Nephrol Dial Transplant (2009) 24: 682–685
doi: 10.1093/ndt/gfn657
Advance Access publication 2 December 2008

Exceptional Case

NDT
Nephrology Dialysis Transplantation

Thrombotic microangiopathy secondary to VEGF pathway inhibition by sunitinib

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Abstract

Background. Drugs targeting the VEGF pathway are associated with renal adverse events, including proteinuria, hypertension and thrombotic microangiopathy (TMA). Most cases of TMA are reported secondary to bevacizumab. It was shown recently that sunitinib, a small molecule inhibiting several tyrosine kinase receptors, including VEGF receptors, can also induce proteinuria, hypertension and biological features of TMA.

Case. A 44-year-old woman with a history of malignant skin hidradenoma was started on sunitinib for refractory disease. She developed hypertension after 2 weeks and low-grade proteinuria after 4 weeks. Renal function remained normal, and biological signs of TMA were absent. A renal biopsy was performed 6 months later as proteinuria persisted, demonstrating typical features of TMA. The patient was given irbesartan, and sunitinib was continued for 3 months after diagnosis. Over this period, blood pressure and renal function remained stable and proteinuria became undetectable.

Conclusion. We report on the first case of histologically documented TMA secondary to sunitinib and provide detailed description of renal histological involvement. This suggests that all anti-VEGF drugs may share a common risk for developing renal adverse events, including TMA. Our case highlights the possible discrepancy between mild clinical manifestation on one hand and severe TMA features on renal biopsy on the other hand and pleads for large indication of renal biopsy in this setting. The renin–angiotensin system blockers may be considered in patients with mild clinical manifestations and in the absence of therapeutic alternative to anti-VEGF drugs.

Keywords: sunitinib; thrombotic microangiopathy; VEGF

Introduction

The development of drugs inhibiting vascular endothelial growth factor (VEGF), a critical factor involved in angiogenesis, has represented a great advancement in the field of oncology over the last few years. However, it has become clear that adverse events, especially renal, are associated with anti-VEGF therapy, many patients developing proteinuria and/or hypertension [1]. Moreover, cases of thrombotic microangiopathy (TMA) have been reported secondary to bevacizumab administration [2,3]. No data are currently available to accurately estimate the proportion of patients developing TMA under antiangiogenic therapy. Sunitinib, a small molecule inhibiting several tyrosine kinase receptors, including VEGF receptors 1–3 and platelet-derived growth factor receptor-beta, is another agent acting on angiogenesis with anti-tumoural effects. Recent data showed that sunitinib can also induce proteinuria and hypertension, and biological features of TMA have been reported [4–6]. However, full histological description of anti-VEGF-induced TMA has been only reported in a few patients receiving bevacizumab. We report on the first case to our knowledge of histologically documented TMA secondary to sunitinib and provide detailed description of renal histological involvement.

Case

A 44-year-old woman with a history of malignant skin hidradenoma was started on sunitinib for refractory disease. Since the diagnosis made 2 years earlier, the cancer was evolutive despite surgical resection, radiotherapy and chemotherapy (Taxol plus Adriamycine). The patient had progressive cervical bone invasion and lung

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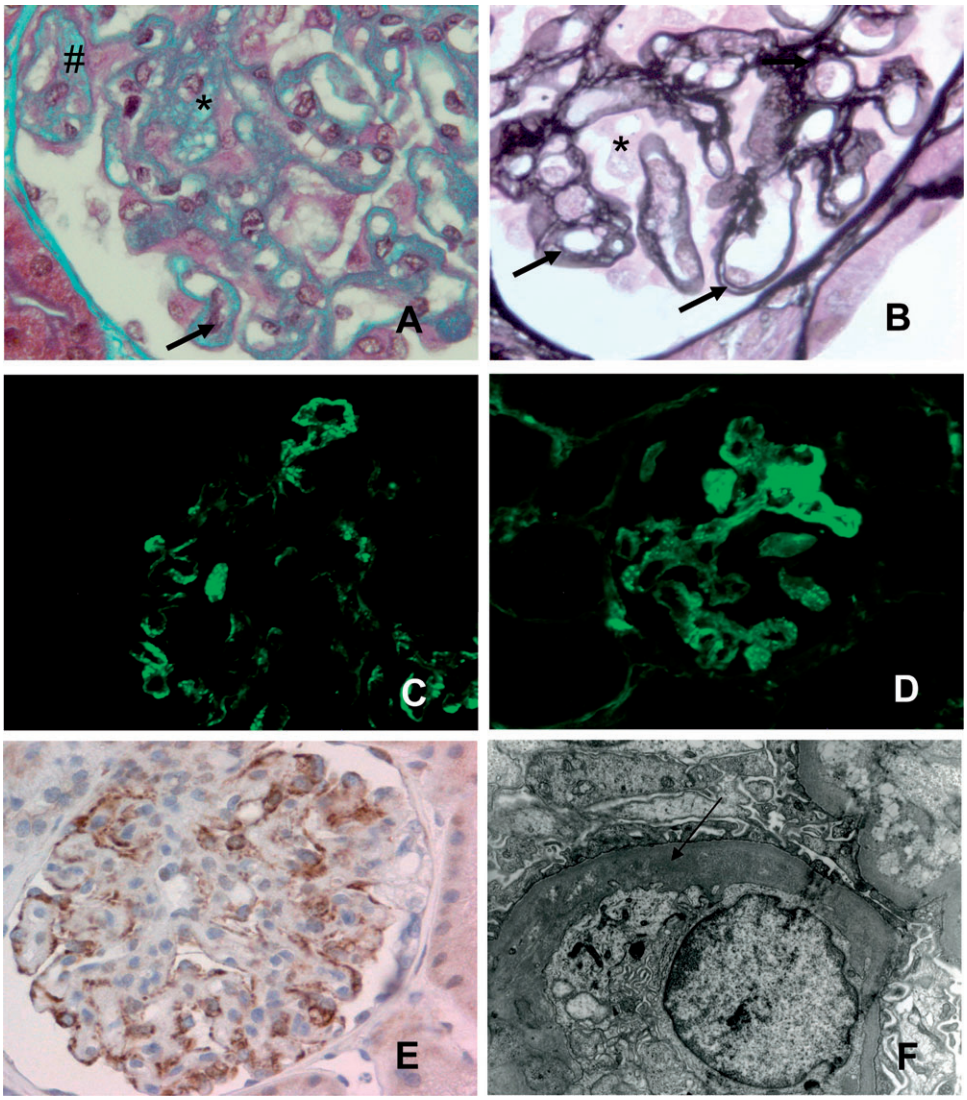

Fig. 1. Histological findings in a renal biopsy. (**A**,**B**) Light microscopy of the renal biopsy. (**A**) Masson's Trichrome stain, 1000× magnification: turgescence of endothelial cells (arrow), mesangiolysis (∗) and subendothelial space widening and clarification (#). No cellular proliferation was observed in glomeruli. Tubules and interstitium displayed no significant alterations. Small arteries and arterioles showed endothelial swelling but no other alterations. (**B**) Silver stain, 1000× magnification: pococyte swelling (∗) and subendothelial mesangial interposition (double contours) of glomerular basement membranes (arrows). (**C**,**D**) Immunofluorescence and immunohistochemistry study of the renal biopsy. (**C**) Immunofluorescence with an anti-IgA antibody, 400× magnification: capillary walls and mesangial deposits. Similar IgG and IgM deposits were also observed. (**D**) Immunofluorescence with an anti-fibrin antibody, 400× magnification: subendothelial deposits consistent with TMA. (**E**) Immunohistochemistry with an anti-VEGF antibody (peroxydase tracing, 400× magnification): the normal pattern of VEGF expression by podocytes. (**F**) Electron microscopy of the renal biopsy, 4000× magnification: electron dense deposits (arrow) in subendothelial space of the glomerular basement membrane.

metastasis. She was given a starting dose of sunitinib of 37.5 mg daily on a 4/2 schedule (4 weeks on treatment followed by 2 weeks off treatment). At baseline, blood pressure was 130/80 mmHg and search for proteinuria was negative. Two weeks after sunitinib initiation, high blood pressure was detected (170/100 mmHg) and treated by diltiazem. One month later, proteinuria was discovered at 1.1 g/day whereas serum creatinine level remained stable at 64 μmol/l and microhaematuria was undetectable. Biological signs of TMA were absent (haemoglobin level 13.3 g/dl, platelet count 146 000/mm^3, schistocytes undetectable, LDH: 581 IU/l). Six months after sunitinib was started, proteinuria remained between 0.25 and 1 g/day and high blood pressure persisted to 150/95 mmHg, necessitating commencement of hydochlorothiazide, as previously no haematological features of TMA had been detected. Antigenic dosages in serum of C3, C4, CH50, Factor H, Factor I and CD46/MCP were in the normal range. ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) activity was also normal. Renal ultrasound showed normal kidneys. A renal biopsy was performed.

The renal biopsy contained 13 glomeruli, none of which were globally sclerotic. Almost all showed typical features of TMA, with widespread duplication of the glomerular basement membranes, endothelial swelling, focal glomerular capillary thrombosis, mesangiolysis and fibrin deposits (Figure 1A, B, D). Immunofluorescence study demonstrated strong diffuse granular IgA and IgM deposits along

Table 1. Clinical and histological presentation of patients with renal biopsy proven TMA secondary to anti-VEGF drugs

Reference number	Drug	Dose	Time	Presentation	Biological TMA	TMA on renal biopsy	Immune deposits	Evolution
[2]	Bevacizumab	7.5 mg/kg/14 day	9 mo	Ht, Pu	Tp	Yes	No	Pu decrease after drug cessation
[2]	Bevacizumab	7.5 mg/kg/14 day	3 mo	Pu	No	Yes	No	Pu decrease after drug cessation
[2]	Bevacizumab	15 mg/kg/21 day	7 mo	RF, Ht, Pu	No	Yes	No	Rapid death due to malignant disease
[2]	Bevacizumab	10 mg/kg/14 day	3 mo	RF, Hu, Pu	No	Yes[a]	Mesangial IgA	RF and Pu normalization after drug cessation
[2]	Bevacizumab	10 mg/kg/14 day	5 mo	RF, Pu	Tp, Sch	Yes[a]	No	RF stabilization after plasmapheresis
[2]	Bevacizumab	15 mg/kg/21 day	9 mo	Pu	No	Yes	Mesangial IgA	Drug continued for 8 mo, stable Pu
[3]	Bevacizumab	Stopped 2 mo before	15 mo	RF, Ht, Pu	Mild Tp	Yes	Subendoth+mesangial IgA predominant	Mild improvement of RF and Pu
[6]	Bevacizumab	10 mg/kg/14 day	2 mo	NS, Ht, RF	Tp, HA	Yes[a]	No	Persistent Pu after drug cessation, relapse under sunitinib
[7]	VEGF trap	4 mg/kg/14 day	1 mo	NS, Hu	NR	Yes[a]	No	Almost complete recovery after drug cessation
This case	Sunitinib	37.5 mg/day	6 mo	Ht, Pu	No	Yes[a]	Subendoth+mesangial IgA, IgM	Sunitinib continued for 3 mo, resolution of Pu under ARB

All patients showed classic features of TMA on renal biopsy, including mesangiolysis, duplication of the glomerular basement membranes, endothelial swelling.

[a]Some patients also presented with arteriolar and/or glomerular capillary thrombosis. Time is the period elapsed from initiation of antiangiogenic therapy to TMA diagnosis (mo = months, Pu = proteinuria, RF = renal failure, Ht = hypertension, NS = nephrotic syndrome, Tp = thrombocytopaenia, Sch = schistocytes, HA = haemolytic anaemia, NR = not reported).

the glomerular basement membrane and less intense IgG, C3 and C1q deposits (Figure 1). Immunohistochemistry using an anti-VEGF antibody showed a normal pattern of expression of VEGF by podocytes (Figure 1E). Electronic microscopy study confirmed subendothelial widening consistent with light microscopy findings and electron dense deposits in the subendothelial space of the glomerular basement membrane (Figure 1F). Podocyte swelling with focal foot process effacement was also seen.

Despite this severe histological involvement contrasting with mild clinical features, sunitinib was continued considering the absence of alternative treatment for controlling tumour, which was stable under antiangiogenic therapy.

In addition to diltiazem and amiloride, the patient was given irbesartan. Subsequently, blood pressure and renal function remained stable and proteinuria became undetectable. However, sunitinib was subsequently interrupted 3 months after renal biopsy as lung metastasis had progressed and switched to anti EGF receptor therapy.

Discussion

Antiangiogenic treatments blocking VEGF are often associated with the occurrence of proteinuria and/or hypertension. Previous studies estimated the incidence of proteinuria to 21–63% and hypertension to 3–36% in patients treated by bevacizumab [1]. Recently, patients under sunitinib developing proteinuria and hypertension and even biological features of TMA have been reported [4–6]. However, no description of renal histology was provided in these reports. We report on the first case of histologically documented TMA secondary to sunitinib.

Our case highlights the possible discrepancy between mild clinical manifestation on one hand and severe TMA features on renal biopsy on the other hand. Indeed, our patient presented with only proteinuria <1 g/day and easily controlled hypertension. This is consistent with reports of biopsy-proven renal TMA secondary to bevacizumab: mild-to-severe renal failure was observed in only half of patients, proteinuria varied from low grade to nephrotic range, and biological features of TMA (e.g. haemolytic anaemia, thrombopaenia, schistocytes) were inconstant. Such renal-localized TMA without typical haematological features have been previously reported, especially in cancer patients after radiation or chemotherapy [7]. Table 1 summarizes cases of renal biopsy-proven TMA occurring under anti-VEGF drugs [2,3,8,9]. TMA is therefore likely underdiagnosed among patients developing mild proteinuria under anti-VEGF therapy. This pleads for large indication of a renal biopsy in these patients, even in the absence of renal failure and biological features of TMA.

Furthermore, our case suggests that sunitinib and bevacizumab (and probably all drugs inhibiting the VEGF signalling pathway) share a similar risk for developing renal adverse events, including TMA. Why only a subset of patients receiving anti-VEGF therapy develop TMA remains unclear. VEGF is constituently synthesized by podocytes, and VEGFR2 is expressed by glomerular capillary endothelial cells [10]. Once synthesized by podocytes, VEGF would be delivered to glomerular endothelial cells against the flow of urinary ultrafiltrate. Disruption of VEGF signalling through drugs or genetic deletion in podocytes has been shown to lead to the loss of the healthy-fenestrated phenotype of glomerular capillaries, microvascular injury and TMA [2]. Endothelial injury caused by VEGF

blocking is also likely to favour hypertension and arterial thrombosis, another side effect related to anti-VEGF drugs [11]. Experimental data suggest that hypertension related to anti-VEGF drugs may occur as a result of decreased NO synthesis by arterial endothelial cells, leading to increased vascular tone [12]. However, at which degree, if any, NO synthesis inhibition is implicated in the pathogenesis of anti-VEGF-induced TMA remains undetermined.

It is unclear whether other factors could favour TMA in patients receiving anti-VEGF agents. Recent advances provided evidence that defective regulation of the complement alternative pathway (CAP) causes defective protection of endothelial cells and TMA [13]. In our case, levels of complement and proteins regulating the CAP were normal. However, mutations in genes encoding CAP proteins (Factor H, Factor I, CD46/MCP, C3) were recently identified in pregnancy-associated HELLP syndrome with normal levels of CAP proteins [14]. Of note, in this setting, glomerular lesions are also induced by low levels of biologically available VEGF (and PIGF) due to increased sFlt1 production by the ischaemic placenta [15]. Further studies should determine whether CAP genes mutations are a predisposition factor to anti-VEGF-induced TMA.

Unexpected glomerular subendothelial deposits of IgA and IgM were observed in our patient. Among cases of TMA-reported secondary to bevacizumab, similar immune deposits were described in one case [3] and mesangial IgA deposits in two cases [2]. The significance and pathogenic role of these deposits remain unclear. However, whereas bevacizumab-associated deposits could have been related to immunization against the monoclonal antibody, the present sunitinib-associated case favours other mechanisms.

VEGF expression by podocytes demonstrated by immunohistochemistry was normal in our case. This was expected since sunitinib does not blunt VEGF production by podocytes but acts on VEGF receptors on endothelial cells.

Renal TMA is a severe complication that should prompt discussing cessation of anti-VEGF drugs in the vast majority of cases. Fortunately, stopping treatment usually results in complete recovery or at least significant improvement of hypertension and renal involvement [2,3,8,9]. However, the occurrence of hypertension has been suggested to reflect efficient VEGF signalling pathway blocking and could be associated with superior antitumoural effect [16]. It is noticeable in our case that renal function remained stable and that proteinuria and hypertension were well controlled by sartan whereas sunitinib was continued for 3 months after renal biopsy. Blocking the renin–angiotensin system has proved effective in other TMA-associated hypertension and proteinuria and could be the first choice in hypertension secondary to antiangiogenic therapy.

Therapeutic alternatives are generally very limited in patients with advanced cancer, and the decision of withholding (or not) anti-VEGF drug should be based on multidisciplinary concertation.

In summary, our case provides evidence that TMA may occur secondary to sunitinib, similarly to previous reports implicating bevacizumab. It is important for clinicians implicated in the management of cancer patients to be aware that TMA must be considered in patients under anti-VEGF developing mild proteinuria, even in the absence of renal failure and biological features of TMA.

Conflict of interest statement. None declared.

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Received for publication: 18.9.08
Accepted in revised form: 31.10.08