Inhibition of tyrosine kinases by sunitinib associated with focal segmental glomerulosclerosis lesion in addition to thrombotic microangiopathy

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Abstract

Sunitinib is an orally administered inhibitor of tyrosine kinases and has become the standard of care for many patients with metastatic renal cell carcinoma. Its use has been associated with renal toxicity in some patients. We report a patient with metastatic clear-cell renal carcinoma who showed arterial hypertension, nephrotic syndrome and azotaemia 10 months after treatment with sunitinib. The renal biopsy revealed focal segmental glomerulosclerosis (FSGS) in addition to thrombotic microangiopathy (TMA), and the complete syndrome disappeared 6 months after sunitinib withdrawal. To our knowledge, this is the first case of FSGS associated to TMA secondary to sunitinib treatment. We discuss the possible glomerular pathomechanism.

Keywords: focal segmental glomerulosclerosis; renal cell carcinoma; sunitinib; thrombotic microangiopathy; tyrosine kinase inhibitors

Background

Sunitinib is an orally administered inhibitor of tyrosine kinases (TKIs) affecting vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) pathways [1]. Sunitinib has become the standard of care for many patients with metastatic renal cell carcinoma. Its use has caused hypertension, proteinuria and azotaemia in some patients [2]. However, the prevalence of TKIs glomerular toxicity could be higher due to a lack of renal biopsy data and routine screening for proteinuria de novo. We report the first case of focal segmental glomerulosclerosis (FSGS) in addition to thrombotic microangiopathy (TMA) in a patient receiving sunitinib for the treatment of clear-cell renal carcinoma, and we discuss the possible glomerular pathomechanism.
Case reports

A 66-year-old White man underwent a right partial nephrectomy for clear-cell renal carcinoma in 2002. No kidney or blood pressure (BP) disorders were documented afterwards. By 2005, pulmonary metastasis appeared. Treatment with interferon-α was started and changed to sunitinib maleate (cycles of 50mg/day during 4 weeks, followed by 2 weeks rest) in 2007. Over the next weeks, BP rose to 200/95 mmHg, requiring three antihypertensive medications (enalapril 40mg/day, amlodipine 10mg/day and hydrochlorothiazide 25mg/day). Ten months later, he showed oedema and oliguria with a serum creatinine of 2mg/dl and proteinuria of 5.4g/24h. Baseline serum creatinine was 0.9mg/dl and proteinuria was 0.1g/24h. Sunitinib was discontinued and enalapril was maintained at the same dosage, whereas hydrochlorothiazide and amlodipine were changed to furosemide 120mg/day and irbesartan 300mg/day, respectively. No further changes were made. Afterwards, platelet count normalized and no schistocytes were present, but nephrotic syndrome and azotaemia persisted. Histologically, an average of 20 glomeruli in the renal cortex was identified, four presented global sclerosis of capillary ball glomerular. The preserved glomeruli had a lesion of focal and segmental distribution consistent in an increased mesangial matrix with capillary occlusion and synechiae to the Bowman capsule. In some of these glomeruli, there were foam cells occupying the lumen of the glomerular capillaries and occasionally hyaline deposits (Figure 1). The glomeruli appeared normal, there was a slightly irregular increase of the mesangial matrix and some capillary loops were thickened with images of double contours (Figure 2). No intra-capillary thrombi were observed. There was a patchy interstitial fibrosis with focal tubular atrophy and minimal inflammatory infiltrates of lymphocytes. Arterioles were seriously injured presenting endothelial swelling and thickness with extensive hyaline–fibrinoid deposits which occasionally completely replaced the muscle cells of the middle layer and occluded the arteriolar lumen (Figure 3). In short, there was a FSGS with hyaline deposits and vascular lesions suggesting TMA. Immunofluorescence and electron microscopy were not performed because of insufficient sample. The complete syndrome disappeared 6 months after sunitinib withdrawal with disappearance of oedema, improvement in BP control and no need of diuretic therapy. Also, serum creatinine and proteinuria decreased to 1.2mg/dl and 0.9g/24h, respectively. However, the tumour progressed and sorafenib was started, which was immediately replaced by temsirolimus due to palmar–plantar erythrodysesthesia.

Discussion

Renal toxicity related to the VEGF pathway has been described with bevacizumab, a VEGF-depleting antibody. Histological confirmation of TMA [3,4], cryoglobuline-
mic glomerulonephritis [5], collapsing glomerulopathy [6], immune complex-associated focal proliferative glomerulonephritis [7] and glomerular TMA with collapsing glomerulopathy and Ig A deposit [8] have been reported after treatment with bevacizumab. The inhibition of TKIs by sunitinib also causes renal toxicity. Obhrai et al. [1] and Patel et al. [2] described seven patients with pre-eclampsia-like syndrome, hypertension and proteinuria who were cured after stopping or decreasing the dose. Kapiteijn et al. [9] reported sunitinib-associated TMA in a patient with gastrointestinal stromal tumour cell, but without renal biopsy data. Recently, Bollée et al. [10] reported the first case of histologically documented TMA in a patient receiving treatment with sunitinib, and Winn et al. [11] reported an acute interstitial nephritis secondary to sunitinib. To our knowledge, we describe the first case of renal toxicity with histological confirmation of FSGS in addition to TMA and subendothelial arteriolar lesions after sunitinib treatment.

VEGF is constitutively expressed by podocytes, and VEGF receptors are present on normal glomerular capillary endothelial cells. The pathogenesis of TMA in patients receiving anti-VEGF therapy likely relates to perturbation of the podocyte–endothelial VEGF axis signalling [3,4].

However, the pathogenesis of FSGS in patients receiving anti-VEGF agents is unclear. In preeclamptic patients with nephrotic syndrome, FSGS is one of the representative glomerular changes [12]. One possible explanation is that the placenta in preeclampsia increases the expression and secretion of fms-like tyrosine kinase 1 (sFlt1), which inhibits VEGF receptors, similarly to the sunitinib mechanism. Also, experimentally, the administration of VEGF-blocking antibodies or an adenovirus-expressing sFlt1 in rodents caused a clinical syndrome with features of preeclampsia [3,8]. This hypothetical mechanism is reinforced by the fact that there are reported patients with clinical pictures of sunitinib-related renal toxicity resembling preeclampsia-like syndrome in which disordered VEGF signaling could play a crucial role [1,2].

A second mechanism for FSGS in the context of arteriolar lesions shown in our patient (Figure 3) may be similar to that found by Greenberg et al. [13]. In this study, FSGS was observed in 63% of the biopsy specimens in patients with nephrotic syndrome secondary to vascular occlusion by cholesterol atheroembolism. The aetiology of this finding is not clear, but both an ischemic injury and a hyperfiltration injury in non-ischemic nephrons may have contributed.

The incidence of renal toxicity associated with VEGF inhibitors is unknown and appears to be partially reversible. We suggest closely monitoring patients receiving VEGF blockers and TKIs. Renal biopsy should be considered to exclude other renal disease, establish pathophysiological mechanisms and indicate appropriate therapy. A new glomerular pathomechanism where new pathways in the paracrine and autocrine relationship between endothelial cells and podocytes interaction must be explored.

Conflict of interest statement. None declared.

References


Received for publication: 1.2.09; Accepted in revised form: 16.11.09