Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, has been widely used in a variety of malignancies offering substantial clinical benefit. Hypertension and proteinuria are the most commonly reported manifestations of bevacizumab-related nephrotoxicity with the risk increasing along with the dose and with the concomitant use of bisphosphonates.

We describe the first case of a patient with small-cell lung cancer who developed diffuse extracapillary necrotizing crescentic glomerulonephritis, temporarily necessitating haemodialysis, following administration of bevacizumab and zolendronate. Renal function improved without any specific treatment and the patient remained off dialysis after withdrawal of bevacizumab–zolendronate.

Special caution is required when VEGF inhibitors are combined with bisphosphonates. Such a combination can cause crescentic necrotizing glomerular lesions. Withdrawal of the offending medications may be adequate for the alleviation of this severe glomerulonephritis.

Keywords: bevacizumab; crescentic glomerulonephritis; zolendronate

Introduction

Neangiogenesis is a mechanism of critical importance in the development and expansion of malignant tumours. Vascular endothelial growth factor (VEGF) is the major representative of molecules mediating the process of angiogenesis [1]. Bevacizumab, a VEGF inhibitor, has been used in a variety of malignancies offering substantial clinical benefit when combined with standard chemotherapy [2]. Overall, the use of bevacizumab appears well tolerated; most of the reported adverse events range from mild to moderate [2]. Occasionally, it has been associated with severe adverse events such as thromboembolic episodes, gastrointestinal perforation, congestive heart failure and haemorrhage [2]. Hypertension and proteinuria are the most frequent manifestations of bevacizumab-related nephrotoxicity displaying a dose-dependent risk [3–5]. Bevacizumab-induced hypertension...
is usually successfully managed by conventional antihypertensive agents. Most proteinuria cases resolve upon treatment discontinuation, although it may prove refractory in few severe occasions [2]. High-dose bisphosphonates have also been associated with nephrotoxicity and proteinuria in patients treated for bone metastases [6], while their combination with bevacizumab has been considered as a risk factor for developing proteinuria [7]. Here, we describe the first case of crescentic glomerulonephritis (CGN) following administration of bevacizumab and zolendronate in a patient with malignant disease.

Case

A 67-year-old Caucasian male smoker, presented with persistent fever and chest pain in May 2005. Further investigation revealed locally extended small-cell lung carcinoma with hepatic metastases. The patient was commenced on first-line chemotherapy with etoposide and cis-diammine-dichloroplatinum. Five months later, he was changed to second-line (alimta and carboplatin) and, subsequently, to third-line chemotherapy (irinotecan and pegylated doxorubicin). He completed eight cycles of third-line chemotherapy and remained stable during the following months. In January 2009, the patient presented with progressive disease in imaging studies. He was started on paclitaxel 90 mg/m²/week for 4 weeks and 2 weeks off and bevacizumab 10 mg/kg every 2 weeks leading to a partial response. He presented, though, neurotoxicity grade II, mild proteinuria (1+) and a slight increase of creatinine from 62 to 97.2 µmol/L. Creatinine fluctuated at these levels over the following 14 months. In September 2009, a routine follow-up revealed brain metastasis for which he received whole brain irradiation; in addition, a new chemotherapy regimen with irinotecan (80 mg/m²/week) and bevacizumab (10 mg/kg/15 days) was administered. In February 2010, magnetic resonance imaging demonstrated disappearance of brain lesions and appearance of bone metastases in the left hip. The patient continued bevacizumab and was restarted on paclitaxel combined with zolendronate (4 mg/month intravenously) and radiation therapy of the left hip. In April 2010, a routine laboratory workup revealed acute renal failure (serum creatinine 186 µmol/L) with minimal proteinuria (1+). The patient also reported a 3-day history of macroscopic haematuria and was admitted to the hospital. During the following days, he developed peripheral oedema, shortness of breath, hypertension (180/95 mmHg) and rapidly deteriorating renal function with serum creatinine reaching 353 µmol/L. A 24-h urine collection showed massive proteinuria (5720 mg/day). Subsequently, the patient was referred to the nephrology department. A renal ultrasound was unremarkable except for slightly increased echogenicity of the cortex and a triplex showed patent renal veins. Laboratory investigation showed normochromic normocytic anaemia with haemoglobin at 9 g/dL.

Fig. 1. Kidney biopsy showed wide interstitial fibrosis and tubular atrophy (A and B). There was severe intimal fibrosis of arteries and mild hyalinosis of arterioles (B). Most glomeruli presented large cellular crescents (A, B, C and D); Periodic acid-Schiff staining.
white blood cells $8.8 \times 10^3/\mu L$ and platelets $290 \times 10^3/\mu L$. Transaminases were within normal limits and lactic dehydrogenase levels, which were consistently increased throughout his illness, were further increased at 869 U/L. Haptoglobin was marginally decreased at 40 mg/dL (normal range 41–160 mg/dL). Clotting times and D-dimers were not affected. One of three repeated blood smears revealed the presence of occasional schistocytes raising the possibility of thrombotic microangiopathy. The urine sediment showed dysmorphic red blood cells, lipid casts and mixed casts containing red and white blood cells. Antinuclear antibodies, anti-dsDNA, antineutrophil cytoplasmic antibodies, myeloperoxidase, proteinase-3, anti-glomerular basement membrane antibodies and serum complement levels were all normal or negative. The patient initially refused to undergo a kidney biopsy and was treated with ramipril 5 mg once a day, amlodipine 10 mg once a day and furosemide. In May 2010, he commenced haemodialysis due to further deterioration of kidney function (serum creatinine 478 μmol/L), oliguria and pulmonary oedema. At this point, he consentingly underwent kidney biopsy. The kidney specimen contained 29 glomeruli, from which 2 were globally sclerotic and 15 showed large crescents (11 cellular, 4 fibrocellular) with segmental necrosis (Figure 1). There was severe intimal fibrosis of arteries, mild hyalinosis of arterioles and wide interstitial fibrosis (60% of parenchyma) associated with focal lymphocytic infiltration and tubular atrophy. Immunofluorescence showed mesangial IgM (2+) and C3 (1+) deposits and segmental staining for fibrinogen (2+) in the crescents. Reactions for IgA, IgG, C1q, kappa and lambda light chains were negative. The diagnosis of diffuse proliferative extracapillary glomerulonephritis was made. A scheduled course of pulse steroids and cyclophosphamide was not ultimately applied since serum creatinine levels improved spontaneously, leading to cessation of haemodialysis 2 weeks after initiation. Over the following 2 months, creatinine levels stabilized at 176.8 μmol/L, proteinuria declined <0.7 g/day and hypertension improved. Despite improvement of kidney disease, the patient’s status deteriorated because of his malignant disease, and he succumbed to respiratory failure shortly thereafter.

Discussion

The use of VEGF inhibitors in cancer treatment has been associated with increased incidence of hypertension (3–36%) and proteinuria (21–63%) [3]. Thrombotic microangiopathy (TMA) is the most frequently encountered renal pathology [8,9]. However, the available histopathological data are limited. Cryoglobulinaemic glomerulonephritis [10] and immune complex-mediated focal proliferative glomerulonephritis [11] have also been described (one case of each).

VEGF signalling is of pivotal importance for the development of physiological glomerulus and the preservation of glomerular integrity and function [1]. VEGF and its receptors are expressed by podocytes and capillary endothelial cells, respectively. [12]. Several mechanisms may underlie VEGF inhibition-related proteinuria [3,12]. However, the precise role of the VEGF pathway remains elusive; there are data suggesting that both increased and diminished VEGF expression may be related to glomerular injury. Disruption of the VEGF pathway is associated with proteinuria accompanied by endotheliosis similar to preeclampsia [12,13], downregulation of nephrin expression and loss of podocytes [13] and may also interfere with the physiological process of renal repair following glomerular injury [1,3]. Conversely, VEGF overexpression has been implicated in the pathophysiology of diabetic nephropathy [14], while podocyte-specific VEGF overexpression is associated with collapsing glomerulopathy [13].

Concerning the clinical diagnosis in our patient, the presence of rare schistocytes in the blood smear in association with bevacizumab treatment pointed towards the diagnosis of TMA, which was not eventually histopathologically confirmed. On the other hand, the rapidly progressive clinical course was in keeping with the pathologic finding of crescentic glomerulonephritis.

The concurrent use of bisphosphonates has been considered as a risk factor for developing proteinuria in patients receiving bevacizumab. Miller et al. [7] reported that proteinuria occurred in 34% of patients receiving combined bevacizumab and pamidronate treatment compared with 18.5% of those administered bevacizumab alone. Pamidronate toxicity appears to target podocytes causing a collapsing form of focal segmental glomerulosclerosis (FSGS) [6]. In contrast, zolendronate appears to affect tubular epithelial cells, causing acute tubular necrosis. Of note, a case of collapsing FSGS following treatment with zolendronate has been reported, indicating that zolendronate may also pose podocytotoxic effects [15]. The distinction that pamidronate targets the podocytes and zolendronate, the tubules may be an oversimplification since renal biopsy findings are not provided in any of the large trials that have documented renal insufficiency following treatment with bisphosphonates. Given the spatial and functional association between podocytes and glomerular endothelial cells, the combination of bevacizumab with zolendronate could affect both cellular compartments, augment toxicity and lead to capillary wall disruption and crescent formation.

Our patient developed mild renal dysfunction soon after initiation of bevacizumab but only after zolendronate addition did renal function rapidly deteriorate necessitating haemodialysis. It is well known that CGN leads to irreversible end-stage kidney failure, unless aggressive immunosuppressive treatment is timely employed. The improvement of renal function after withdrawal of bevacizumab and zolendronate suggests a pathogenetic role of these drugs for the observed histological lesions. To the best of our knowledge, this is the first case of CGN associated with bevacizumab–zolendronate treatment ever reported.

Because of the concerns raised by previous studies regarding the increased incidence of nephrotoxicity from the combination of bevacizumab–bisphosphonates as well as due to the severity of kidney involvement in our patient, we felt it important to bring this case to the attention of nephrologists and oncologists. A low threshold for renal biopsy may help identify similar cases and shed more light onto the effects of VEGF inhibition on kidney structure and function.
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References


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