Paraneoplastic Peripheral Nervous System Manifestations of Renal Cell Carcinoma: A Case Report and Review of the Literature

Ingrid Yang\textsuperscript{a}  Joanna Jaros\textsuperscript{b}  Danny Bega\textsuperscript{c}

\textsuperscript{a}Rehabilitation Institute of Chicago, Northwestern Feinberg University School of Medicine, Chicago, IL, USA; \textsuperscript{b}University of Illinois College of Medicine, Chicago, IL, USA; \textsuperscript{c}Northwestern Feinberg University School of Medicine, Chicago, IL, USA

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Renal cell carcinoma · Paraneoplastic manifestations · Polyneuropathy · Plexopathy

Abstract
Neurologic symptoms secondary to a paraneoplastic syndrome may be the presenting manifestation of a previously undiagnosed cancer, and alertness to these syndromes may provide an opportunity for early detection and treatment of a cancer. Paraneoplastic weakness is a rare manifestation of renal cell carcinoma and may present with variable electrophysiological features. We present a case of a patient with progressive weakness, sensory changes, and urinary retention, with electrophysiological features suggestive of a complex peripheral nervous system syndrome. Ultimately, a renal cell mass was detected and resected, resulting in significant clinical improvement. We review the literature, cataloging the known neurologic syndromes and antibodies associated with renal cell carcinoma. This case highlights that paraneoplastic neurological disorders associated with RCC can take on many features and provides a resource to practitioners for early detection of a neurologic paraneoplastic syndrome arising from renal cell carcinoma.

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Ingrid Yang
Rehabilitation Institute of Chicago
345 E. Superior
Chicago, IL 60611(USA)
E-Mail ingrid.yang@northwestern.edu
Introduction

Paraneoplastic disorders are autoimmune, nonmetastatic syndromes that have been associated with various cancers. Central and peripheral nervous system disorders associated with paraneoplastic antibodies are relatively common oncological phenomena but occur in only 0.5–1% of the patients with renal cell carcinoma (RCC) [1]. In the peripheral nervous system, paraneoplastic antibodies have been associated with impairment along the entire pathway, from motor neuron, to neuromuscular junction, to peripheral nerves and ion channels, and finally to muscle. Frequently, these neurological syndromes may be the presenting symptom of a previously undiagnosed cancer, and alertness to these syndromes may provide an opportunity for early detection and treatment of a cancer.

Paraneoplastic syndromes are estimated to occur in 10–40% of the patients with RCC but more often present with endocrine or neuroendocrine effects, rather than neurologic symptoms [2]. The few neurological syndromes associated with peripheral nervous system manifestations of RCC that have been described are limited mainly to case reports. These syndromes are diverse and include motor neuron disease [3–5], demyelinating polyneuropathies [2], and myopathies [6, 7]. We present a case of clear-cell RCC associated with unique peripheral nervous system characteristics, including features of a demyelinating polyneuropathy and plexopathy as part of a physiologically complex paraneoplastic syndrome. We report the electrophysiological abnormalities in this case and review the literature as it relates to paraneoplastic neurologic manifestations of RCC. This case highlights the importance of considering RCC in the context of complex peripheral nervous system manifestations.

Case Presentation

A 61-year-old female with a history of type II diabetes presented to the emergency department for evaluation of several days of urinary retention and inability to ambulate, in the setting of 1 year of progressive lower-extremity weakness and a 100-lb, unintentional weight loss. The patient’s weakness began in her proximal left leg approximately 1 year prior to presentation and gradually involved the right leg and both hands over the following months. She reported numbness and tingling in her feet progressively worsening over the course of the year and preventing her from standing without assistance. She did not complain of any pain related to her weakness. She had declined from independent ambulation to ambulating only with the assistance of a walker over the first few months and then started to require the use of a wheelchair within 6 months prior to presentation. She denied flank pain, hematuria, fevers, changes in vision, speech, cognition, or difficulty in swallowing.

On examination, she was alert, fully oriented, and provided a clear history. She appeared comfortable. She had a soft, nontender abdomen. The remainder of her general examination was unremarkable. Cranial nerves II–XII were intact. She had weakness in her bilateral hip flexors, knee flexors, knee extensors, and intrinsic hand muscles. She also had atrophy in the hands and thighs bilaterally. Table 1 displays her detailed motor examination. Sensory examination revealed a reduced sensation to light touch over her feet bilaterally. Vibration and proprioception were slightly impaired in her feet as well. She did not have a sensory level.
Coordination was intact. Reflexes were 2+ in her upper extremities but absent in her patellars and ankles bilaterally. Plantar responses were flexor bilaterally.

Catheterization revealed 1.8 L of retained urine. Complete blood count was normal, and basic chemistry was remarkable for a sodium level of 117 mmol/L and chloride level of 87 mmol/L. Her blood urea nitrogen was 0.89 mg/dL, and creatinine was 25 mg/dL. Urine was negative for protein or bacteria. Spinal tap revealed total protein 175 mg/dL, glucose 105 mg/dL, 1 white blood cell (billion cells/L), and 0 × 10^6 red blood cells. Cytology from a single large-volume collection of the cerebrospinal fluid did not show evidence of malignancy. Lyme, autoimmune panel, and paraneoplastic panel (antineuronal nuclear antibody [types 1, 3], amphiphysin antibody, antiglial nuclear antibody type 1, Purkinje cell cytoplasmic antibody [types 1, 2, TR], CRMP immunoglobulin G, striational antibody, P/Q type calcium channel antibody, N-type calcium channel antibody, acetylcholine receptor-binding antibody, acetylcholine receptor ganglionic neuronal antibody, neuronal V-G potassium channel antibody) were negative. Hemoglobin A1c was elevated to 6.5 g/dL.

On day 4 of hospitalization, electromyography and nerve condition studies were performed and demonstrated decreased amplitudes in the median motor, median sensory, peroneal motor, tibial motor, and sural sensory responses on the left, consistent with axonal injury. Slowed conduction velocities were noted in the median motor and peroneal motor responses pointing to potential demyelination of these nerves. Prolonged distal latency was recorded in the median motor, ulnar motor (mild), and median sensory on the left. Responses were absent in the ulnar and superficial peroneal sensory nerves in the left lower extremity. Limited electromyography was performed on the right side with similar findings, suggesting bilateral dysfunction. These features were thought to be suggestive of a chronic length-dependent sensorimotor demyelinating polyneuropathy with superimposed chronic lumbosacral plexopathy. Results of the study are shown in Table 2. Magnetic resonance imaging of the pelvis demonstrated bilateral femoral nerve enlargement without enhancement. Given the suspicion for malignancy based upon the time course, results of the workup, significant weight loss, and blood found in urinalysis, computed tomography (CT) imaging of the abdomen and pelvis was obtained. Ultimately, the CT scan revealed a 1.2-cm right renal parenchymal mass.

On day 13 of hospitalization, the patient underwent a robotic partial nephrectomy. Pathology revealed a RCC, clear-cell type, Fuhrman grade 2, measuring 1.5 × 1.4 × 1.3 cm [8]. The patient received a tapered course of steroids over 2 months and 90 g of intravenous immunoglobulin treatment over 2 days, and was discharged to subacute rehabilitation for ongoing therapy. Approximately 6 months following resection, the strength in her hands and proximal lower extremities had markedly improved, and she advanced from using a wheelchair to ambulating with a single-point cane. Her follow-up motor examination is displayed in Table 1 and shows improvement in her strength particularly in her distal upper extremities and proximal lower extremities. Her sensory examination remained impaired with reduced light touch and vibration sensation in the feet. Her reflexes had fully returned in her lower extremities. Ten months after resection, she was ambulating freely without assistance, and her urinary retention had completely resolved.
Discussion and Review of the Literature

It is estimated that over 62,000 new cases of renal cancer were diagnosed in the United States in 2016, with mortality rates exceeding 14,000 per year [9, 10]. Clear-cell RCC is the most common form of renal cancer, accounting for 9 out of 10 cases [10]. RCC is classically associated with flank pain, hematuria, and a palpable abdominal mass, but this “classic triad” is found in less than 15% of the patients [11]. In fact, 15–48% of the RCC cases are diagnosed incidentally during evaluation for an unrelated disorder [5, 12]. Early identification improves mortality [13], and in some instances such as the case described here, paraneoplastic manifestations may be the earliest presenting symptom. This case highlights the potential complexity of the neuromuscular syndrome associated with RCC and the positive outcome associated with early detection.

The neuromuscular characteristics of paraneoplastic RCC are not well described. We searched the PubMed database for all English language articles from inception to June 2, 2016, to identify the characteristics of paraneoplastic manifestations of RCC. The search was conducted independently by 2 reviewers (I.Y. and J.J.). The majority of articles identified were case reports or case series. A total of 298 journal articles describing RCC associated with paraneoplastic syndromes were identified. The most common syndromes included liver dysfunction, hyperglycemia, hypercalcemia, and hypertension [5]. In further narrowing the search, we identified 22 cases of paraneoplastic neurologic manifestations related to RCC, summarized in Table 3.

Our patient presented with peripheral weakness, sensory deficits, and bladder dysfunction. Proximal and distal weakness with abnormal nerve conduction studies and elevated protein in the spinal fluid were consistent with a chronic demyelinating polyneuropathy. However, atypical features included bladder dysfunction suggestive of possible autonomic involvement and diffuse asymmetric fibrillations on electromyography. The differential was broadened to include carcinomatous meningitis as well as painless amyotrophy. However, the patient’s unintentional 100-lb weight loss also raised concern for an oncologic etiology and paraneoplastic syndrome. Ultimately, the mixed symptomology prompted further evaluation with an abdominal and pelvic CT, and a renal mass was found. This case highlights the importance of abdominal imaging in patients presenting with unexplainable neuromuscular manifestations over a subacute time course.

The role of paraneoplastic antibodies in RCC remains unclear and is a topic of ongoing investigation in the current literature [14]. Onconeural antibodies occur only in a small proportion of patients with cancer who develop peripheral neuropathy [7]. Previous case reports of paraneoplastic neuropathies associated with RCC have also described negative antibody screens preceding RCC diagnosis [2, 6, 15, 16, 17, 18–20]. Likewise, our patient was seronegative for common paraneoplastic antibodies including anti-Hu, anti-Ma, and anti-CV2 [21]. The question remains whether these antibody-negative cases are truly immune-mediated or whether these antibodies have simply not been identified yet. However, we highlight that failure to identify an antibody marker should not exclude a paraneoplastic process [22, 23], particularly if resolution of the neurologic syndrome follows the removal of the tumor. Of the 22 cases of paraneoplastic neurologic syndromes associated with RCC, 10 patients were not screened for paraneoplastic antibodies and 8 were negative for all antibodies tested [2, 4, 9, 15–17, 19, 20]. Of those who tested positive, all were nonspecific in-
cluding 3 that were positive for antinuclear antibody at 1:80 [21, 24, 25] and 1 who was positive for anti-GAD [14].

Identification of paraneoplastic RCC is challenging given the rare and nonspecific presentations and the lack of definitive paraneoplastic antibody markers. This report demonstrates that, if identified in a timely manner, prompt treatment of an underlying malignancy could reverse the underlying paraneoplastic disorder and prevent disability.

Conclusion

Paraneoplastic weakness in RCC is rare, and the electrophysiological features are variable. The antibodies associated with the disease are not well described. Our case underscores that, in the setting of significant weight loss and rapid progression of weakness, a paraneoplastic etiology should be considered regardless of whether or not antibodies are detected. This is the first case report of RCC presenting with features of several neuromuscular syndromes simultaneously and underscores the potential complexity of the paraneoplastic syndrome. The complexity of the syndrome itself may be a reason to suspect a paraneoplastic process.

Statement of Ethics

The authors confirm that the patient has agreed to the publication.

Disclosure Statement

The authors declare that they have no conflicts of interest regarding the contents or publication of this paper.

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Table 1. Physical examination findings

| Motor examination       | On admission | 6-month follow-up |
|-------------------------|--------------|-------------------|
|                         | right | left | right | left |
| Shoulder abduction     | 5     | 5     | 5     | 5     |
| Elbow flexion          | 5     | 5     | 5     | 5     |
| Elbow extension        | 5     | 5     | 5     | 5     |
| Finger flexion         | 5     | 5     | 5     | 5     |
| Finger abduction       | 4+    | 4+    | 5     | 5     |
| Finger grip            | 4+    | 4+    | 5     | 5     |
| Hip flexion            | 2     | 2     | 3     | 3     |
| Knee extension         | 5     | 3     | 5     | 4     |
| Knee flexion           | 3     | 3     | 3     | 4+    |
| Dorsi flexion          | 4     | 4     | 3     | 3     |
| Plantar flexion        | 5     | 5     | 5     | 5     |
### Table 2. Electromyography and nerve condition study results (day 4 of admission)

| EMG results                  | SIA  | Fibs | PSW  | Fasc | HF  | Amp | Dur | PPP | RP  |
|------------------------------|------|------|------|------|-----|-----|-----|-----|-----|
| L. vastus lateralis          | None | 3+   | 3+   | None | None| None| 2+  | 2+  | Red.|
| L. tibialis anterior         | None | 1+   | 1+   | None | None| None| 2+  | 2+  | Red.|
| L. peroneous longus          | None | 2+   | 2+   | None | None| None| 2+  | 1+  | Red.|
| L. gastrocnemius medius      | None | 1+   | 1+   | None | None| 1+  | 2+  | 1+  | Red.|
| L. adductor longus           | None | 3+   | 3+   | None | None| None| 3+  | 3+  | Red.|
| R. vastus lateralis          | None | None | None | None | None| None| 1+  | N   | Red.|
| R. tibialis anterior         | None | 1+   | 1+   | None | None| None| 2+  | 2+  | Red.|
| L. lumbar paraspinal         | None | None | None | None | None| None| None| None| None|
| L. biceps                    | None | None | None | None | None| None| None| None| None|

### Motor NCS

| Nerve/sites                   | Rec. site | Lat, ms | Amp, V | Area, mVms | Segments | Distance, cm | Vel, m/s | Temp, °C | Dur, ms |
|-------------------------------|-----------|---------|--------|------------|----------|--------------|----------|----------|---------|
| **L Hand**                    |           |         |        |            |          |              |          |          |         |
| Median wrist                  | APB       | 6.67    | 3.0    | 10.2       | Median wrist – APB | N/A       | N/A      | 32.9    | 6.41    |
| Median elbow                  | APB       | 12.29   | 2.7    | 9.3        | Elbow – median wrist | 20.5      | 36.4     | 33      | 7.24    |
| Ulnar wrist                   | ADM       | 3.85    | 5.1    | 20.4       | Ulnar wrist – ADM   | N/A       | N/A      | 33.3    | 8.39    |
| B. elbow                      | ADM       | 9.06    | 4.1    | 16.4       | B. elbow – ulnar wrist | 19        | 36.5     | 33.3    | 9.48    |
| A. elbow                      | ADM       | 12.29   | 3.5    | 15.4       | A. elbow – B. elbow  | 10        | 31       | 33.3    | 10.42   |
| **L Leg**                     |           |         |        |            |          |              |          |          |         |
| Peroneal ankle                | EDB       | 5.31    | 0.4    | 1.1        | Per. ankle – EDB    | N/A       | N/A      | 30.3    | 6.41    |
| B. knee                       | EDB       | 14.11   | 0.2    | 1.5        | B. knee – Per. ankle | 29        | 32.9     | 30.4    | 10.42   |
| A. knee                       | EDB       | 15.63   | 0.2    | 1.6        | A. knee – B. knee   | 7         | 46.3     | 30.6    | 11.35   |
| Post tib ankle                | AH        | 5.05    | 1.0    | 2.7        | Post tib ankle – AH | N/A       | N/A      | 30.7    | 8.07    |

### Sensory NCS

| Nerve/sites                   | Rec. site | Onset Lat, ms | Peak Lat, ms | NP Amp | Segments | Distance, cm | Temp, °C |
|-------------------------------|-----------|---------------|--------------|--------|----------|--------------|----------|
| **L Hand**                    |           |               |              |        |          |              |          |
| Median wrist                  | Dig II    | 4.06          | 5.05         | 5.2    | Median wrist – Dig II | 13        | 33.1     |
| Ulnar wrist                   | Dig V     | NR            | NR           | NR     | Ulnar wrist – Dig V  | 11        | 33.1     |
| **L Leg**                     |           |               |              |        |          |              |          |
| Sural                         | Calf      | 3.39          | 4.11         | 4.11   | Sural – calf  | 14        | 30.6     |
| Sup peron                     | Lat leg   | NR            | NR           | NR     | Sup peron – Lat leg | 14        | 30.6     |

A. elbow, above the elbow; A. knee, above the knee; ADM, Abductor digiti minimi; AH, abductor hallicus; Amp, amplitude; APB, Abductor pollicis brevis; B. elbow, below the elbow; B knee, below the knee; Dig, digit; Dur, duration; EDB, extensor digitorum brevis; EMG, electromyography; Fasc, fasciculations; Fibs, fibrillations; HF, high frequency; Lat, latency; Lat leg, lateral leg; L, left; N/A, not applicable; NCS, nerve conduction study; NP Amp, nerve potential amplified; NR, not read; Onset Lat, onset latency; Peak lat, peak latency; Per. ankle, peroneal ankle; Post tib ankle, posterior tibial ankle; PPP, polyphasic potentials; PSW, positive sharp waves; R, right; Rec, recorded; Red., reduced; RP, reduced potentials; SIA, small irregular activity; Sup peron, superior peroneal; Temp., temperature; Vel, velocity.
Table 3. Paraneoplastic neurologic disorders and renal cell carcinoma

| Symptom/syndrome                        | First author [ref.], year | Cases reported, n | RCC subtype       |
|-----------------------------------------|---------------------------|-------------------|------------------|
| Limbic encephalitis                     | Harrison [15], 2015       | 1                 | Clear cell       |
|                                         | Bell [24], 1998           | 11                |                  |
| Lower motor neuropathy                  | Forman [26], 1999         | 1                 | Not specified    |
| Ballismus/chorea                        | Kujawa [16], 2001         | 1                 | Not specified    |
| ALS                                     | Turk [5], 2009            | 1                 | Clear cell;      |
|                                         | Evans [4], 1990           |                   | not specified    |
| CIDP                                    | Sufit [2], 2011           | 1                 | Papillary        |
| Polyneuritis                            | Swan [27], 1963           | 1                 | Not specified    |
| Motor neuron disease                    | Evans [4], 1990           | 1                 | Not specified,   |
|                                         | Buchanan [3], 1973        |                   | clear cell       |
| Myasthenia gravis                       | Torgerson [17], 1999      | 1                 | Clear cell       |
| General myopathy                        | Solon [7], 1994           | 1                 | Not specified    |
| Necrotizing myopathy                    | Naert [6], 2015           | 1                 | Clear cell       |
| Polymyalgia rheumatica                  | Sidhom [25], 1993         | 1                 | Not specified    |
| Opsoclonus-myoclonus                    | DeLuca [18], 2001         | 1                 | Clear cell;      |
|                                         | Koukoulis [19], 1998      |                   | papillary;       |
|                                         | Vigliani [20], 2001       |                   | papillary        |
| Stiff Person syndrome                   | McHugh [14], 2007         | 1                 | Not specified    |
| Acute demyelinating polyradiculopathy   | Roy[21], 2002             | 1                 | Clear cell       |
| Dermatomyositis                         | Schaefer [28], 2004       | 1                 | Not specified    |
| Cerebellar ataxia                       | Hagel [29], 2005          | 1                 | Clear cell;      |
|                                         |                           |                   | Clear cell       |
| Frontal lobe disorder                   | Hagel [29], 2005          | 1                 | Clear cell       |

ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy.