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Case Report

Acute renal failure after treatment with sunitinib in a patient with multiple myeloma

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Abstract

Sunitinib is a multiple tyrosine kinase receptors inhibitor that is approved for the treatment of advanced renal cell carcinoma. Amongst its targets are fetal liver tyrosine kinase receptor 3 (FLT 3) and vascular endothelial growth factor receptor (VEGFR). Renal toxicity has not been reported from the trials, but several patients have been reported to develop a pre-eclampsia-like syndrome. We report the first case of acute tubular necrosis in a patient with multiple myeloma following treatment with sunitinib.

Keywords: acute renal failure; drug toxicity; sunitinib

Introduction

Sunitinib is a small-molecule inhibitor of multiple tyrosine kinase receptors approved for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumour (GIST). Phase II trials have been performed in other solid tumours including breast, lung and colon cancer [1]. Trials in haematologic malignancies including multiple myeloma are currently under study [2]. Most common side effects included left ventricular dysfunction, haemorrhage, hypertension, fatigue and diarrhoea [1]. Mucositis, hand-foot syndrome, hair and skin discoloration, hypothyroidism and rash have also been reported. Renal toxicity was not reported from the trials, but a pre-eclampsia-like syndrome (hypertension, proteinuria and renal insufficiency) was reported in seven patient receiving sunitinib or sorafenib [3]. We report a case of acute renal failure (ARF) after initiation of sunitinib without the pre-eclampsia-like syndrome.

Case report

A 50-year-old male with a history of hypertension and diabetes mellitus presented with abdominal discomfort in January 2006. X-rays revealed a pathologic fracture in the left fourth rib and multiple lytic bone lesions. Serum protein electrophoresis found 6.2 g/dL of a monoclonal IgGκ. A bone marrow biopsy showed 70% κ-restricted CD-20 negative plasma cells and a labelling index of 1.8%. The initial κ serum-free light chain (sFLC) was 327 mg/dL. The patient was treated with lenalidomide followed by autologous stem cell transplantation with a good response. The disease relapsed in July 2007, and bortezomib and dexamethasone were started. Despite a good response, the regimen had to be discontinued because of painful dysesthesia. The patient's M-spike again rose to 4.9 g/dL and κ sFLC to 585 mg/dL. He agreed to enrol in a phase II study with sunitinib monotherapy. Sunitinib was started on 19 December 2007 with a serum creatinine (Scr) of 1.3 mg/dL.

On 21 January 2008, the patient complained of congestion, cough, malaise and low-grade fever. Levofloxacin 500 mg was started every other day. The next day, labs revealed a WBC of 2.5×10^9/L, Ca 7.2 mmol/L, K 5.8 mmol/L, uric acid 11.3 mg/dL and a Scr 7.4 mg/dL (Figure 1). Apart from levofloxacin and sunitinib that were new, his medications included nifedipine (13 years), lisinopril (13 years), oxycodone hydrochloride (2 years), trimethoprim–sulfamethoxazole (3 months) and pamidronate (2 years). He had a blood pressure of 138/80 mmHg at admission that never required any support and at no time did he appear septic. M-spike was 7.5 g/dL and κ FLC was 1270 mg/dL. Urine protein was 2.4 g/day down from 3.2 g/day in December. The patient was admitted to the hospital for haemodialysis. A renal biopsy was performed.

The renal biopsy showed mild mesangial expansion and hypercellularity in the glomeruli. Tubules were dilated with oedema and a mild mononuclear infiltrate present in the interstitium. No interstitial eosinophils were identified. Tubular epithelial cells showed vacuolization of the cytoplasm; mitotic figures were prevalent (Figure 2A and B). No atypical casts were seen. Bright linear staining with IgG and κ was noted on the glomerular and tubular basement membranes (Figure 3). Electron microscopy showed very mild foot process effacement and no deposits in the glomeruli or tubular basement membranes. Findings were consistent with a severe acute tubular injury and evidence of light heavy chain deposition disease.

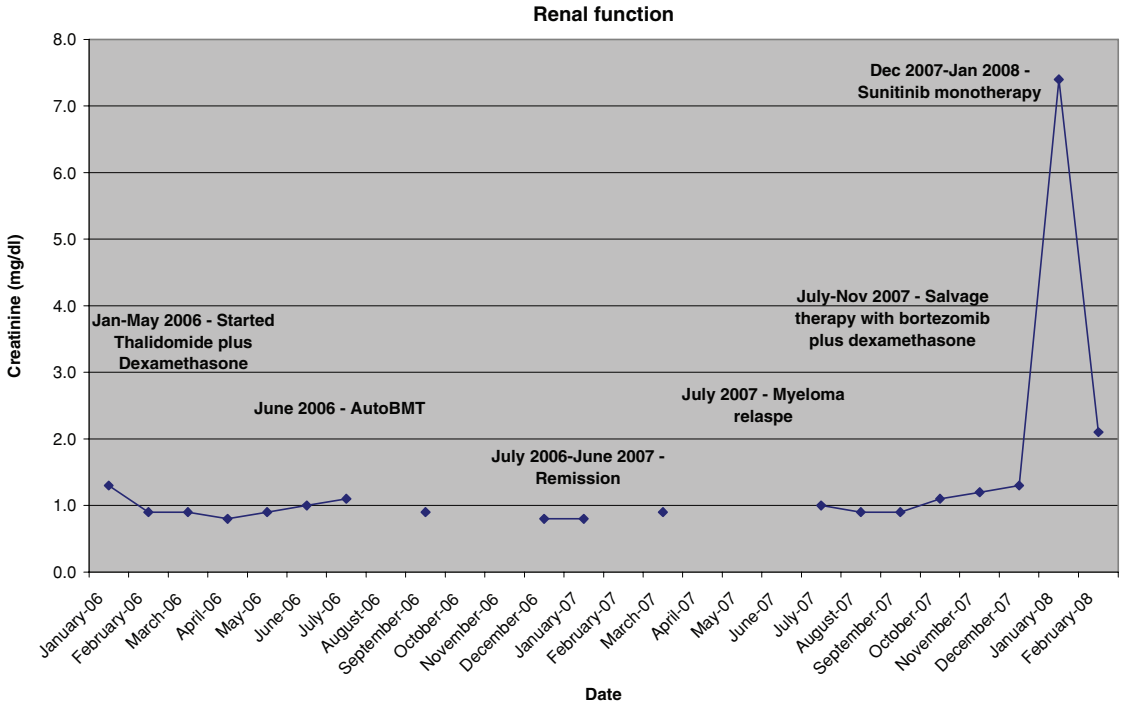

Fig. 1. The patient's renal function over time.

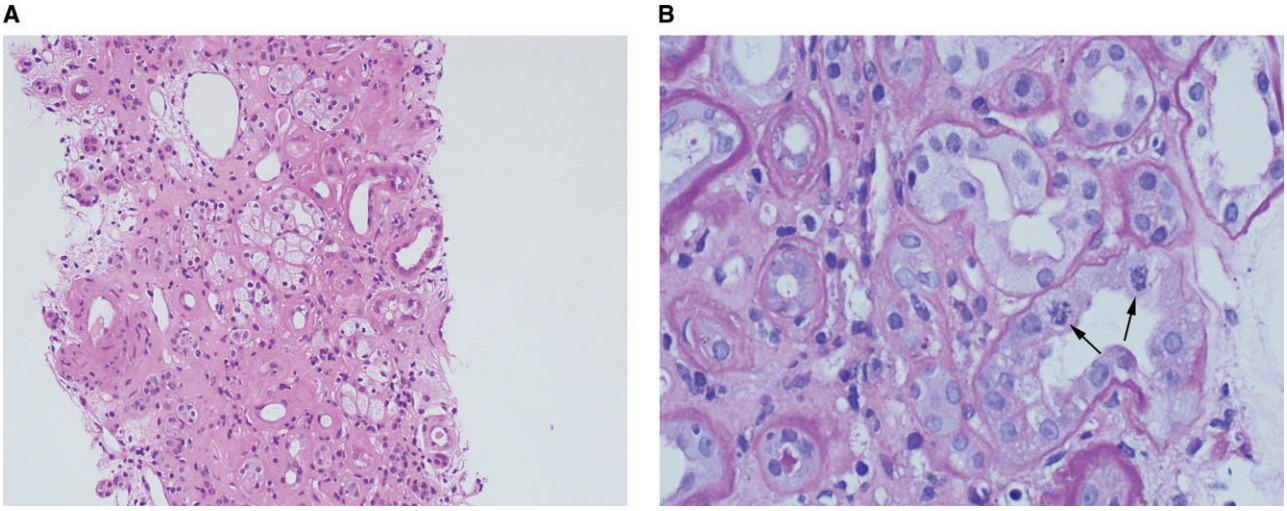

Fig. 2. (**A**) Light microscopy showing vacuolization of the epithelial cytoplasm (haematoxylin and eosin). (**B**) Mitotic figures in the tubular epithelial cells (periodic acid-Schiff).

Sunitinib was discontinued and his renal function started to recover after 1 week of dialysis. Myeloma therapy was switched to bortezomib and doxorubicin. The combination resulted in tumour lysis syndrome on two separate occasions requiring temporary dialysis. In May 2008, lenalidomide was added that finally brought his κFLC <1000 mg/dL. Serum creatinine stabilized at 1.7 mg/dL with an iothalamate clearance of 39 ml/min/1.73m^2. All of the previous medications except sunitinib were restarted without any problems. His most recent Scr was 0.9 mg/dL, 15 months after his episode of acute renal failure.

Discussion

The targets of sunitinib include stem cell factor receptor (KIT), Fms-like tyrosine kinase 3 and colony-stimulating factor receptor type 1 and glial cell line-derived neurotrophic factor receptor (RET), platelet-derived growth factor receptor (PDGFR), fetal liver tyrosine kinase receptor 3 (FLT 3) and vascular endothelial growth factor (VEGFR) 1, 2 and 3 [1]. These cell surface receptors are involved with regulation of growth, differentiation, survival of various cell types as well as neoangiogenesis

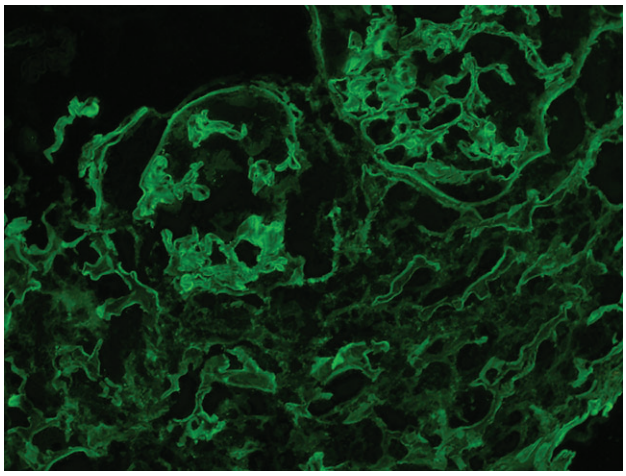

Fig. 3. Immunofluorescence study showing linear staining with antibodies to kappa light chain. Lambda staining was negative (not shown). By electron microscopy, however, no deposits typical of monoclonal immunoglobulin deposition disease were identified.

that are the bases for sunitinib's anti-neoplastic activity. Like other VEGF inhibitors (bevacizumab), hypertension is common (15–28%). Proteinuria was not reported but peripheral oedema was noted in 12.2–16% in two of the early trials [4,5]. More recently, a pre-eclampsia-like syndrome manifested by hypertension, oedema and proteinuria was reported in seven patients treated with either sunitinib or sorafenib [3]. These symptoms appeared after a median of 24 weeks of therapy with an estimated incidence of 2.3%. Other reports of renal injury include a case of possible allergic interstitial nephritis in a patient who developed ARF and peripheral eosinophilia [6]. Although no biopsy was obtained, the symptoms recurred when the patient was re-challenged with the drug. Thrombotic microangiopathy, hypertension and reversible posterior leukoencephalopathy syndrome was reported in a patient receiving sunitinib for GIST. The patient presented with loss of vision, seizure and renal failure [7]. In nearly every case, the symptoms improved with either discontinuation of the drug or dose reduction [3,6,7].

The renal injury reported to date with VEGF inhibitors mainly involves the glomerular compartment. Evidence from animal and human studies suggests that VEGF is necessary for the health of the podocytes [8]. VEGF is produced by podocytes while VEGF receptors 1 and 2 are found on glomerular endothelial cells. The inhibition of VEGF production or its receptors produces characteristic podocyte injury (endotheliosis, mesangiolysis, microthrombi and thrombotic microangiopathy).

Our patient is the first case of acute tubular necrosis reported with sunitinib. Although the injury in our patient was confined to the tubular compartment, the role of VEGF cannot be completely excluded. While the function of VEGF in healthy adult kidney remains incompletely understood, it may be important in ischaemic protection [9]. Studies have shown that hypoxia increases VEGF that increases renal blood flow. This may help explain the ARF in our patient. Kidneys of myeloma patients have increased sensitivity to the vasoconstriction caused by drugs such as non-steroidal anti-inflammatory drugs (NSAID) and intravenous iodinated contrast agents. The ability to stimulate reactive oxygen species and MCP-1 by light chains may be a contributing factor [10]. The inhibition of VEGF in our patient may have further reduced the kidney's ability to cope with the stress of the myeloma proteins. The possibility that the injury was due to inhibition of the other tyrosine kinase receptors also cannot be ruled out.

To the best of our knowledge, this is the first case of acute tubular injury associated with sunitinib. Other medications could not have played a role in the acute renal failure, since the patient was able to restart every medication except sunitinib without any sequelae. Without any light chain casts on the renal biopsy, cast nephropathy is ruled out. Improvement in his renal function despite uncontrolled κ light chain levels does not support light heavy chain deposition disease as a cause of the renal failure. The role of the myeloma, however, cannot be completely ruled out, as the inhibition of VEGF may have compromised the renal haemodynamics resulting in the tubular injury. Administration of sunitinib and other VEGF inhibitors in patients with multiple myeloma or other pre-renal pathophysiology should be done with caution. Patients should be closely monitored for changes in their renal function.

Conflict of interest statement. None declared.

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