Resolution of a Debilitating Paraneoplastic Parkinson-like Neurological Syndrome Following Tyrosine Inhibitor Therapy and Consolidative Nephrectomy in a Patient with Advanced Clear Cell Renal Cell Carcinoma

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Paraneoplastic syndromes are commonly encountered in renal cell carcinoma, but neurological manifestations are rare. Herein we report a case of a patient with locally advanced renal cell carcinoma who presented with Parkinson-like symptoms which prohibited surgery due to poor performance status. However, a significant improvement was noted after tyrosine kinase inhibitor therapy, allowing the patient to proceed to curative surgery.

Introduction

Although paraneoplastic syndromes are commonly encountered in patients with renal cell carcinoma, neurological manifestations are rare and can present a diagnostic dilemma. We report a case of a patient with locally advanced renal cell carcinoma who presented with Parkinson-like symptoms. Definitive surgery was deferred in light of debilitating neurological symptoms, however a remarkable improvement was observed after commencement of systemic therapy with tyrosine kinase inhibitors, thus allowing the patient to undergo a curative radical nephrectomy and lymphadenectomy.

Case presentation

A 74-year old Caucasian male was diagnosed with cT1aN0M0 Stage I clear cell renal cell carcinoma (RCC) upon laparoscopic renal biopsy and concomitant laparoscopic cryoablation (Fig. 1a). Magnetic Resonance Imaging of the abdomen 2 years later demonstrated a heterogeneous 5.7 x 7.7 x 5.6 cm enhancing right renal mass (Fig. 1b) with associated right retrocaval lymphadenopathy (Fig. 1c) consistent with locally advanced RCC recurrence. Around the time of this imaging study, the patient and family described a rapid decline in the patient's performance status. In a matter of months, the patient transformed from a fully functioning and interactive septuagenarian to one who was largely non-communicative, sedentary, and suffering from severe gait ataxia and progressive motor weakness. Upon presentation to our institution for a second opinion, the patient was wheelchair bound outside the home (ECOG PS = 3). On exam, he was noted to display bradykinesia, was unable to get up to sit on the exam table, had a shuffling gate and lacked facial expression.

Furthermore, the patient exhibited low-grade nocturnal fevers and unintentional weight loss. A CT of the head with and without contrast demonstrated no specific pathology, while an MRI of the cervical spine revealed multilevel spondylosis but no cord edema. Endocrinologic and metabolic interrogation was within normal limits and included an aldolase (6.3), B12 (311) and TSH (4.4). Patient’s ESR was elevated to 135 (nl < 20) and CRP to 135 (nl < 1).

With a presumed diagnosis of Parkinson’s disease, the patient was started on Carbidopa-Levodopa 25 mg - 100 mg three times a day during a hospitalization for failure to thrive, but medications were stopped shortly after discharge, as it did not affect the patient’s symptoms. At this point, given a negative neurological workup, his symptoms were clinically attributed to paraneoplastic manifestations of RCC.

As such, the patient was initiated on therapy with pazopanib hydrochloride 600 mg a day, a multikinase inhibitor of VEGFR,
PDGFR, FGFR and c-KIT. The patient developed grade 3 palmar-plantar erythrodysesthesia (PPE) and after an unsuccessful attempt at dosage reduction, he was switched to the TKI axitinib which he was able to tolerate at the lowest dose. Interim scans demonstrated reduction in the size of the renal mass and resolution of retrocaval lymphadenopathy (Fig. 2a). The CRP normalized, his ESR decreased by 50% and his fevers resolved. Importantly, the patient’s gait and strength improved; he became more interactive and began to gain weight. Seven months after initiating TKI therapy, patient, family, and treatment team decided to proceed with right radical nephrectomy and retrocaval lymphadenectomy. Histology revealed a 3.0 cm area of viable clear cell RCC, Fuhrman nuclear grade 4, with 10% sarcomatoid features extending to the renal pelvis and ureter. An associated 3.5 cm area of necrosis with chronic inflammation consistent with history of previous cryoablation was also noted. No lymphovascular invasion was present; all margins were negative, the adrenal gland which was removed was uninvolved and no tumor was seen in 4 hilar lymph nodes and 4 para- and retrocaval lymph nodes. The patient had an uneventful post-operative course. More than 2.5 years from resection, the patient is radiographically disease free (Fig. 2b). His performance status is now back to his pre-illness baseline (ECOG 1). Importantly, he has no residual Parkinson-like symptoms.

**Discussion**

Renal cell carcinoma constitutes 2–3% of all cancers in adults in the United States. Paraneoplastic syndromes are commonly encountered in RCC, but neurologic manifestations are rare. Several pathophysiological models have been proposed for paraneoplastic symptoms. The most widely accepted mechanism is immune mediation, where tumor cells express antigens normally expressed in other organs with a subsequent autoimmune response being mounted against these antigens. Another possible mechanism includes cross-reacting proteins, which by virtue of their molecular mimickery with endogenous hormones cross react with...
hormone receptors in normal tissue. Central and peripheral nervous system, neuromuscular junction and muscles themselves can become affected. Several non-specific changes in the CSF such as increased pleocytosis, elevated protein and IgG levels can occur, as well as the occasional finding of various serum antibodies such as anti-Yo, anti-Hu and anti-Ri.

Although paraneoplastic syndromes occur in 10–40% of RCC patients, paraneoplastic neurological manifestations are rare and are limited to only a few case reports. In the present case, the patient developed neurological symptoms upon disease recurrence and regional progression 2 years following failure of initial focal therapy. The symptoms complex for this particular patient was remarkable and unique, clinically greatly resembling Parkinson’s disease.

As a result of his symptoms, all surgery was deferred due to rapidly worsening performance status. Ultimately, systemic therapy was initiated as a last resort effort to potentially improve symptoms and slow disease progression. Due to marked radiographic response, symptoms and performance status improvement, the patient was able to go on to receive consolidative surgery and be disease free over two years later.

Neo-adjuvant TKIs have been evaluated in at least three prospective phase II trials in RCC, both in the advanced and localized settings. Both pazopanib and axitinib have been found safe and feasible to administer prior to either a curative or cytoreductive nephrectomy. However, the use of TKI therapy to improve performance status and resolve Parkinson-like neurologic paraneoplastic manifestations in order to proceed to a nephrectomy has not been previously reported.

**Conclusion**

TKIs have the potential to improve or resolve paraneoplastic neurological syndromes associated with renal cell carcinoma as demonstrated by this case, and should be considered as an option prior to consolidative surgery in those with a poor performance status due to paraneoplastic manifestations.

**Conflict of interest**

None.

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