Myasthenia gravis improvement in a patient receiving sunitinib for metastatic renal cell carcinoma

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Abstract

We present a case of a 59-year-old gentleman with myasthenia gravis and metastatic renal cell carcinoma that resolved on sunitinib. The clear temporal relationship between the patient receiving sunitinib for renal cell carcinoma and the resolution of his myasthenia gravis suggests that the improvement was due either to a paraneoplastic condition responding to treatment of the underlying malignancy or to a direct effect of sunitinib.

Keywords

Renal cell carcinoma; kidney cancer; myasthenia gravis; sunitinib.

Case report

A 59-year-old white man presented to his urologist with recurrent urinary infections in January 2007. Investigations revealed G1 pT2a bladder transitional cell carcinoma (TCC) and an incidental mass of the left kidney was seen on ultrasound. A month later, laparoscopic left radical nephrectomy was performed. Histology of the tumour demonstrated grade 2 pT2 N0M0 renal carcinoma with glandular differentiation and sarcomatoid elements. Five months after the operation, he developed an intermittent vertical diplopia, worse when he was tired. Eight months after surgery (September 2007), he developed intermittent dysarthria and dysphagia, a persistent productive cough, a weak voice and fatigue, often worse in the evening. He was hypertensive and social history was positive for occasional pipe smoking until 2003. He also had significant asbestos exposure, having previously worked with boilers and asbestos lagging. He was taking alfuzosin XL 10 mg and bendroflumethiazide 2.5 mg daily. Basic eye examination showed minimum diplopia and dextrodepression with a possible minimal under action of the left medial rectus muscle. Investigations showed full blood count, liver function tests, urea and electrolytes, and coagulation screen were unremarkable, except for an increased level

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thyroid-stimulating hormone 9×10 mU/L (normal 0.35–5.00 mU/L). Serum anti-acetylcholine receptor antibodies were markedly increased at 8.48 nmol/L (normal <0.40 nmol/L). No serum paraprotein was found on serum electrophoresis. A diagnosis of mild, generalised myasthenia gravis was made and the patient was started on a titration dose of pyridostigmine (Mestinon) 30 mg three times daily. Magnetic resonance imaging of the head was normal. However, chest radiograph showed increased shadowing in the mid-zone of the right lung and chest computed tomography (CT) confirmed multiple, predominantly right-sided pulmonary nodules, mediastinal lymphadenopathy and dense, confluent consolidation in the right upper lobe. Abdomino-pelvic CT was normal. CT-guided needle biopsy of the right lower lobe lung mass confirmed metastatic renal cell carcinoma.

The patient commenced the multi-targeted kinase inhibitor, sunitinib 50 mg once a day for 28 days out of every 42 day cycle as treatment for his metastatic disease in December 2007. Two weeks after commencing sunitinib, his myasthenic symptoms were very much improved and he commenced a reduced dose of pyridostigmine (30 mg three times daily) because of diarrhoea, although this could also be a side effect of sunitinib. During cycle 2 day 1 of sunitinib treatment 6 weeks later, he reported complete resolution of his cough and dysphagia. He had a reduced requirement for pyridostigmine. One month later (during cycle 3 day 1), he reported complete resolution of his myasthenic symptoms and the pyridostigmine was eventually discontinued in March 2008. This coincided with CT imaging of the chest (Fig. 1), showing partial response of the metastatic renal disease with no significant mediastinal lymphadenopathy remaining. Residual

Fig. 1. (a) CT imaging of the chest, (b) showing partial response of the metastatic renal disease with no significant mediastinal lymphadenopathy remaining.
changes only were noted in the right lung with adjacent pleural thickening. Myasthenia gravis symptoms did not recur despite subsequent progression of metastatic disease in the lung and brain, for which the patient received everolimus. However, the patient’s serum anti-acetylcholine receptor antibodies remained increased at 7.62 nmol/L. The patient’s condition deteriorated and he died in October 2009.

Myasthenia gravis is an autoimmune disorder mainly caused by antibodies to the nicotinic acetylcholine receptors (AChR) of the neuromuscular junction[11]. Loss of these receptors from autoimmune destruction leads to a defect in neuromuscular transmission with muscle weakness and fatigability, the hallmarks of this disorder. Late onset myasthenia gravis is characterized by bulbar, ocular, neck, and respiratory symptoms. As a paraneoplastic phenomenon, it is most commonly caused by a thymoma and has not been definitively associated with other cancers[26]. AChR antibodies, when identified, offer the highest specificity for the diagnosis of myasthenia gravis[31]. They are positive in about 85% of patients[31]. Some studies have found no direct correlation between AChR antibody levels and disease activity or response to treatment[4–6], although this is controversial[7]. The classic electromyographic finding is an increased decrement in the evoked compound muscle action potential in response to repetitive supramaximum nerve stimulation[8]. It is important to distinguish myasthenia gravis, present in this patient, from myasthenic syndrome (Eaton–Lambert syndrome, LEMS). LEMS is caused by an antibody response to voltage-gated calcium channels, accounting for its different clinical features.

Myasthenia gravis is treated with anti-acetylcholinesterases, surgical treatment of underlying neoplasm and/or immunosuppression. Intravenous immunoglobulins and humanized monoclonal anti-CD 20 antibody (rituximab) have also been used, and future developments may include immunologically active monoclonal antibodies (e.g. anti-CD 52 and campath-1) [9]. Sunitinib (Sutent, also called SU11248; Pfizer) is an orally administered anti-angiogenic multi-targeted tyrosine kinase inhibitor[10]. It is widely used as first-line therapy in patients with metastatic renal carcinoma.

Paraneoplastic symptoms are found in 20% of patients with renal cell carcinoma at initial presentation[11]. However, paraneoplastic neurological disorders are uncommon and occur in only 0.5–1.9%[12]. The multitude of neuromuscular symptoms associated with renal cell carcinoma includes polymyositis[13], polymyalgia rheumatica[14], motor neuron disease[15], opsoclonus–myoclonus syndrome[16] and myopathy[17]. Cytokine treatment-induced oculo-bulbar myasthenia gravis has been reported in a patient with metastatic renal cell carcinoma[18]. To our knowledge, only one case of myasthenia gravis as a paraneoplastic complication of renal cell carcinoma has been reported before, and the patient did not have any antibodies to the acetylcholine receptor[19]. This patient’s myasthenia gravis was resolved after surgical treatment. Whilst it is interesting to note renal carcinoma and myasthenia gravis occurring simultaneously in a patient, it is not possible to establish a causative link between the conditions on the strength of this case report.

Teaching point

It is not clear whether sunitinib resolved the myasthenic symptoms directly or indirectly from controlling the metastatic disease or whether the myasthenia gravis resolved spontaneously. The temporal relationship of resolution of myasthenic symptoms following the commencement of sunitinib suggests a link between the two[20]. Sunitinib acts by inhibiting the vascular endothelial growth factor receptor and other tyrosine kinases, including the platelet-derived growth factor, c-kit and Flt-3 receptor at nanomolar concentrations[21,22]. In addition, sunitinib inhibits a wide range of receptor tyrosine kinases and has been shown to have immunomodulatory properties[23–25]. It is therefore possible that the resolution of the myasthenic symptoms may have been an off-target effect of sunitinib.

References


