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Case Report

Acute Confusional Syndrome as Direct Adverse Effect of Sunitinib Therapy for Metastatic Renal Cell Carcinoma

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Keywords

• Confusional syndrome; Sunitinib; Heart disorders; Renal cell carcinoma; Complete response

Abstract

Sunitinib is an anti angiogenic agent used in the first line treatment of metastatic renal cell carcinoma (mRCC), which is associated to a high incidence of adverse effects, although neurological adverse effects are uncommon. We describe the case of 76-year-old male with mRRC and severe aortic and mitral valve disease treated with sunitinib, who presented acute confusional syndrome (ACS) during sunitinib treatment without organic condition that, explains his status. After 24 months of sunitinib discontinuation, the patient remains completely recovered from the ACS and showed complete radiological response.

ABBREVIATIONS

Mrcc: Metastatic Renal Cell Carcinoma; ACS: Acute Confusional Syndrome; CT: Computerized Tomography; BP: Blood Pressure

INTRODUCTION

Sunitinib is an anti angiogenic agent from the tyrosine kinase group targets the vascular endothelial growth factor used as first line treatment of metastatic renal cell carcinoma (mRCC). The most frequent adverse effects of sunitinib treatment include asthenia, hypertension, digestive and skin toxicity [1]. Neurological side effects are uncommon, although reversible posterior leukoencephalopathy [2] and some cognitive disorders [3] had been previously described, but acute confusional syndrome is exceptional (ACS).

CASE REPORT

76 year-old male with previous history of hypertension, hypercholesterolemia, type II diabetes mellitus and hypertrophic cardiopathy with severe aortic and mitral stenosis, but intact left ventricular ejection fraction. He was diagnosed with left renal mass and multiple pulmonary metastases by tomography (CT) as the result of a study of acute pulmonary edema due to extra-hospital pneumonia. Regular treatment included omeprazole 20 mg, atorvastatin 80 mg, metformin, telmisartan 40 mg, lorazepam 1 mg and acetylsalicylic acid 100 mg.

The baseline CT showed multiple nodular opacities, the largest was 15 mm, compatible with metastases (Figure 1a), and an 11x9 cm left renal mass dependent of the upper pole. The pathological diagnosis of the percutaneous biopsy taken of the renal mass was conventional renal cell carcinoma. Due to the patient's poor performance status at diagnosis (Karnofsky PS 60%), cytoreductive nephrectomy was ruled out and treatment with Sunitinib 50 mg/day 4/2 schedule was initiated. Additionally, atorvastatin, a cytochrome P450 inhibitor (CYP 34A), which hypothetically could increase the availability of sunitinib, was replaced by ezetimibe.

The control CT after 3 cycles of sunitinib showed partial response of the lung M1 (two 6mm nodular opacities in lower left lobe) and stability of the primary renal tumor, and the patient showed considerable improvement in overall status with a Karnofsky PS of 90%, so he was subject to laparoscopic radical left nephrectomy after the 4th cycle of sunitinib. The histological analysis of the nephrectomy specimen revealed clear cell carcinoma, Fuhrman 4, with a maximum diameter of 11 cm and extensive necrotic areas, no extra-capsular extension or invasion of renal sinus fat. The adrenal gland was normal and there were tumour-free hilaradenopathies, stage pT2b.

Twelve days after surgery treatment with sunitinib 50mg/day was resumed, observing a complete radiological response after 3 cycles post-nephrectomy (7th cycle in all) (Figure 1b). During the 8th post-nephrectomy cycle (12th cycle in all), the patient was admitted to hospital to syncope, without loss of consciousness, and asthenia, hyporexia, cough, expectoration without fever and weakening. The family referred repeated syncopes in the previous week and occasional disorientation in the previous month. In a first assessment in the emergency room, he presents BP 90/50 mmHg, heart rate 85 bpm and temperature 35ºC. When assessed in the hospital, parameters were: BP 147/93 mmHg, heart rate 85 bpm and temperature 36.6ºC. biochemical and hematological parameters were normal. Sunitinib was

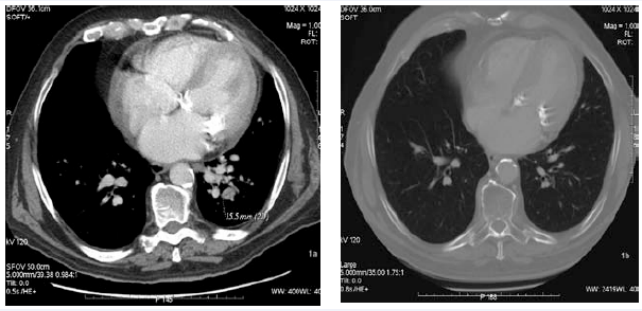

Figure 1 a: Major metastatic lung node in basal tomography, previous sunitinib treatment. b: Complete radiological response, after 7 cycles of treatment with sunitinib (3 cycles after nephrectomy).

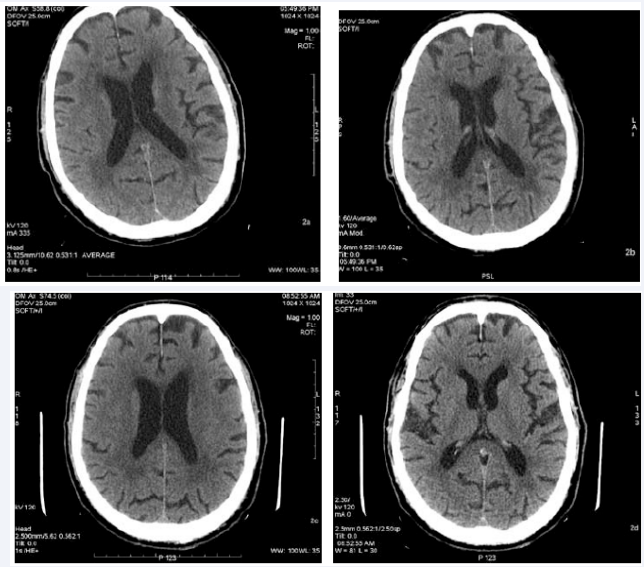

Figure 2 a and b-Baseline cranial tomography (before sunitinib therapy) c and d: Cranial tomography during episode of acute confusional syndrome. Both tomographies show small vessel ischemic of leukopathy syndrome without acute lesions.

suspended. The disorientation worsened in the following 3 days, presenting agitation and visual hallucinations, and he remains with normal serum parameters, including glucose and thyroid hormones levels, and new cranial CT showed data similar to pre-sunitinib therapy (Figure 2). Two months later, the patient presented total recovery from the delirium episode.

The patient continues in periodic follow-up, without active oncologic treatment for the last 24 months. He has not presented syncope or neurological disorders again and continues in radiological complete response.

DISCUSSION

Treatment with sunitinib has a high incidence of adverse events, primarily comprising asthenia, hypertension, digestive, hematological and skin toxicity, but neurological toxicity is exceptional [1]. In this case, we describe an ACS with Naranjo probability score [4] of 6 indicates a probable adverse sunitinib reaction.

Disturbance of consciousness and attention are identified as core symptoms of ACS. The associated symptoms consist of mixture of various cognitive dysfunctions, thought and language disturbances, psychopathological, perceptual and affective symptoms. In this case, we have to make the differential diagnosis with dementia and depression. ACS can be differentiated from dementia as dementia has a gradual onset and persists for more than one month. Dementia occurs in clear consciousness with no fluctuations in cognitive functions and it is not associated with decreased alertness. Depression can be distinguished from ACS by the absence of altered cognitive functions and decreased consciousness. Multiple neurologic conditions such as cerebral metastases, stroke, drug-induced delirium, metabolic disorders, limbic encephalitis or reversible posterior leukoencephalopathy, can be clinically mistaken for ACS. Magnetic resonance imaging was not available in this case, but the CT performed during the ACS episode showed lesions similar to those of the CT performed before sunitinib therapy, which are typical of age-related cerebral degeneration, ruling out organic conditions and cerebral metastases. Another of the described causes of ACS is hyponatremia and decreased levels of thyroid hormones, which do not apply in this case. On the other hand, treatment with sunitinib is associated to hypertension, due to the antagonist effect on the vascular endothelial growth factor, which causes vasoconstriction and increases peripheral vascular resistance. Syncope and hypotension episodes are described in our patient; his severe double valve disease explains both phenomena due to reduced cardiac output. Hypertension has been described as a cause of ACS, but that is not the case of hypotension.

Another interesting point in this case is the suitability of sunitinib therapy in a patient with double cardiac valve disease. Heart disease is not a contraindication in itself, but it is a condition that requires precaution when indicating this treatment. Significant cardiac toxicity is very uncommon, with left ventricle dysfunction being the main adverse effect, with grade III/IV in 1-2% of patients [1]. It is therefore a very safe drug from the cardiac perspective with the pertinent controls.

Finally, we highlight the complete radiological response of the pulmonary metastatic disease 24 months after sunitinib discontinuation. This fact has been previously documented [5], and represents a feasible alternative both for the tumour control and the patient's quality of life. However, all authors agree that the mechanism of this phenomenon is unknown and further well-designed studies are required to show its suitability.

CONCLUSIONS

Neurological toxicity with sunitinib is rare and there a few described cases of ACS, all of them in the context of reversible posterior encephalopathy, limbic encephalitis or secondary to brain metastases. However, it could also be a direct adverse effect associated to treatment with sunitinib. Sunitinib withdrawal is the safe options in patients who present this serious adverse effect, without it involves an unfailing progression of the mRCC.

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