BJMHR
British Journal of Medical and Health Research
Journal home page: www.bjmhr.com

Myasthenia Gravis and Rhabdomyolysis in A Patient with Advanced Renal Cell Cancer Treated With Nivolumab: A Case Report And Review of the Literature

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ABSTRACT

Nivolumab is a fully human monoclonal antibody against programmed cell death 1 receptor (PD-1). Acting as an immune checkpoint inhibitor, it has emerged as a promising therapeutic method for advanced malignancy, inducing durable responses in patients with solid tumors. It can be associated to very unusual immune mediated toxicity against multiple tissues. Here, we describe a patient with metastatic clear cell renal cell carcinoma, who received nivolumab as fourth line therapy and experienced muscular weakness and pain secondary to rhabdomyolysis and myasthenia gravis. This case portrays a very uncommon yet potentially fatal side effect of nivolumab, seen in less than 1% of patients across all clinical trials. As immunotherapy evolves and its efficacy is proven in more tumor types, the overall use of this class of drugs will increase and their uncommon side effects may be evident more frequently. To our knowledge, this is the first case of fatal myasthenia gravis reported in a patient with renal cell carcinoma treated with anti-PD1 therapy.

Keywords: (Myasthenia gravis, rhabdomyolysis, renal cell carcinoma, nivolumab, anti PD-1 blockade immune mediated side effects)

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Received 20 October 2015, Accepted 29 October 2015

Please cite this article as: Calvo A *et al.*, Myasthenia Gravis and Rhabdomyolysis in A Patient with Advanced Renal Cell Cancer Treated With Nivolumab: A Case Report And Review of the Literature. British Journal of Medical and Health Research 2015.

INTRODUCTION

Renal cell carcinomas, which originate within the renal cortex, are responsible for 80 to 85 percent of all primary renal neoplasms[1]. Globally, the incidence of renal cell carcinoma varies widely from region to region[2]. With the highest incidences occurring in northern Europe, Czech Republic and North America[3,4.]

Each year, an estimated of 338,000 new cases of renal cell carcinoma are diagnosed worldwide[5] and approximately 25% to 30% of patients present with metastatic disease at the time of diagnosis[6]. A number of targeted therapies have been approved for the treatment of metastatic renal cell carcinoma. Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. Interaction between PD-1 and PD-L1 or PD-L2 results in inhibition of the cellular immune response against malignant cells. Previous studies have shown that PD-L1 expression is associated with a poor prognosis in renal cell carcinoma, presumably because of its immunosuppressive function. It has been postulated that PD-L1 expression would be associated with improved overall survival in response to nivolumab therapy, because disruption of PD-1 and PD-L1 signaling by this agent leads to restored antitumor immunity[7,8]. Adverse events such as pulmonary disorders (pneumonitis), renal disorders (acute renal failure and tubulointerstitial nephritis), hepatic disorders (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation), gastrointestinal disorders (colitis and diarrhea), skin disorders (rash, vitiligo, and pruritus) and endocrinopathy (hypothyroidism) are well known adverse effects. Other rare immune mediated side effects such as myasthenia gravis and rhabdomyolysis have also been sparingly described with the use of anti-PD-1 therapy[9].

Case Presentation

A 65-year-old Caucasian man was diagnosed with renal cell carcinoma following a history of back pain that led to identification of a right renal mass via ultrasound. He underwent a radical nephrectomy along with a right adrenalectomy for a single metastatic adrenal lesion. Pathology reported an 11-cm clear renal cell carcinoma (T2b) Fuhrman Nuclear grade II tumor with clear surgical margins and a non-contiguous 1 cm adrenal metastasis. CT imaging studies were consistent with small, bilateral pulmonary metastases. He was treated with sunitinib for 9 months until toxicity led to its discontinuation. He remained asymptomatic with stable bilateral sub centimeter, non-calcified lung nodules for 3 years. At that point there was evidence of disease progression with enlarging lung nodules, mediastinal adenopathy, a pancreatic mass and two soft tissue masses, one in the right supraclavicular fossa and one in

the distal aspect of the right biceps muscle. Biopsy of the right supraclavicular mass confirmed metastatic clear cell carcinoma. Therapy with temsirolimus was started with excellent tolerance and minimal toxicity. Three months into this treatment he was found to have a solitary cerebellar metastasis that was treated with radiosurgery. A PET-CT scan done 6 months after initiation of temsirolimus showed a partial response. Twelve months later -due to recurrent infections and severe weakness- temsirolimus was stopped. He was referred for evaluation to an academic cancer center. He did not qualify for a clinical trial so axitinib was recommended. He experienced an objective response to axitinib with decrease in size of all soft tissue tumors. Unfortunately, he developed drug-induced erythrocytosis, progressive weakness, diarrhea and weight loss. After 9 months of therapy, axitinib was stopped due to excessive adverse effects. After all that toxicity resolved, he was started on nivolumab 3 mg/kg given intravenously every 2 weeks. Twenty-four hours after receiving his second dose of nivolumab, he was admitted to the hospital complaining of dyspnea, diplopia, bilateral ptosis, back pain and progressive muscular weakness. Upon examination by a neurologist, the patient scored 3 out of 5 on strength of the upper extremities (neck flexion, neck extension, deltoid and biceps) and 4 out 5 of the lower extremities but in the next 24 hours his muscle strength worsened significantly. It was noted that his serum creatine kinase (CK) was 6,321U/L (normal, 39–308) on admission. Creatine kinase levels gradually normalized by hospitalization day 14. (Fig.1.)

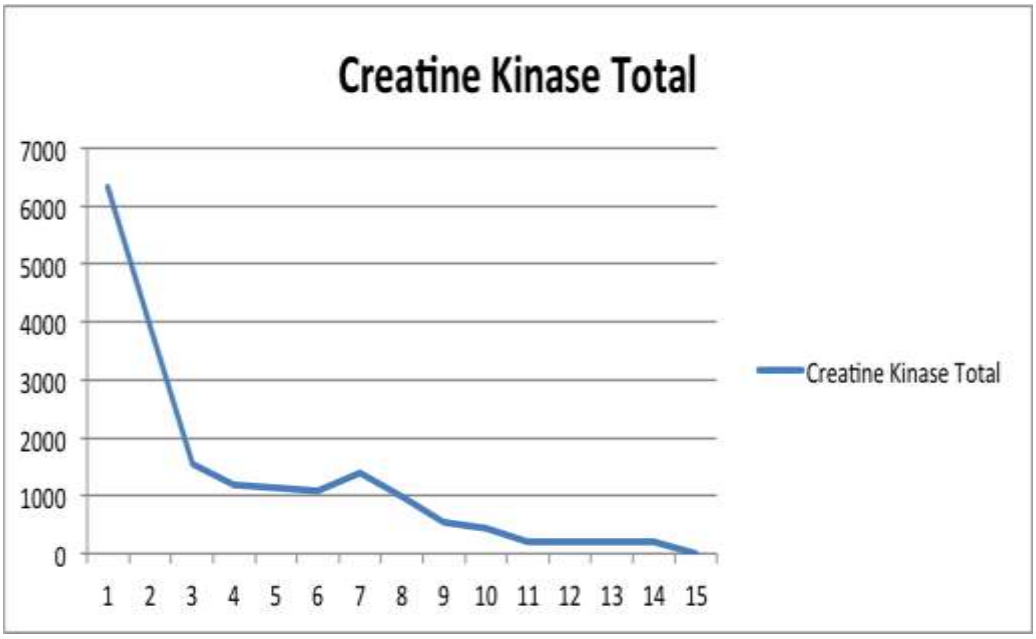

Figure. 1 Creatine Kinase levels through hospitalization day 1 to 14

Based on the clinical and laboratory findings the patient was found to have myositis and possibly acute peripheral neuropathy of autoimmune origin. He also had acute on chronic renal failure. Thyroid function tests were normal. High dose steroids were started on the

second day of admission, despite this, over the course of 7 days he experienced progressive muscle weakness and dyspnea, eventually leading to respiratory failure. Physical examination showed bilateral horizontal and vertical gaze paresis. Motor examination showed upper greater than lower extremity motor strength loss. Electromyography showed diffuse neuropathic changes in the upper extremities with evidence of mild distal, symmetric demyelinating greater than axonal sensorimotor polyneuropathy. On his 10th day of hospitalization he was started on intravenous immunoglobulin daily for five days. His muscular strength improved partially and transiently. On day 17, the patient condition deteriorated, he developed lethargy and additional loss of muscle strength. The patient and family refused any further aggressive medical care. Palliative care was provided and the patient expired on hospital day 18. Serologic tests reported 4 days after his death were strongly positive for acetylcholine receptor muscle binding antibody and acetylcholine receptor muscle modulating antibody consistent with myasthenia gravis. His paraneoplastic antibody panel was negative. (Table 1.)

Table 1. Paraneoplastic antibody Panel

Test	Result	Normal
ACh Receptor Muscle Antibody	98 nmolL	<= 0.02 nmolL
ACh Receptor Muscle Antibody Modulating	2.72 nmolL	<= 0.02 nmolL
Antinuclear antibody	Negative	
Striational	Negative	
P/Q Type calcium channel antibody	0 nmol/L	<= 0.02 nmol/L
Anti-Neuronal Nuclear Antibody 1 S, ANNA -1 S	Negative	< 1:240
Reflex	None	
Anti-Neuronal Nuclear Antibody 2 S, ANNA - 2 S	Negative	< 1:240
Anti-Neuronal Nuclear Antibody 3 S, ANNA - 3 S	Negative	< 1:240
Anti-glial nuclear antibody, AGNA -1 S	Negative	< 1:240
Purkinje cell antibody – 1S, PCA -1 S	Negative	< 1:240
Purkinje cell antibody – 2 S, PCA - 2 S	Negative	< 1:240
Purkinje cell antibody – TR, S PCA – TR, S	Negative	< 1:240
Amphiphysin AB, S	Negative	< 1:240
Collapsin response-mediator family, CRMP – 5 IGG, S	Negative	< 1:240

RESULTS AND DISCUSION

Nivolumab targets PD-1 a co-inhibitory receptor expressed on activated T cells, B cells, monocytes and natural killer cells. This results in an enhanced immune response not only to tumor cells, but occasionally also directed towards normal host tissues, constituting about 50% of nivolumab related toxicity.

The rapid progression to respiratory failure seen in our patient highlights the potential risk of severe rhabdomyolysis and myasthenic crisis associated with nivolumab. The mechanism by which this drug causes myasthenia gravis is unclear, but it is suspected to be due to cytotoxic T-lymphocyte activation. The association of nivolumab with rhabdomyolysis and myasthenia

gravis was previously reported in one patient with non-small cell lung cancer in the CheckMate-012 Trial[10].

Presence of low titers of acetylcholine receptor antibodies has been also reported in the serum of a patient with melanoma who developed nivolumab-induced myasthenia gravis. These antibodies were present before treatment, with a significant titer elevation after exposure to the drug [11]. Thus is it possible that PD1 blockade would cause activation of subclinical myasthenia gravis in selected patients– those that are already predisposed to autoimmune diseases and more specifically myasthenia gravis.

The association of nivolumab and rhabdomyolysis secondary to acute hypothyroidism has previously been reported[12]. In our case, there was no acute thyroid dysfunction therefore a different etiology for rhabdomyolysis had to be present, likely direct autoimmune muscle damage. Even though rhabdomyolysis and myasthenia gravis are rare complications; they can be fatal if unrecognized.

CONCLUSION

Protocols for nivolumab administration already include monitoring thyroid function tests. In addition, clinicians should be alerted to recognize the wide variety of autoimmune- related adverse effects of these medications. Evidently, it is important to be aware of myasthenia gravis and rhabdomyolysis as side effects and thus include periodic clinical evaluations of muscle strength, creatine kinase and aldolase levels if indicated. The goal being to intervene early with drug discontinuation, high dose steroid and immunoglobulin therapy. Timely intervention could avoid fatal cases of checkpoint inhibitor-induced myasthenic crisis and rhabdomyolysis.

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