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CASE REPORT

Aflibercept-induced Nephrotic Syndrome

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ABSTRACT

Aflibercept is a high-affinity ligand trap for vascular endothelial growth factor (VEGF) and is used as second-line therapy against metastatic colorectal cancer. It has a similar but potentially less favourable toxicity profile compared with other anti-angiogenic agents. We report a Chinese woman with metastatic colorectal cancer who developed nephrotic syndrome after a single dose of aflibercept (4 mg/kg) with FOLFIRI (leucovorin, fluorouracil, and irinotecan). On days 11 and 18, 24-hour urine collection showed urine protein of 6.07 and 8.72 g/day, respectively. Renal biopsy revealed chronic interstitial nephritis due to underlying obstructive uropathy. The nephrotic syndrome resolved after stopping aflibercept. This illustrates the reversible nature of aflibercept-induced proteinuria, especially when detected and treated early. It is important to monitor the urine protein level in patients prescribed aflibercept, even in those who tolerate other anti-VEGF therapies without significant proteinuria.

Key Words: *Aflibercept; Colorectal neoplasms; Nephrotic syndrome; Proteinuria*

中文摘要

阿普西柏誘發的腎病綜合症

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阿普西柏是血管內皮生長因子（VEGF）的配體陷阱，並用作二線治療轉移性結腸直腸癌。與其他抗血管生長藥相比，它具有相似但可能更不利的毒性。本文報導一名患轉移性結腸直腸癌的華籍女性，在接受單劑量的阿普西柏（4 mg / kg）及FOLFIRI (leucovorin, fluorouracil, and irinotecan) 後出現腎病綜合症。在第11天和第18天，24小時尿液收集顯示尿蛋白分別為每天6.07和8.72 g。腎活檢顯示阻塞性尿道症引致慢性間質性腎炎。腎病綜合症在停藥後緩解。這說明了此症的可逆性，檢測和治療及時尤為明顯。定期監測尿蛋白水平很重要，包括曾接受其他抗VEGF療法且沒有蛋白尿的患者。

INTRODUCTION

Aflibercept is a high-affinity ligand trap for vascular endothelial growth factor (VEGF) and is used as second-line therapy in combination with FOLFIRI (leucovorin, fluorouracil, and irinotecan) for metastatic colorectal cancer that has progressed beyond an oxaliplatin-based

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regimen.[1] Aflibercept works as a decoy receptor that binds human VEGF-A, VEGF-B, and placental growth factor and thus inhibits binding of these growth factors to their receptors. The mechanism of action is primarily through anti-angiogenesis. Similar to bevacizumab, aflibercept improves survival in patients with metastatic colorectal cancer. Despite its toxicity profile typical of anti-angiogenic agents, aflibercept is pertinent to proteinuria. We report a case of grade-4 proteinuria secondary to a single dose of aflibercept (4 mg/kg) combined with FOLFIRI.

CASE REPORT

In April 2014, a 52-year-old Chinese woman with a history of hypertension (controlled with amlodipine) was diagnosed with adenocarcinoma of the rectosigmoid colon and metastasis to lung and left pelvic lymph nodes. The left pelvic lymph nodes caused extrinsic compression of the left ureter resulting in left hydronephrosis. Palliative anterior resection of the rectum, ureteric segmental excision, and primary ureteroureterostomy were performed. A double J stent was inserted into the left ureter. Pathology was poorly differentiated adenocarcinoma with *KRAS* mutation at exon 2 (G13D). Six cycles of palliative chemotherapy with XELOX (capecitabine plus oxaliplatin) and bevacizumab (oxaliplatin 130 mg/m^2 on day 1, capecitabine 1000 mg/m^2 twice daily on days 1-14, bevacizumab 7.5 mg/kg every 3 weeks) were given. During all six cycles of bevacizumab, urine dipstick testing remained negative for protein with stable serum creatinine levels. After the sixth cycle, positron emission tomography computed tomography showed a new bone metastasis at the T1 vertebra and a new pelvic mass on the right side.

In November 2014, second-line chemotherapy using FOLFIRI and aflibercept (irinotecan 180 mg/m^2 on day 1, 5-fluorouracil 400 mg/m^2 as bolus and 600 mg/m^2 as 22-hour infusion on days 1-2, and aflibercept 4 mg/kg on day 1 every 2 weeks) was started. On day 1, routine pre- and post-aflibercept urine dipstick testing was negative and 2+ (grade-2 proteinuria), respectively. On days 11 and 18, 24-hour urine collection showed urine protein of 6.07 and 8.72 g/day, respectively (Table). The patient complained of new-onset bilateral ankle oedema and frothy urine suggestive of nephrotic syndrome. Her serum albumin was 28 (reference range, 39-50) g/l, and total cholesterol was 6.5 (reference level, <5.2) mmol/l.

Aflibercept was terminated, and 5 mg of ramipril daily was started (in addition to 2.5 mg amlodipine for hypertension). A nephrologist was consulted for suspected membranous glomerulonephritis. Her serum immune markers, immunoglobulin (Ig) G, IgA, IgM, C3, C4, anti-nuclear antigen, and anti-neutrophil cytoplasmic antibody were negative. Serum electrophoresis and urine culture were unremarkable. Biopsy of the left kidney showed no evidence of glomerulonephritis. Immunofluorescence studies showed no deposits of IgG, C3, or C1q, whereas deposits of IgA and IgM were focal and equivocal. The renal arterioles and interlobular arteries displayed marked intimal fibrous thickening, medial hypertrophy, and hyalinosis. No evidence of thrombotic microangiopathy was noted. A pathological diagnosis of chronic interstitial nephritis secondary to underlying obstructive uropathy was made. The patient received further doses of FOLFIRI alone without subsequent anti-VEGF therapy. Proteinuria resolved gradually over the 3-month observation period, and ramipril was stopped. Her blood pressure remained well controlled throughout.

Table. Urine protein increases on days 11 and 18 after administration of a single dose of aflibercept and gradually decreases over the following months, while serum creatinine level remains stable.

Time after aflibercept administration	Urine protein (g/day)	Serum creatinine (mmol/l)
Day 11	6.07	94
Day 18	8.72	89
Month 1	6.00	80
Month 2	1.32	75
Month 3	0.89	79

DISCUSSION

The VELOUR study[1] is a phase-III randomised controlled trial to establish the role of aflibercept as second-line treatment for patients with metastatic colorectal cancer that has progressed beyond an oxaliplatin-based regimen. In patients treated with aflibercept plus FOLFIRI, 62% developed proteinuria, and 8% of which were grade 3 or 4. In controls, only 41% developed proteinuria, and only 1% of which were grade 3 or 4. Interestingly, only 23% and 0% of patients in the aflibercept group developed any grade or grade-3 or -4 serum creatinine increase, respectively. This suggests that aflibercept-induced proteinuria is common but rarely results in severe renal function derangement.

Proteinuria is a class effect of anti-VEGF therapy.[2] It has been reported in patients prescribed bevacizumab,

regorafenib, pazopanib, sunitinib, and axitinib. The underlying mechanism is multifactorial. One postulation is that inhibition of VEGF signalling down-regulates nephrin (a critical glomerular endothelial protein) and results in swelling and detachment of glomerular endothelial cells from the basement membrane, and thus disruption of the glomerular filtration barrier.[3] Another postulation is that the increased intra-glomerular pressure seen in systemic hypertension (a common side-effect of anti-VEGF therapy) is caused by the lack of stimulation of the nitric oxide pathway and reduced density of the microvascular beds.[3]

Most cases of anti-VEGF–induced proteinuria are reversible,[4] and hence renal biopsy is not usually indicated and study of pathological correlation is scarce.[2] Most renal pathologies are caused by bevacizumab.[3] Renal pathological findings of grade-3 or -4 proteinuria in patients with anti-VEGF therapy vary; they include 12 cases of thrombotic microangiopathy, two cases of collapsing focal segmental glomerulosclerosis (likely caused by concomitant pamidronate), one case of cryoglobulinemic glomerulonephritis, one case of immune complex glomerulonephritis, one case of mesangioproliferative glomerulonephritis, one case of glomerular endotheliosis, and one case of sorafenib-induced acute interstitial nephritis.[3]

To the best of our knowledge, our patient is the first reported case of anti-VEGF–induced proteinuria associated with chronic interstitial nephritis, which is known to cause proteinuria by itself.[5] The single dose of aflibercept may have exacerbated the proteinuria. The patient had received six prior cycles of XELOX (capecitabine plus oxaliplatin) with bevacizumab without any proteinuria. The severity of proteinuria and the occurrence of nephrotic syndrome following a single dose of aflibercept was unexpected. In a meta-analysis of 4596 patients in 16 clinical trials,[6] the relative risk of developing all-grade or high-grade proteinuria was significantly higher after administration of aflibercept than bevacizumab (2.37 vs. 1.85). Aflibercept is a more potent VEGF blocker that binds circulating VEGF-A, VEGF-B, and placental growth factor. Thus proteinuria occurred after administration of aflibercept but not bevacizumab.

Risk factors for anti-VEGF–induced proteinuria include poor renal reserve with pre-existing renal disease, history of hypertension, and renal cell carcinoma.[3] Our patient had no history of renal disease or uncontrolled hypertension. Nonetheless, in the presence of her long-standing left hydronephrosis, her renal function reserve may have been compromised despite a relatively normal serum creatinine level. The tubular dysfunction in chronic interstitial nephritis secondary to obstructive uropathy may contribute to proteinuria by reducing reabsorption of protein in tubular fluid and altering the tubulo-glomerular reflex.[5] Nonetheless, severe proteinuria and nephrotic syndrome are extremely rare. Aflibercept may have significantly exacerbated the proteinuria. Aflibercept-induced nephrotic syndrome may occur in patients who have tolerated other anti-VEGF therapies. Aflibercept should be given with caution in patients with prior obstructive uropathy. Full recovery of nephrotic syndrome in our patient illustrates the reversible nature of aflibercept-induced proteinuria, especially when detected and treated early. It is important to monitor the urine protein level in patients prescribed aflibercept or anti-VEGF therapy.

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