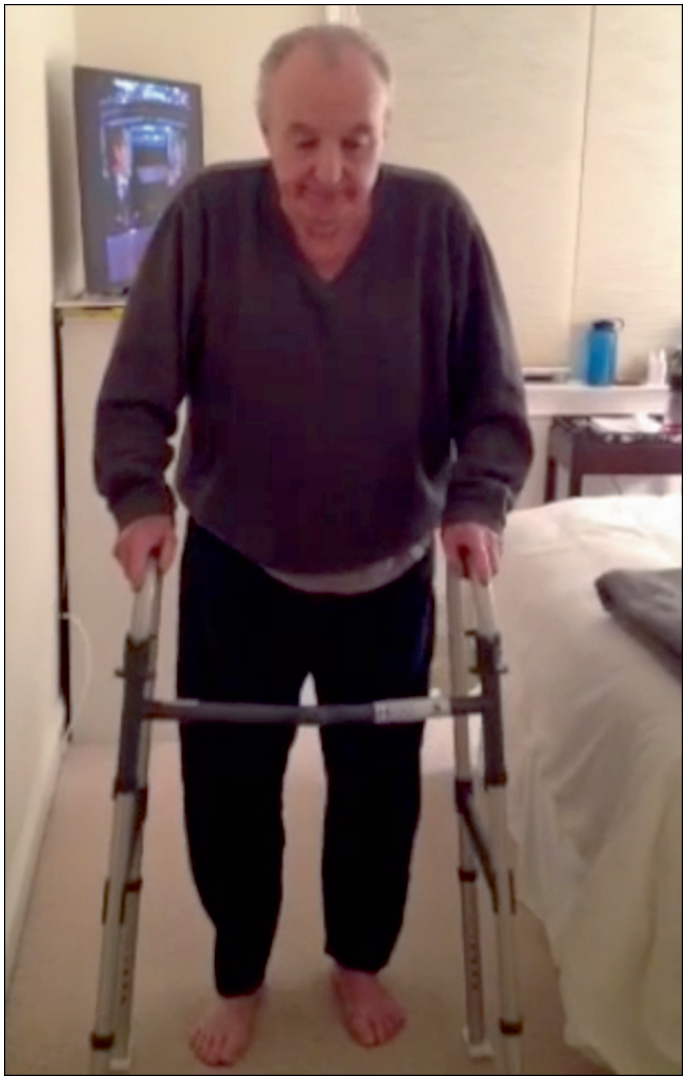
A 74-year-old man was diagnosed with prostate cancer in 2010 and underwent an uncomplicated laparoscopic prostatectomy. Histopathologic examination revealed adenocarcinoma, and abiraterone acetate in combination with prednisone was started for treatment. Three weeks after surgery, he became aware of 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



Video 1. Patient 1 before and 1 Month after Initiation of Sodium Oxybate. **Segment 1. Pre-sodium Oxybate**. The examination in Segment 1 was performed 2 years after the onset of myoclonus. In this segment, myoclonus of the right leg, not present at rest, emerged when the patient stretched his leg out in a seated position. The myoclonus was prominent and mainly generated from the proximal leg. It was also present when standing and walking, and limited his ability to perform these activities. Bearing weight on the right foot (such as when standing on the right foot only) also triggered the myoclonus. After this visit, sodium oxybate was initiated and titrated up to 1.5 g twice a day. He had moderate benefit in dose-dependent fashion (not shown in the video at the lower dose). **Segment 2. After Initiation of Sodium Oxybate.** Segment 2 demonstrates Patient 1 after taking sodium oxybate for 1 month. The examination was performed 2 hours after the last dose. Myoclonic jerks of the right leg were moderately improved, and his ability to perform daily activities improved as well. He was able to walk independently, but still required his wife by his side due to fear of falling.

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.



Video 2. Patient 2. Segment 1. The Examination Performed 1 Year after the Onset of Myoclonus (2 Years after the Diagnosis of Prostate Cancer). There was no myoclonus at rest. When he pushed the left thigh or extended the left knee against the examiner's hand, prominent myoclonic jerks of the left leg emerged, especially from the proximal region around the hip joint. In one part of the video, he attempted to counter the jerks with his right leg. Upon arising from the chair and standing, myoclonic jerks of the left proximal leg became prominent leading to difficulty performing these activities and walking. **Segment 2. Home Video Demonstrating Walking Immediately after Ingesting Two Glasses of Wine.** Although walking with his walker, mild intermittent myoclonus of the left leg, mainly generated from the proximal region, was present; however, he was able to ambulate.

Patient 2

A 76-year-old male presented for evaluation of involuntary movements of the left leg. He had been diagnosed with metastatic

adenocarcinoma of the prostate with diffuse bony metastases 2 years previously and had been treated with leuprolide. He did not undergo any surgical intervention or local radiation. One year after the cancer diagnosis, he developed involuntary jerking movements of the left leg, especially around the hip joint. Movements were triggered by moving the leg when seated, and especially by attempting to stand. Because of the severity of the movements he was confined to a wheelchair for 6 months. Imaging of the spine and CSF examination revealed no evidence of metastatic disease. Serum ESR and CSF white blood cell count and protein were within normal limits (personal communication with his outside neuro-oncologist and neurologist). Serum and CSF commercial testing for known paraneoplastic antibodies was negative. He had been treated with IVIG 2 g/kg/course) without apparent benefit. On examination, there was no myoclonus at rest or with stimuli. Violent action myoclonus of the left leg was generated when he attempted to move the leg while in the chair, and was especially noticeable when he tried to stand (Video 2, Segment 1). His neurologic examination was otherwise notable only for 3+ reflexes in both knees and ankles with crossed adductor signs.

Given our prior therapeutic experience in Patient 1, we suggested that he try a small amount of alcohol to evaluate his level of response. His myoclonus was markedly improved with alcohol (Video 2, Segment 2). Unfortunately, we were unable to obtain insurance approval for sodium oxybate, and a therapeutic trial could not be attempted.

Discussion

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.[2] Of note, alcohol responsivity is a feature of other forms of subcortical myoclonus, including myoclonus–dystonia syndrome (DYT11) and subcortical posthypoxic myoclonus, as well as essential tremor and spasmodic dysphonia, among others.[3–5] Administration of sodium oxybate, a derivative of γ-hydroxybutyric acid, as a symptomatic therapy in alcohol-responsive movement disorders has been studied.[3–5] 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 neurapraxia involving the ulnar, median, obturator, and femoral nerves, as well as the lumbosacral plexus have been reported after laparoscopic prostatectomy,[6–8] 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.[9,10] 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 antimyoclonic agents, and unlikely to cause myoclonus.

Lack of evidence of inflammation in the CSF also does not exclude the possibility of paraneoplastic neurologic syndrome. Psimaras et al.[11] found no inflammatory CSF in 7% of 295 patients in their series. Malter et al.[12] 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.[13]

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.[14] 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

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

Reference	Phenomenology	Neurologic Syndrome	Age (yrs)	T Dx→Syn (yrs)	Tumor Stage	Tumor Histopath	Antibody (Site of Sample)	Treatment[1] (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 oxybate (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 mvmts, 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 mvmts with relatively preserved vertical eye mvmts	66	5	Multiple pelvic lymphadenopathies but negative bone scan	Adeno	Unknown	DZP, VPA, baclofen LZP (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 1° 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; pseudobulbar palsy, diplopia, transient migratory paresis of rt inferior rectus, rotatory nystagmus	67	0.25 (3 mo)	T3NxM0[2]	"Poorly differentiated"	Unknown	Rx of the 1° tumor only	Stable cerebellar syndrome; progression of eye mvmts, thought to be "opsoclonus myoclonus"
Clouston et al. [20]	Ataxia—trunk and gait	Cerebellar syndrome—subacute, cerebellar atrophy on neuroimaging LEMS	68	5	Bony 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. Continued

Reference	Phenomenology	Neurologic Syndrome	Age (yrs)	T Dx→Syn (yrs)	Tumor Stage	Tumor Histopath	Antibody (Site of Sample)	Treatment[1] (Response)	Outcome
Matschke et al.[21]	Ataxia—limbs and gait	Cerebellar syndrome—unsteadiness, scanning dysarthria, nystagmus, saccadic dysmetria	79	−0.5 (6 mo)	T4N1M1	Adeno with focal 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 1° tumor with bicalutamide and tamoxifen	Remained markedly impaired despite the 2nd course of IVIG and no progression of underlying malignancy
Stern and Hulette[24]	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 PLEx; Rx of the 1° 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 pruritus, 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), PLEx (no)	Rituximab led to respiratory arrest; leukopenia from CTX

Abbreviations: 1°, Primary; Abs, Antibodies; Adeno, Adenocarcinoma; Ag, Antigen; ANNA1, Anti-neuronal Nuclear Antibody Type 1; Aza, Azathioprine; bil, Bilateral; BoNT, Botulinum Toxin Injections; ca, Carcinoma; CLZ, Clonazepam; CSF, Cerebrospinal Fluid; CTX, xxx; CV2/CRMP5, Collapsing Response Mediator Protein 5; 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; PLEx, 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).

Table 1. This table demonstrates previously reported cases of PMDs in prostate cancer in the literature, with the addition of our cases (in dark pink). PMDs in prostate cancer are classified based on the phenomenology and neurologic syndromes. Among these cases, two phenomenologies have been reported including myoclonus (in shades of pink) and ataxia (in shades of green). Neurologic syndromes associated with myoclonus include isolated alcohol-responsive unilateral leg action myoclonus (in dark pink), brainstem syndromes (in light pink) and limbic encephalitis (in medium pink), whereas ataxia has been reported in cerebellar syndromes (in light green in the middle of the table), limbic encephalitis (dark green), and recurrent brainstem syndrome (in light green at the bottom).

In each case, age, time from tumor diagnosis to the onset of the neurologic syndromes (T Dx→Syn, in years), tumor stages, tumor histopathology (histopath), antibodies (with sites from which the samples were obtained), treatments (with responses in parentheses), and outcomes are listed. Note that a negative number of T Dx→Syn indicates that the neurologic syndromes were diagnosed before tumor diagnosis.

[1]Treatments to the primary tumor were also given in every patient unless indicated "none" (in one case).

[2]This case was staged according to Union for International Cancer Control classification in 1978.

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,[15] 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.[16] Brain metastases are rare in prostate cancer.[16] 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).[1] 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.[17–26] Ataxia has been reported in cerebellar syndromes, limbic encephalitis, and brainstem syndromes.[19–26] 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.[17,18] Of note, myoclonus is very rare in paraneoplastic syndromes with the exception of opsoclonus–myoclonus syndrome and NMDA encephalitis.[27]

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,[28] our review showed that most PMDs were associated with adenocarcinoma. A VGCC antibody was found in a case with LEMS and cerebellar degeneration.[20] 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.[21–23] One patient with ataxia in the setting of limbic encephalitis had positive anti-Hu antibody (or anti-neuronal nuclear antibody 1, ANNA 1).[25] An intraneuronal antibody was identified in one patient with gait ataxia and a recurrent brainstem syndrome; however, the exact antigen is unclear.[26] 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);[21,25] initially good but non-sustained responses in cases with anti-CV2/CRMP5 and unidentified intraneuronal antibodies;[23,26] and sustained responses in cases with anti-mGluR1.[22] These findings may indicate a poor response for cell-mediated processes to intraneuronal/onconeuronal 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.[17] 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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